Going with the Flow – The Use of Continuous Processing in Organic Synthesis

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Center for Continuous Flow Synthesis and Processing (CCFLOW) - RCPE GmbH
Graz, Austria

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Continuous Processing – A Hot Topic in Both Industry and Academia

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

Continuous Processing has Arrived in Big Pharma

Novartis to give MIT $65m to find new way to produce drugs

The Boston Globe

Focus on manufacturing

By Todd Wallack, Globe Staff | September 28, 2007

Drug giant Novartis AG says it will give its Cambridge neighbor, MIT, $65 million over 10 years to create a research program, likely to be the biggest in the world aimed at revolutionizing the way drugs are made.

The goal is to help companies move from making drugs in batches to using a continuous high-tech process that will save time and money.

GSK commits to continuous processing

Witty says it could be used on up to half of the company's drugs

February 19, 2013 | By Eric Palmer

The Mainstreaming of Continuous Flow API Synthesis

The pharma industry is moving toward commercial-scale continuous processes for small-molecule API manufacturing.

Jul 02, 2014 By Cynthia A. Challener
Pharmaceutical Technology
Volume 38, Issue 7

Vertex, J&J, GSK, Novartis all working on continuous manufacturing facilities

FDA supports the move as a way to improve quality in manufacturing

February 9, 2015 | By Eric Palmer

Lilly takes to continuous manufacturing with $40m Irish investment

By Dan Stanton

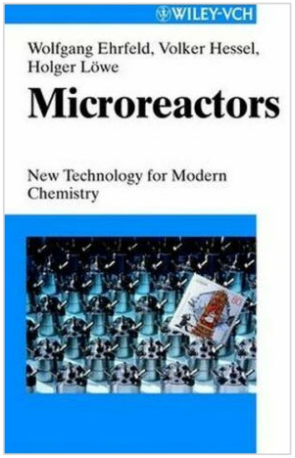
05-Apr-2016 - Last updated on 06-Apr-2016 at 11:03 GMT

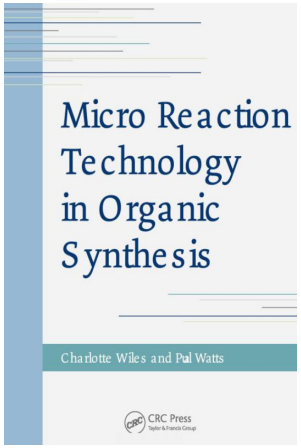
GSK completes $95m investment for continuous manufacturing in Singapore

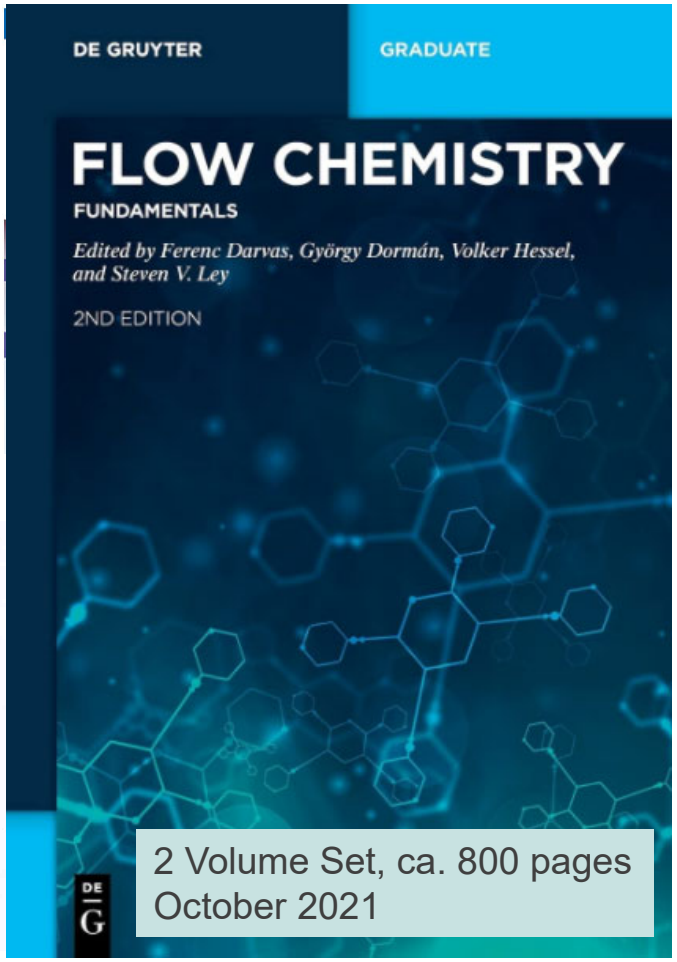
By Ben Hargreaves

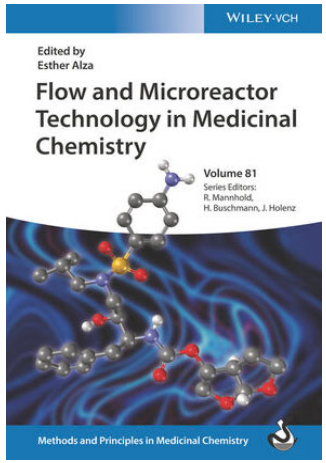
06-Aug-2019 - Last updated on 06-Aug-2019 at 16:18 GMT

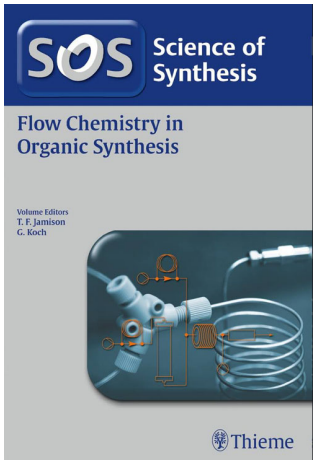
Literature on Flow Chemistry, Microreactors and Continuous Processing

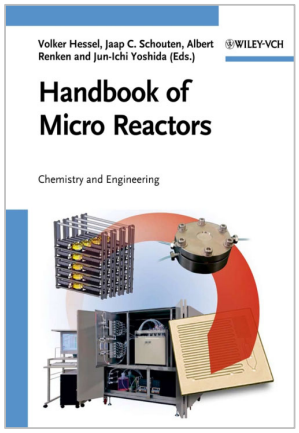


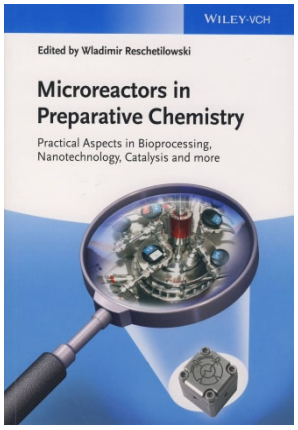


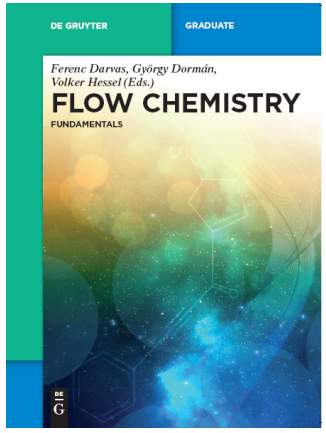


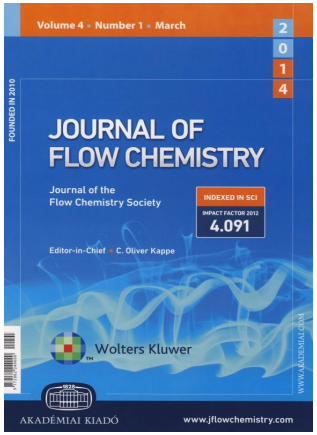






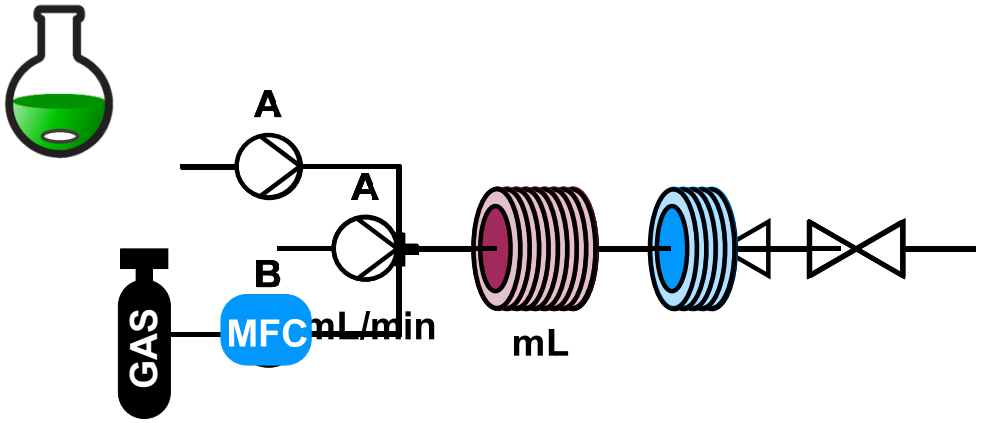


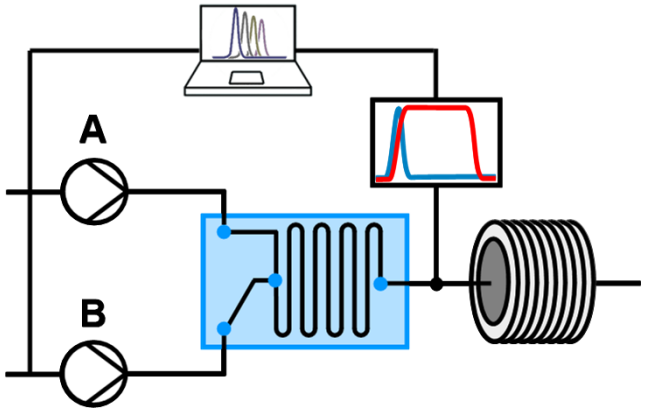


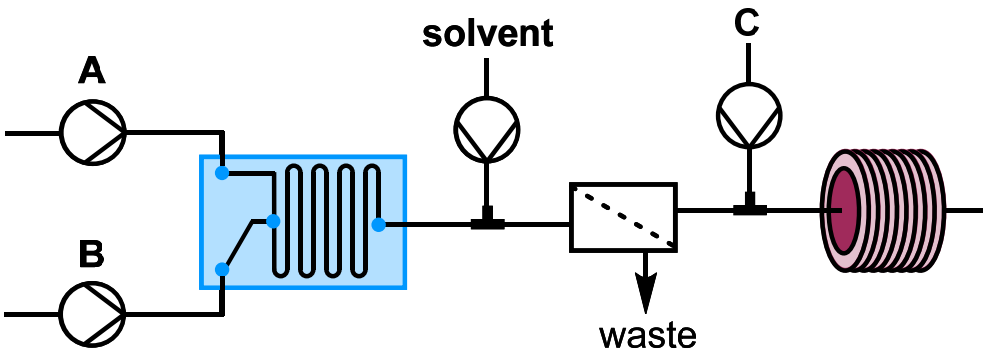


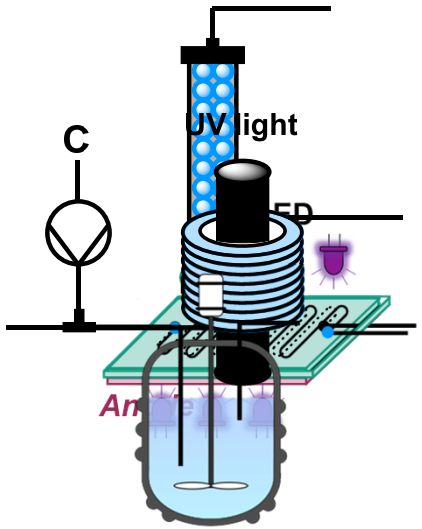
General Flow Chemistry Principles

The Hitchhiker's Guide to Flow Chemistry,
Seeberger, P. H. et al. *Chem. Rev.* **2017**, 117, 11796









Typical Flow Reactors (Lab Scale)

THALESNANO

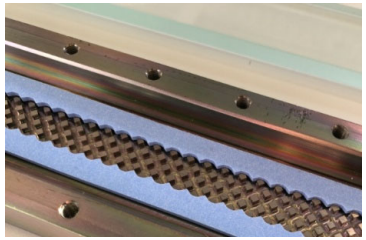
H-Genie
Phoenix Pro

www.thalesnano.com

CREAFLOW

HANU Reactor

www.creaflow.be



Anton Paar

3D Printed Reactors

www.anton-paar.com

vapourtec

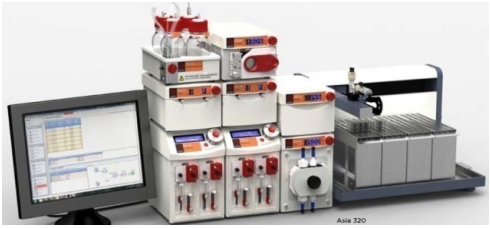
E-Series Flow System

www.vapourtec.com

UNIQSIS

FlowSyn

www.uniqsis.com



syrris

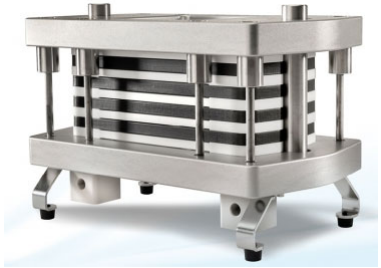
Asia System

www.syrris.com

CORNING

Advanced Lab Flow Reactor

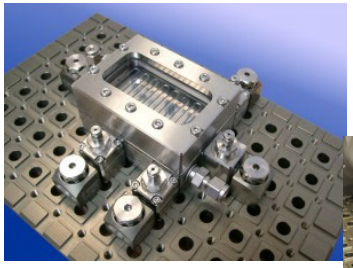
www.corning.com



CHEMTRIX

Protrix

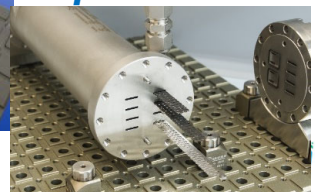
www.chemtrix.com



EHRFELD Mikrotechnik

Lonza FlowPlate
Miprowa

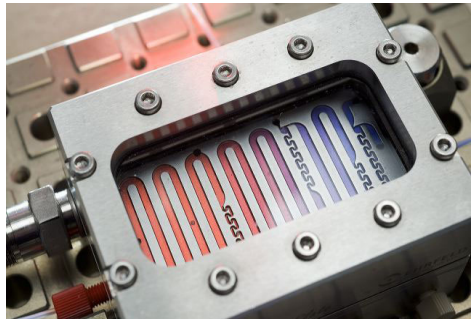
www.ehrfeld.com



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)

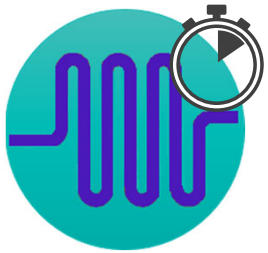
Microreactor for Flow Processing



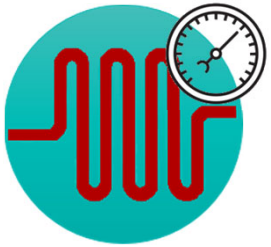
Scale-Up by Smart Dimensioning

Flow Chemistry in the Kappe Lab – Scalability and Manufacturability (CoG/Sustainability)

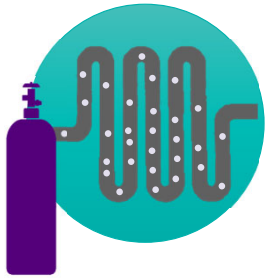
Flash Chemistry



High-T/p



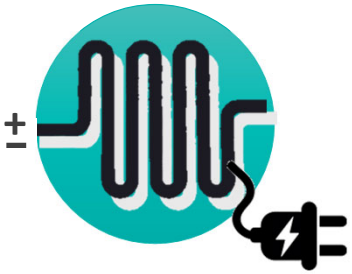
Gas-Liquid



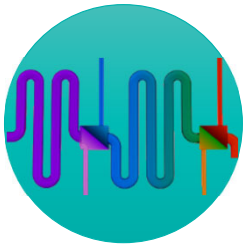
Hazardous Chemistry

Photochemistry

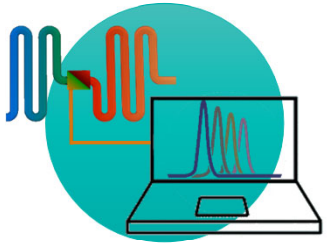
Electrochemistry



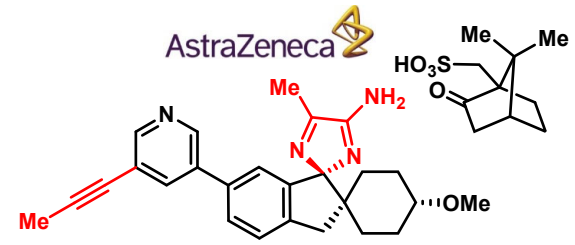
Multi-step/APIs



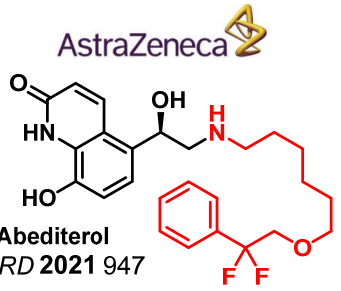
PAT/Process Control



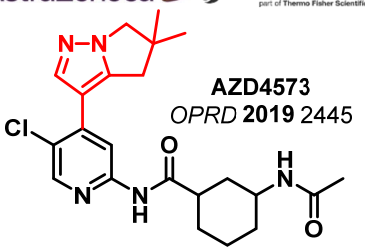
APIs/Intermediates (Clinical Studies and Marketed Drugs)



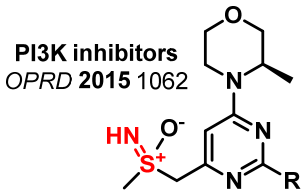
Lanabecestat
JFC **2017** 29, *OPRD* **2017** 878, *OPRD* **2018** 633



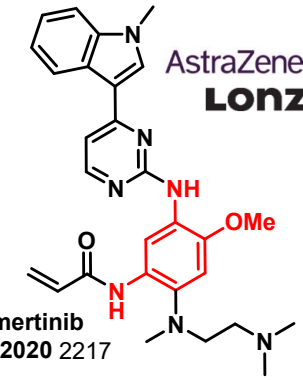
Abediterol
OPRD **2021** 947



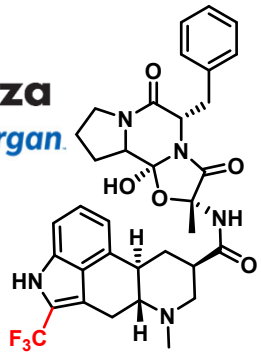
AZD4573
OPRD **2019** 2445



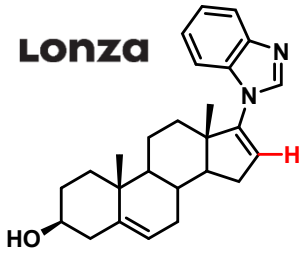
PI3K inhibitors
OPRD **2015** 1062



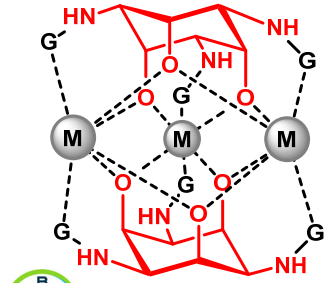
Osimertinib
OPRD **2020** 2217



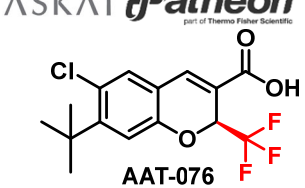
5-HT agonist
CEJ **2017** 176



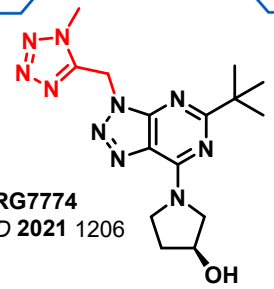
Galeterone
ACIE **2014** 11557



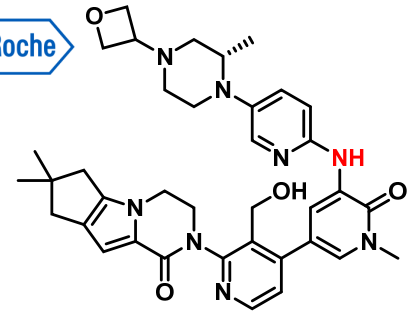
X-Ray Imaging
OPRD **2014** 1360



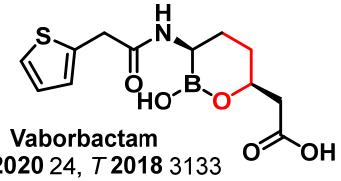
AAT-076
CEJ **2022** e202200741



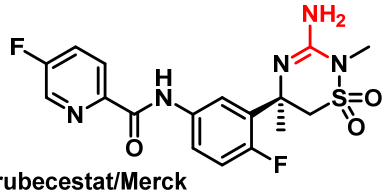
RG7774
OPRD **2021** 1206



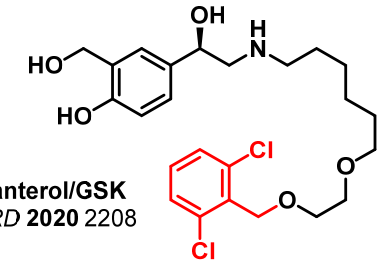
Fenebrutinib
OPRD **2021** 1988



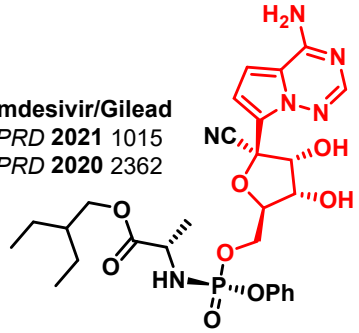
Vaborbactam
CO **2020** 24, *T* **2018** 3133



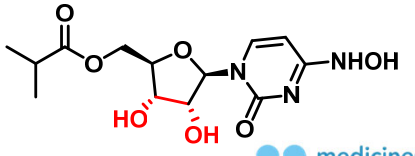
Verubecestat/Merck
ACIE **2017** 13786



Vilanterol/GSK
OPRD **2020** 2208

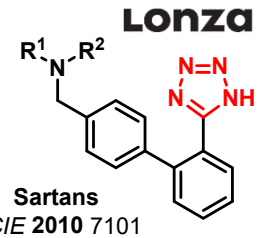


Remdesivir/Gilead
OPRD **2021** 1015
OPRD **2020** 2362

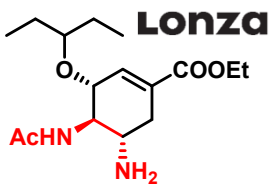


Molnupiravir/Merck
EJOC **2020** 6736

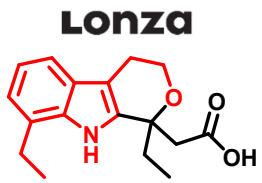
APIs/Intermediates (Generics)



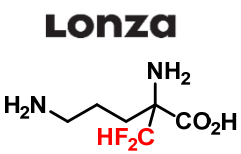
Sartans
ACIE **2010** 7101



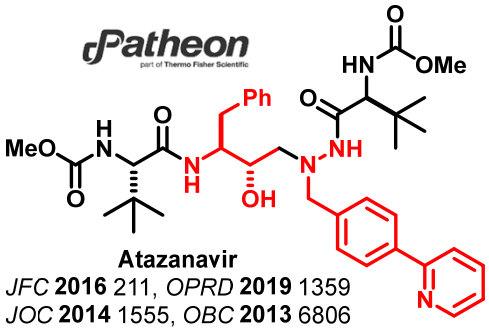
Oseltamivir
CEJ **2011** 13146



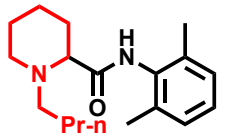
Etodolac
OPRD **2013** 294



Eflornithine
OPRD **2018** 1553
GC **2018** 108, *JFC* **2017** 46

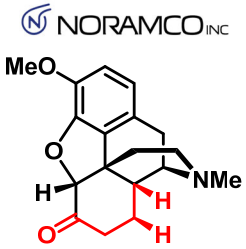


Atazanavir
JFC **2016** 211, *OPRD* **2019** 1359
JOC **2014** 1555, *OBC* **2013** 6806

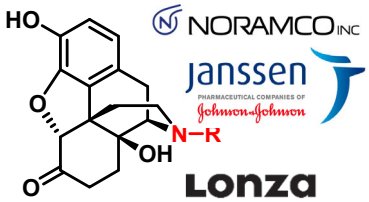


Bupivacaine
EJOC **2017** 6511

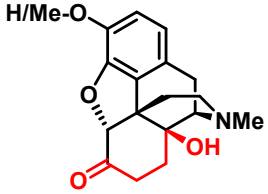
Levetiracetam
OBC **2019** 1552



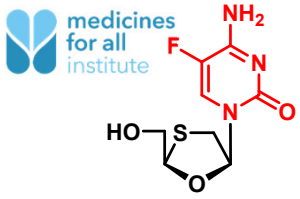
Hydrocodone
OPRD **2016** 376



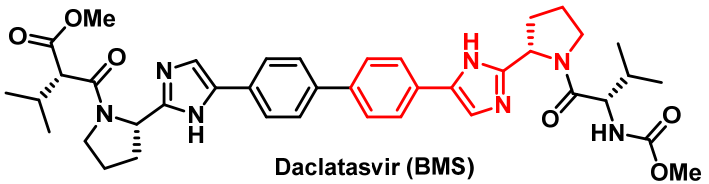
Naloxone/Naltrexone
ACSSCE **2016** 6048
CEJ **2016** 10393, *EJOC* **2017** 914
ACSSCE **2022** 8988



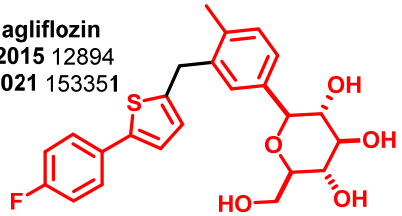
Oxymorphone/Oxycodone
EJOC **2017** 6505, *JFC* **2021** 707



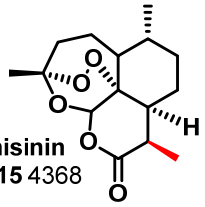
Emitricitabine
ACSCHS **2022** 165



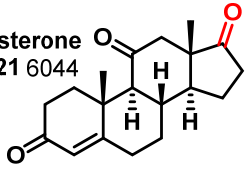
Daclatasvir (BMS)
ACSSCE **2015** 3445



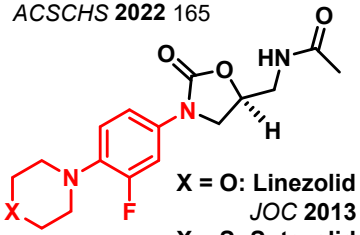
Canagliflozin
CEJ **2015** 12894
THL **2021** 153351



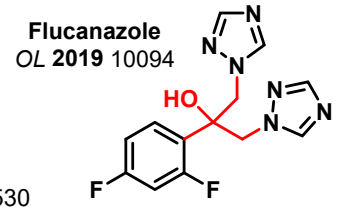
Artemisinin
CEJ **2015** 4368



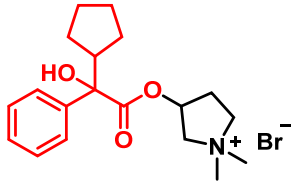
Adrenosterone
CEJ **2021** 6044



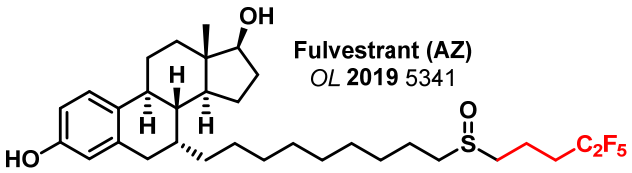
X = O: Linezolid
JOC **2013** 4530
X = S: Sutezolid
OPRD **2022** 2532



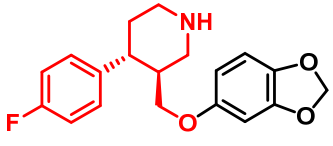
Flucanazole
OL **2019** 10094



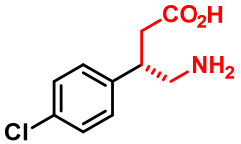
Glycopyrronium Bromide
JFC **2018** 109



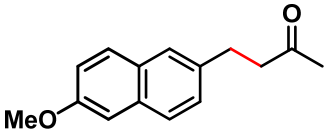
Fulvestrant (AZ)
OL **2019** 5341



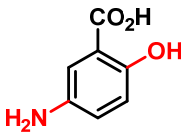
Paroxetine
CS **2019** 11141



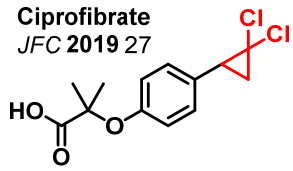
Baclofen/Rolipram
OL **2020** 8122; **2022** 1066



Nabumetone
OPRD **2011** 858

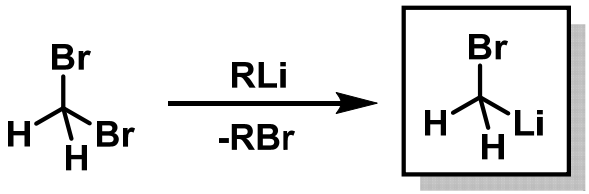


Mesalazine
ACIE **2021** 8139



Ciprofibrate
JFC **2019** 27

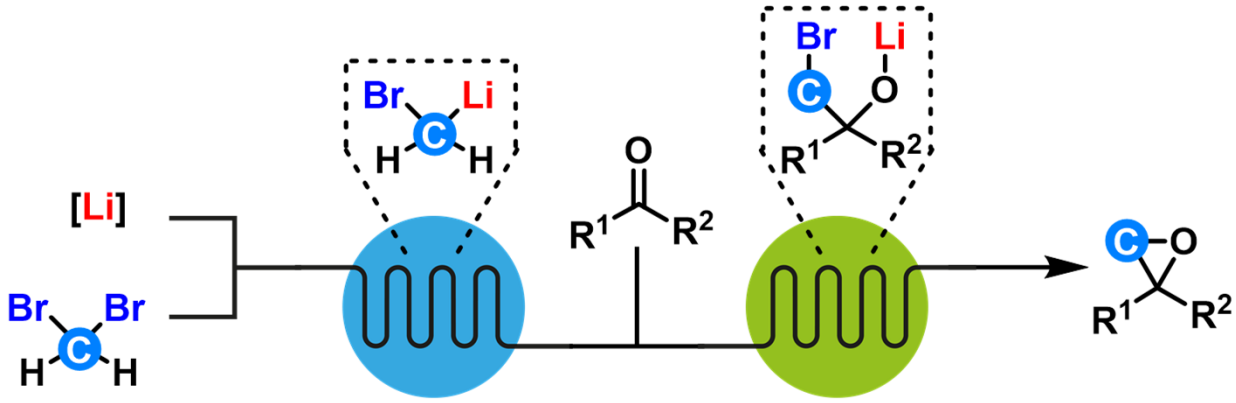
Flash Chemistry - Synthesis of Epoxides via (Bromomethyl)lithium



lithiummethane to react with carbonyl compounds to give oxiranes more easily than the corresponding chloroderivative.

$LiCH_2Br$ however is very unstable and is practically impossible to prepare even at −110°. We tried therefore to prepare it *in situ* in the presence of the carbonyl compound. For this purpose an equimolar solution of 5α-cholest-3-one and CH_2Br_2 in THF were treated at −78° with a mole of BuLi in hexane. Work up yielded 20% of the expected oxirane together with the carbinol derived from the direct addition of BuLi to the carbonyl group.

Cainelli, G. et al. *Tetrahedron*, **1971**, *27*, 6109
Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631



Challenges – Map of Side-Reactions

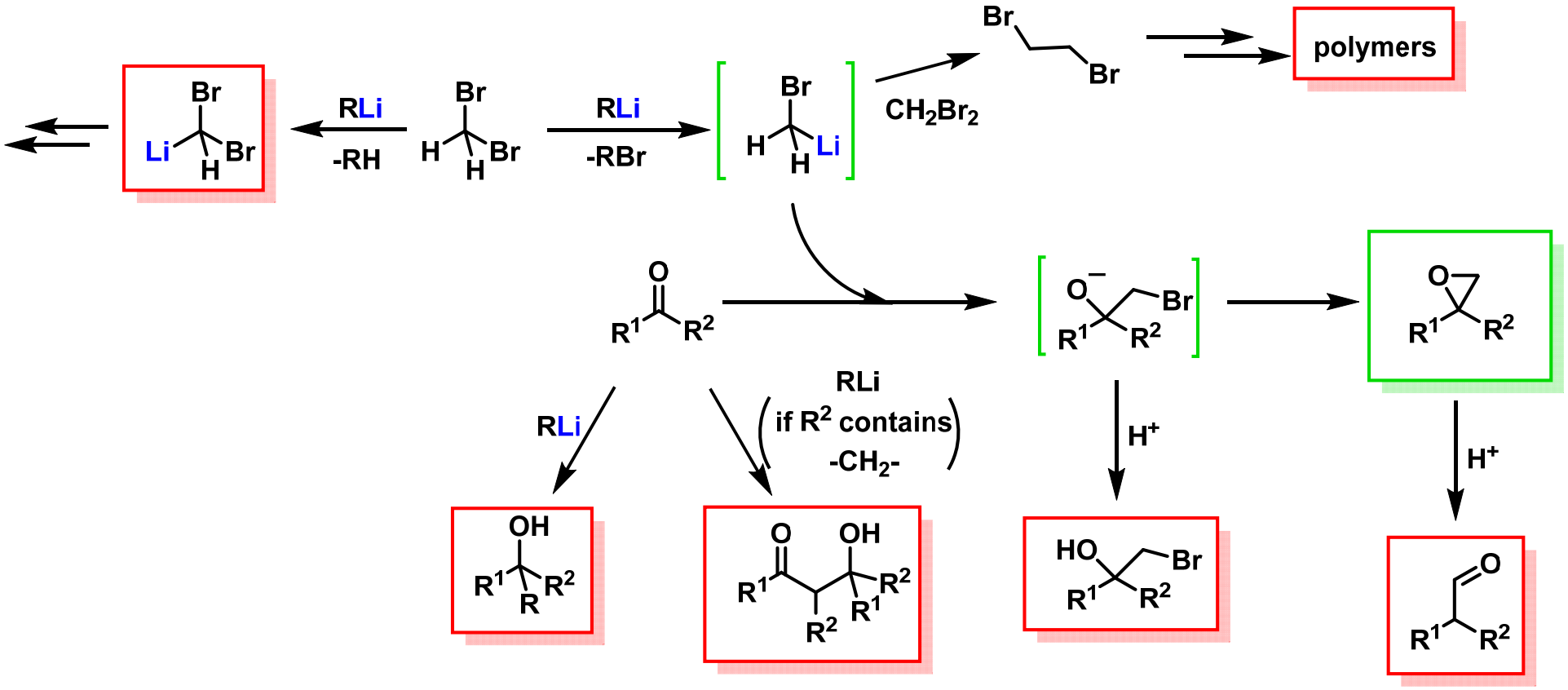
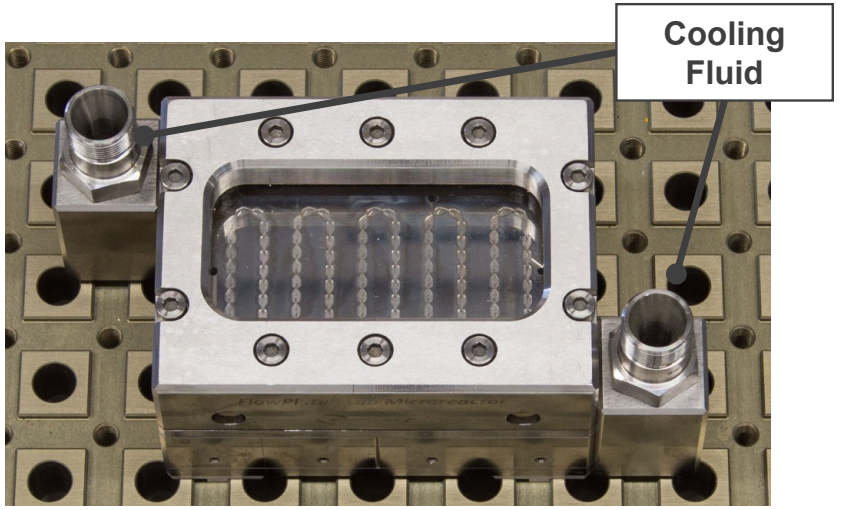


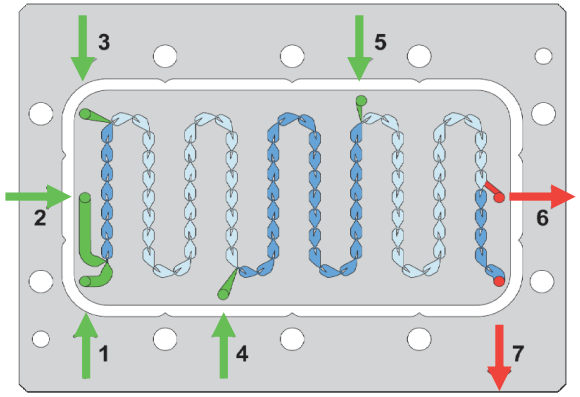
Plate Reactors (Ehrfeld)

Lonza FlowPlate

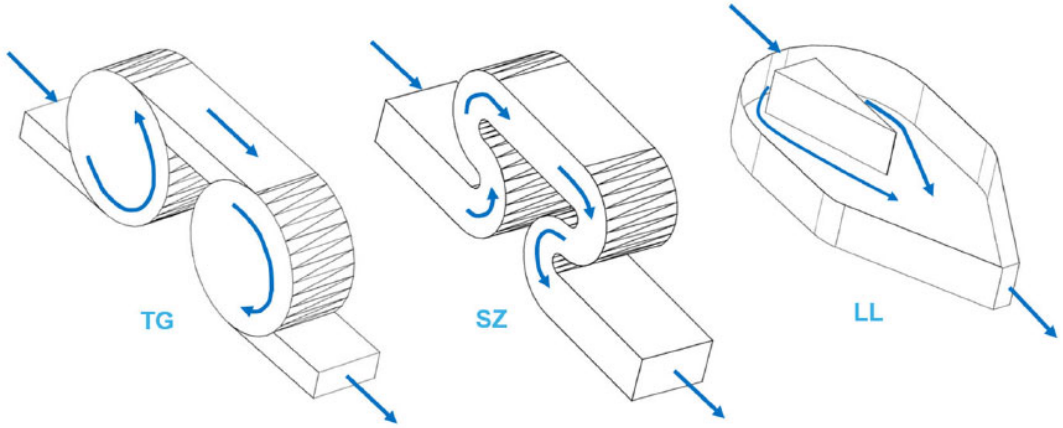
- Very fast reactions (flow rate >1.5 ml/min)
  - Yield affected by heat exchange and mixing
- Plate-type heat exchanger
- Structured mixing channel



LL-Mixer 0.24 mL

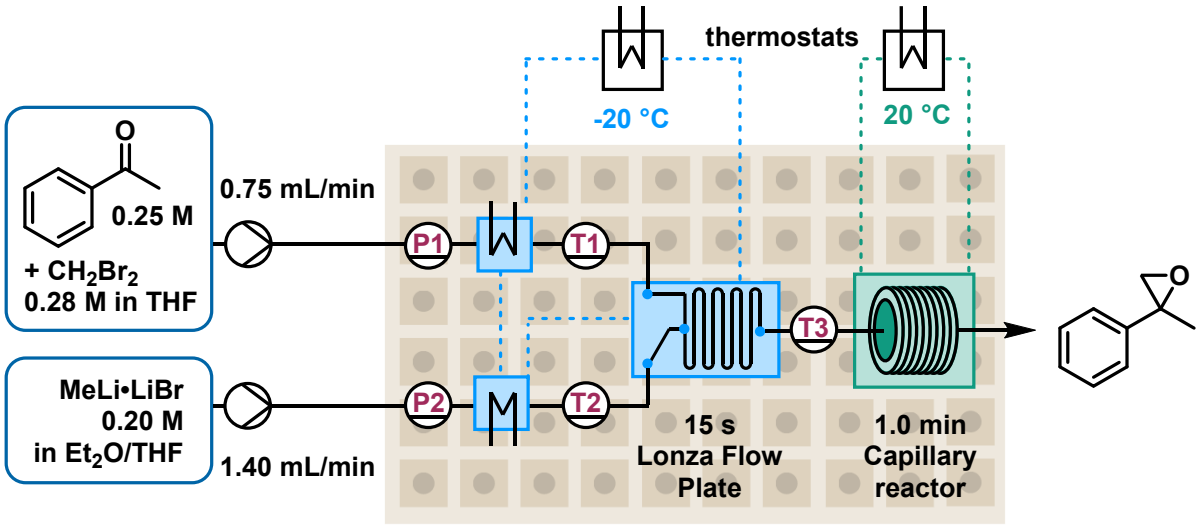


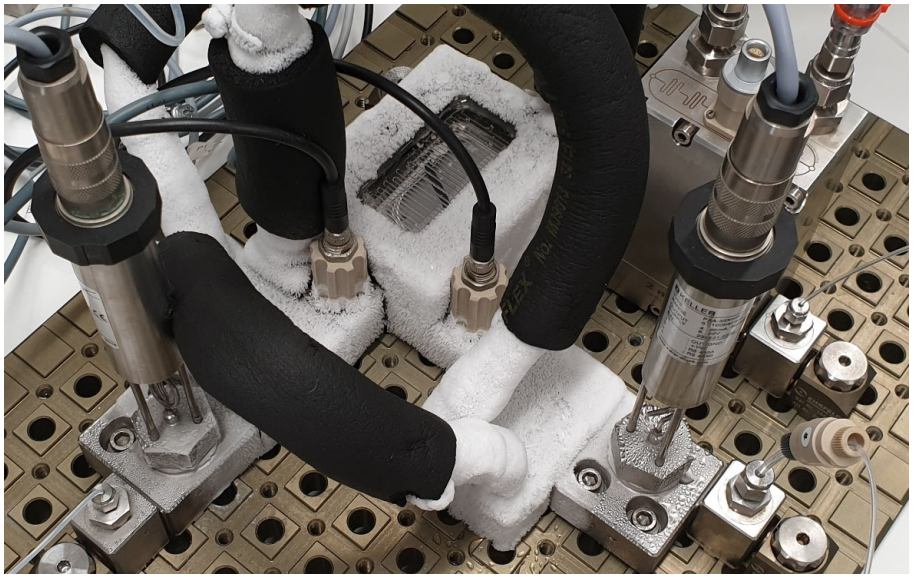
Mixing Structures

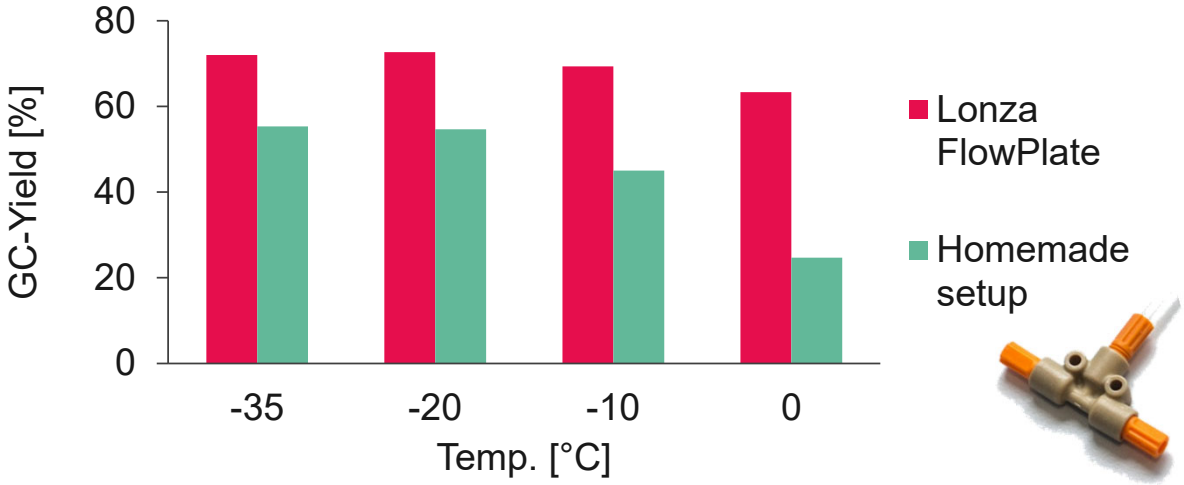


Plouffe, P. et al. *Org. Process Res. Dev.* **2014**, *18*, 1286; Plouffe, P. et al. *Chem. Eng. J.* **2016**, *300*, 9

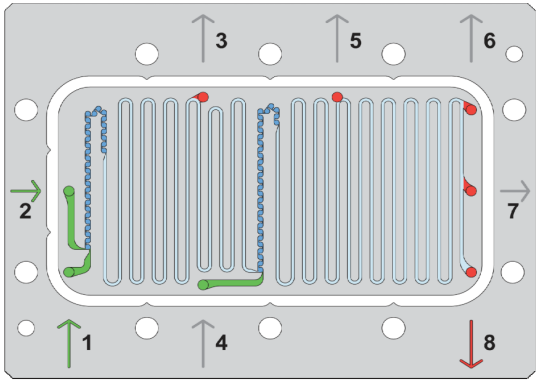
Tubing vs Lonza FlowPlate



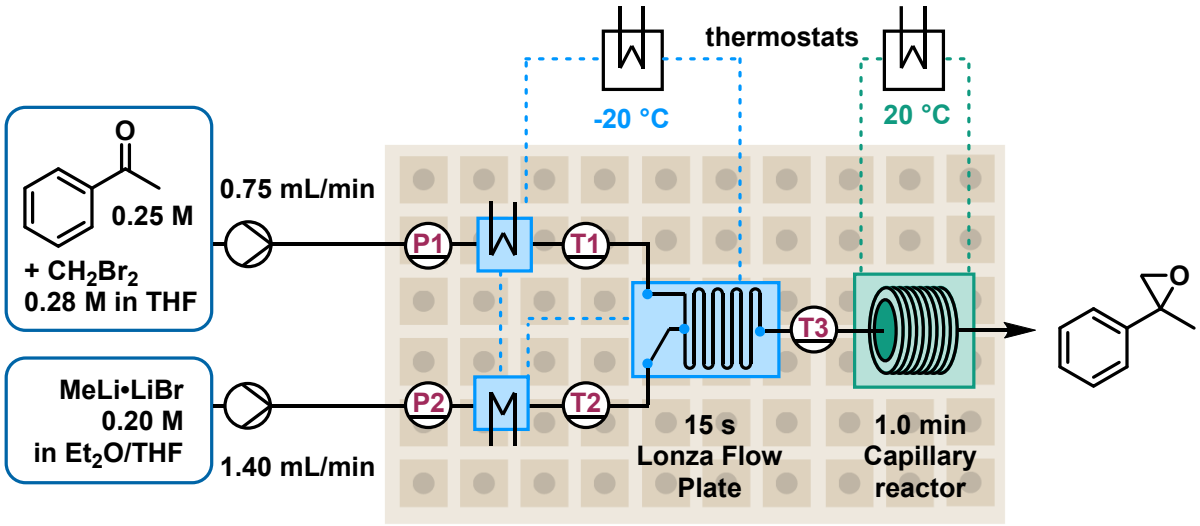


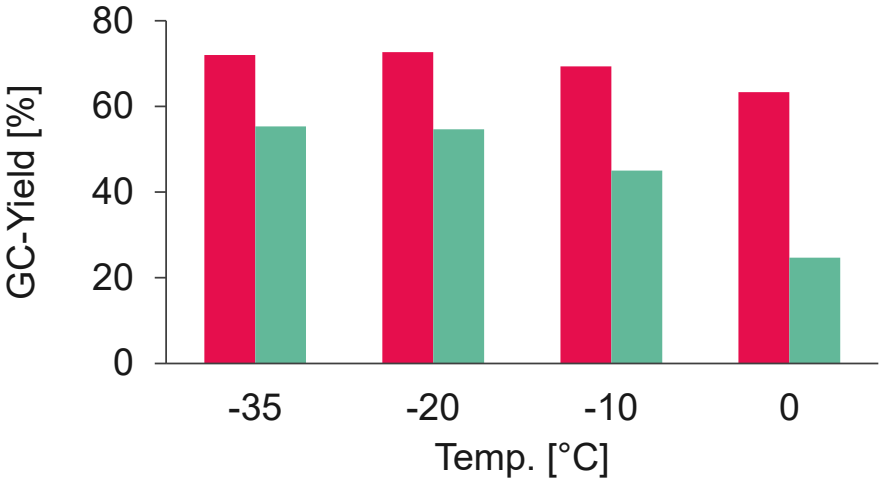


TG-Mixer 0.35 mL
Channel width 0.2-0.6 mm
Channel depth 0.5 mm

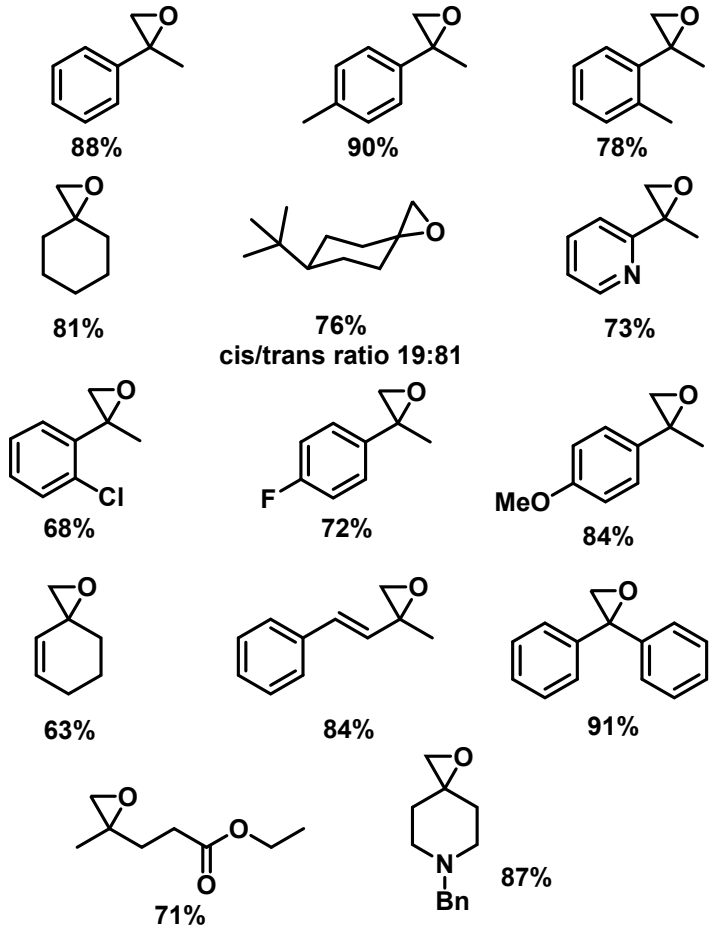


Tubing vs Lonza FlowPlate



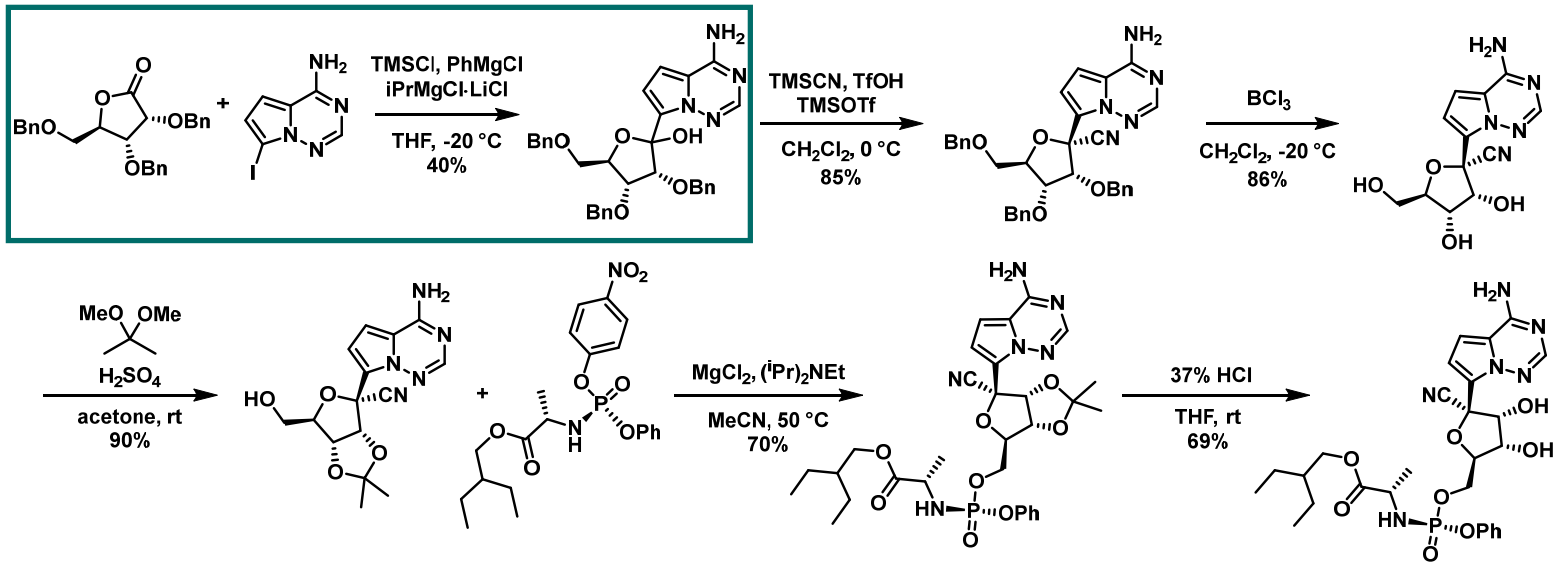


Scope



von Keutz, T. et al. *Org. Lett.* **2019**, *21*, 10094

Manufacturing Route to Remdesivir (COVID-19)



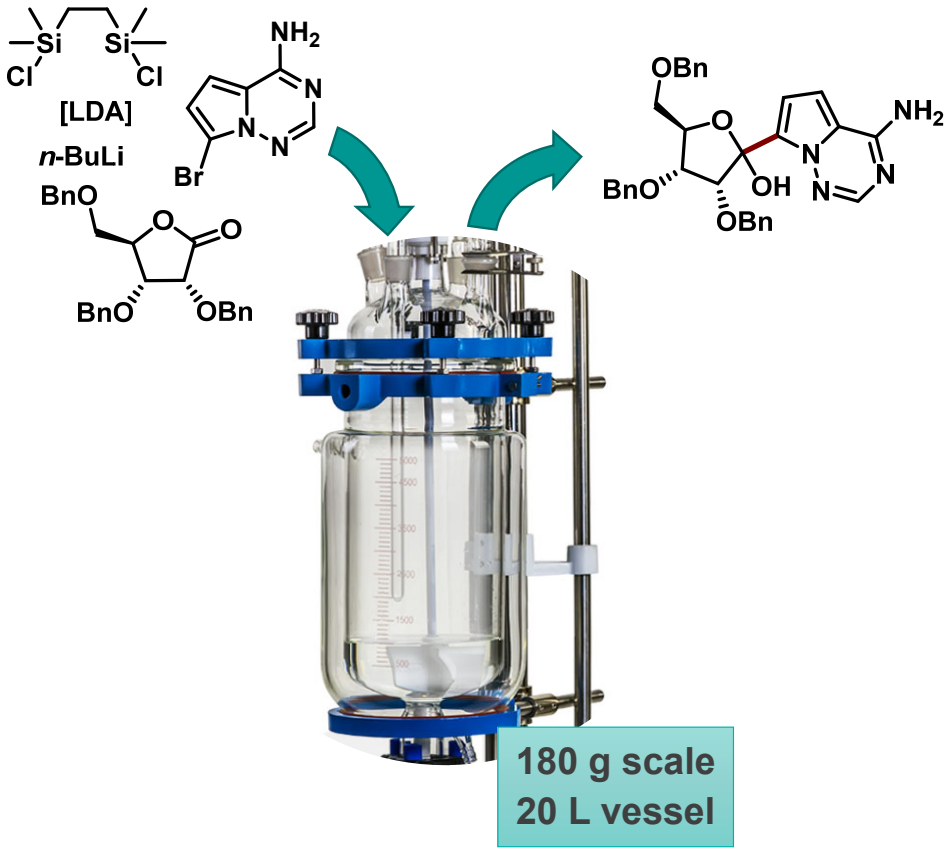
Warran, T. K. et al. *Nature* **2016**, *531*, 381
cf. organolithium method: Siegel, D. et al. *J. Med. Chem.* **2017**, *60*, 1648 (~20% yield)
cf. flow *C*-glycosylation (Mg): von Keutz, T. et al. *Org. Process Res. Dev.* **2020**, *24*, 2362

"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

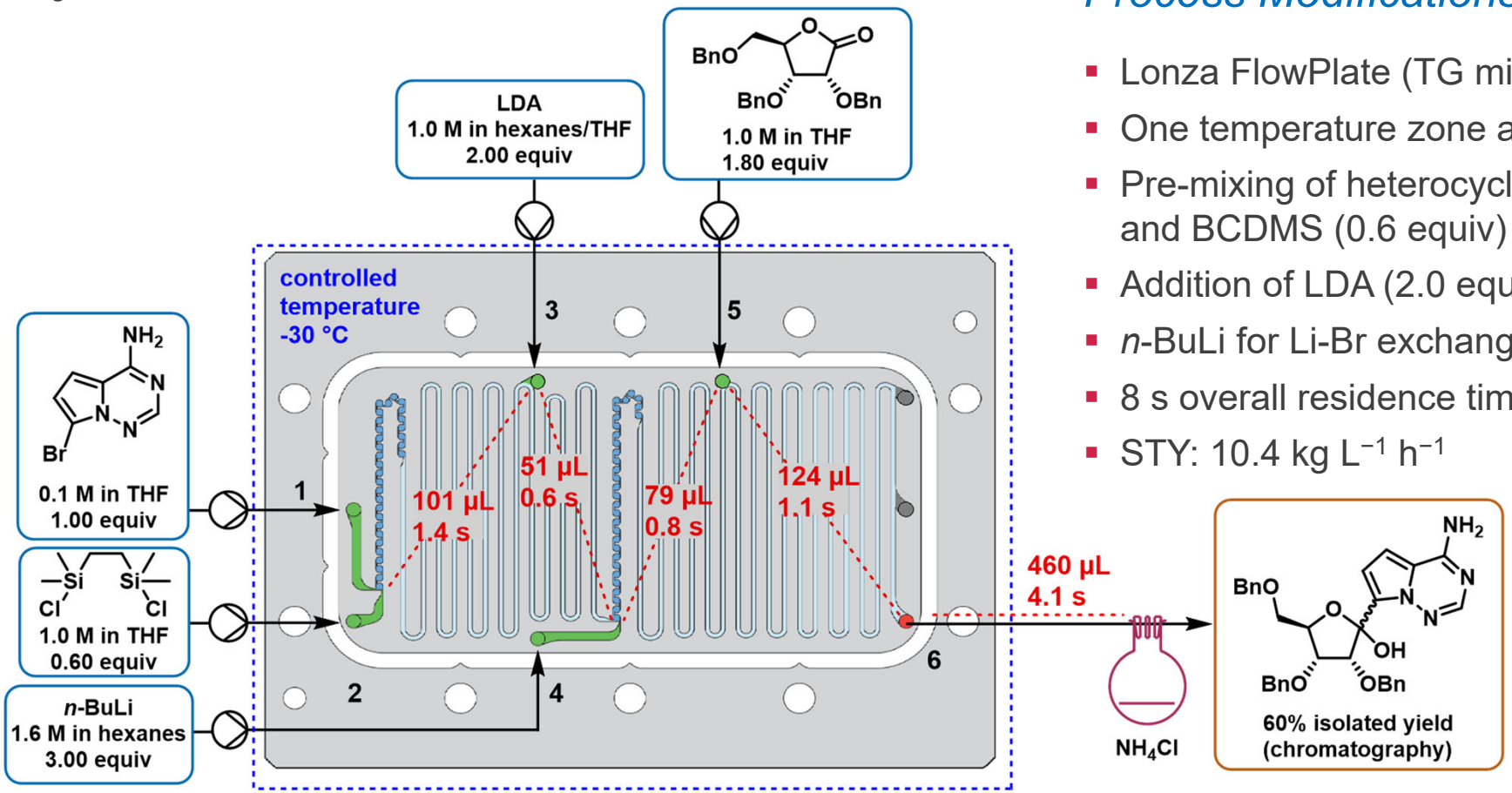


1. charge heterocycle (0.845 mol) and anhydrous THF (1.44 L) to oven-dried reactor under N_2 at 20 °C
2. stir for **10 min**
3. charge BCDMS (1.1 equiv) in THF (360 mL)
4. stir for **15 min**
5. charge diisopropylamine (1.1 equiv)
6. cool to -85 °C to -78 °C (**?? 1 h ??**)
7. charge *n*-BuLi (2.5 M 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

- Lonza 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}

Scalability Concept (Smart Dimensioning)

Research & Development

0.05 - 10 mL/min

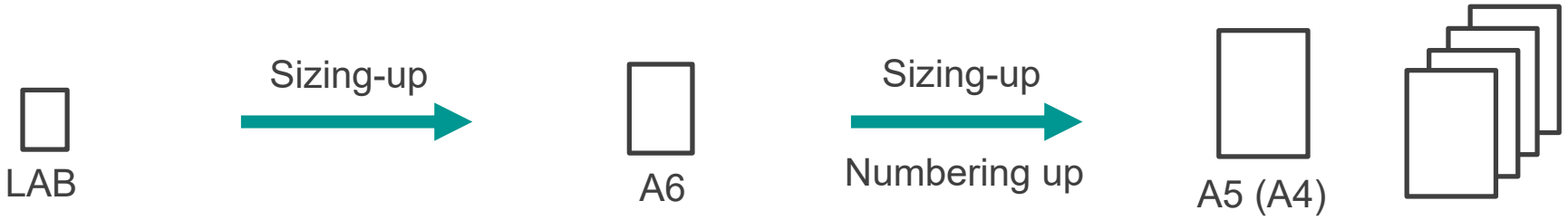
Pilot scale

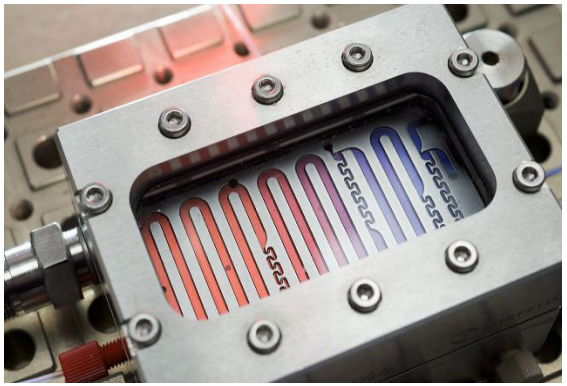
15 - 150 mL/min

Production Scale

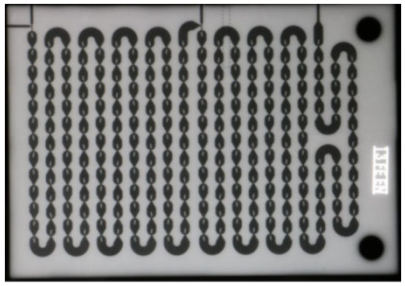
150 - 600 mL/min

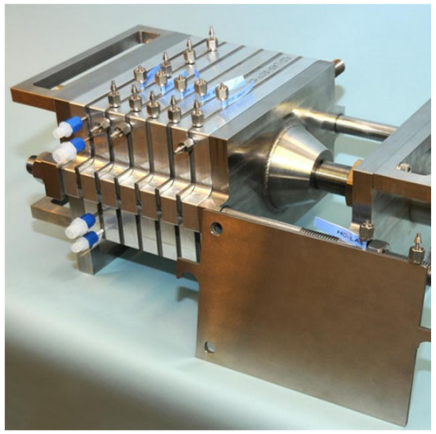
FlowPlate





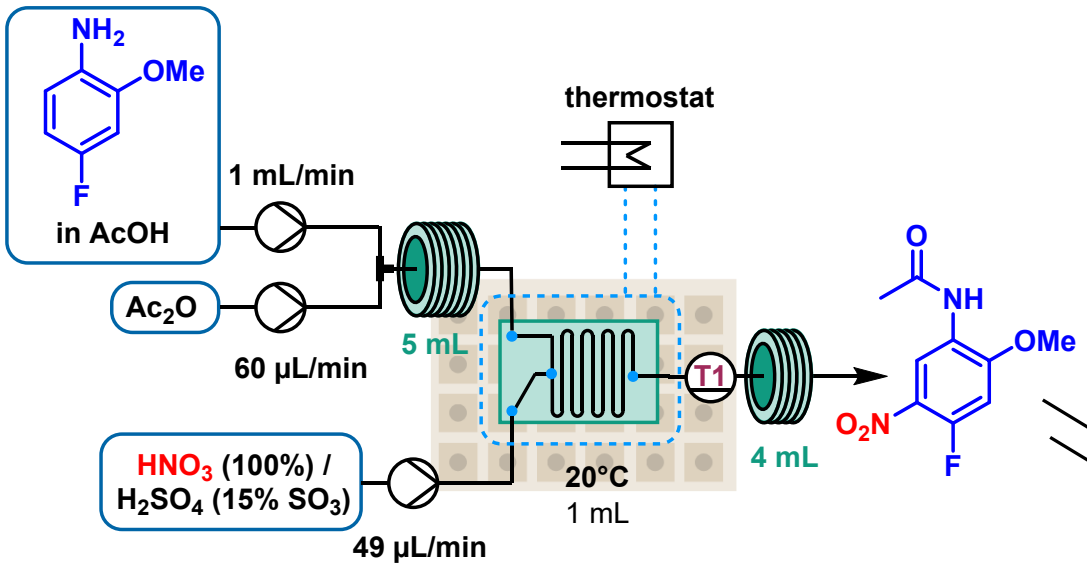
Example of Channel structure

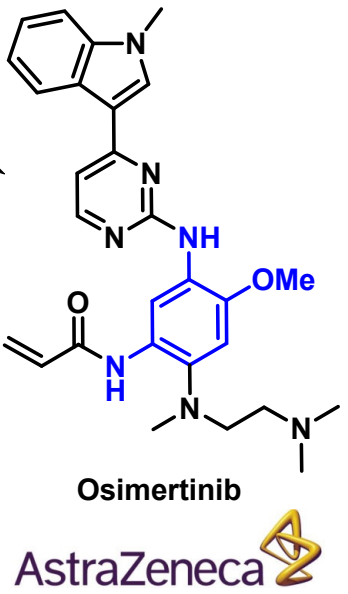




Roberge, D. M. et al. *Chim. Oggi/Chem. Today* **2009**, *27*, 8

Continuous Nitration Towards Osimertinib Intermediate (Lab Scale)

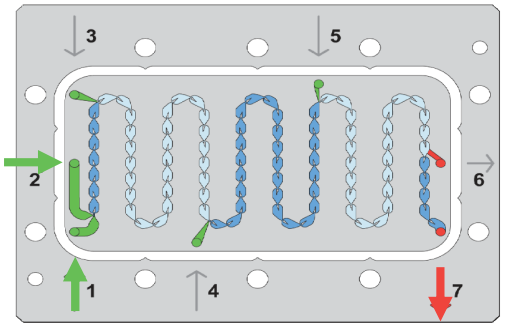




Osimertinib

- 5.6 g/h throughput
- 130 g/day

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

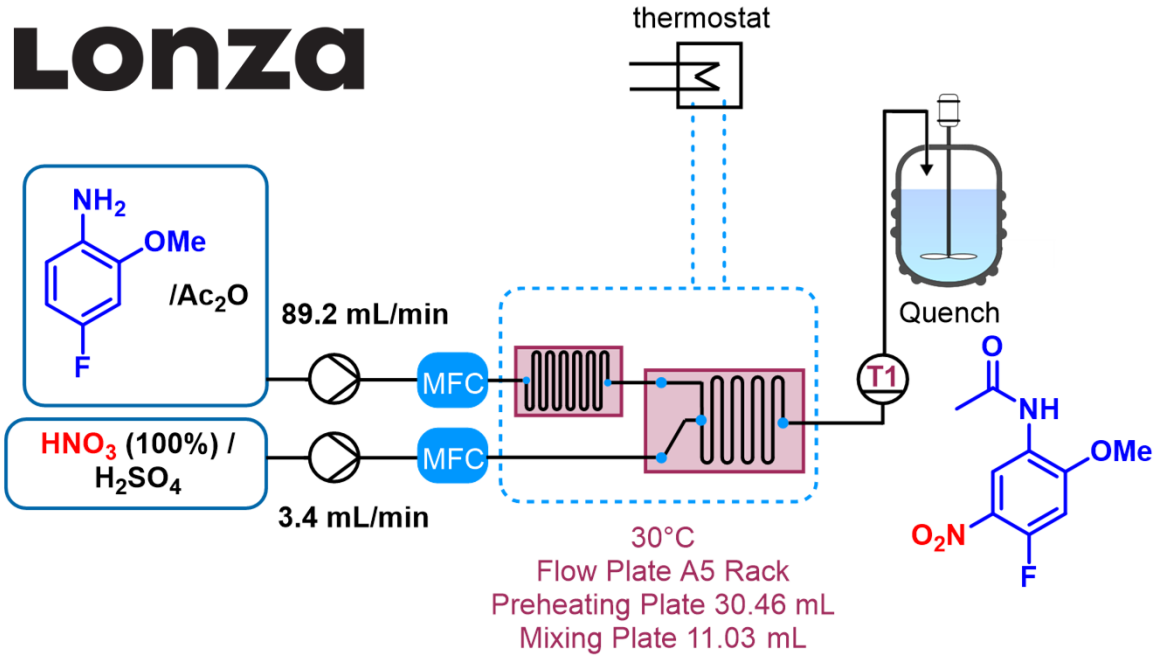


- reaction needs to be absolutely water free
- arene/Ac_2O/H_2SO_4/HNO_3 = 1/1.2/1.15/1.15 (mol)
- residence time in plate mixer ~13 s
- 82% isolated yield (7.5 g)

AstraZeneca

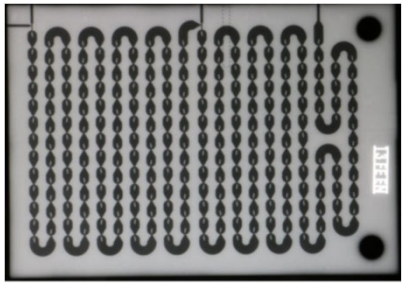
Continuous Nitration Towards Osimertinib Intermediate (Pilot Scale)

Lonza



- **0.45 kg/h**
- **~11 kg/day**

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

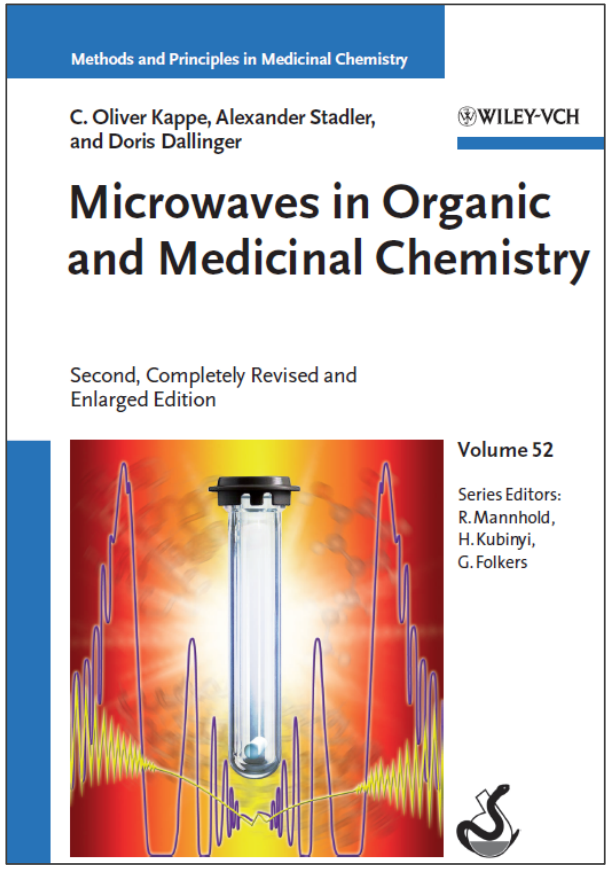


- arene/Ac_2O/H_2SO_4/HNO_3 = 1/1.2/1.1/1.1 (mol)
- residence time ~7 s (full mass transfer limited)
- 83% isolated yield (HPLC assay >99%)

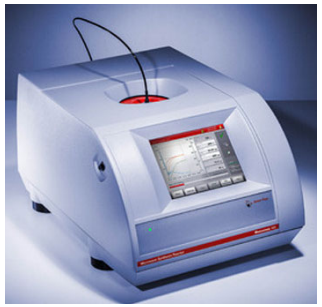
larger structure of A5 LL-Mixers (~25 mL)
width 0.7 mm × depth 1.75 mm
(4 × A5 plates in series, ~100 mL)

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

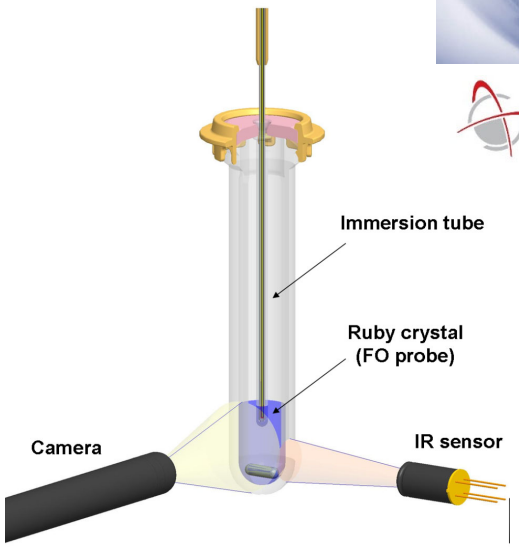
Process Intensification - Translating Microwave Batch to Flow



- 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



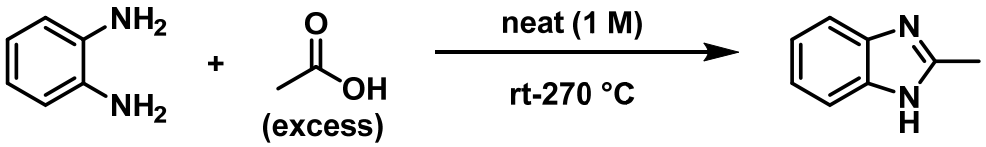
Anton Paar



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**)
Kappe, C. O. *Chem. Rec.* **2019**, *19*, 15

Why High-T/p Processing? Speeding Up Chemistry (Arrhenius Law)

Batch Microwave 2-Methylbenzimidazol Synthesis

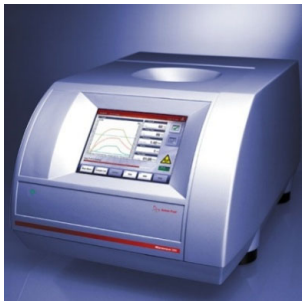


$k = A\, e^{-Ea/RT}$

$E_a = 73.4$ kJ mol^{-1}
$A = 3.1 \times 10^8$

Temperature [°C]		t >99% conv (HPLC)
CONV	25	9 weeks
CONV	60	5 days
CONV	100	5 h
MW	130 (2 bar)	30 min
MW	160 (4 bar)	10 min
MW	200 (9 bar)	3 min
MW	270 (29 bar)	“1 s“

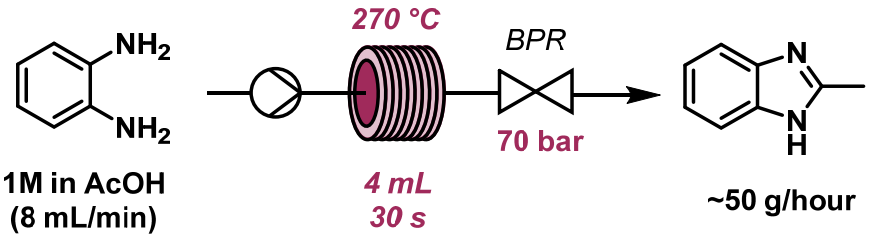
Batch Microwave Reactor (300 °C, 30 bar)

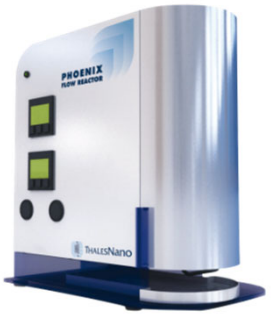


Damm, M. et al. *Org. Process Res. Dev.* **2010**, *14*, 215
cf. essay on microwave effects: Kappe, C. O. et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 1088

Converting Batch Microwave to Continuous Flow Processing

Benzimidazole Synthesis



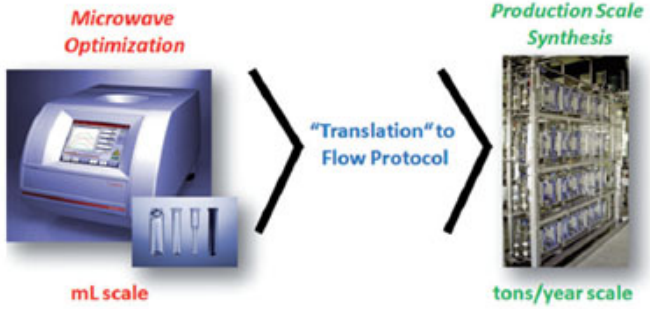


Damm, M.; Glasnov, T, N.; Kappe, C. O. *Org. Process Res. Dev.* **2010**, *14*, 215

Flow Chemistry

*T. N. Glasnov,**
*C. O. Kappe**..... 11956-11968

The Microwave-to-Flow Paradigm: Translating High-Temperature Batch Microwave Chemistry to Scalable Continuous-Flow Processes



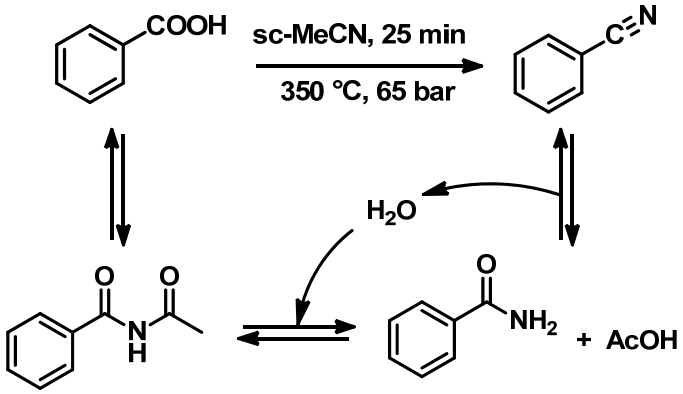
Microwaves not required! Conventionally heated flow reactors (coils or chips) fitted with back-pressure regulators can mimic the high temperatures and pressures attainable in a sealed-vessel microwave instrument. Such devices can therefore be used to perform otherwise difficult to scale microwave chemistry (see scheme).

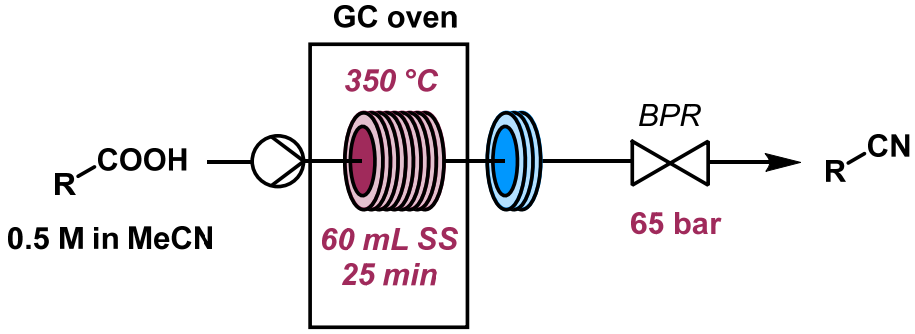
CHEMISTRY
A EUROPEAN JOURNAL

Glasnov, T.; Kappe, C. O.
Chem. Eur. J. **2011**, *17*, 11956

Accessing “Forbidden” (and “Forgotten”) Chemistries

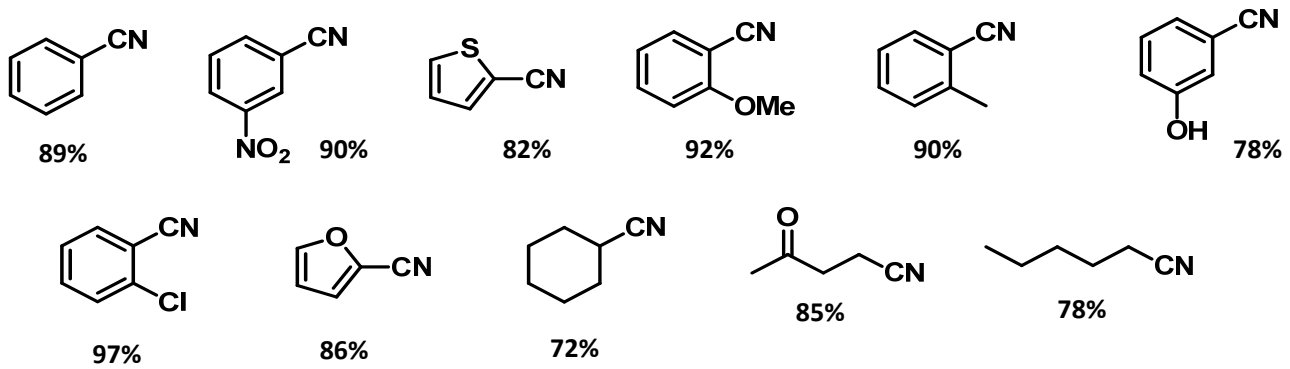
Acid-Nitrile Exchange Reaction





cf. Becke, F.; Burger,
Liebigs Ann. Chem. **1968**, *716*, 78
(Ag-lined or Ta autoclave, 300 °C)

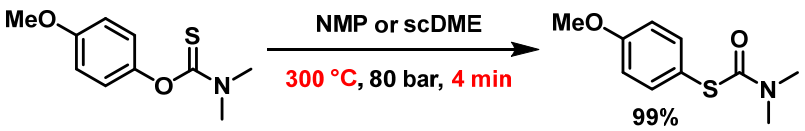
Scope



Cantillo, D. et al.
J. Org. Chem. **2013**, *78*, 10567

More High-T/p Flow Chemistry (Lab Scale)

Newman-Kwart Rearrangement

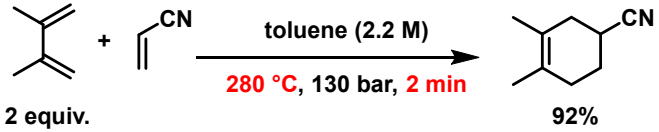


Eur. J. Org Chem. **2009**, 1321

Methylations Using Dimethylcarbonate

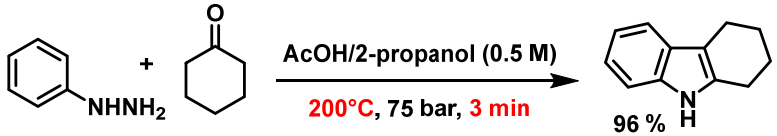
Green Chem. **2012**, *14*, 3071

Diels-Alder Reactions



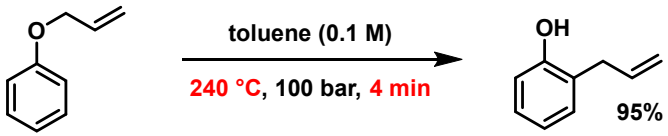
Org. Process Res. Dev. **2010**, *14*, 215

Fischer Indole Synthesis



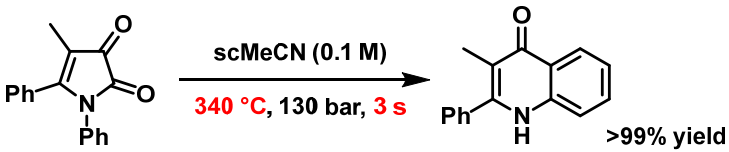
Eur. J. Org Chem. **2009**, 1321

Claisen Rearrangement



Chem. Eng. Technol. **2009**, *32*, 1702

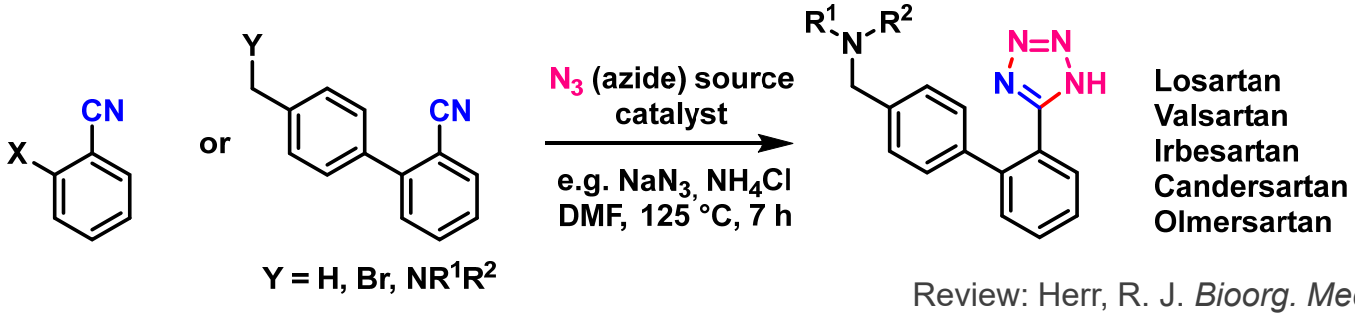
"Flash Flow Pyrolysis"



J. Org. Chem. **2012**, *77*, 2463

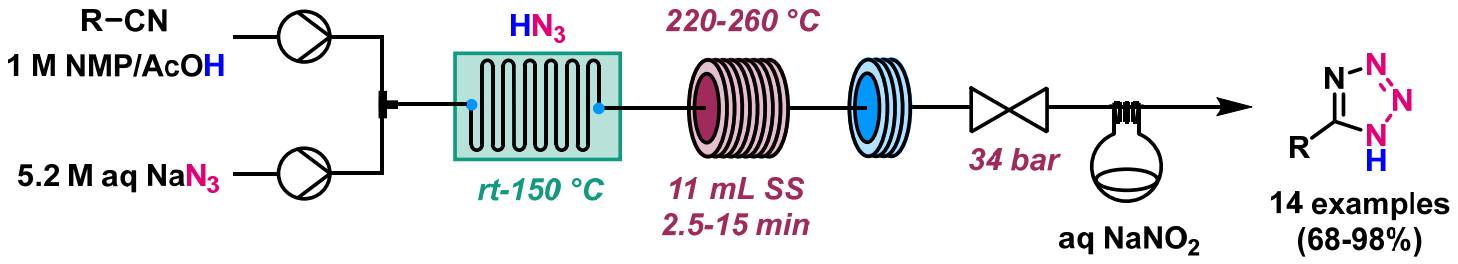
Tetrazole Synthesis in Flow under High-T/p Conditions

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

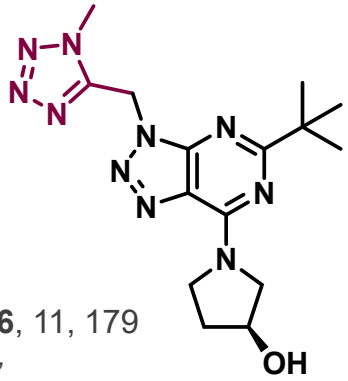
Gutmann, B. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 7101; *J. Flow Chem.* **2012**, *2*, 8
Mechanism: Cantilo, D. et al. *J. Org. Chem.* **2012**, *77*, 10882; *J. Am. Chem. Soc.* **2011**, *133*, 4465

Tetrazole Synthesis in Flow under High-T/p Conditions

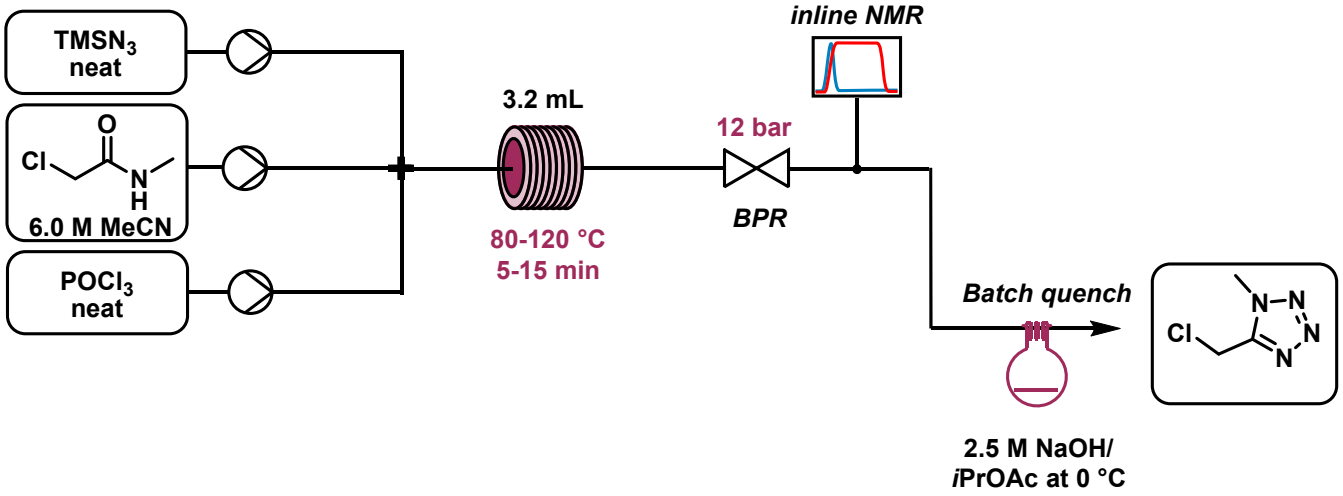
Cannabinoid Receptor 2 (CB2) Agonist (RG7774)

- 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)

Roche



Nettekoven, M. et al.
ChemMedChem **2016**, 11, 179
"diabetic retinopathy"



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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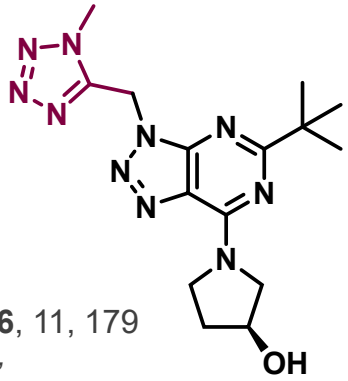
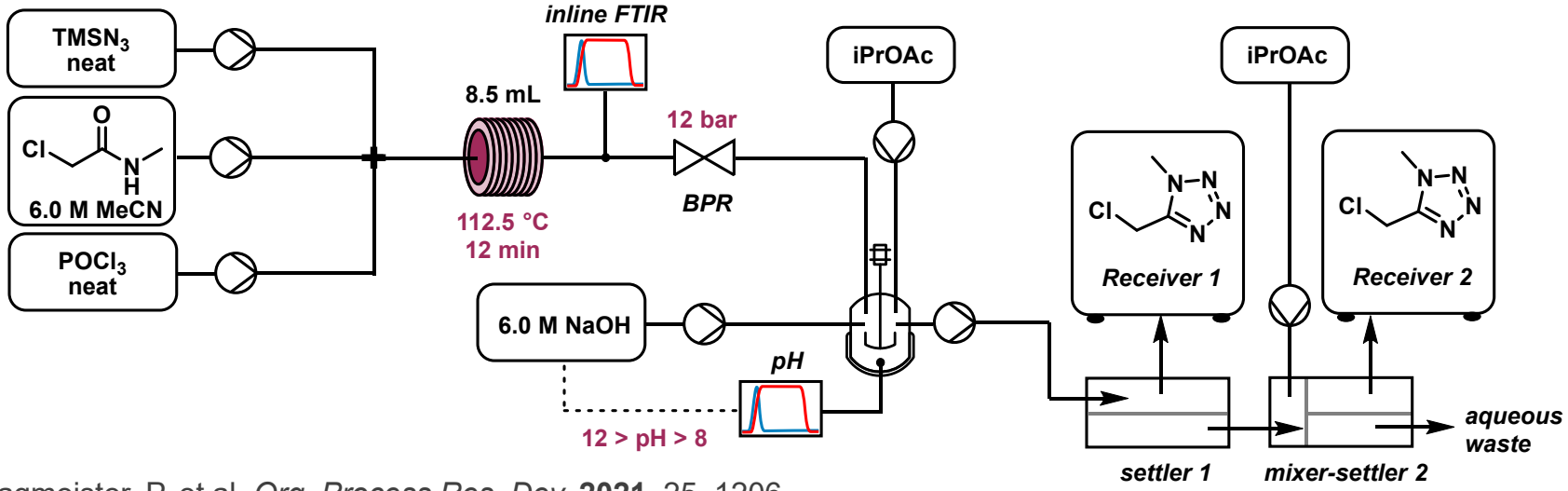


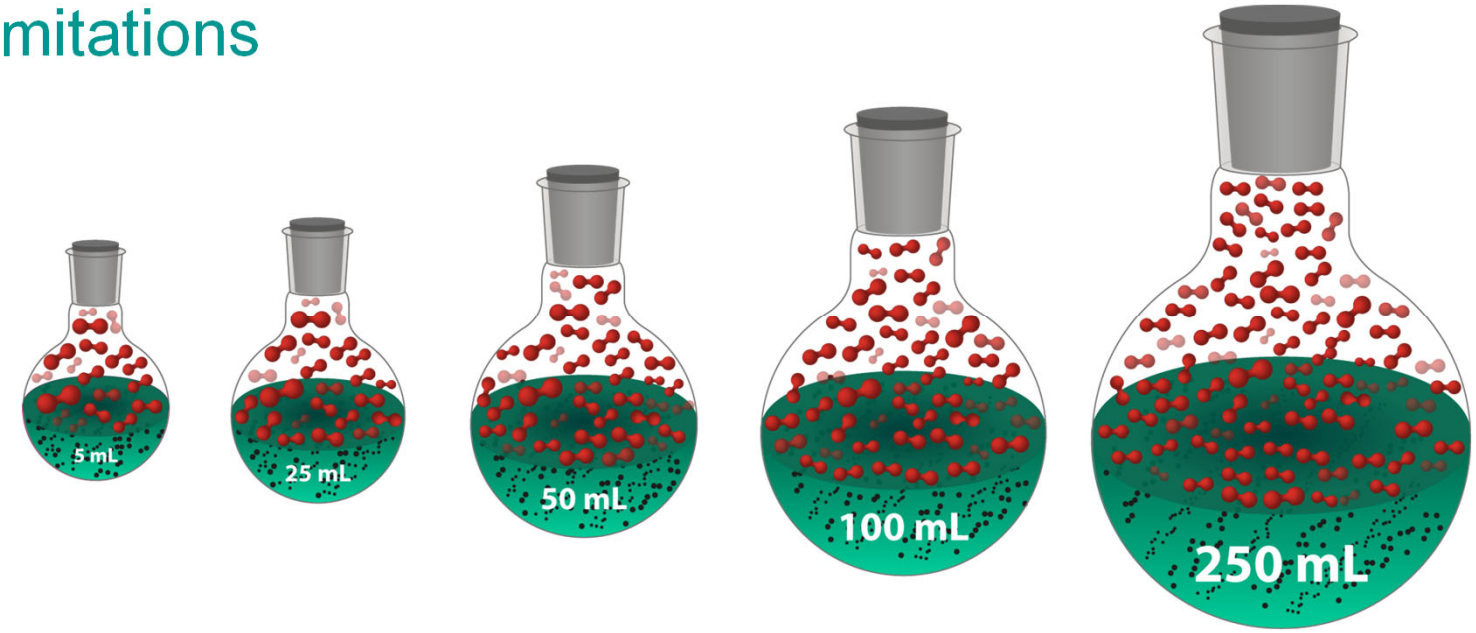
Nettekoven, M. et al.
ChemMedChem **2016**, 11, 179

"diabetic retinopathy"



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

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

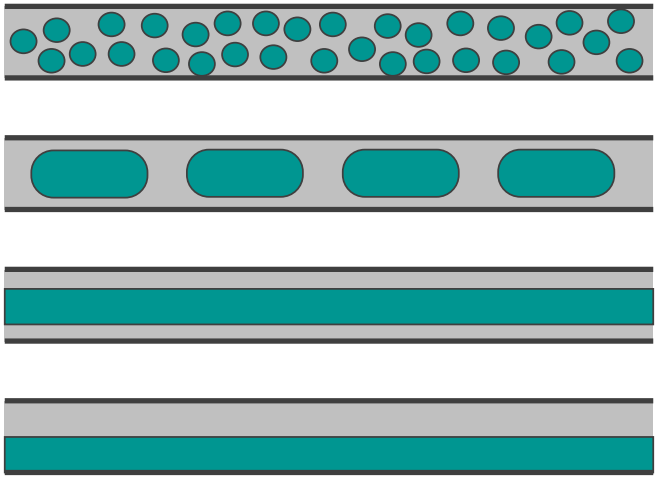
Review: Mallia, C. J.; Baxendale, I. R. *Org. Process Res. Dev.* **2016**, *20*, 327

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



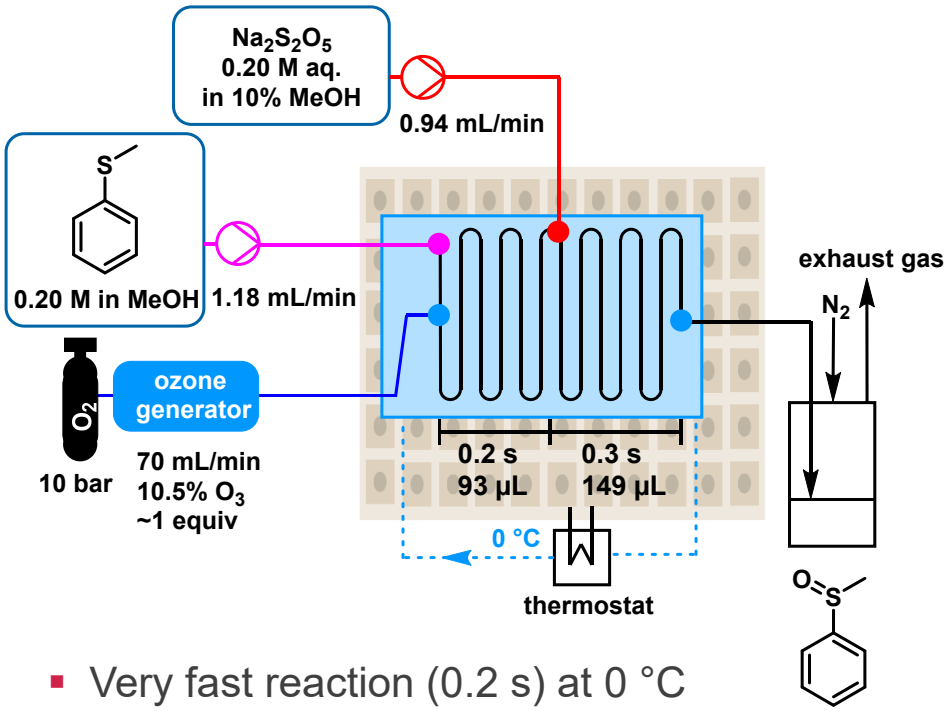
Other Factors

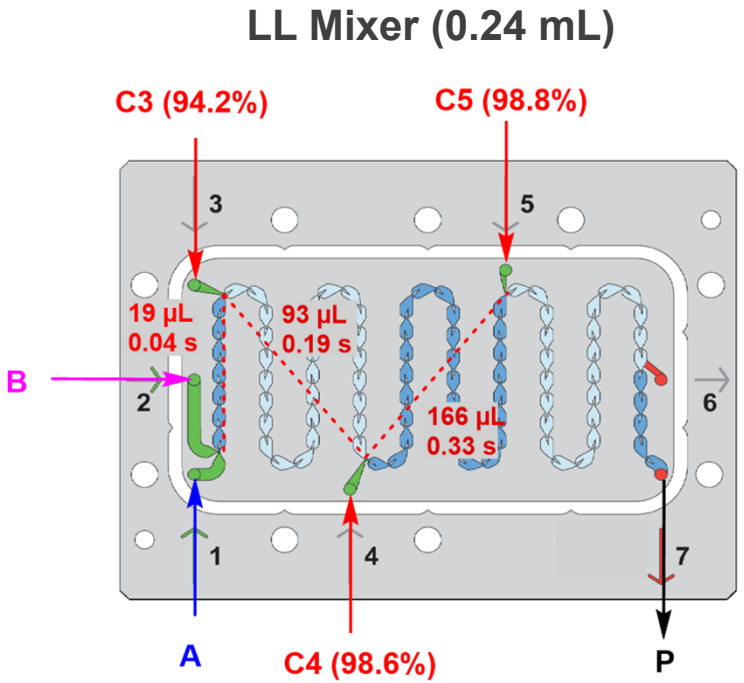
- higher solubility of gases in pressurized reactors (Henry's law)
- exact dosing using mass flow controllers, use of large stoichiometric excess (headspace) avoided
- safety aspects

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

Switching Quench Inlets



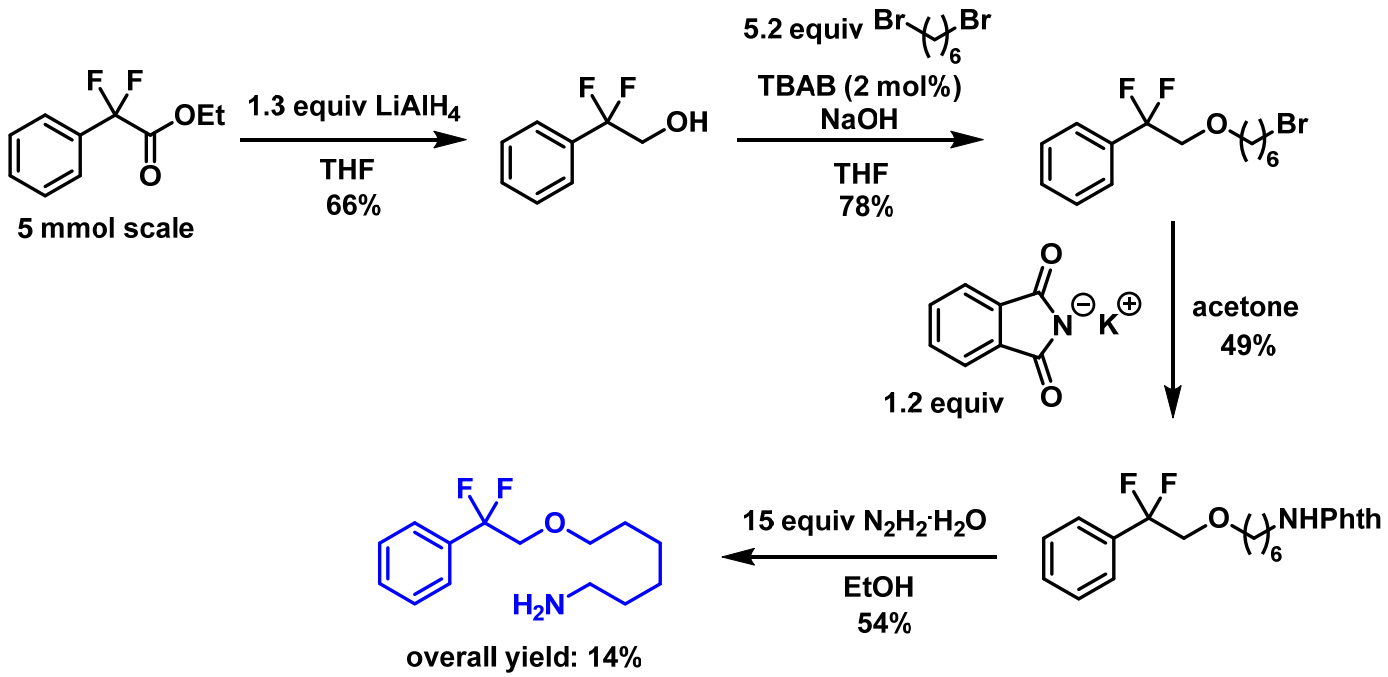


- Very fast reaction (0.2 s) at 0 °C
- Intensive gas-liquid mixing

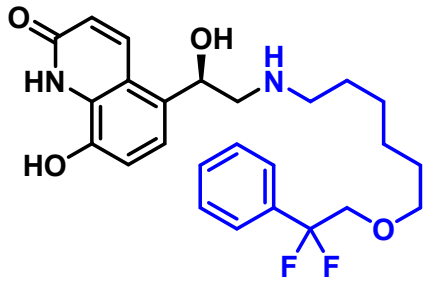
Polterauer, D. et. al. *React. Chem. Eng.* **2021**, *6*, 2253
cf. flow ozonolysis in tubing (22 s): Irfan, M. et al. *Org. Lett.* **2011**, *14,* 984

Continuous Flow Approaches to the Abediterol Side Chain

Original Batch Procedure (Almirall)



AstraZeneca



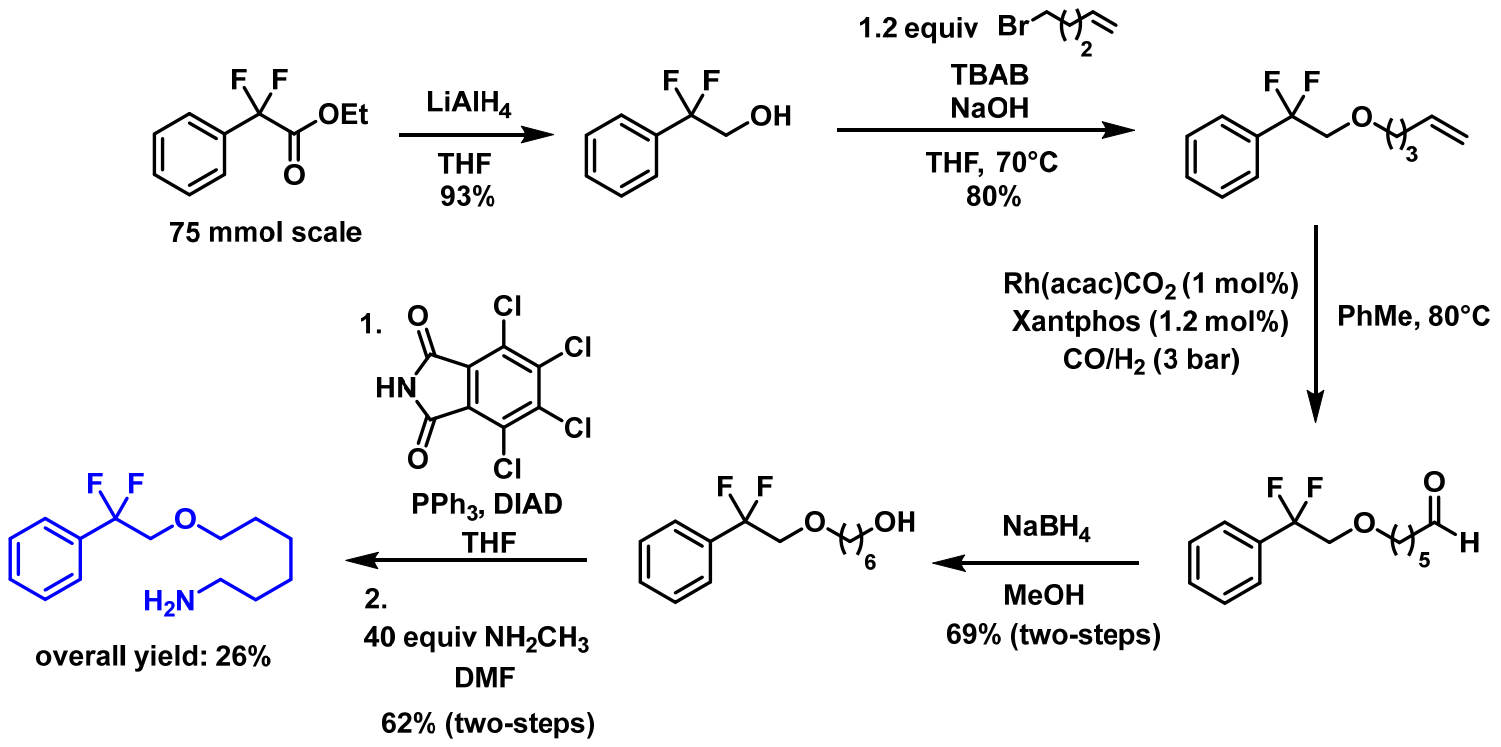
(Abediterol, AZD0548)

very high potency β2-adrenoceptor agonist (kg demand)

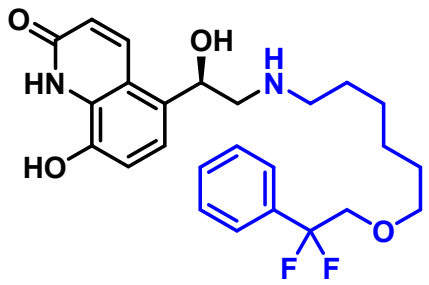
Duran Puig, C. et al. (Almirall) WO2006/122788

Continuous Flow Approaches to the Abediterol Side Chain

Alternative Batch Procedure (AstraZeneca)



AstraZeneca



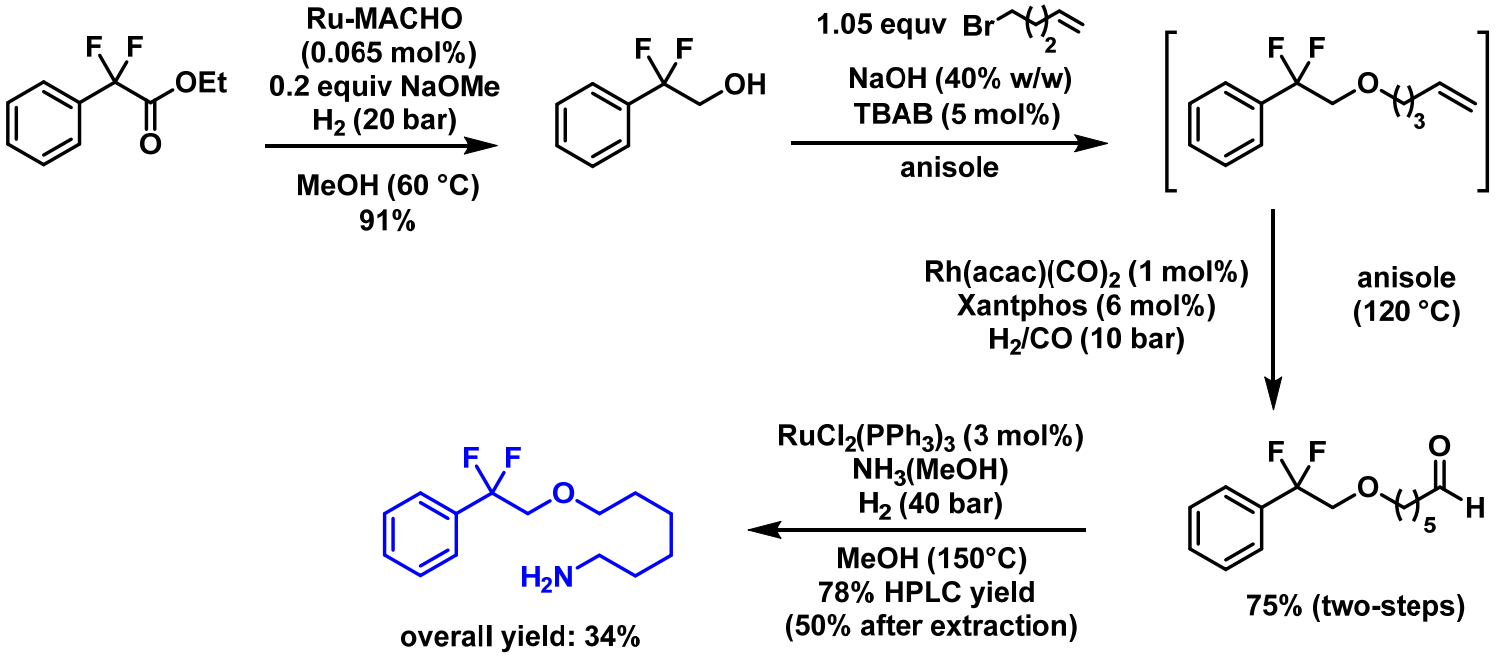
(Abediterol, AZD0548)

very high potency β2-adrenoceptor agonist (kg demand)

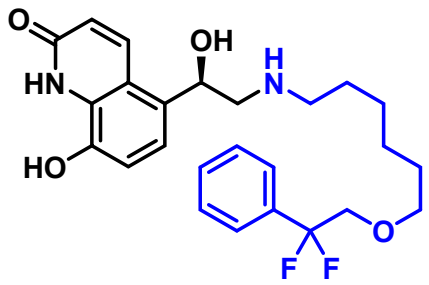
Munday, R. H. et al. (AstraZeneca) *Tetrahedron Lett.* **2019**, *60*, 606

Continuous Flow Approaches to the Abediterol Side Chain

"Telescoped" Flow Procedure



AstraZeneca



(Abediterol, AZD0548)

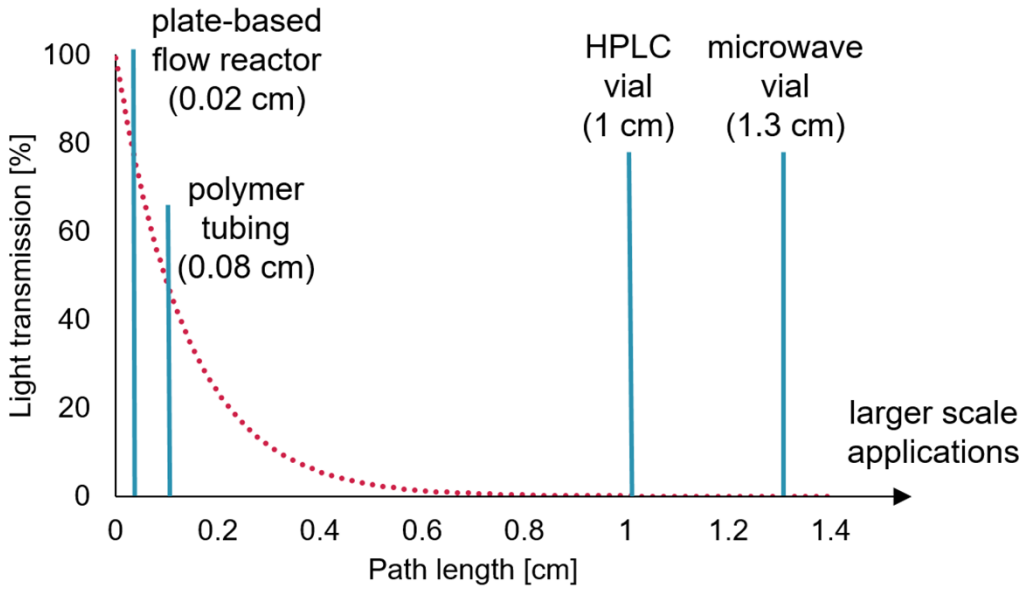
very high potency
β2-adrenoceptor agonist
(kg demand)

Prieschl, M. et al. *Green Chem.* **2020**, *22*, 5762 (step 1)
García-Lacuna, J. et al. *Org. Process Res. Dev.* **2021**, *25*, 947 (steps 2-4)

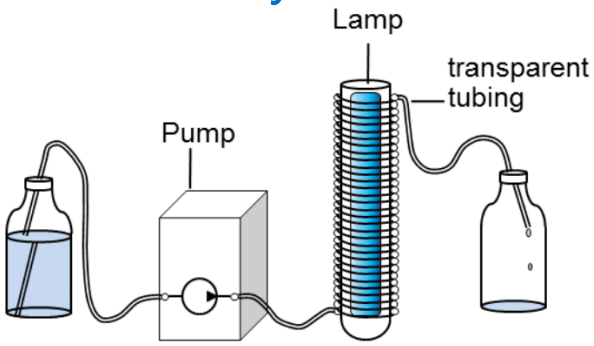
Continuous Flow Photochemistry

Advantages of Light-Induced Reactions

- clean and safe method of activation
- economical
- generates complexity otherwise difficult to obtain
- but: difficult to scale (Beer-Lambert Law)



Flow Photochemistry

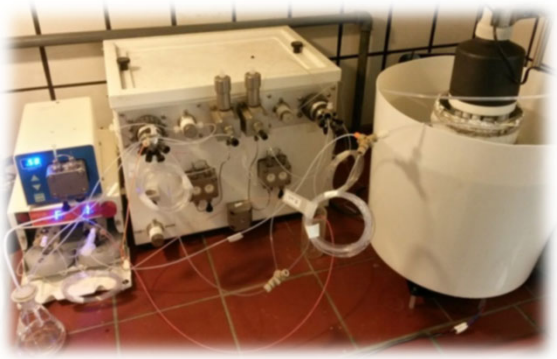


- uniform irradiation
- accurately controlled exposure time (flow rate)
- small amounts of solvent near to lamp (safe)
- scalable

Reviews: Politano, F.; Oksdath-Mansilla, G. *Org. Process Res. Dev.* **2018**, *22*, 1045
Cambie, D. et al. *Chem. Rev.* **2016**, *116*, 10276; Buglioni, L. et al. *Chem. Rev.* **2022**, *122*, 2752
Elliott, L. D. et al. *Chem. Eur. J.* **2014**, *20,* 15226; Bonfield, H. E. et al. *Nat. Comm.* **2020**,*11*, 804
Booker-Milburn, K. I. et al. *Beilstein J. Org. Chem.* **2012**, *8*, 2025

Building Capability: 10 Years of Flow Photochemistry in the Kappe Group

Home-Built Reactors



since 2013

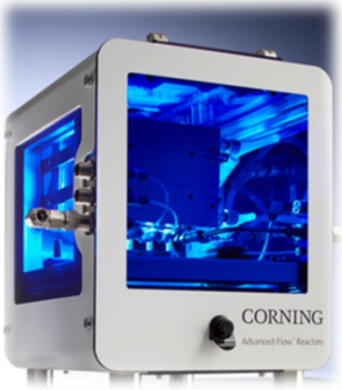
- large selection of light sources (CFL, LEDs, blacklight)
- simple and versatile

Vapourtec UV150

since 2015

- tubing-based reactor
- LEDs and medium pressure Hg lamp

Corning Advanced-Flow Lab Photo Reactor

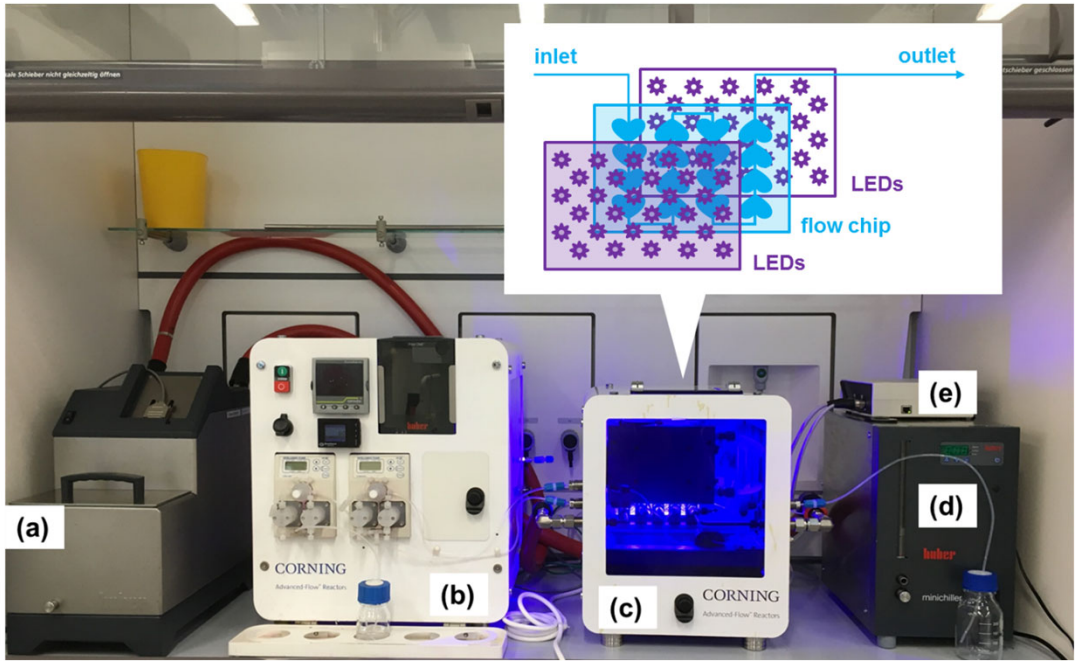


since 2018

- plate-based reactor
- LED arrays with a choice of 12 wavelengths

Combined capability to cover *the whole spectrum* of UV and visible photochemical transformations

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

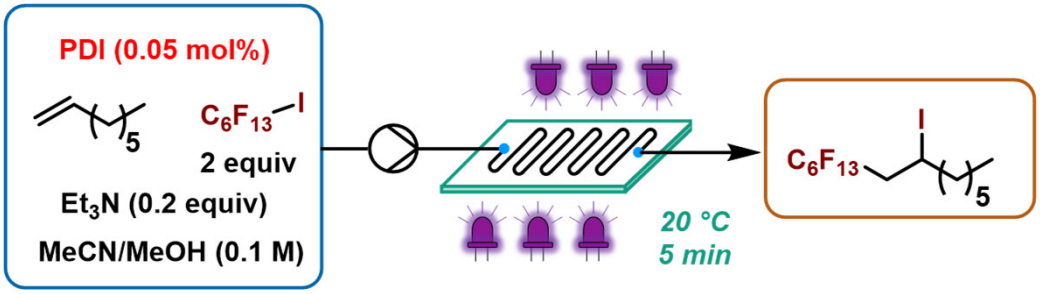
d) Thermostat (LED plate temp. control)

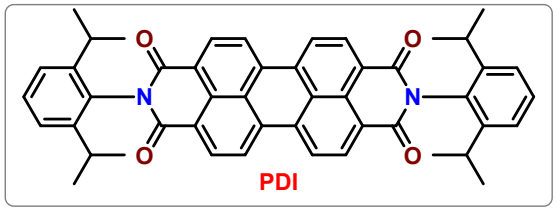
e) Lamp control module

- 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)

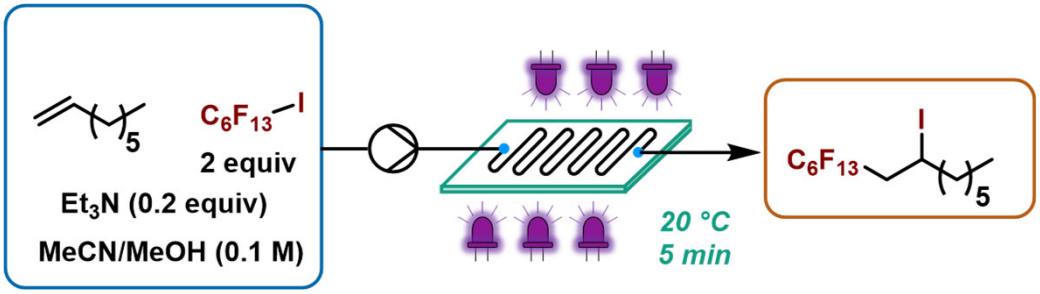


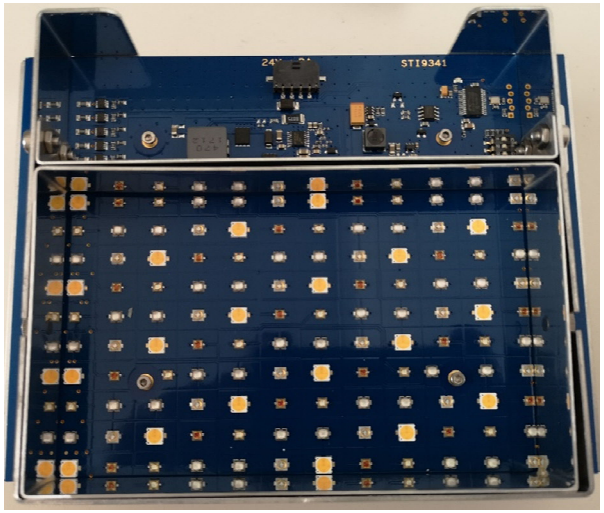


Wavelength	Yield [%]
365 nm	95
385 nm	97
405 nm	97
422 nm	95
450 nm	95
540 nm	88
610 nm	0

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

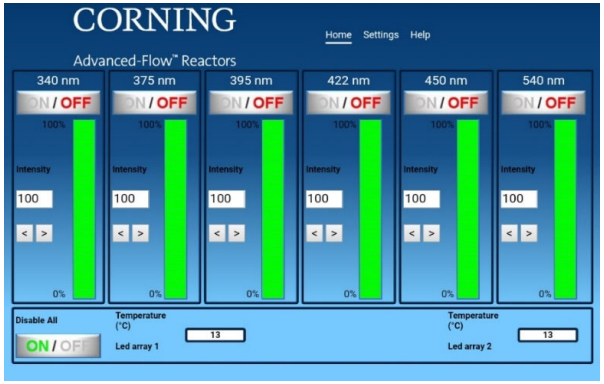
Iodoperfluoroalkylation of Alkenes (ATRA)



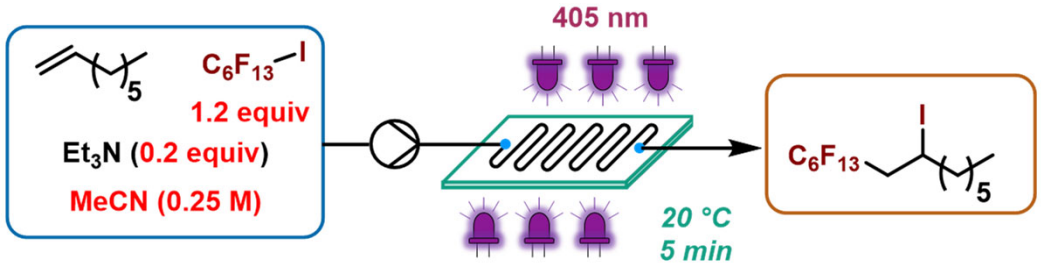


Wavelength	Yield [%]
365 nm	95
385 nm	97
405 nm	97
422 nm	95
450 nm	95
540 nm	88
610 nm	0

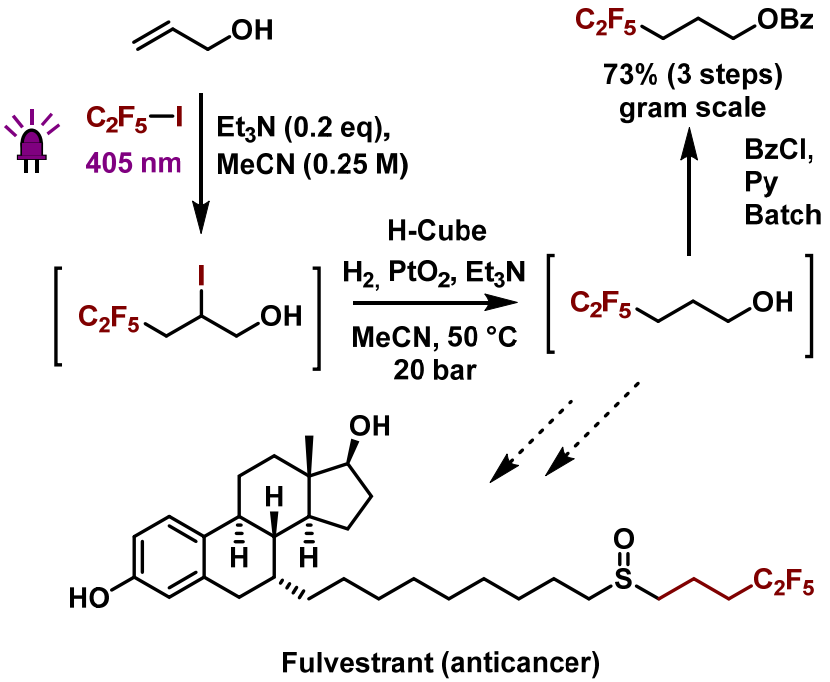
Wavelength	Yield [%]
365 nm	94
385 nm	94
405 nm	94
422 nm	34
450 nm	0
540 nm	0
610 nm	0



Iodoperfluoroalkylation of Alkenes (ATRA)



- 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

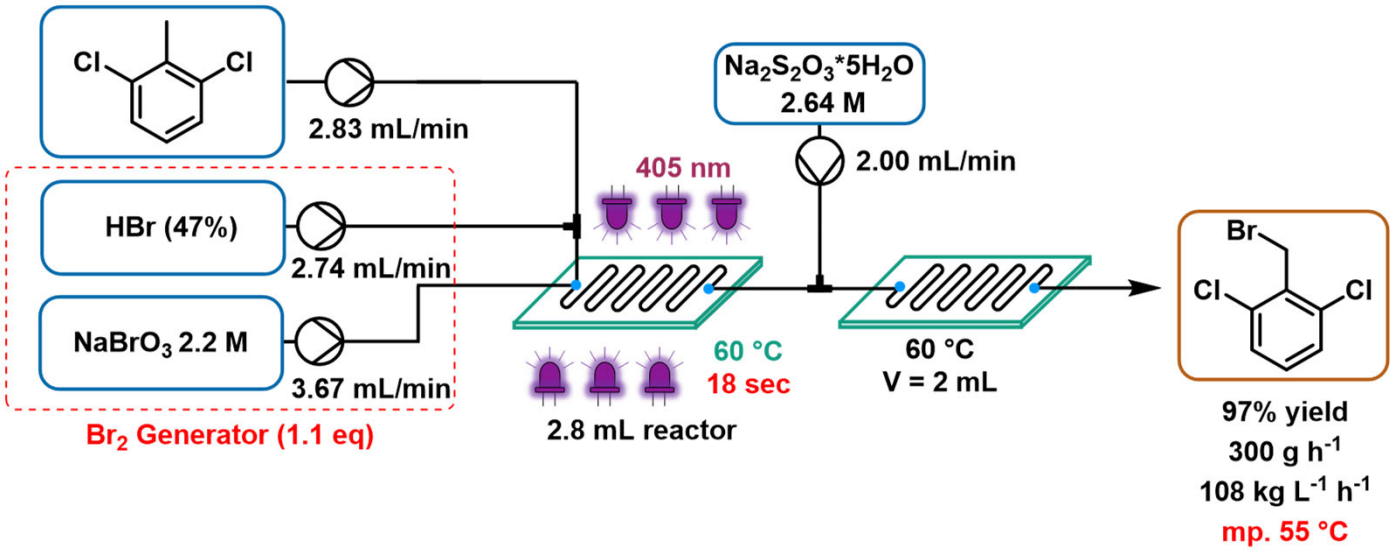


Fulvestrant (anticancer)

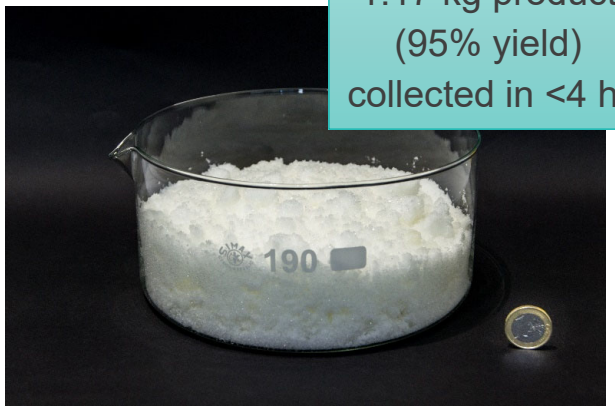
Rosso, C. et al. *Org. Lett.* **2019**, *21*, 5341

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

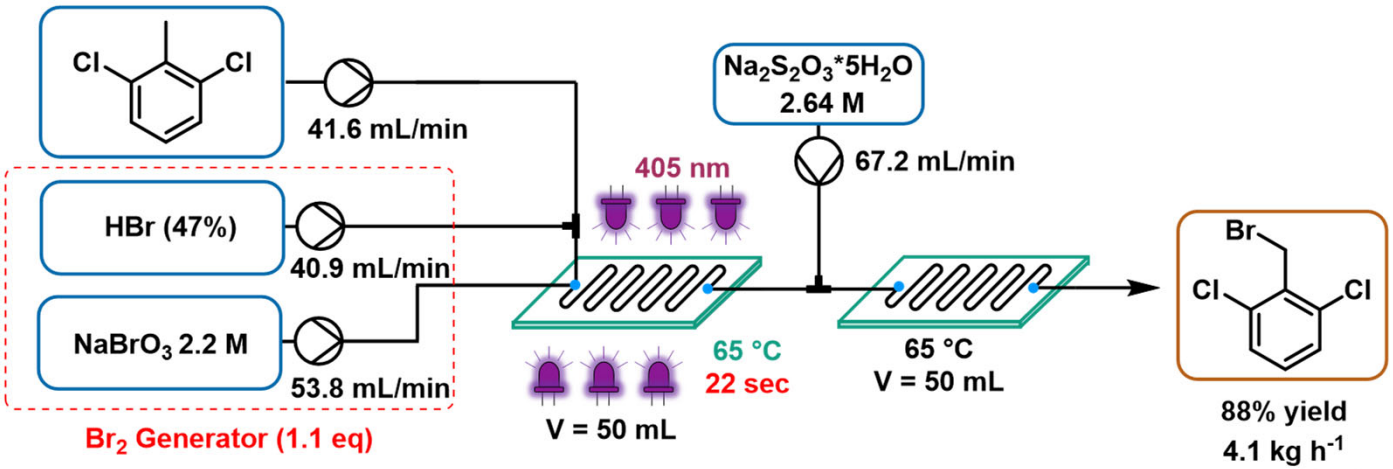


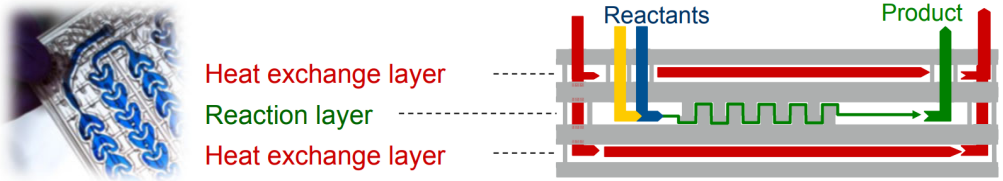
1.17 kg product
(95% yield)
collected in <4 h!

cf. BrCN/Br_2 generator: Glotz, G. et al. *Angew. Chem. Int. Ed*. **2017**, *56*, 13786
Steiner, A. et al. *Green Chem*. **2020**, *22*, 448

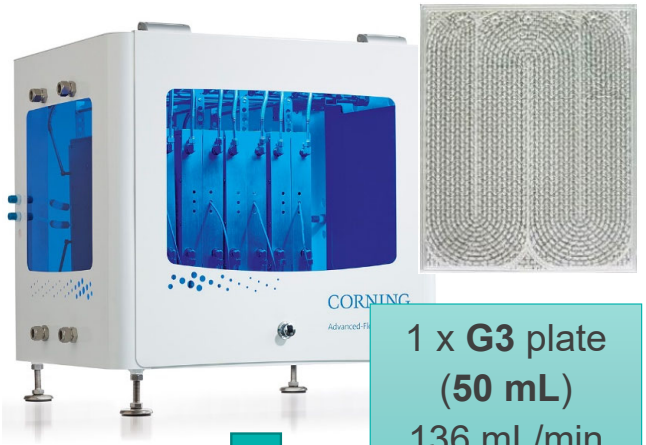
Continuous Benzylic Bromination – Production Scale

2,6-Dichlorobenzylbromide (API Intermediate)





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



1 x **G3** plate
(**50 mL**)
136 mL/min

Throughput:
27 kg/h
~750 kg/day

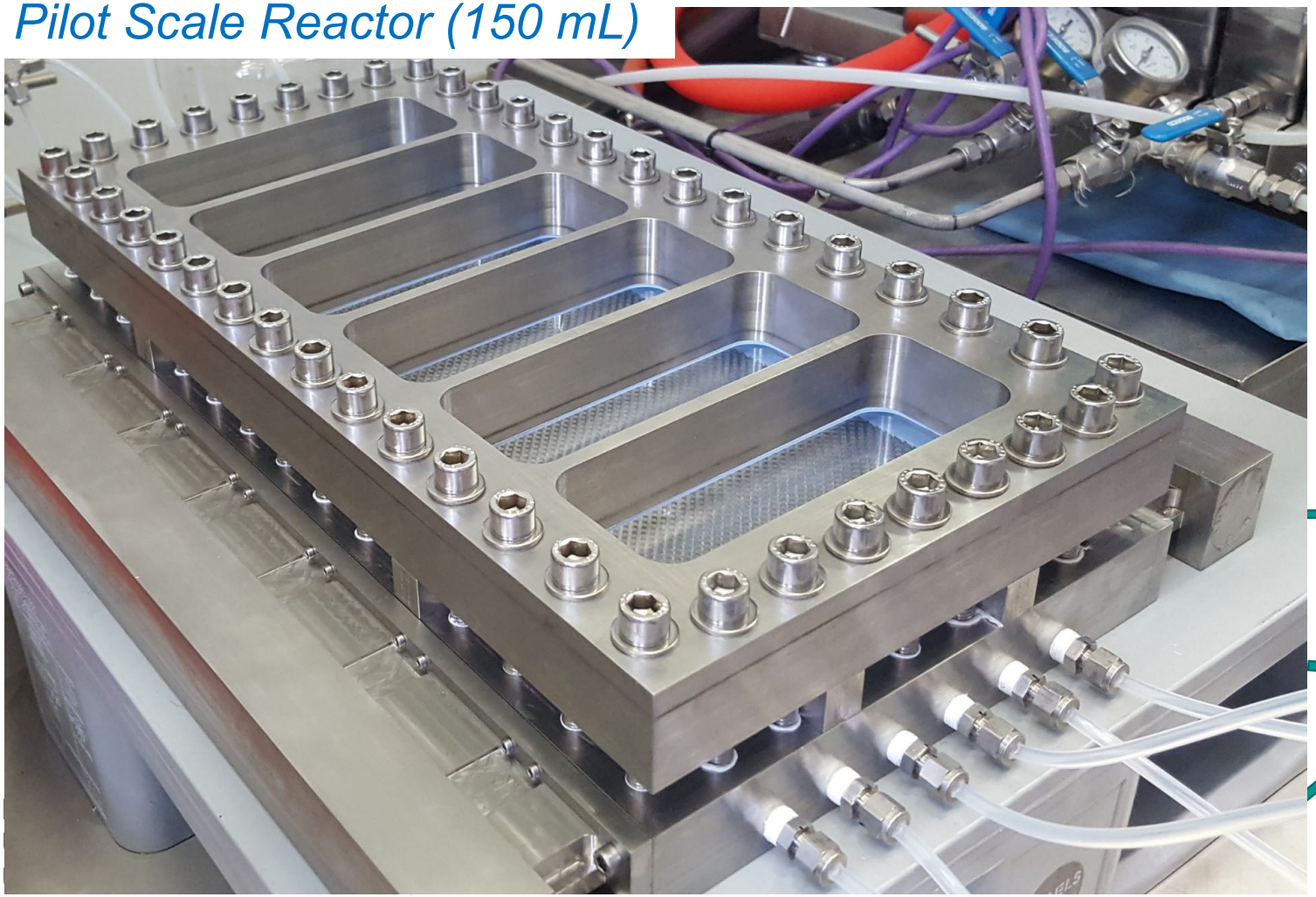
5 x **G3** plate
(**250 mL**)
680 mL/min

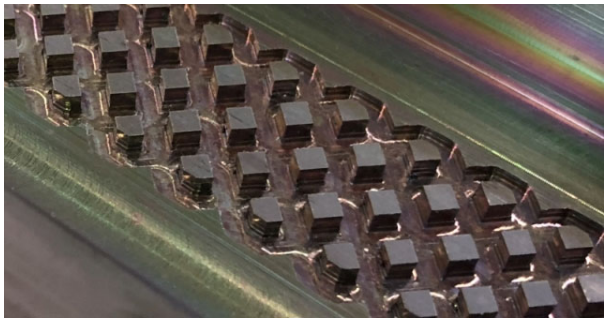
HANU Reactor – Handling Solids in Flow

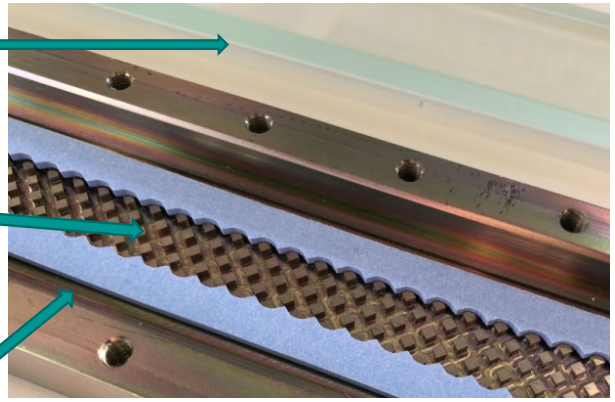
Pilot Scale Reactor (150 mL)

CREAFLOW

www.creaflow.be

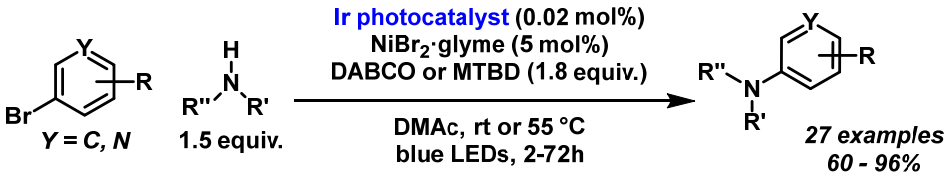




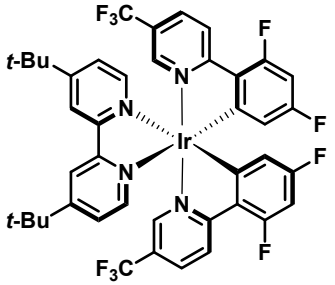


Dual Nickel/Photocatalytic C-N Cross-couplings

Iridium Complexes as Photocatalysts (Buchwald, MacMillan)

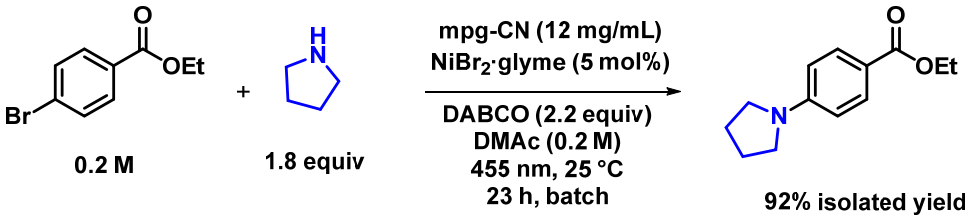


Corcoran, E. B. et al. *Science* **2016**, *353*, 279

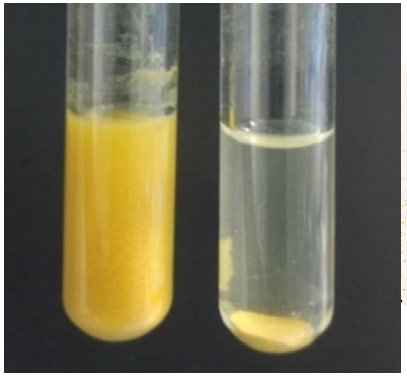


Iridium photocatalyst
Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$
800 €/g Sigma-Aldrich

Carbon Nitrides as Photocatalysts (Antonietti, König, Pieber)

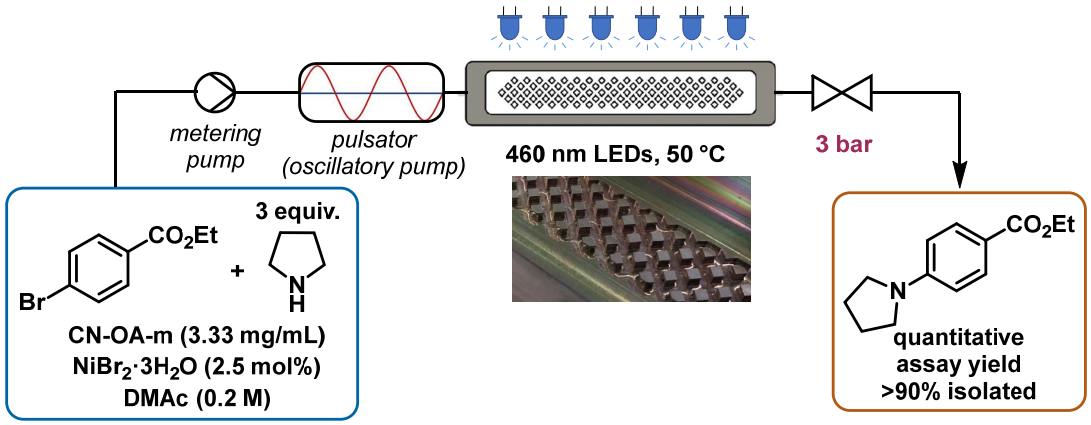


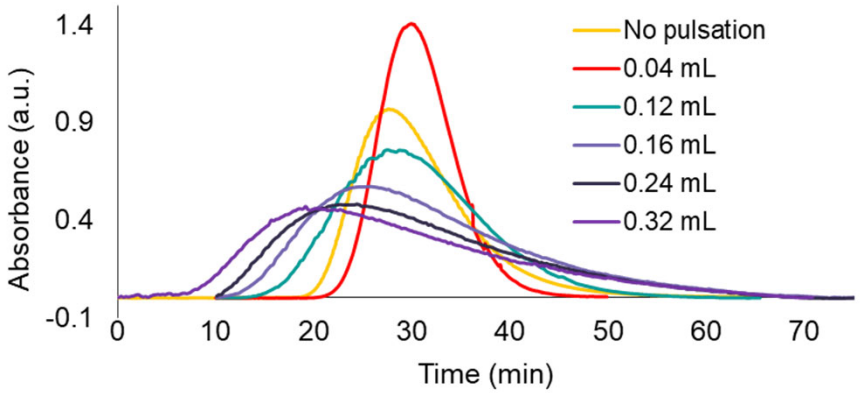
Gosh, I. et al. *Science* **2019**, *365*, 360
cf. Pieber, B. et al. *Nature Catal.* **2020**, *3*, 611; *Angew. Chem. Int. Ed.* **2019**, *58*, 9575



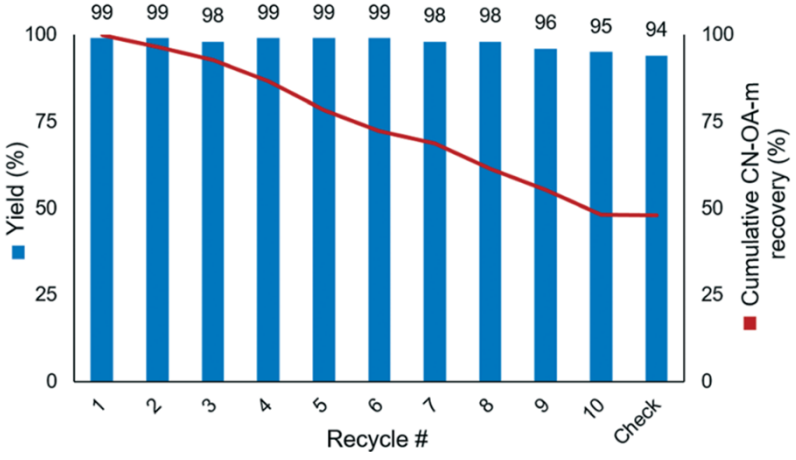
mpg-CN
inexpensive, solid, recycable

Semi-heterogeneous Photoredox Catalysis in the HANU Reactor

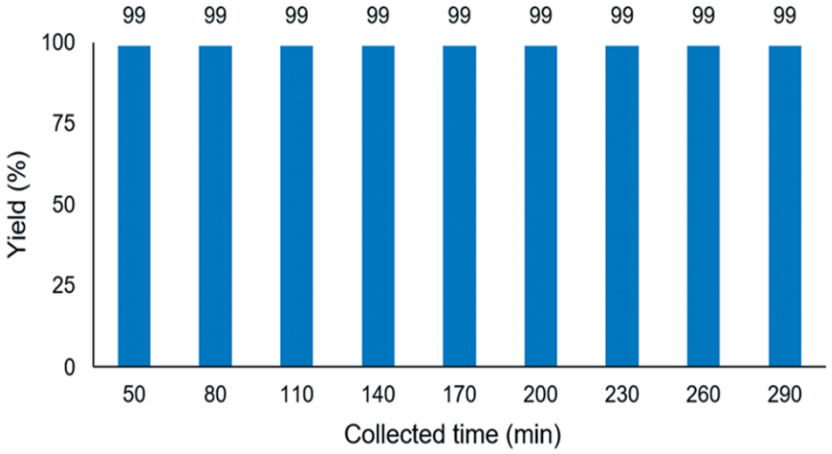




- Pulsation characteristics optimized for narrow RTD



- 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

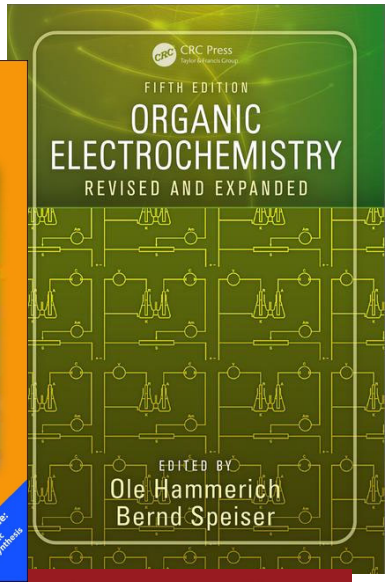


Rosso, C. et al. *React. Chem. Eng.* **2020**, *5*, 597

Electroorganic Synthesis – A Renaissance

Book

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



Electroorganic Synthesis – Advantages and Opportunities

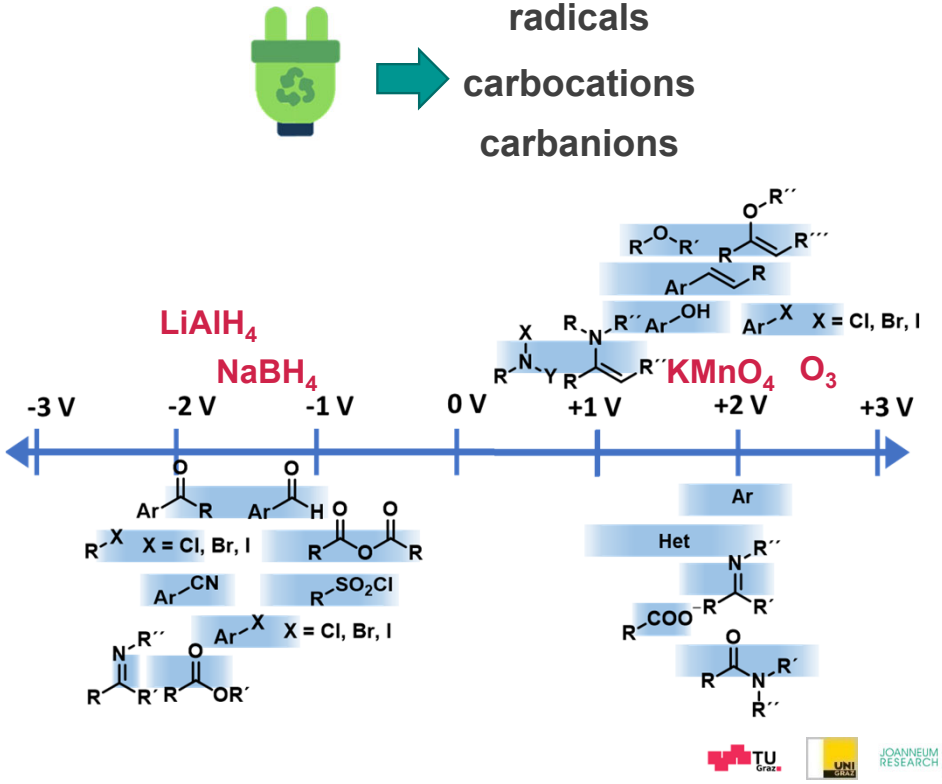
Sustainable and Cost-Efficient

vs

$KMnO_4$ 1-2 €/mol
$LiAlH_4$ 8 €/mol
mCPBA 7 €/mol

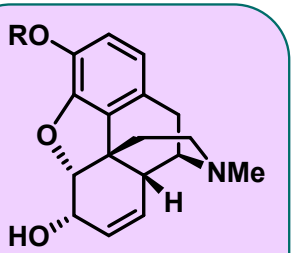
1 mol e^- (2 V cell) = < 0.01 €/mol

Enabling

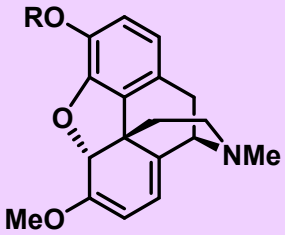


Important Opioid APIs

Opiates



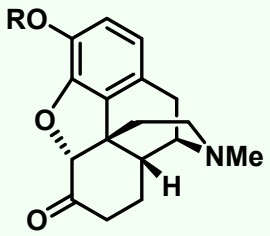
R=H: morphine
R=Me: codeine



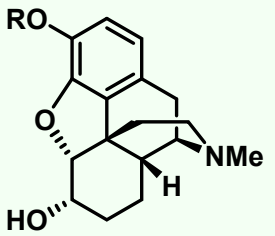
R=H: oripavine
R=Me: thebaine

Semisynthetic Opioids

Analgesic Drugs



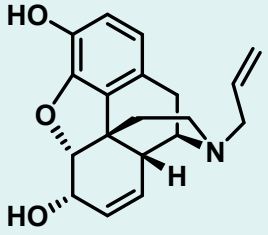
R=H: hydromorphone
R=Me: hydrocodone



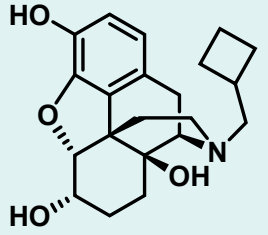
R=H: dihydromorphine
R=Me: dihydrocodeine

R=H: oxymorphone
R=Me: oxycodone

Mixed Agonist–Antagonists

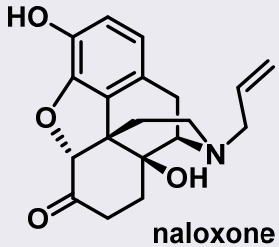


nalorphine



nalbuphine

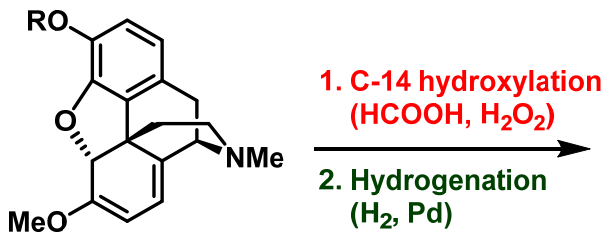
Pure Antagonists



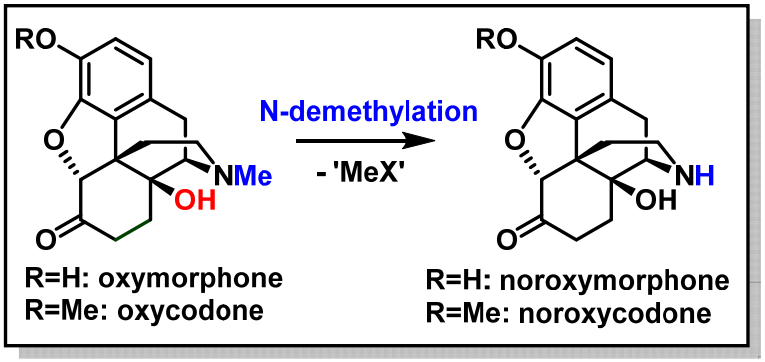
naloxone
(WHO essential medicine)

naltrexone

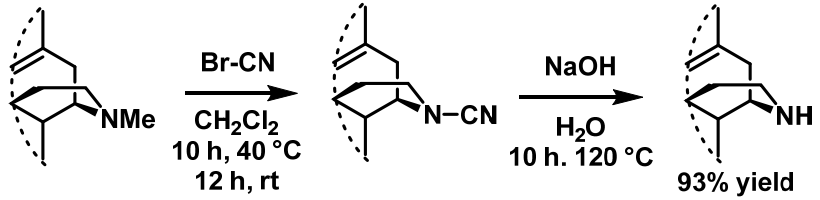
Common Opioid *N*-Demethylation Methods



J. Flow Chem. **2021**, *11*, 707

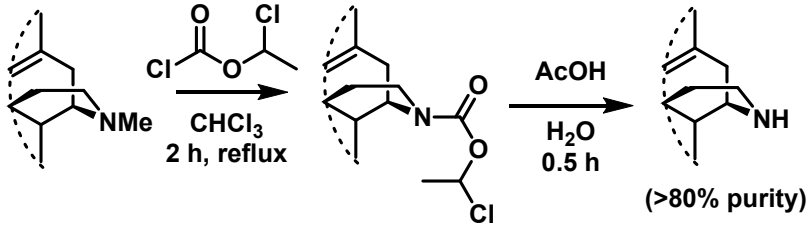


von Braun Reaction (1918)



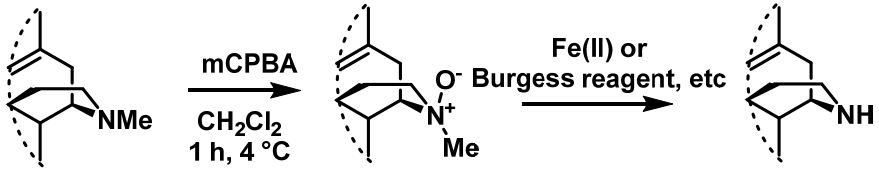
Johnson Matthey (WO2013050748A2)

Chloroformates



Mallinckrodt (US20090156818A1)

Polonovski Type Reactions

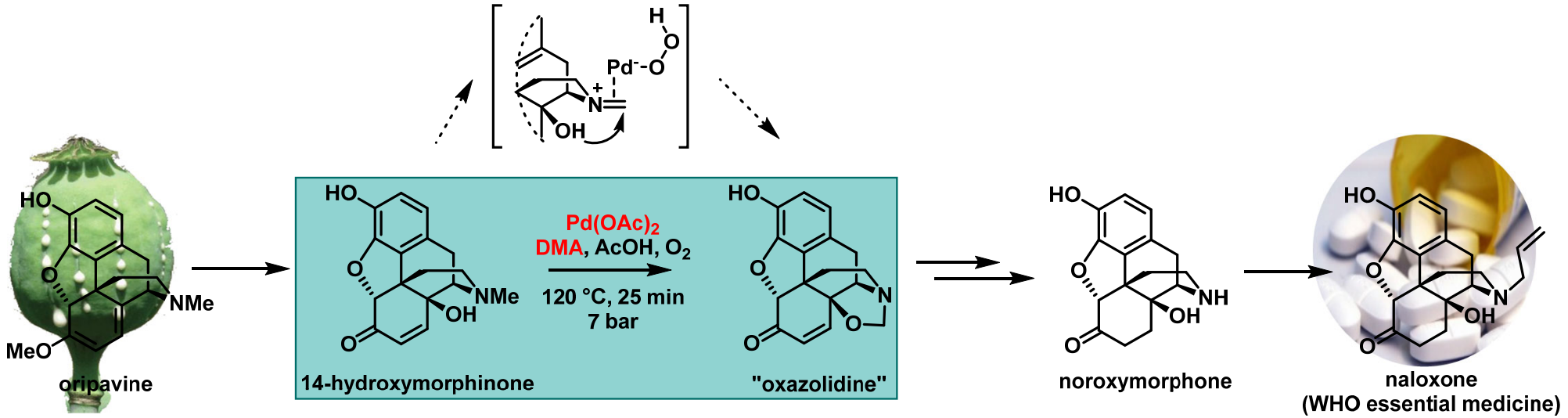


e.g. Brock University (WO2012149633A1)

- Stoichiometric amounts of reagents (toxic and corrosive)
- Stoichiometric quantities of waste

Continuous Manufacturing of Opioid Derived APIs

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

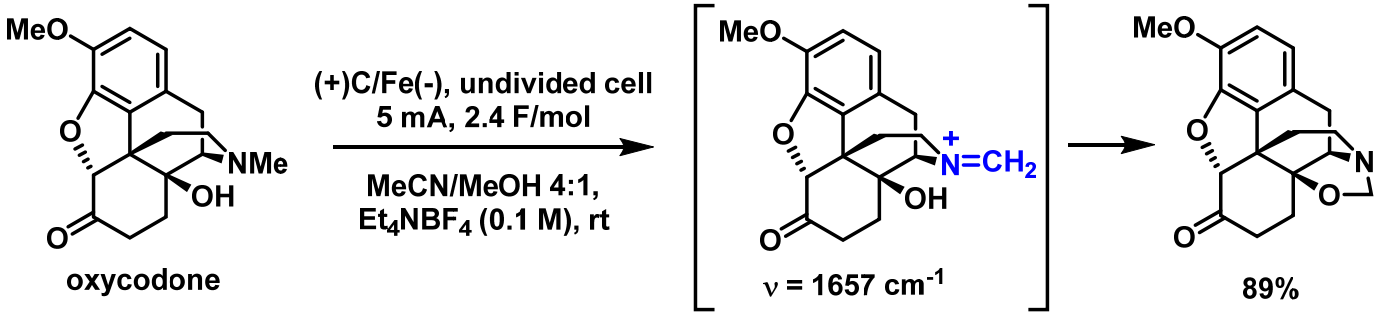
NORAMCO

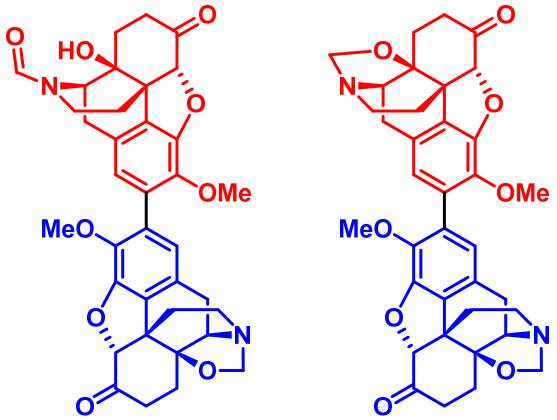
Janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Lonza

TU Graz | UNI GRAZ | JOANNEUM RESEARCH

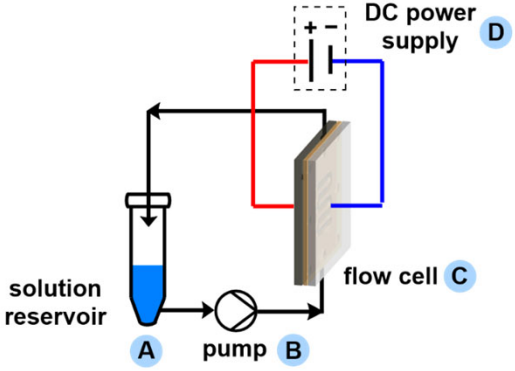
Electrochemical *N*-Demethylation of Oxycodone

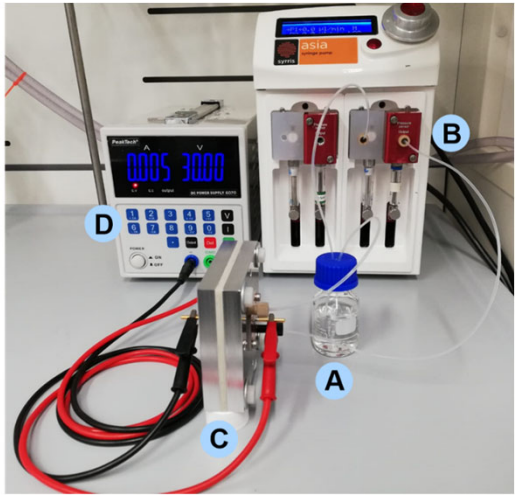


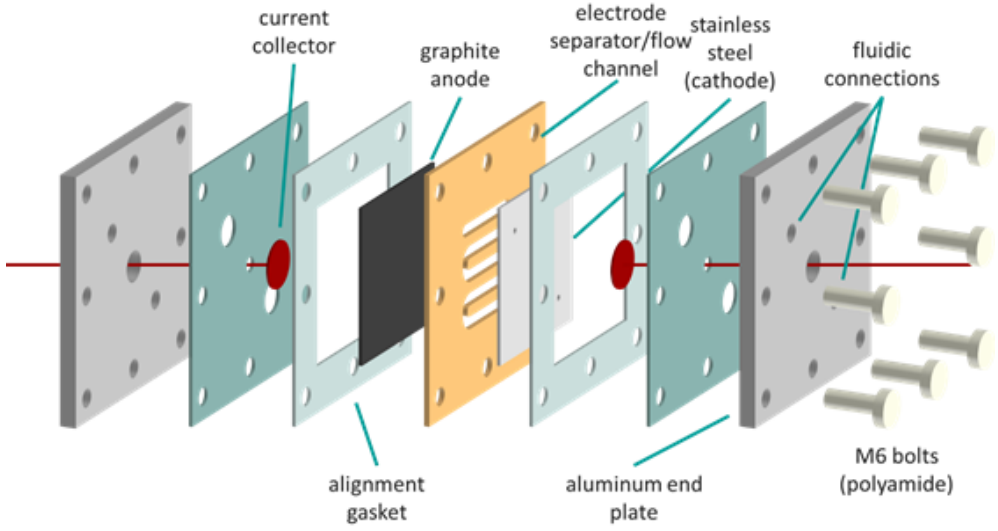


Glotz, G. et al. *Org. Lett.* **2020**, *22*, 6891

Flow Set-Up

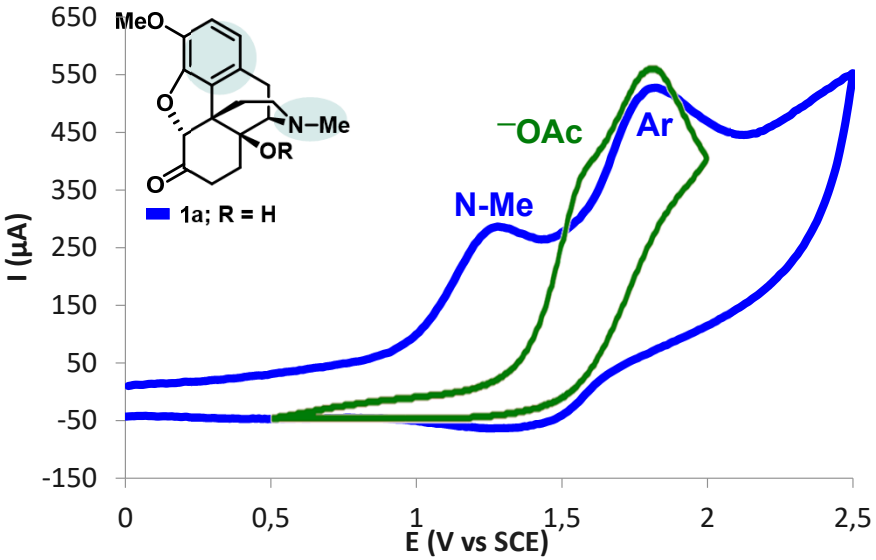






Jud, W. et al. *Chem. Methods* **2021**, *1*, 36

Electrochemical *N*-Demethylation of Oxycodone



Original Electrolysis

0.05 M in MeCN/MeOH

0.1 M Et_4NBF_4

89% yield

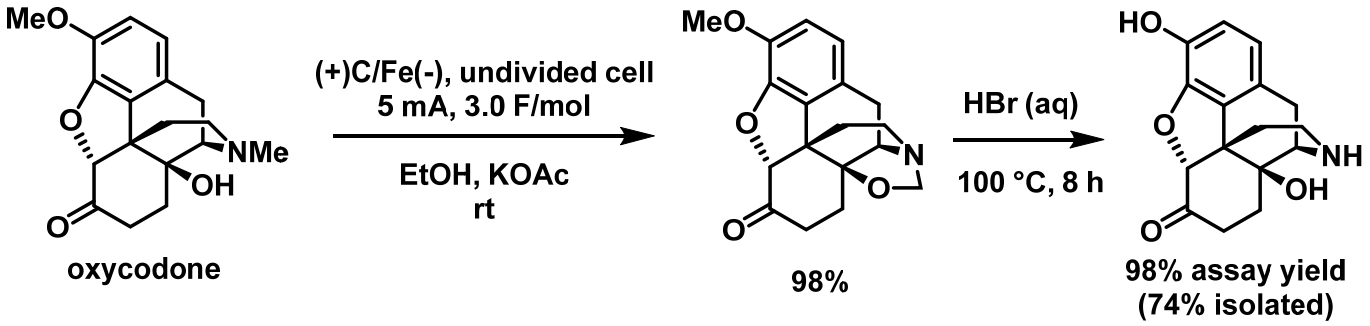
Improved Process

0.2 M in EtOH

0.1 M KOAc

98% yield

dimerization suppressed



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

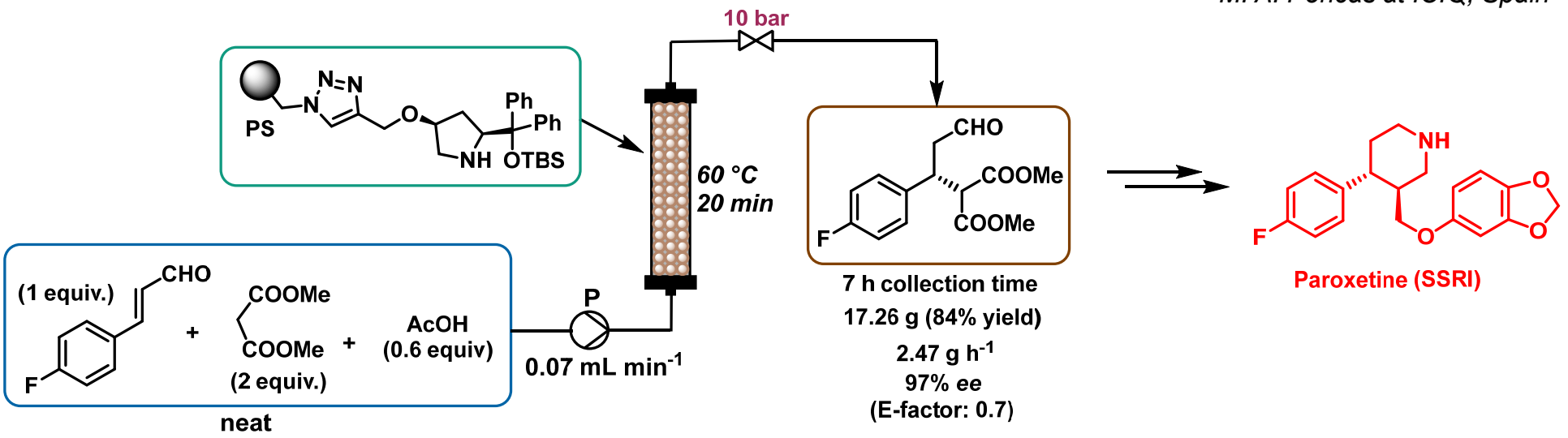
Comparison of Conventional and Electrochemical Procedures

	EtOCOCl	Electrochemical A	Electrochemical B
Type of reaction	Stochiometric Reagent	Electricity (Et_4NBF_4)	Electricity (KOAc)
T [°C]	60	rt	rt
Workup	Extraction	Chromatography	Extraction
Solvent	$CHCl_3$	MeCN/MeOH	EtOH
Yield [%]	60	89	98
Quench	50 L H_2O/kg oxycodone	-	-
Atom Economy	12	35	81
PMI (without solvent)	3.5	2.9	1.2
PMI	37	62	15
EcoScale	49	60	90

Immobilized Organocatalysts for Chiral API Synthesis

Asymmetric Conjugate Addition

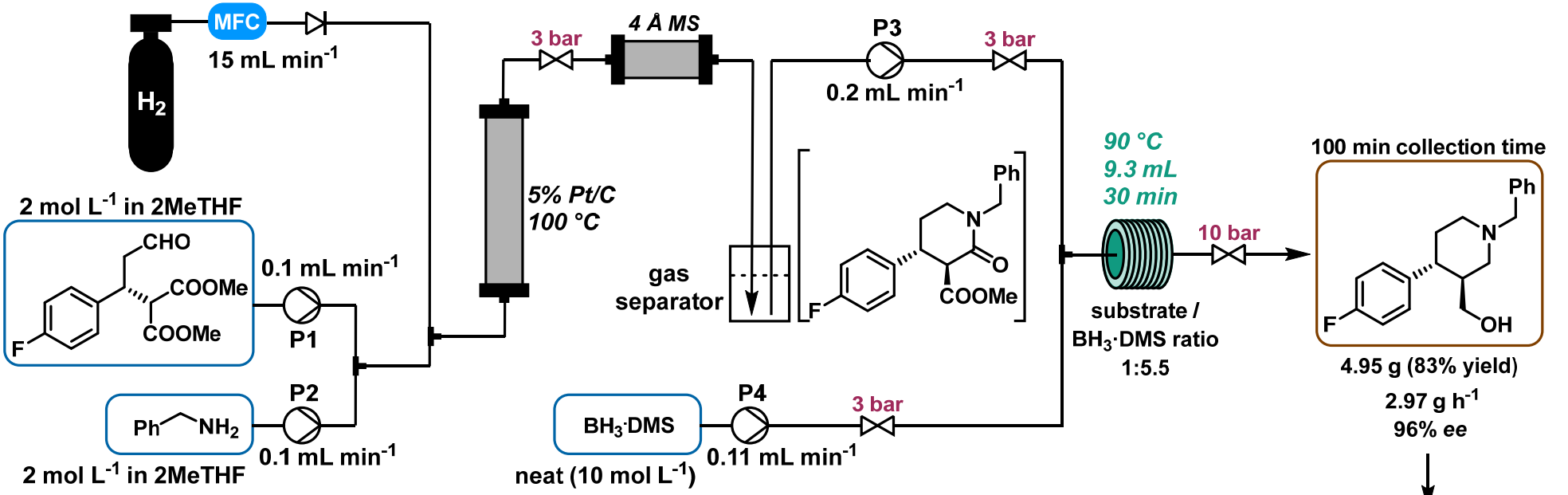
In collaboration with
M. A. Pericas at ICIQ, Spain



- Flow organocatalysis under solvent-free conditions
- 7-h long experiment under optimum flow conditions
- Isolation of analytically pure product by evaporation

Ötvös, S. et al. *Chem. Sci.* **2019**, *10*, 11141
Review: Ötvös, S.; Kappe, C. O. *Green Chem.* **2021**, *23*, 6117

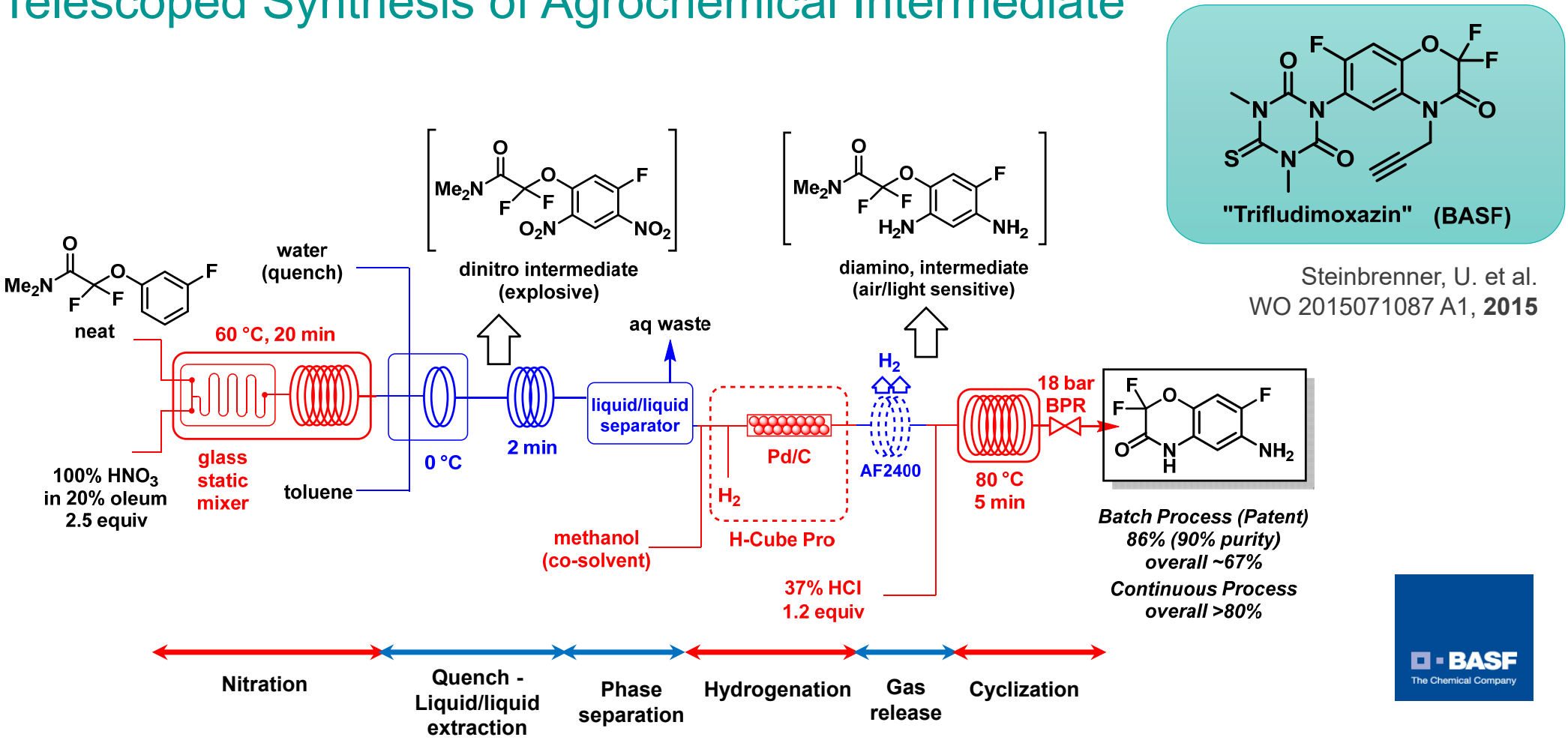
Telescoped Reductive Amination–Lactamization–Amide/Ester Reduction



- Both steps in 2-MeTHF – no solvent switch necessary
- Sufficiently pure lactam formed – no in line purification
- Water removal by 4 Å MS column to prevent BH_3·DMS decomposition

Ötvös, S. et al. *Chem. Sci.* **2019**, *10*, 11141; *ChemSusChem* **2020**, *13*, 1800; *Org. Lett.* **2022**, *24*, 1066

Telescoped Synthesis of Agrochemical Intermediate

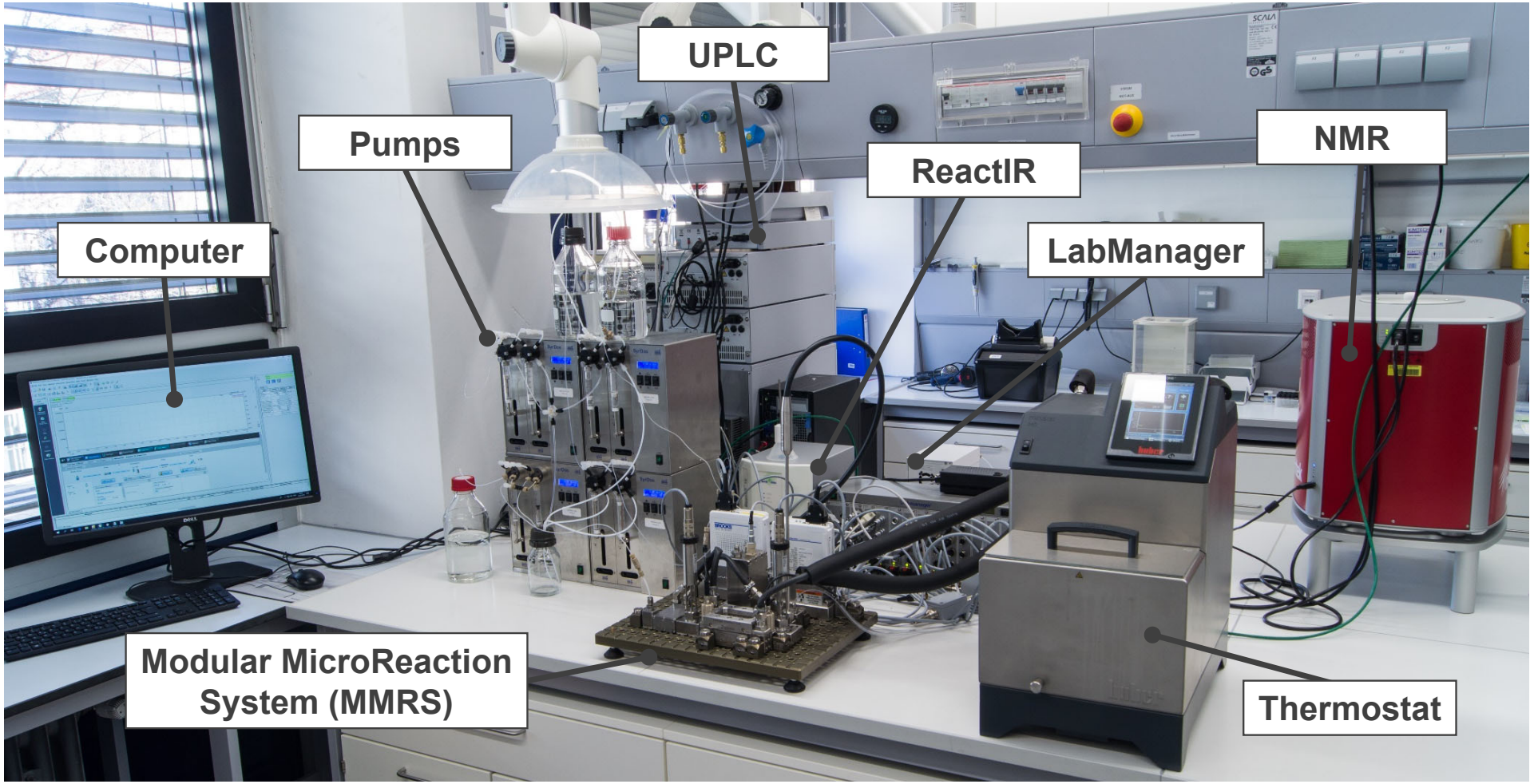


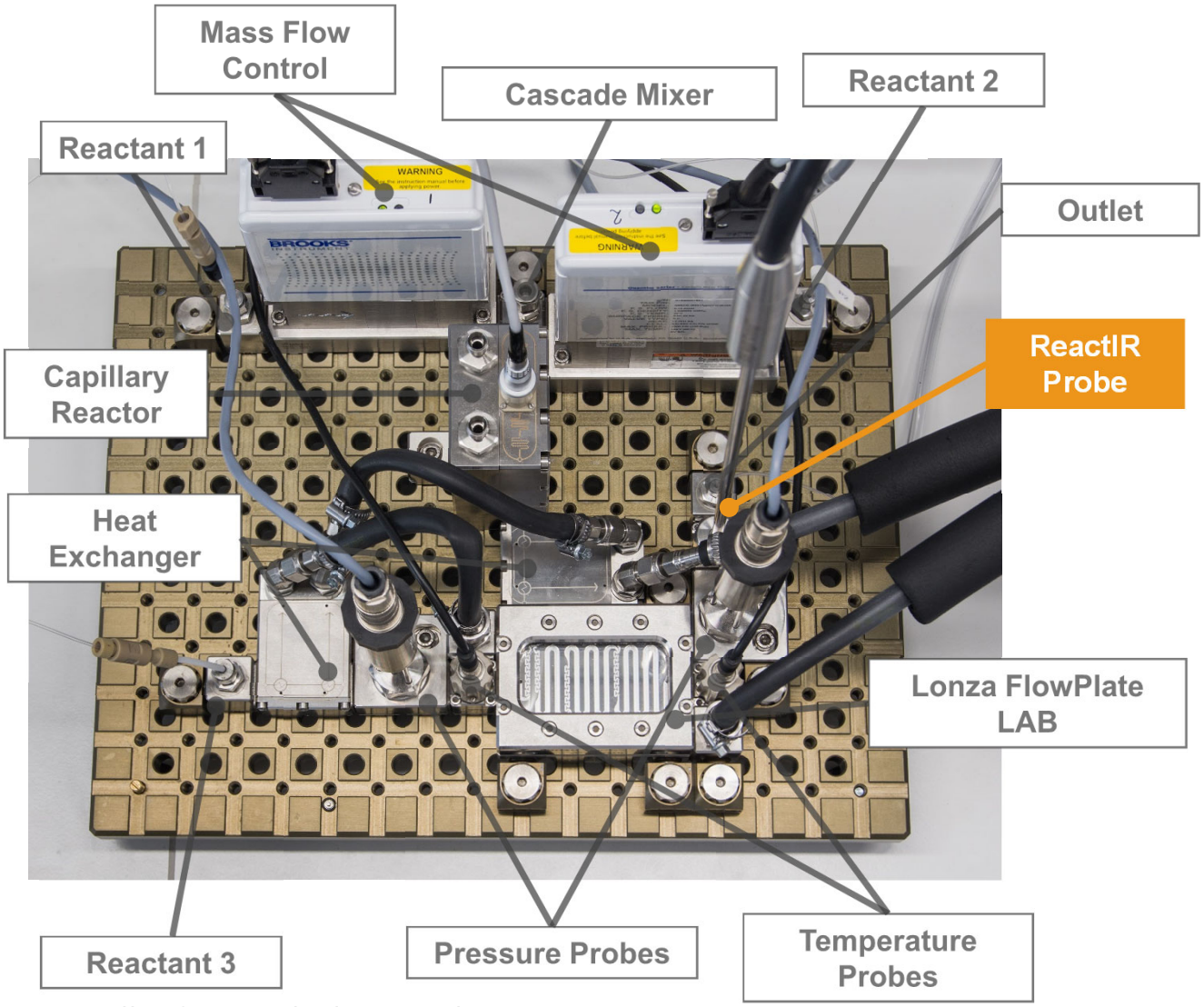
"Trifludimoxazin" (BASF)

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

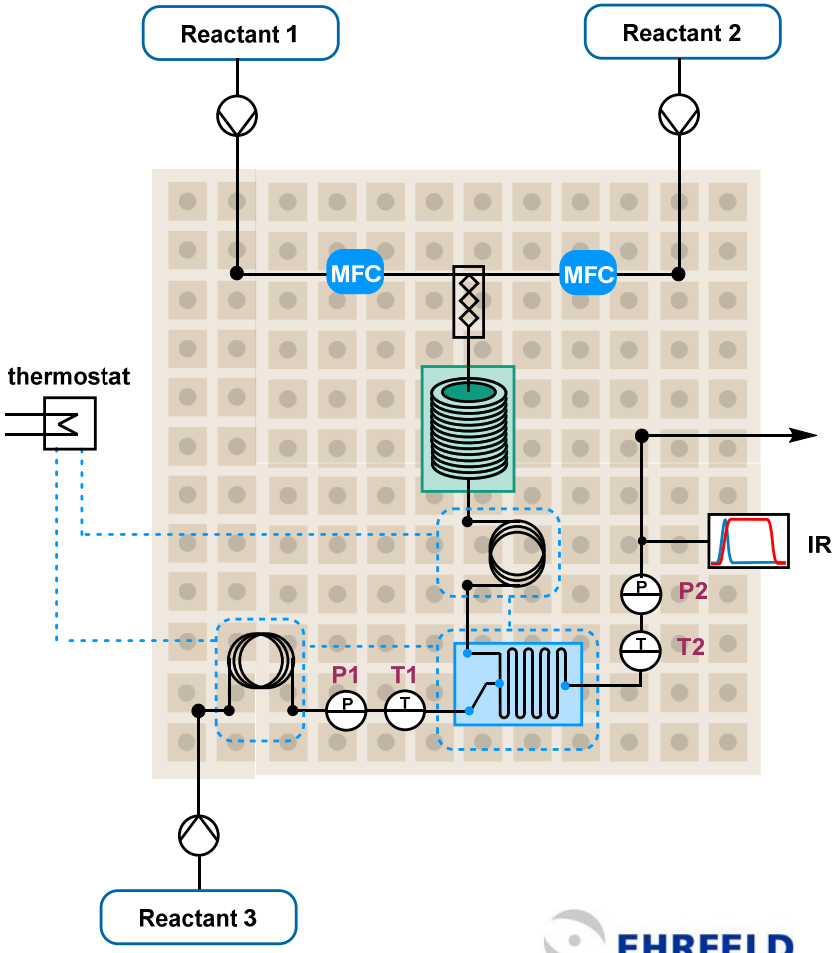
EP 15201920.4
Cantillo, D. et al. *Org. Process Res. Dev.* **2017**, *21*, 125

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



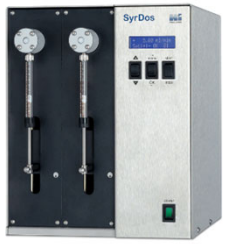


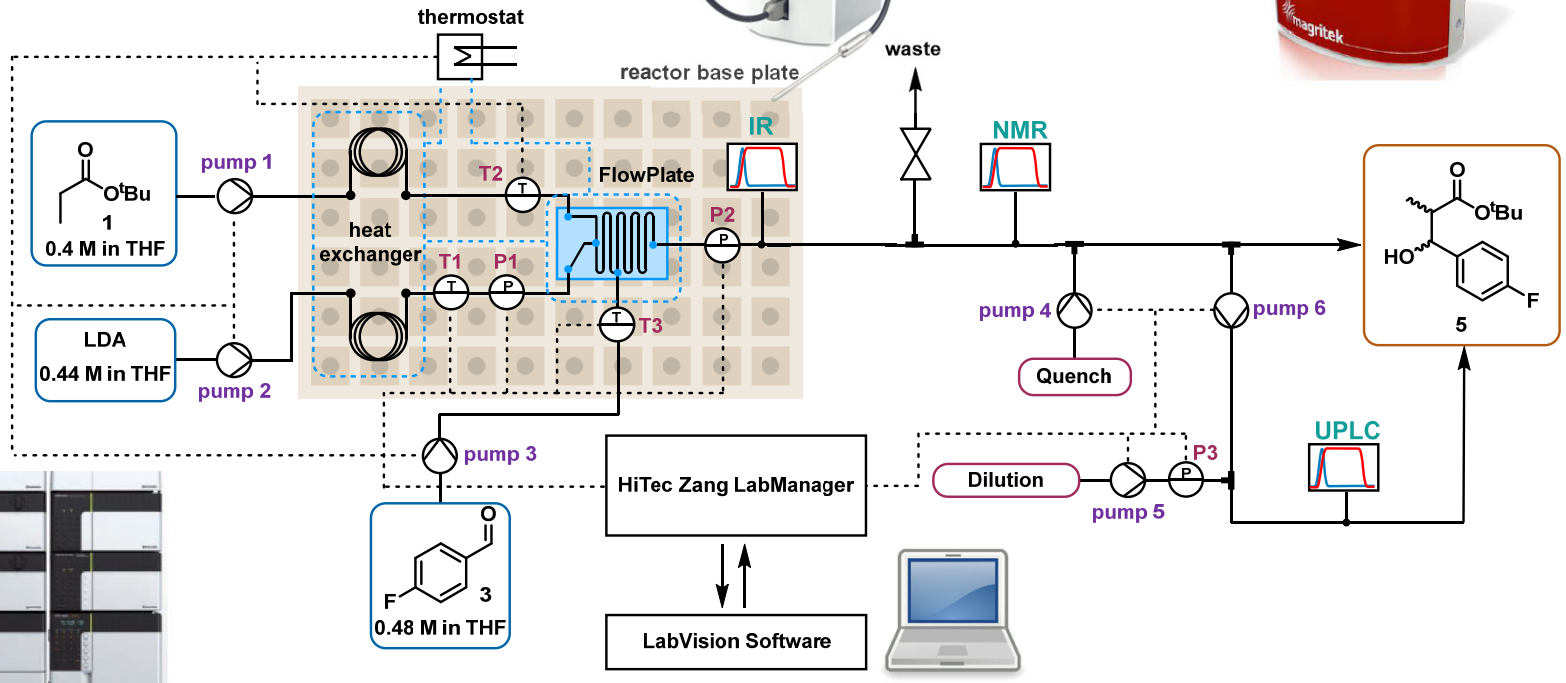
https://ehrfeld.com/en/products/mmrs.html



EHRFELD Mikrotechnik

Laboratory of the Future: A Modular Flow Platform with Multiple Integrated PAT Tools for Multistep Reactions

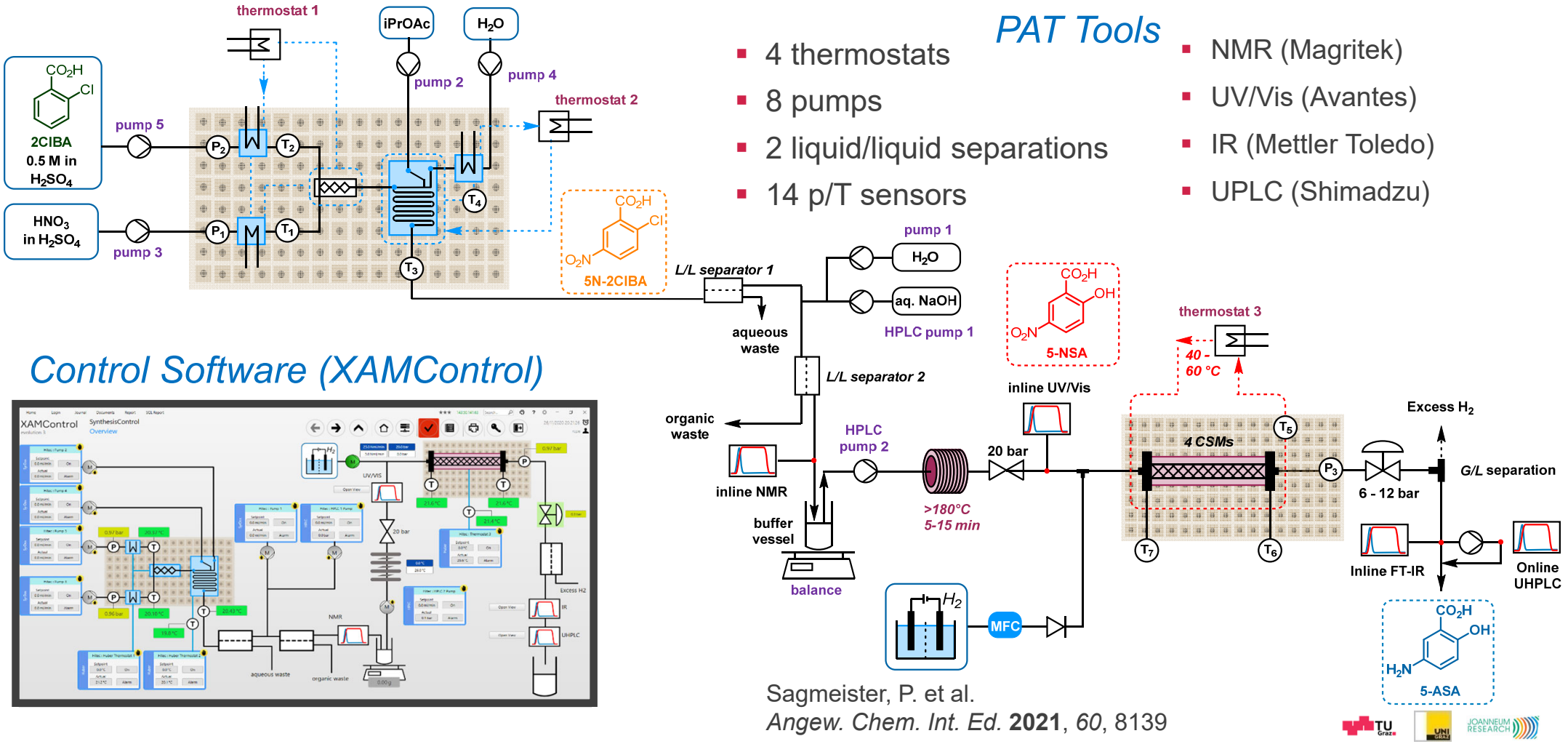




70%, 4.2 g h^{-1}

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

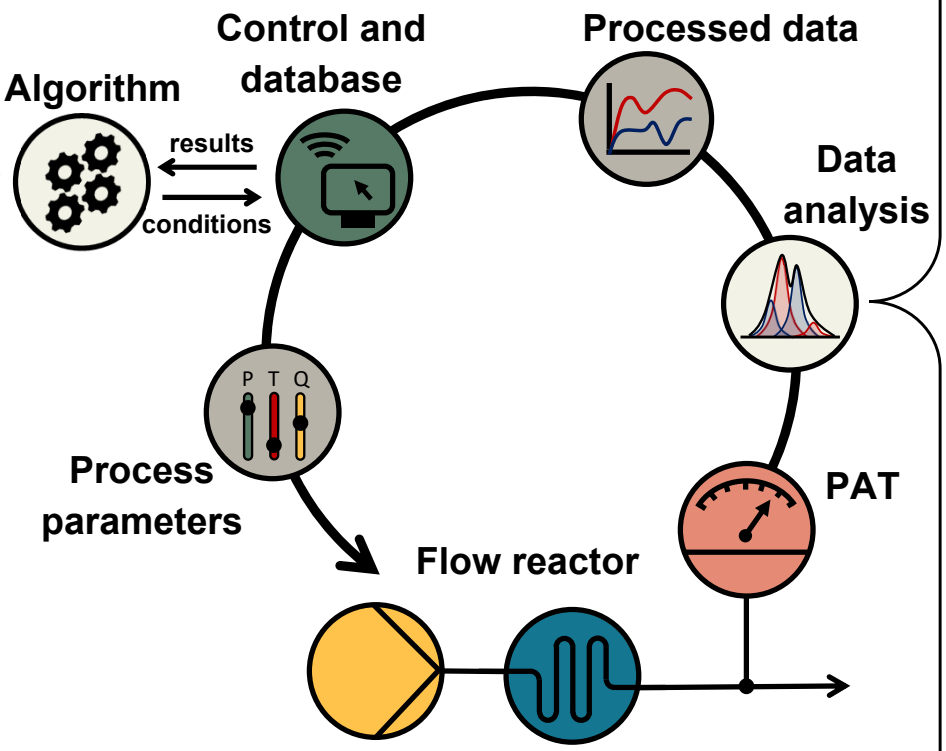
Sagmeister, P. et al.
manuscript in preparation

Iterative Model Building

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

Model Predictive Control (MPC)

Sacher, S. et al. *Chem. Eng. Res. Des.* **2022**, *177*, 493



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

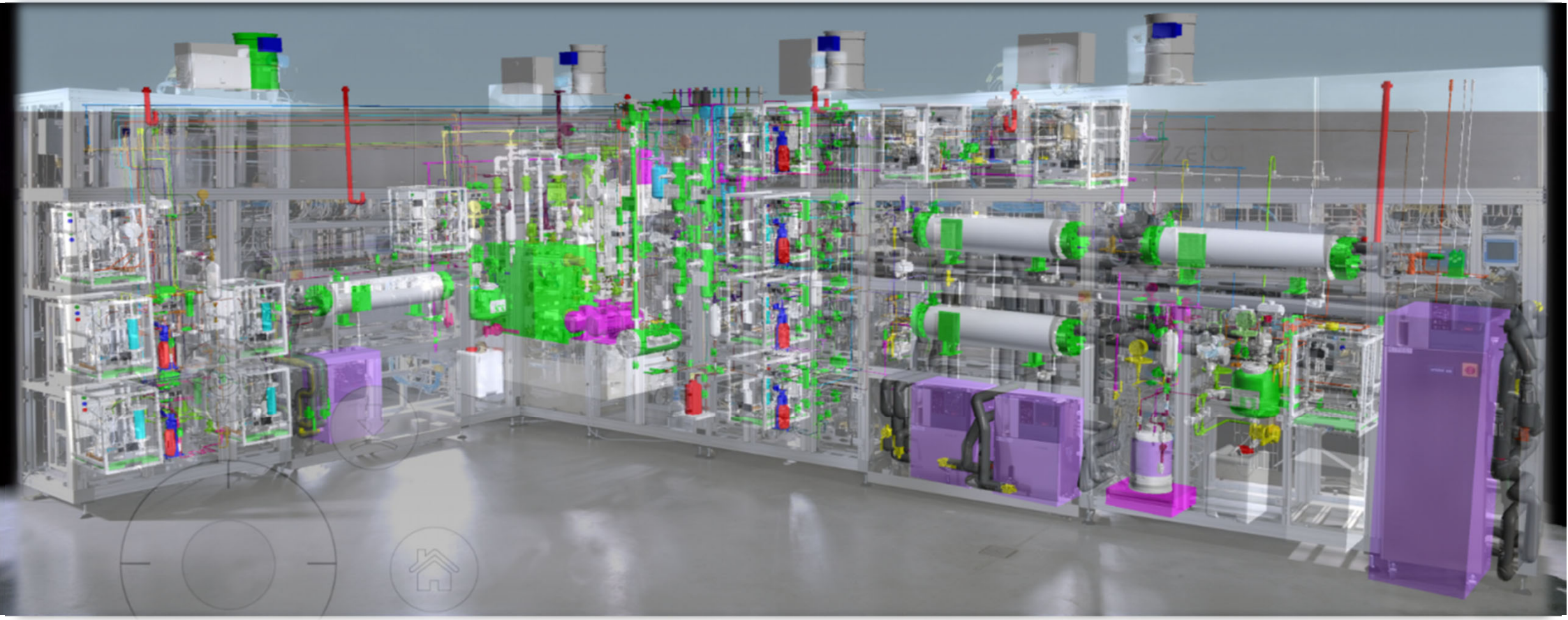
Indirect Hard Modeling (IHM)

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

Artificial Neural Network (ANN)

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

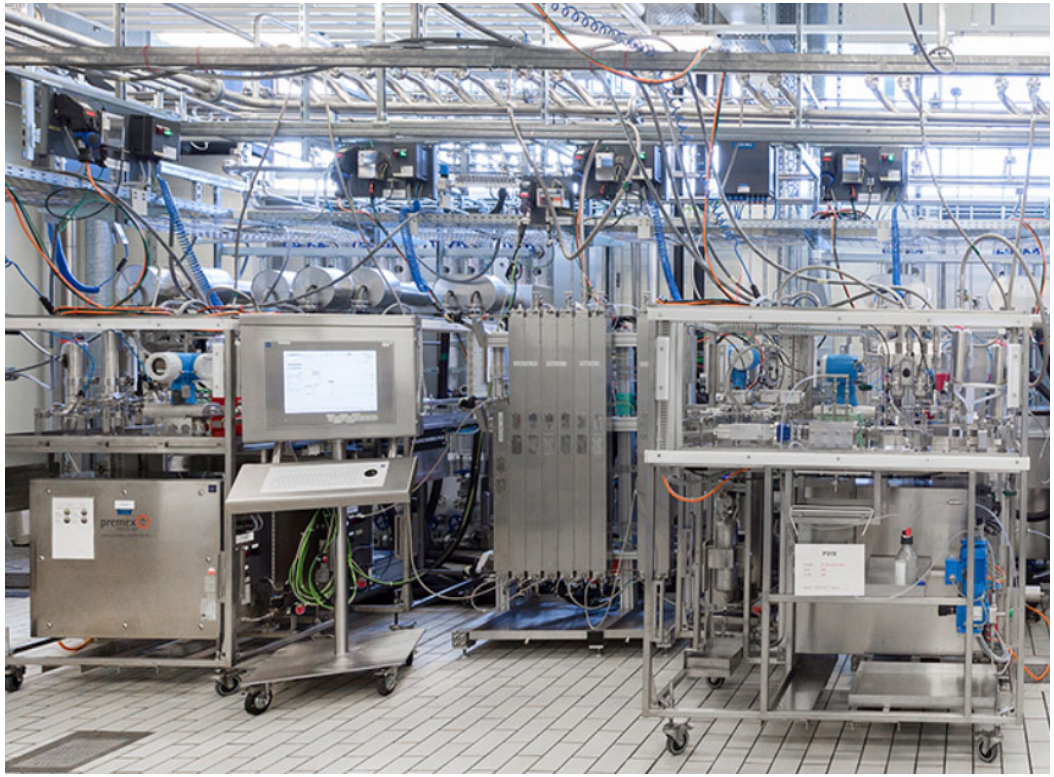
GSK Continuous API Manufacturing (Singapore)



Allford, G.; Hagger, B. *7th Symposium on Continuous Flow Reactor Technology for Industrial Applications,* Delft, Netherlands, Sept 29-Oct 1, **2015**
See also: Roberts, K. *Chemistry and Industry Magazine* **2016** (*6*), p. 31-33

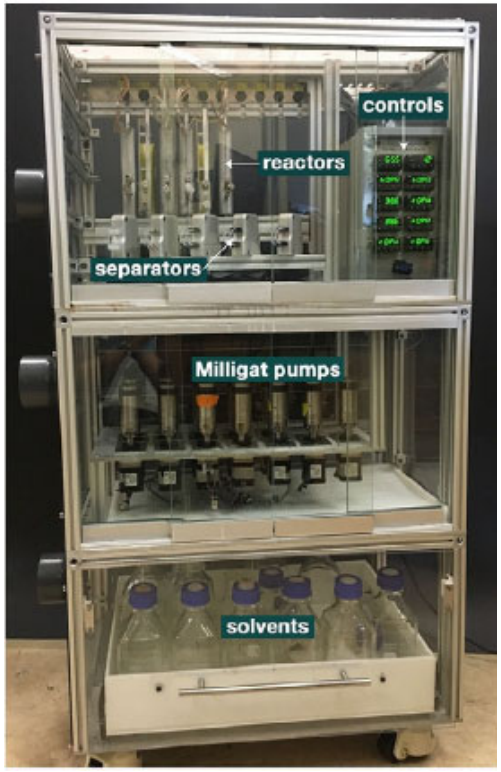
End-to-End Continuous Manufacturing (MIT)

Novartis CM Facility (Basel)



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

Pharmacy on Demand (DARPA)



Adamo, A. et al. *Science* **2016**, *352*, 61
Zhang, P. et al. *Chem. Eur. J.* **2018**, *24*, 2776
cf. Coley, C. et al. *Science* **2019**, *365*, Issue 6453, eaax1566

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” 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 2010-2022

Pharma

Allergan — *CEJ* **2017** 176

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

ASKAT — *CEJ* **2022** e202200741

AZAD PHARMA AG — *ACSSCE* **2022** xxxx

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 / MSD

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

Pfizer — *OPRD* **2022** 1486

Roche — *OPRD* **2021** 1206
OPRD **2021** 1988

SANOCHEMIA DEVELOP.PRODUCE.SUPPLY

ucb

willow

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

umicore materials for a better life

syngenta

CMO/CDMO

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

Lonza — *ACIE* **2010** 7101….
RCE **2021** 2253 (19)

mi micro innova efficient processing — *OPRD* **2011** 858….
OPRD **2020** 2208 (3)

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

SEQENS

Acknowledgements: CCFLOW Team and Funding Agencies

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

FFG Forschung wirkt.
SFG NEUES DENKEN. NEUES FÖRDERN.
FWF Der Wissenschaftsfonds.
Das Land Steiermark
BILL & MELINDA GATES foundation
austria wirtschaftsservice aws
UNI GRAZ
TU Graz