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MINAKEM®
FINE SERVICES FOR LIFE

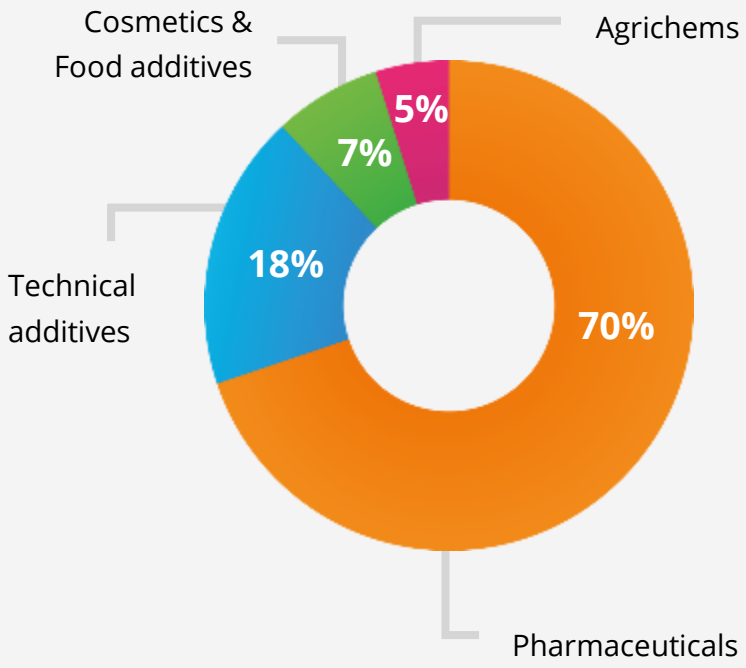
Innovation through process development, enabling technologies and collaborations

SCF 2023 - 27/06/2023

Dominique Delbrayelle, *Scientific Director*

2021 KEY FIGURES

Acting as a Global Player



€ 236M
revenue
(2021)

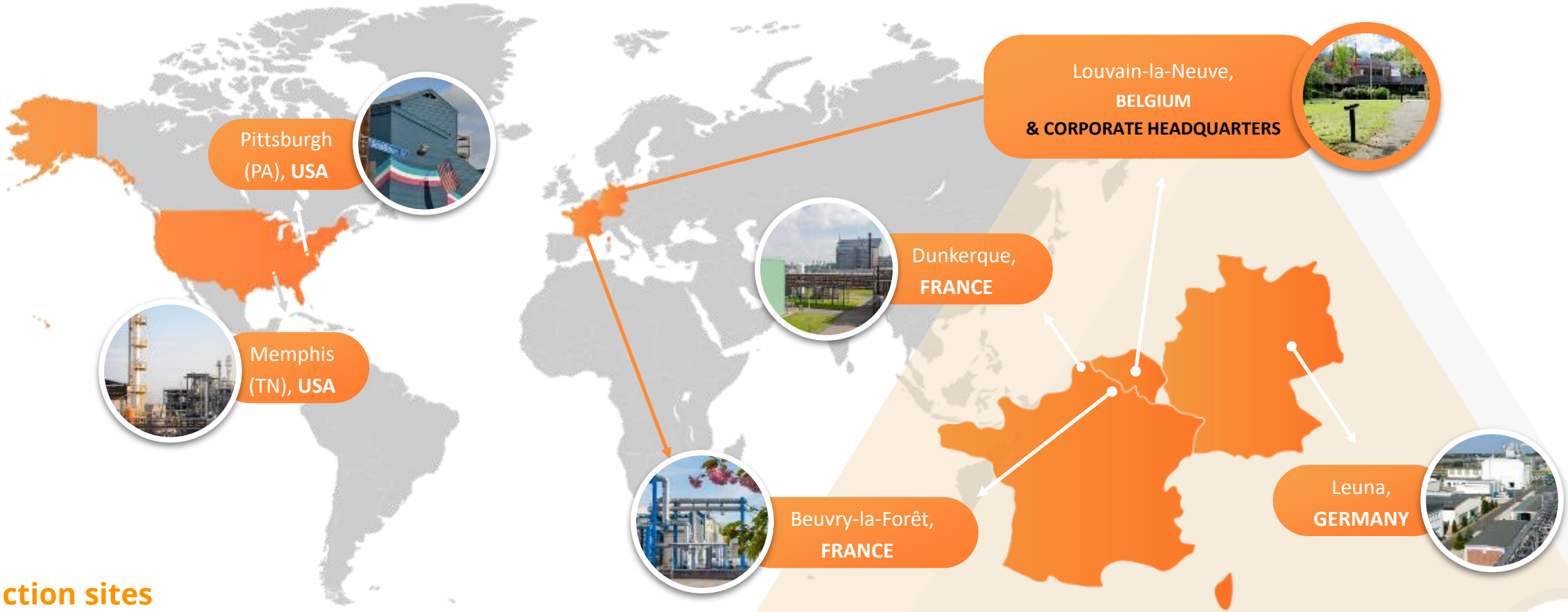
€ 42M
EBITDA
(2021)

98
R&D
resources

860
employees

4 EU & 2 US
sites

WE HAVE EXPANDED GLOBALLY SINCE 2004



6 Production sites
Corporate Headquarters in Belgium

Our organization
3 DIVISIONS – 7 BUSINESS UNITS

Health chemistry division
Minakem CDMO
Minakem Generics

Green Chemistry division
Pennakem
Minasolve
EcoXtract

Challenging Chemistry division
Minascent Technologies
Pressure Chemical

Organization by division

Health Chemistry Division
130 M€ sales – 540 FTE

Pharma

MINAKEM

Green Chemistry Division
80 M€ sales – 160 FTE

Green chemistry

PENNAKEM

Cosmetics

MINASOLVE

Green extraction

ecoXTRACT

Challenging Chemistry Division
26 M€ sales – 160 FTE

High Pressure & Polymers

PRESSURE CHEMICAL

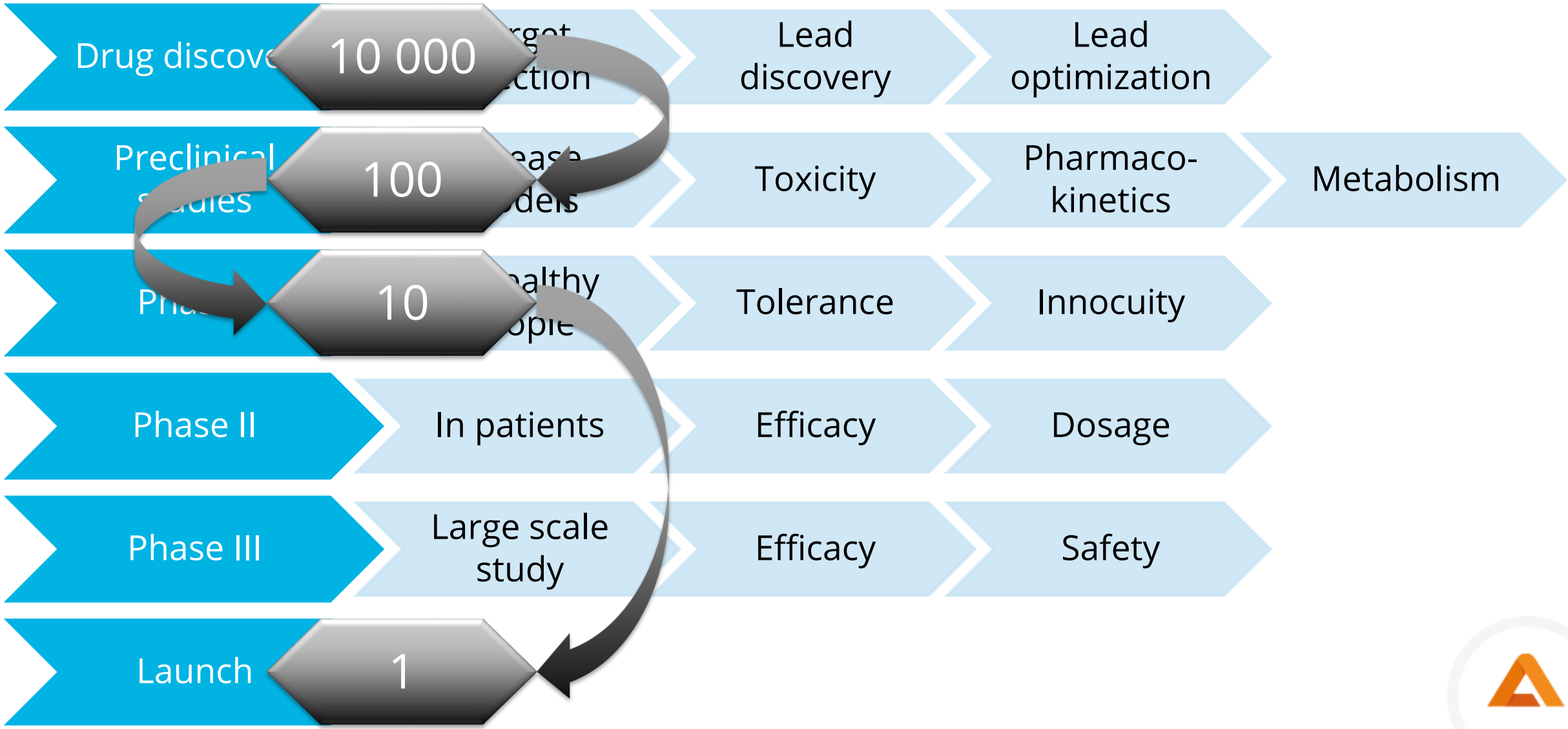
Demanding Chemicals

MINASCENT TECHNOLOGIES

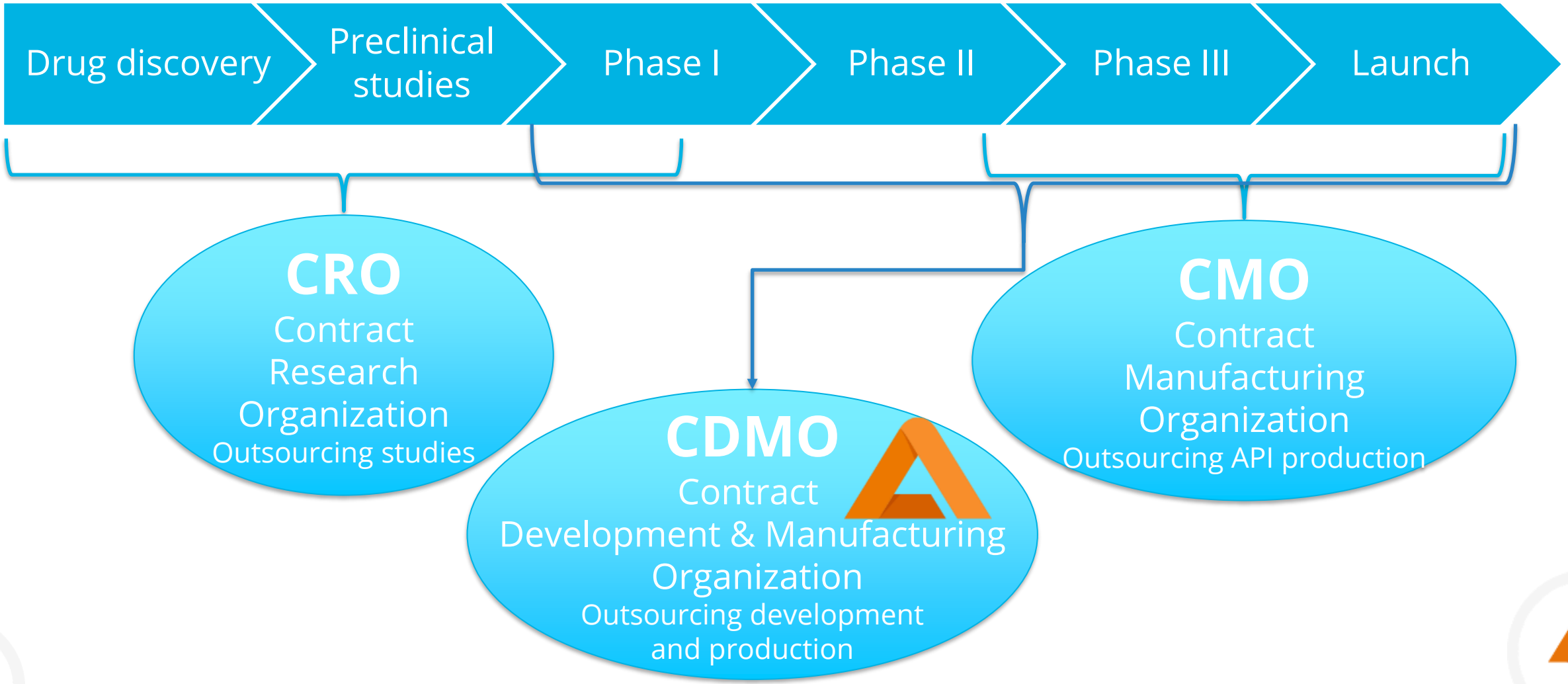
MINAKEM® CDMO

CDMO – What is it ?

Development steps for a drug candidate



Sub-contracting in the pharma industry



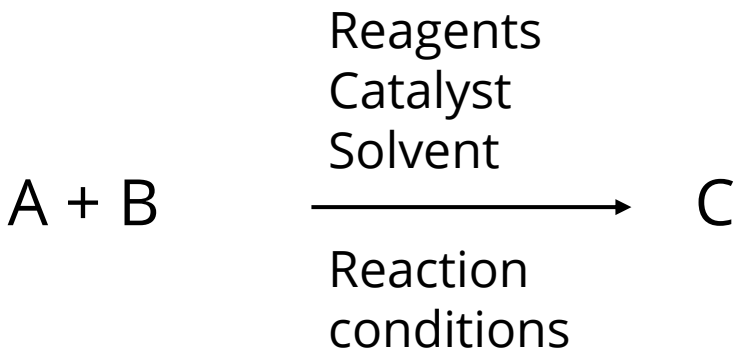
Process development to enable large scale production

	Qty	Synthesis	Location
Drug discovery	10 mg-10 g	Expeditious	Lab
Initial development	10 g-10 kg	Practical	Kilo-lab
Development	10 kg-100 kg	Efficient	Pilot
Launch	100 kg ++	Optimal	Plant

Process development

The chemical reaction is only part of the process...
and often not the most difficult!

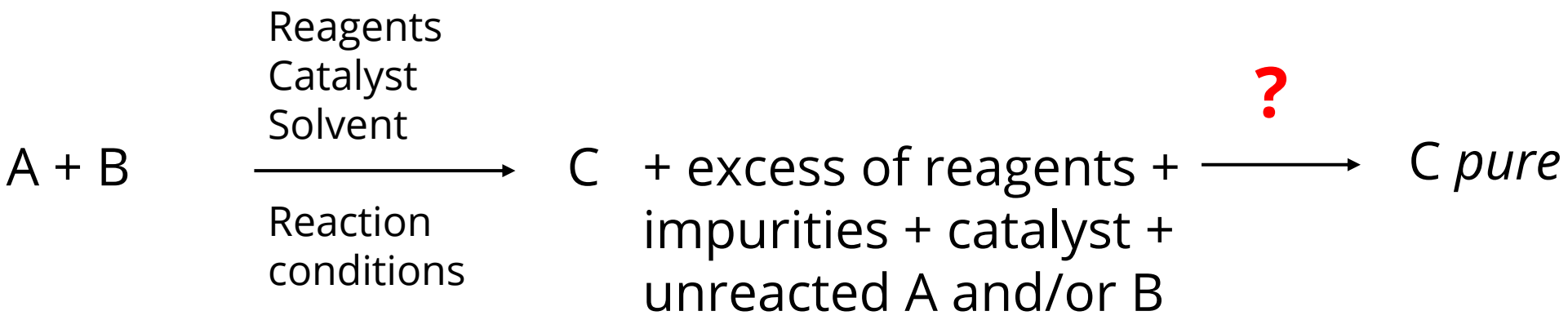
The "theory":



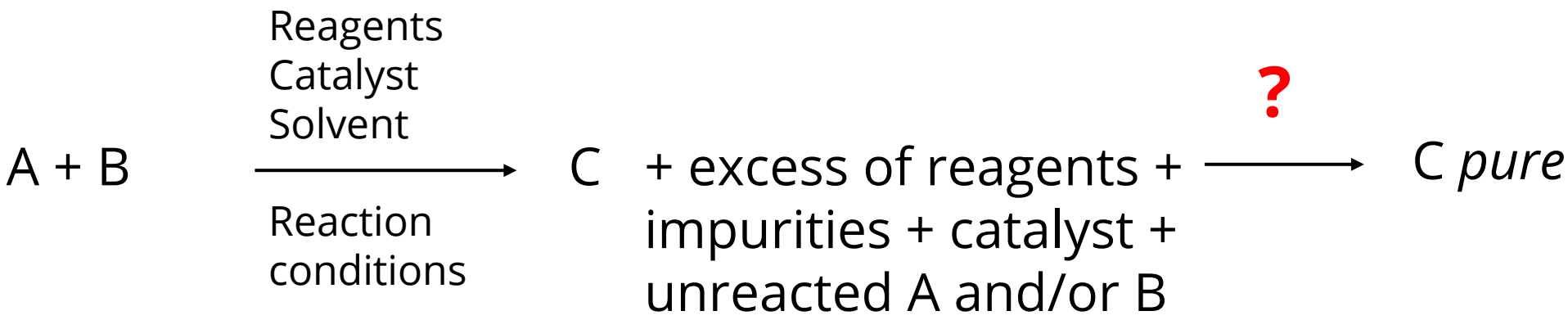
Process development

The chemical reaction is only part of the process…
and often not the most difficult!

In practice:

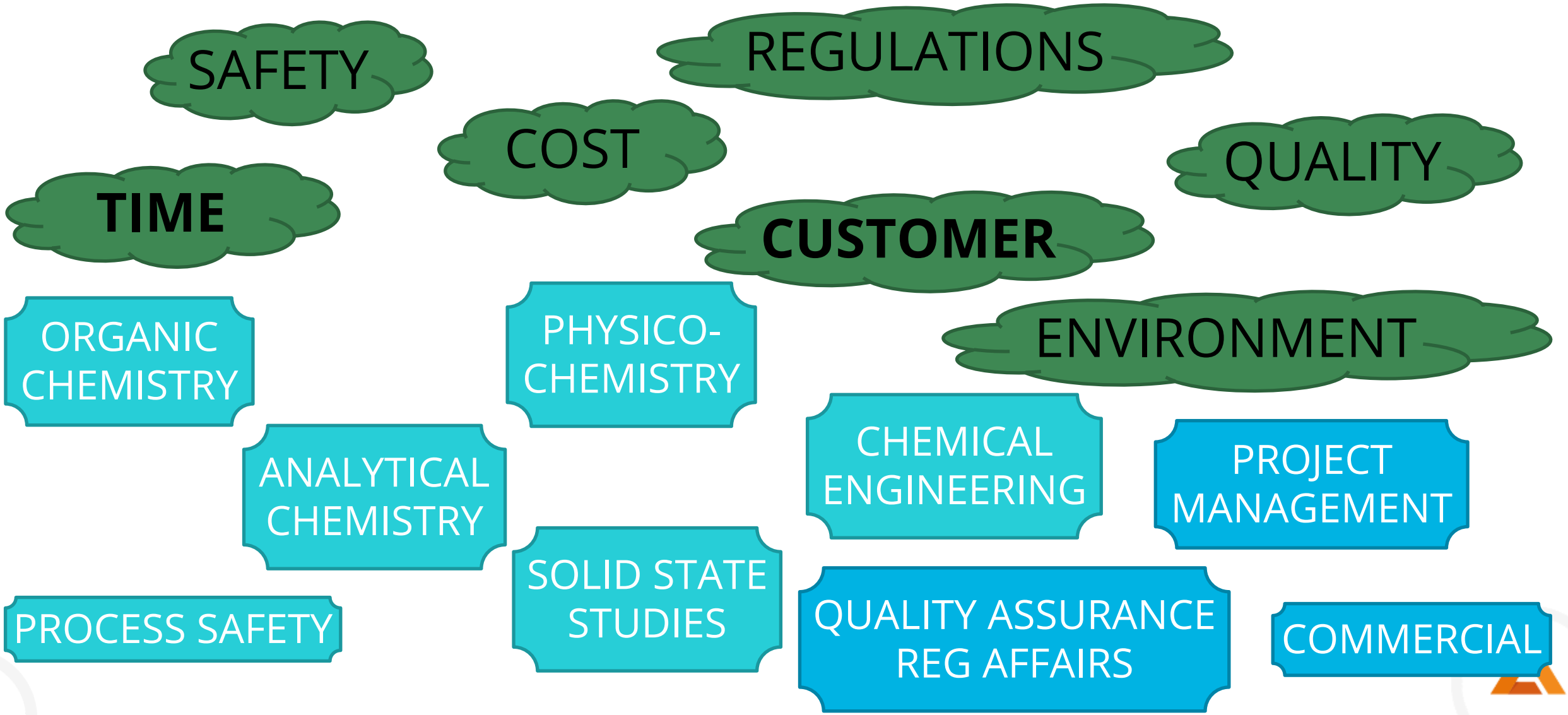


Process development



- Choosing solvent and reagents
- Reaction conditions: parameters, operation (safety)
- Reaction workup: implementation, removal of impurities
- Obtaining the product: crystallization, telescoping steps

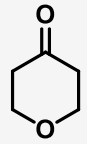
Process development



Process development – Case study

Presentation

Tetrahydro-4*H*-pyran-4-one

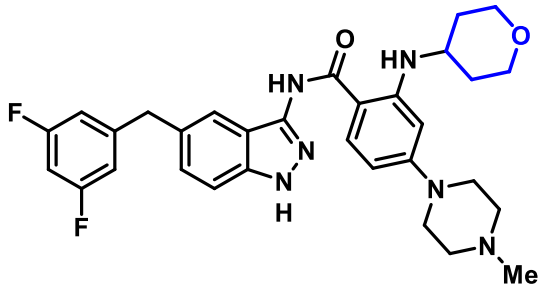


THP

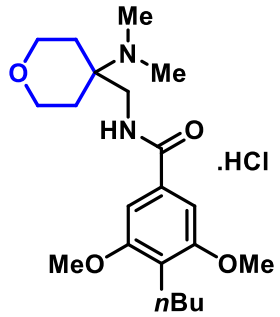
[Key building block]

[Linchpin molecule]

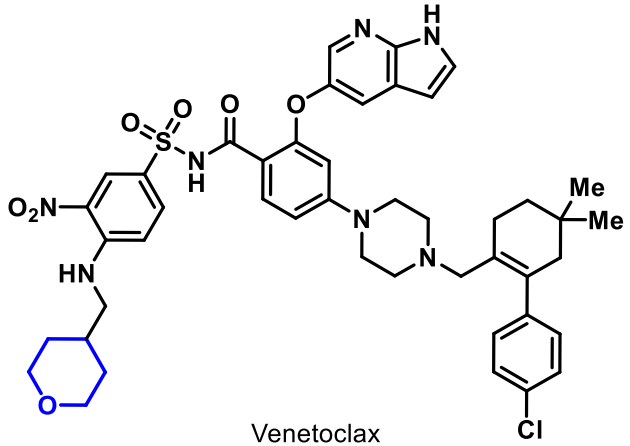
APIs bearing 4-tetrahydropyranyl motif



Entrectinib
[anti-cancer]

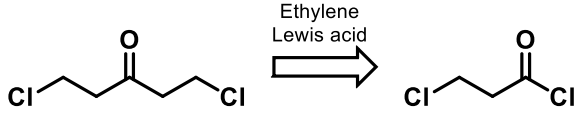


Opiranserin.HCl
[non-opiod analgesic]



Venetoclax
[anti-cancer]

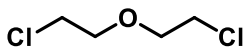
Previous approaches



Cyclization with H_2O
Extraction ten times to get acceptable yield

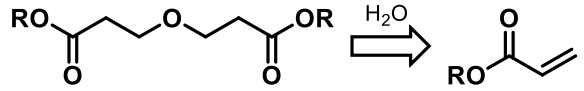
Stoichiometric amounts of Lewis acid for ethylene insertion

J. Chem. Soc. C **1970**, *17*, 2401



Oxygenated equivalent of mustard gas

CN108912081



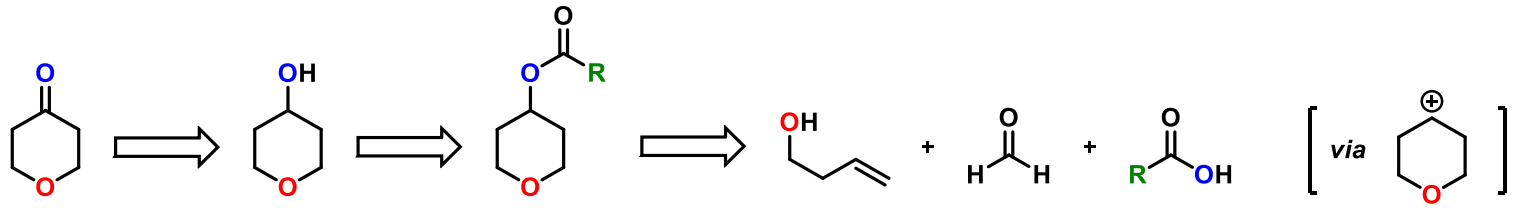
Use of acrylate: HSE issue
Poor atom efficiency

Bull. Soc. Chim. Fr. **1976**, 995 / CN104496858

Process development – Case study

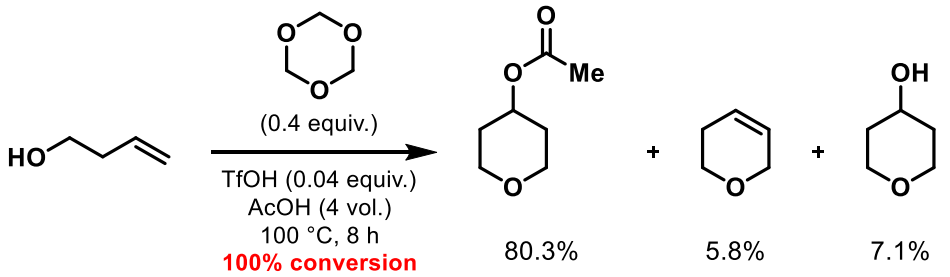
Our strategy

Seminal work (Ube): WO2003104215 / JP2006036707



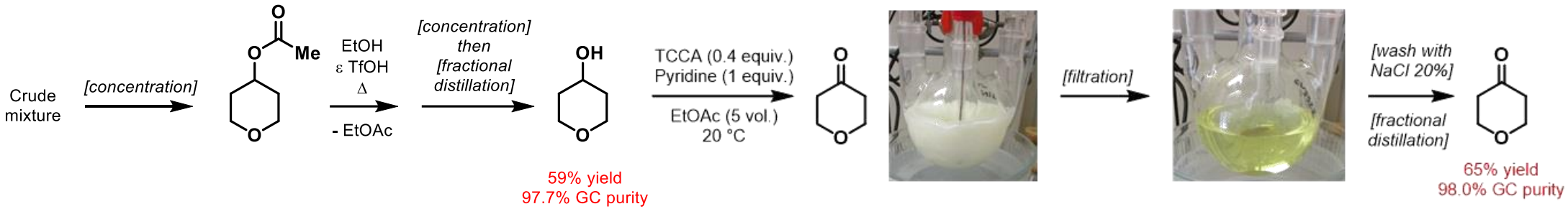
Prins-type cyclization

- Reaction optimization using OFAT and DoE approaches:



Process development – Case study

First route

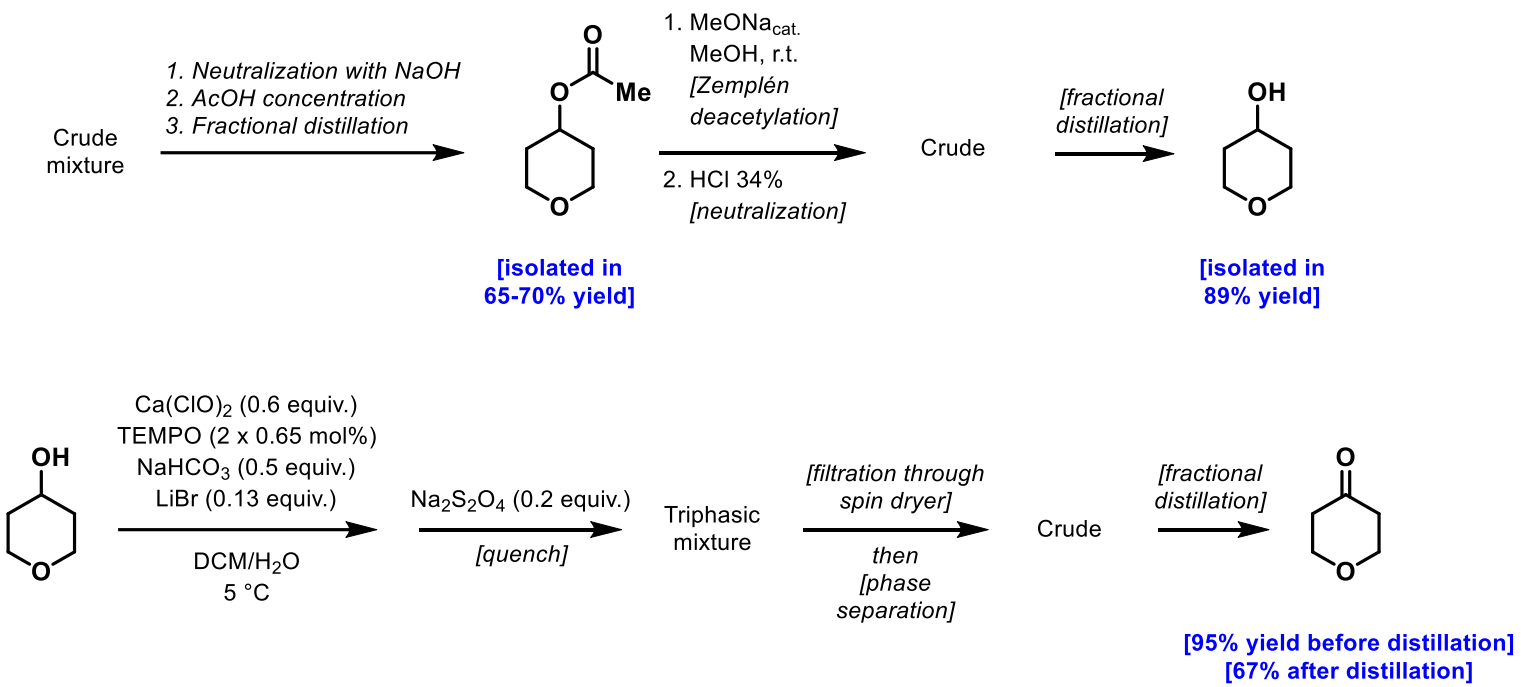


- Performed on 50-100 g-scale
- Water-free acetate deprotection → Ethanol mediated transesterification catalyzed by the remaining triflic acid
- Main drawbacks:
  - Degradation of the distillation residue during the various distillations in the presence of triflic acid
  - Oxidation of 1 kg of alcohol would give a 3 L cake made of pyridine hydrochloride and cyanuric acid

Oxidation with TCCA/pyridine: *Synth. Commun.* **1992**, *22*, 1589 / *Tetrahedron Lett.* **2017**, *58*, 2720

Process development – Case study

Final route



- 16 kg of THP produced at pilot plant (99.6% GCAP)
- First route: 38% overall yield, 98.0% GC purity, unscalable process
  Final route: 42% overall yield, 99.6% GC purity, scalable process

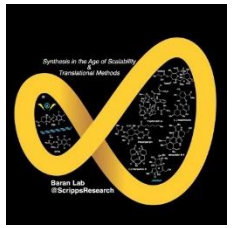
Zahim, S.; Delacroix, K.; Carlier, A.; Berranger, T.; Bergraser, J.; Echeverria, P.-G.; Petit, L. *Org. Process Res. Dev.* **2022**, *26*, 199

Process Development
Safety
Robustness
Sustainability
Cost

Enabling Technologies
Photochemistry
Electrochemistry
Continuous processes

Synergies

Collaborations
Academia
Technology platforms



Prof. Phil Baran (SCRIPPS, CA, US)

Electrosynthesis

Lancaster, NY, US

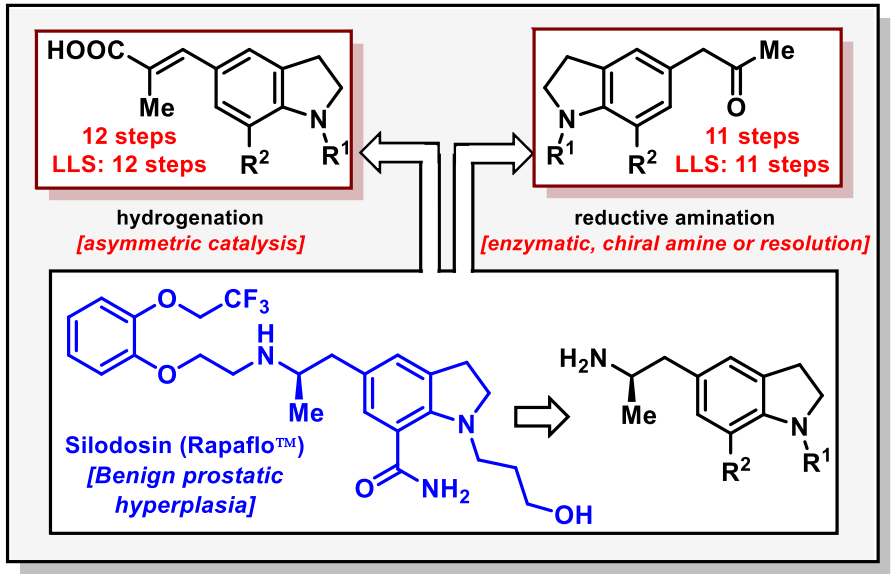
Chimie Paris ParisTech | PSL

ParisFlowTech, France

Serpier, F.; Delbrayelle, D.; Petit, L.; Echeverria, P.-G. *L'Actualité Chimique* **2023**, 482, 26-33

Modern chemistry – Cross-electrophile coupling

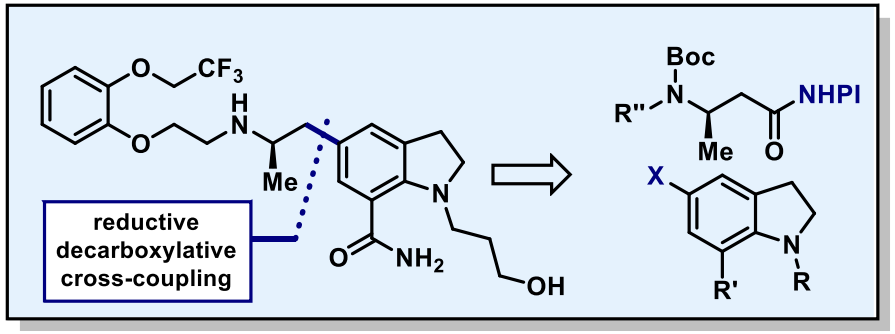
Prior synthetic approaches



- Hydrogenation/Curtius pathway
- Reductive amination tactics (enzymatic, diastereoselective, resolution)
- Routes proceed in a linear fashion

Tetrahedron Lett. **2013**, *54*, 1449 / *Tetrahedron: Asymm.* **2014**, *25*, 284 / *Eur. J. Org. Chem.* **2015**, 6011 / *Tetrahedron* **2013**, *69*, 2834

New disconnection approach

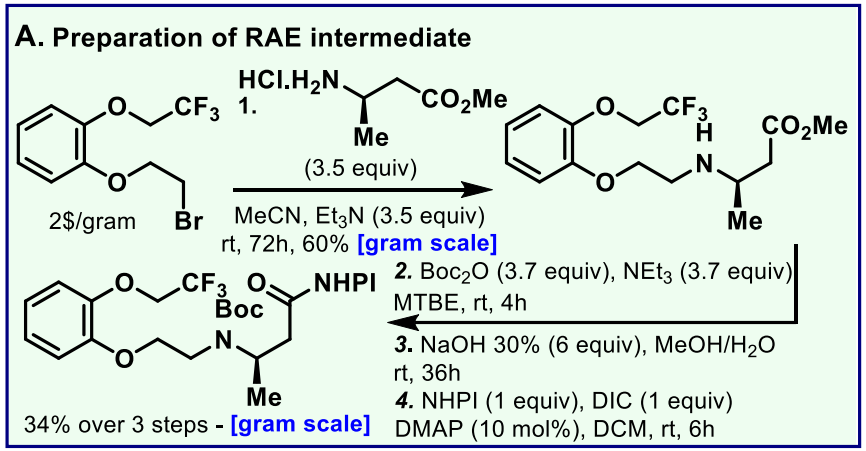


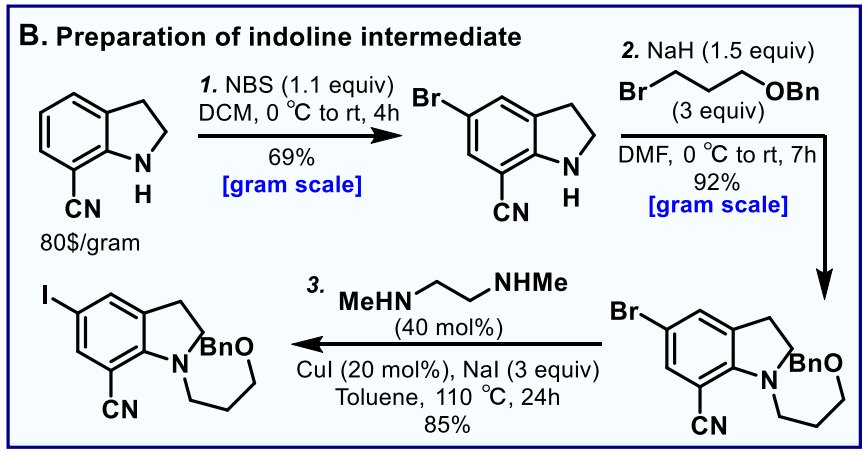
- Radical retrosynthesis → Decarboxylative cross-electrophile coupling
- Convergent approach
- Chiral pool strategy to introduce chiral amine

JACS **2016**, *138*, 5016 / *Org. Lett.* **2018**, *20*, 1338 / *Org. Lett.* **2019**, *21*, 816 / *Chem. Eur. J.* **2020**, *26*, 186

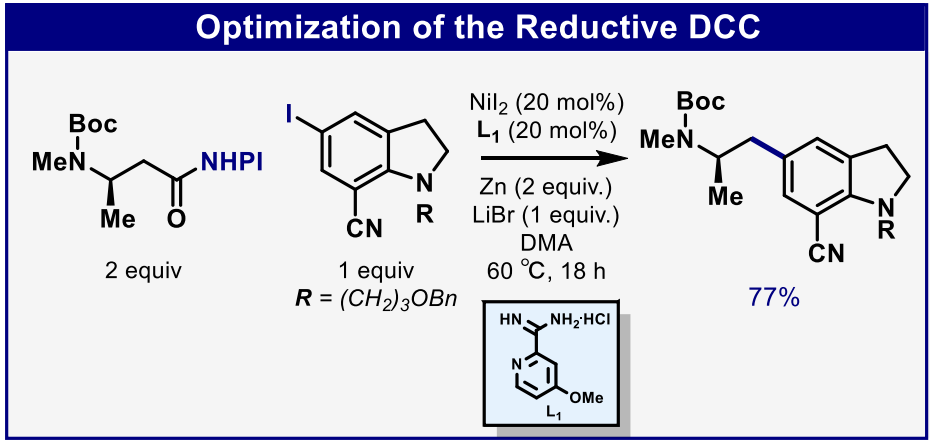
Modern chemistry – Cross-electrophile coupling

Synthesis of coupling partners





Key DCC – Model substrate

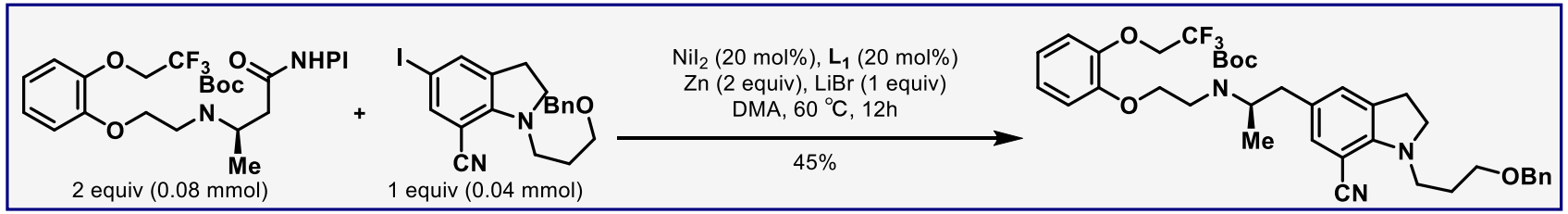


- ~ 50 ligands tested (HTE)
- Best reductant: Zn / Best additive: LiBr
- No chirality erosion

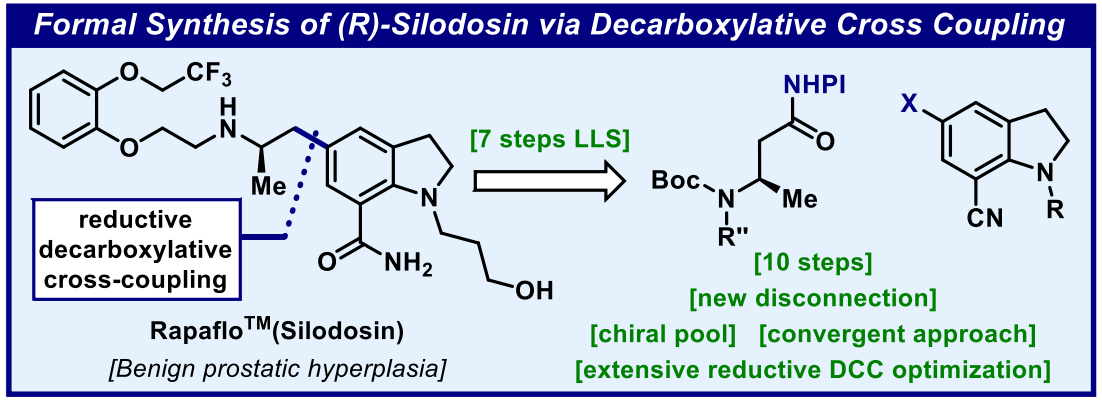
Weix/Pfizer ligand: *Nat. Chem.* **2016**, *8*, 1126

Modern chemistry – Cross-electrophile coupling

Formal synthesis of Silodosin



Conclusions

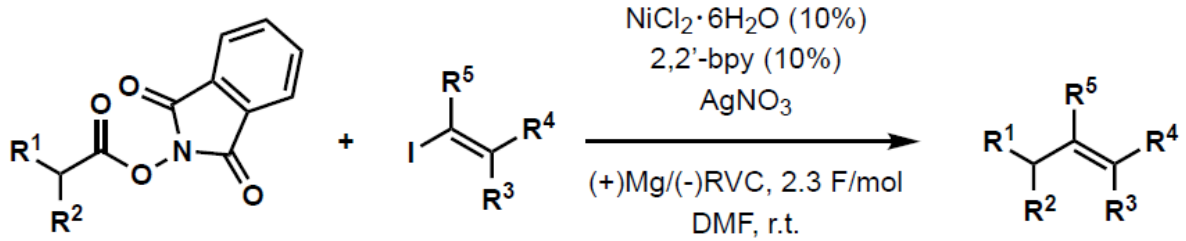


- Synthetic approach patented (WO2021205023)
- First DCC for the synthesis of an active compound
- Main limitation: heterogeneous reductant (see *OPRD* **2020**, 1141)

Chen, T.-G.; Mele, L.; Jentzer, O.; Delbrayelle, D.; Echeverria, P.-G.; Vantourout, J. C.; Baran, P. S. *Tetrahedron Lett.* **2021**, *79*, 153290

Modern chemistry – Cross-electrophile coupling

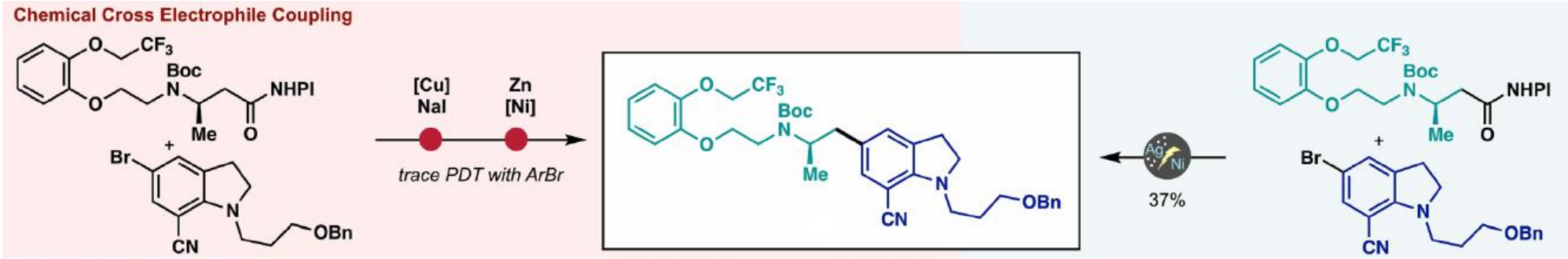
Terpene synthesis with Ag-Ni electrocatalysis



Science **2022**, *375*, 745

- Key role of $AgNO_3$ → Ag nanoparticles layer on the cathode
- Lowers the overpotential → preventing catalyst overreduction & inhibition of the formation of Ni(I)-alkenyl intermediates

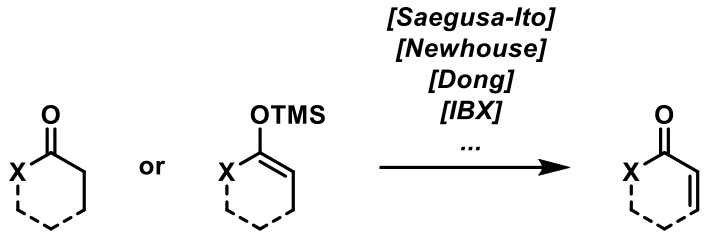
Electrochemical coupling



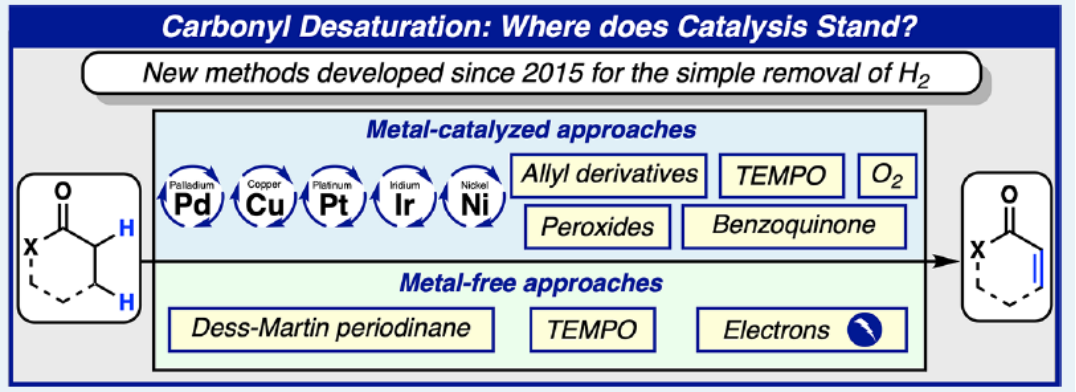
Palkowitz, M. D.; Laudadio, G.; Echeverria, P.-G.; Biogen; Bristol Myers Squibb; Pfizer; Leo Pharma; Baran, P. S. *JACS* **2022**, *144*, 17709

Electrochemical desaturation

Limitations of the current methods

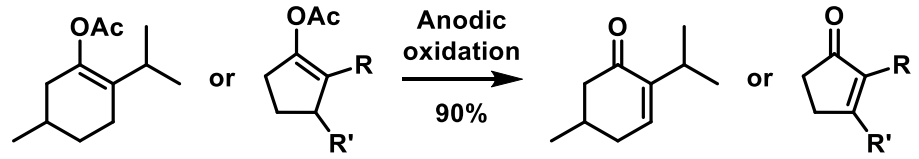


Unscalable
Scope limited
Harsh conditions
Expensive



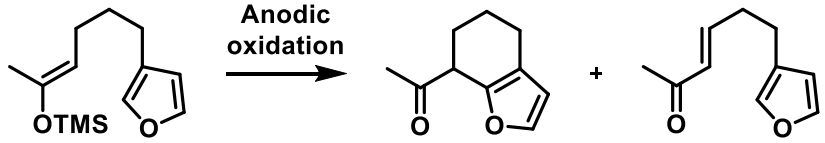
Gnaim, S.; Vantourout, J. C.; Serpier, F.; Echeverria, P.-G.; Baran, P. S. *ACS Catal.* **2021**, *11*, 883

Few precedents



[limited to substituted ketones]

Shono: *JACS* **1974**, *96*, 3532 / *JACS* **1975**, *97*, 6144

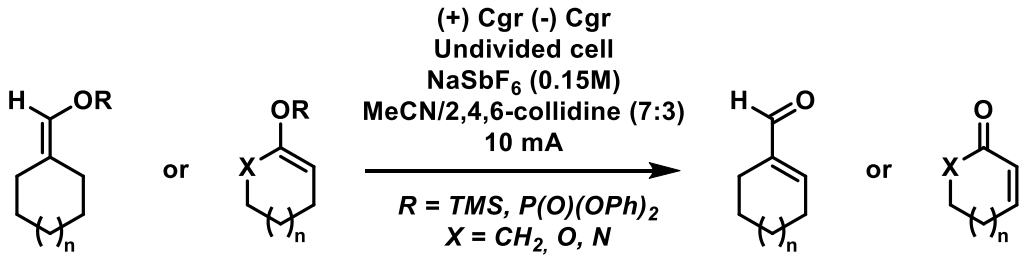


[traces]

Moeller: *Tetrahedron* **2001**, *57*, 5183 / *Chin. J. Chem.* **2019**, *37*, 672
Wright: *JOC* **2004**, *69*, 3726

Electrochemical desaturation

Reaction optimization

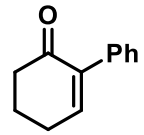


Key features:

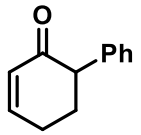
- Non-nucleophilic salts with Na counter cation proved optimal → **$NaSbF_6$**
- The use of a **graphite anode was found to be essential** whereas several materials were suitable for the cathode
- MeCN, acetone, DMA, and DMF could be employed but **MeCN gave the highest yield**
- Heteroaromatic amines proving most promising as base → **2,4,6-collidine emerged as optimum**
- **Excess of base** was necessary to get high yield
- **Reaction tolerates exogenous air and moisture**

Electrochemical desaturation

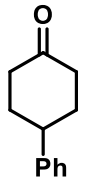
Scope



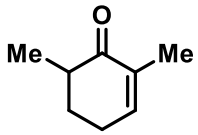
[e-desaturation]: 78%
[Saegusa-Ito]: n.d.
[Newhouse]: n/a
[Dong]: n/a
[IBX]: 9%



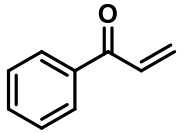
[e-desaturation]: 72%
[Saegusa-Ito]: 45%
[Newhouse]: 71%
[Dong]: 52%
[IBX]: 19%



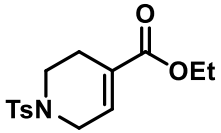
[e-desaturation]: 62%
[Saegusa-Ito]: 85%
[Newhouse]: 71%
[Dong]: n/a
[IBX]: 70%



[e-desaturation]: 81%
[Saegusa-Ito]: 46%
[Newhouse]: 75%
[Dong]: traces
[IBX]: n.d.



[e-desaturation]: 46%
[Saegusa-Ito]: 56%
[Newhouse]: n/a
[Dong]: n.d.
[IBX]: 34%



[e-desaturation]: 81%
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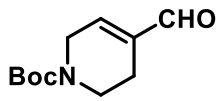
[Newhouse]: 42%
[Dong]: n.d.
[IBX]: n/a



[e-desaturation]: 50%
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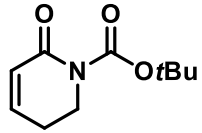
[Newhouse]: n/a
[Dong]: n/a
[IBX]: n.d.

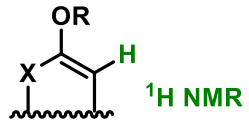


[e-desaturation]: 69%
[Saegusa-Ito]: n/a
[Newhouse]: n/a
[Dong]: 32%
[IBX]: n/a

Reactivity prediction

5.1 ≥ δ ≥ 4.6 ppm

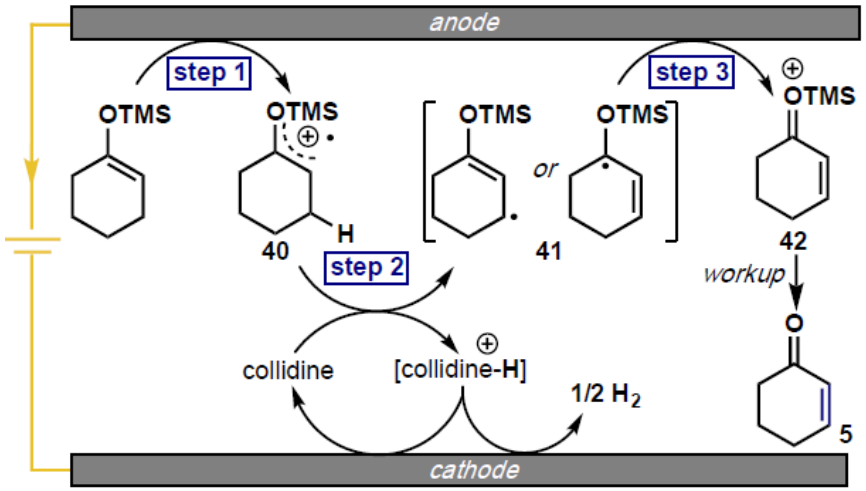
[low reactivity]
[high oxidation potential]



^{1}H NMR

[by-products: dimer, hydrolysis,...]
[low oxidation potential]

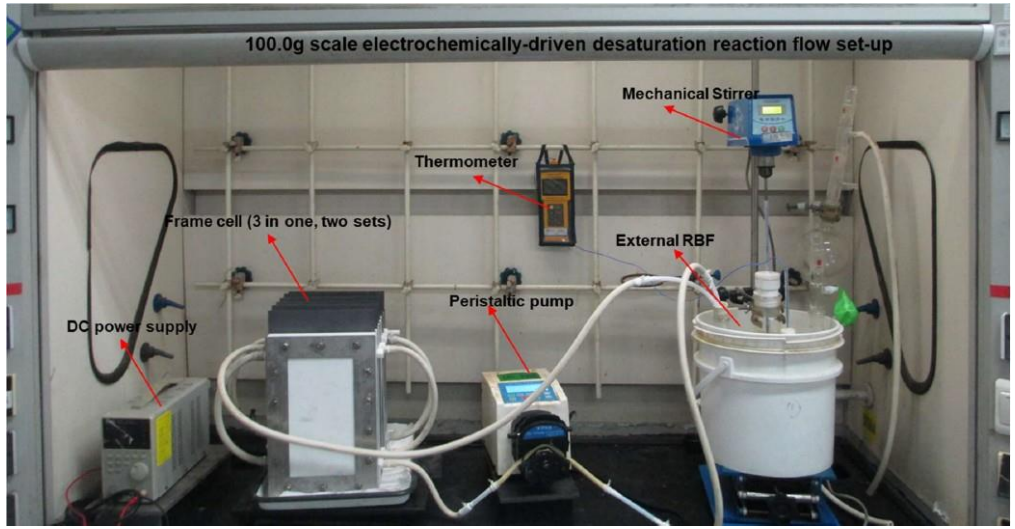
Mechanism

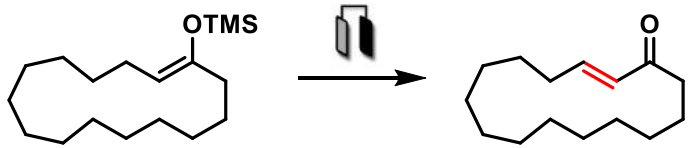


Gnaim, S.; Takahira, Y.; Wilke, H. R.; Yao, Z.; Li, J.; Delbrayelle, D.; Echeverria, P.-G.; Vantourout, J. C.; Baran, P. S. *Nat. Chem.* **2021**, *13*, 367

Electrochemical desaturation

Scale-up





[Key intermediate in the synthesis of (*R*)-muscone]

- Flow system with recirculation mode
- Numbering-up strategy (8 graphite plates)

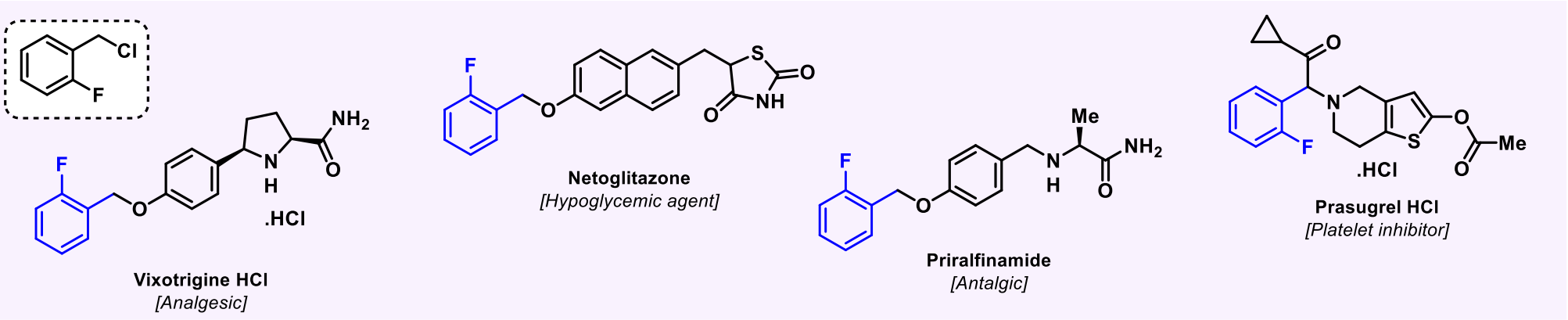
  (minimal amount of reoptimization)
- Increase current value → I = 3.6 A
- 61% yield (27% recovered SM)

Conclusions/Outlook

- Efficient, scalable, predictable e-desaturation
- Broad scope including ketones, esters and lactams
- Simple and fast translation to continuous mode

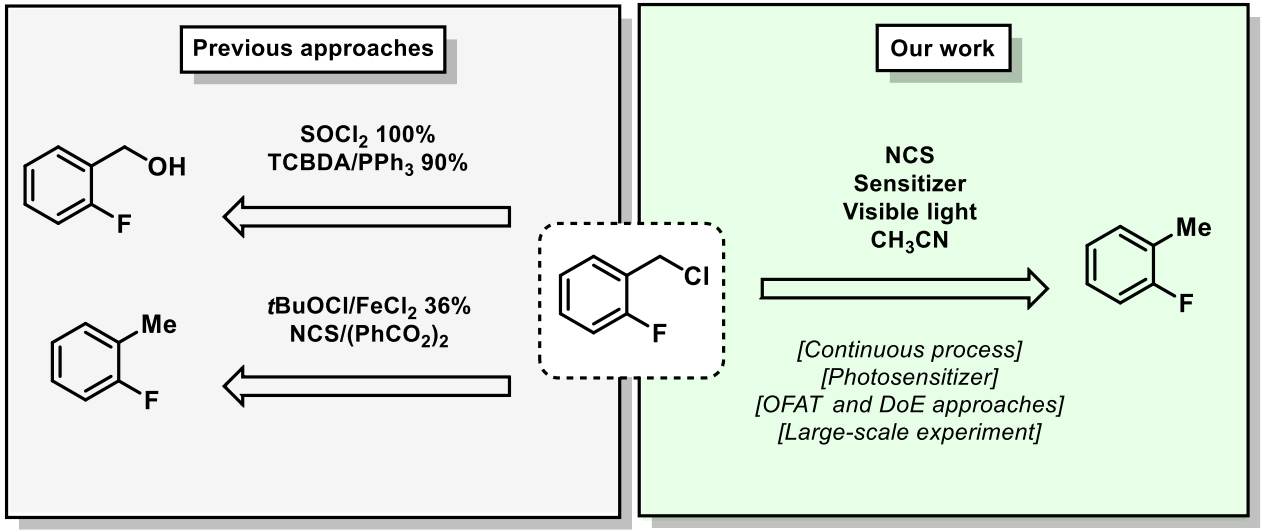
Flow photochemistry

2-FBC as key starting material

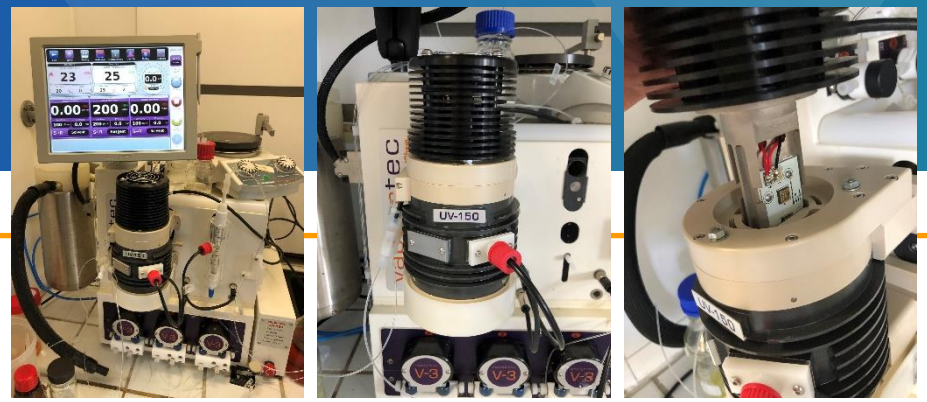


2-FBC as key starting material

- Expensive benzyl alcohol
- Poor atom economy
- Poor yield
- Runaway reactions

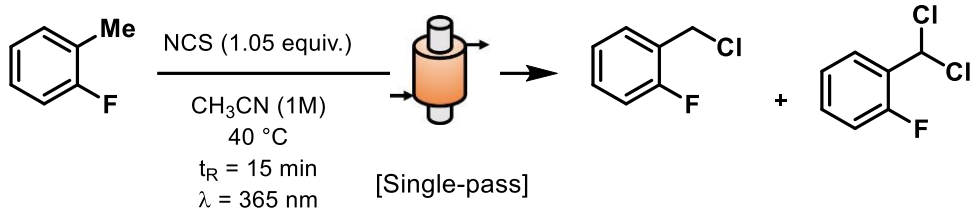


Flow photochemistry



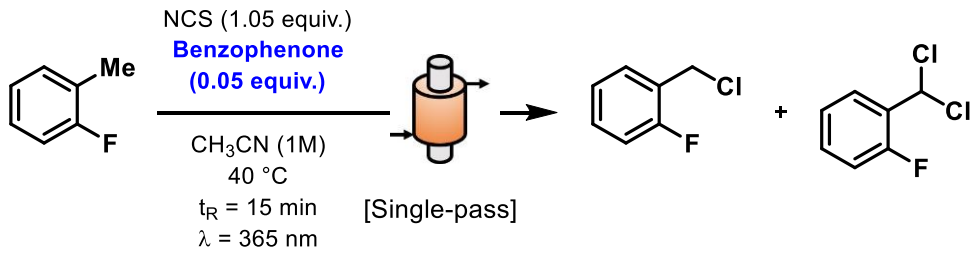
Optimization with Vapourtec® photoreactor

- OFAT and DoE methodologies
- Experiment without sensitizer:



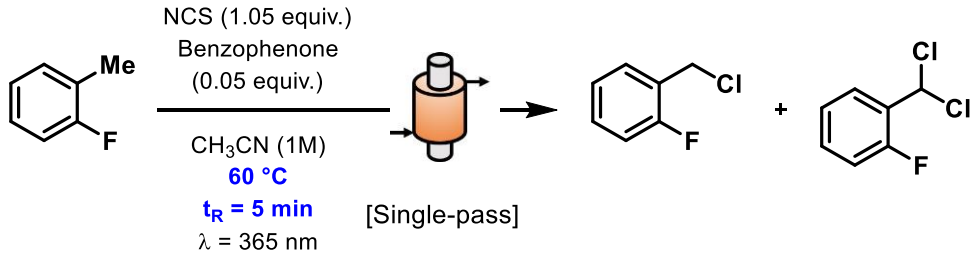
Conversion = 34%

- Addition of benzophenone:



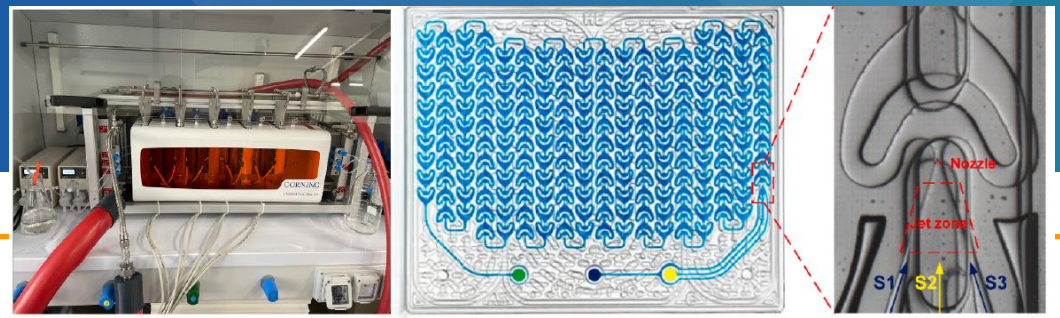
Conversion = 88%
Mono/Di = 14/1

- Significant reduction of the residence time:

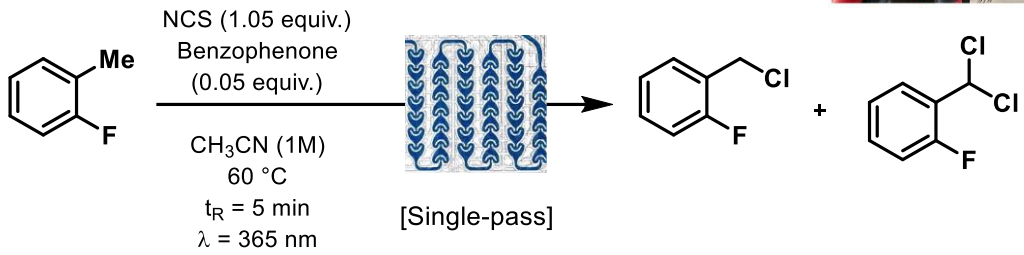


Conversion = 87%
Mono/Di = 11/1

Flow photochemistry



Scale-up using Corning® G1LF



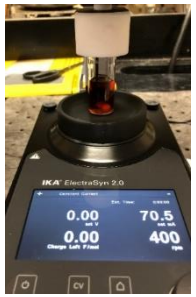
Conversion = 87%
Mono/Di = 21/1

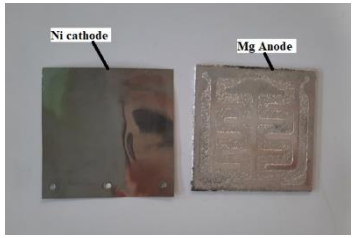
- Similar performance Vapourtec® vs Corning®
- Reaction performed on 55 g of 2-fluorotoluene
- Azeotrope mixture between 2-fluorotoluene and acetonitrile
- Close boiling points of mono- and di-chlorinated compounds
- Pure product obtained after distillation → 61% yield / 100.0% GCAP
- Room for improvement to increase the yield

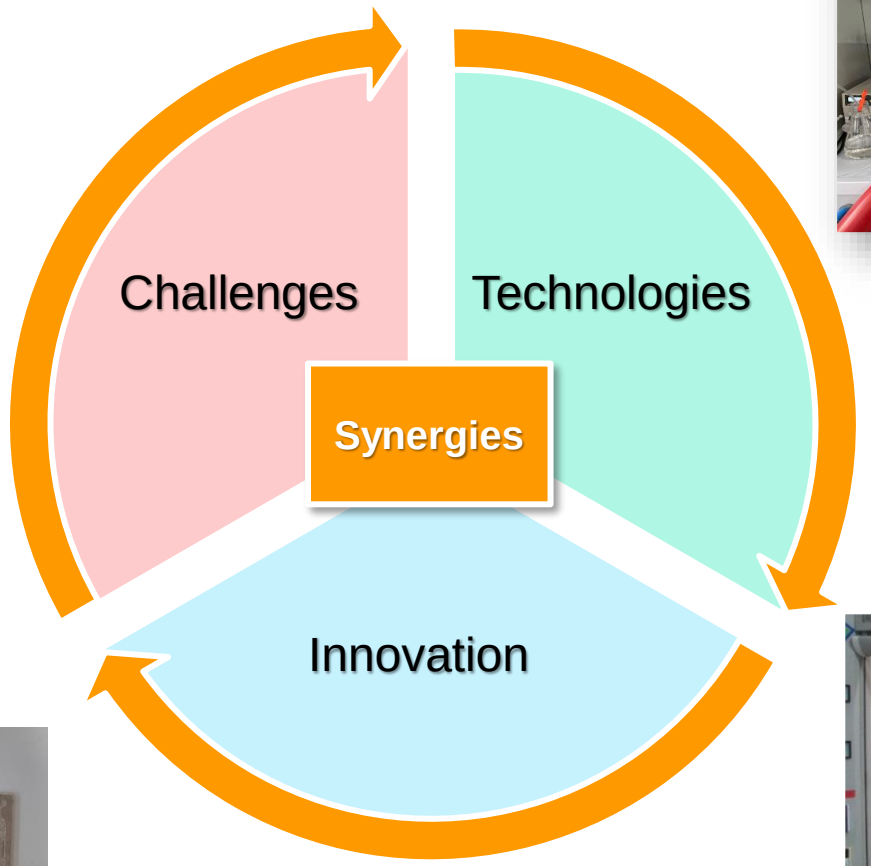
  → Quench before distillation + Distillation improvements
- Next step: Corning G3 for our Phoenix platform at Minakem

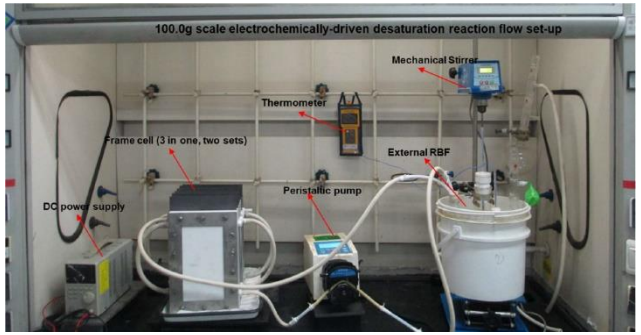
Radjagobalou, R.; Imbratta, M.; Bergraser, J.; Gaudeau, M.; Lyvinec, G.; Delbrayelle, D.; Jentzer, O.; Roudin, J.; Laroche, B.; Ognier, S.; Tatoulian, M.; Cossy, J.; Echeverria, P.-G. *OPRD* **2022**, *26*, 1496

Conclusions/Outlook









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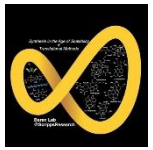

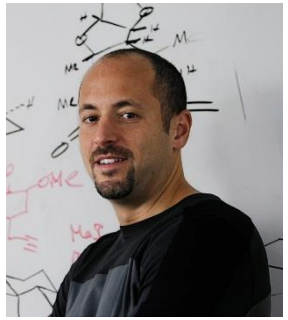

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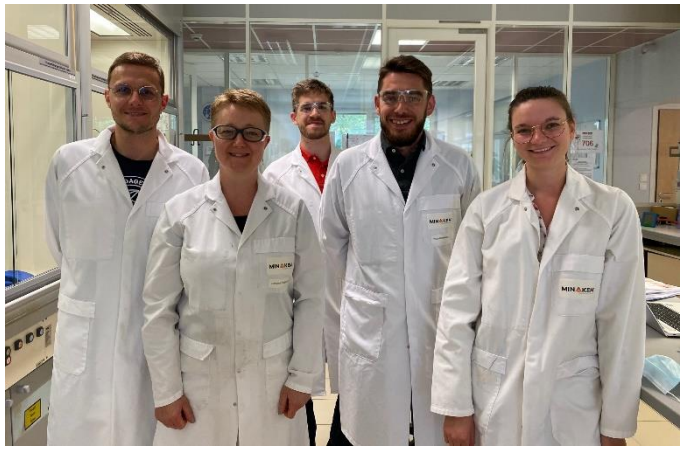

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