UNIVERSITEIT VAN AMSTERDAM

NRG
NOËL RESEARCH GROUP

From Batch to Flow: Advancing Synthetic Organic Chemistry through Technological Innovation

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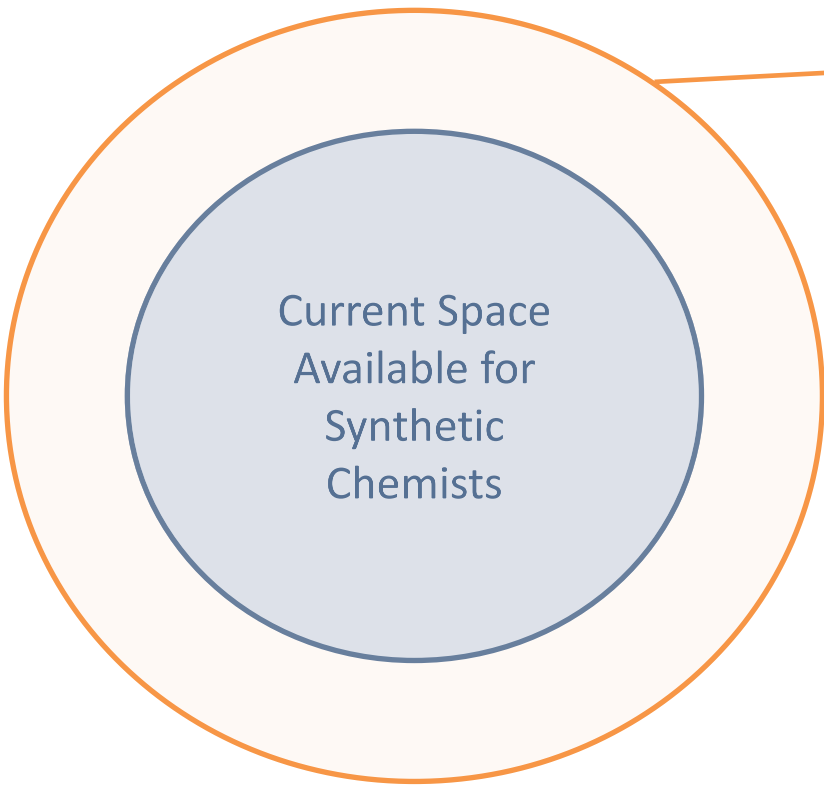
Reimagining Synthetic Chemistry



Our mission:

Expanding the available chemical space by embracing technology to the fullest extent

by

1) *Developing new synthetic transformations using reagents or conditions that are difficult to handle*
2) *Developing new tools to make synthesis easier*
3) *Showing unique selectivity and reactivity*

How?

by merging
organic chemistry and chemical engineering

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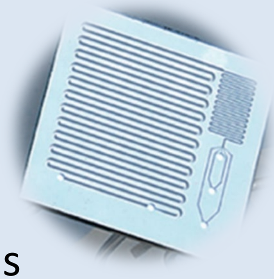
How can flow make an impact?

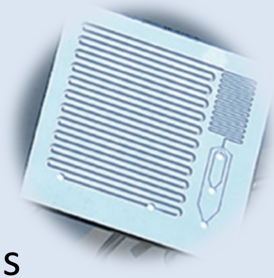
Inherent advantages of microscale flow reactors:



Enhanced mass transfer	Gas-liquid reactions
Enhanced heat transfer	Taming exothermic reactions
High reproducibility	Reaction kinetics
Multistep flow sequences	Time-gain, labor reduction
Automation	Minimizing human error
Safety	New processing windows
Scalability	From mg to kg in same device

Selected reviews: (i) Capaldo, Wen, Noel, *Chem. Sci.* **2023**, *14*, 4230-4247. (ii) Laybourn, Robertson, Slater, *J. Am. Chem. Soc.* **2023**, *145*, 4355-4365. (iii) Plutschack, Pieber, Gilmore, Seeberger, *Chem. Rev.* **2017**, *117*, 11796-11893.

How can flow make an impact?



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Problem: In general, people resist change.

Education is Key!

OPINION

Flow into the chemistry curriculum

BY TIMOTHY NOEL | 27 SEPTEMBER 2019

There's more to chemistry than the round-bottomed flask

It's ironic that chemists are experts at change, except when it comes to their own practice. Mark Gilligan recently wrote about chemists' reluctance to adopt flow chemistry as an example of this innate resistance to change. I have seen that same resistance, and I understand it. Why would you suddenly change your habits and embrace an expensive new technology?

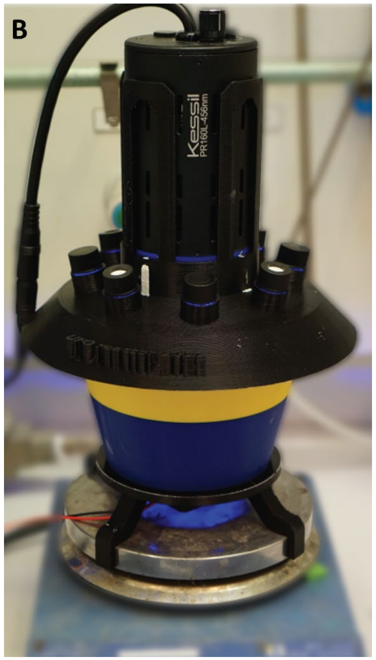
"Put flow chemistry in your curriculum and give students the broadest experience of making molecules. Let them decide which ideas have a future."

For an opinion article: Noël, *Chemistry World* **2019**, https://www.chemistryworld.com/opinion/flow-into-the-chemistry-curriculum/4010382.article .

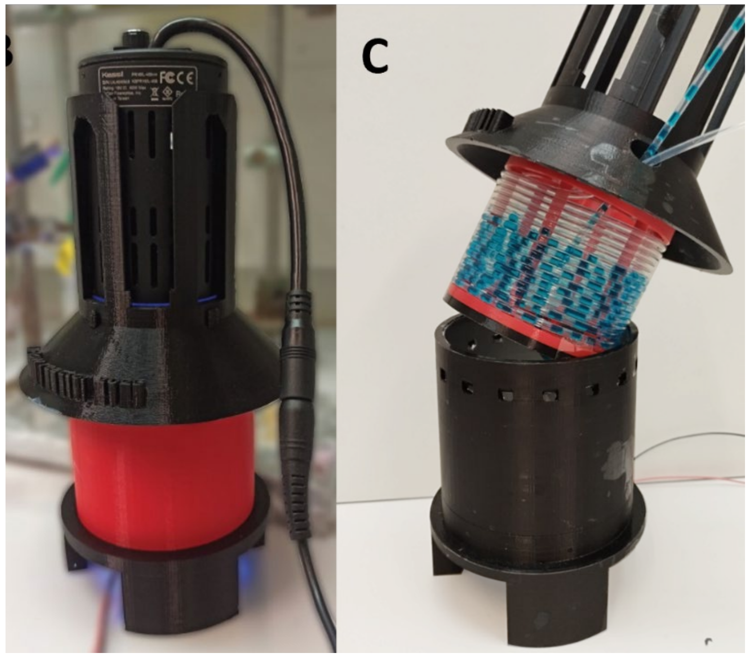
For our undergrad flow experiments: Kuijpers, Weggemans, Verwijlen, Noël, *J. Flow Chem.* **2021**, *11*, 7-12.

Democratization of Flow Chemistry

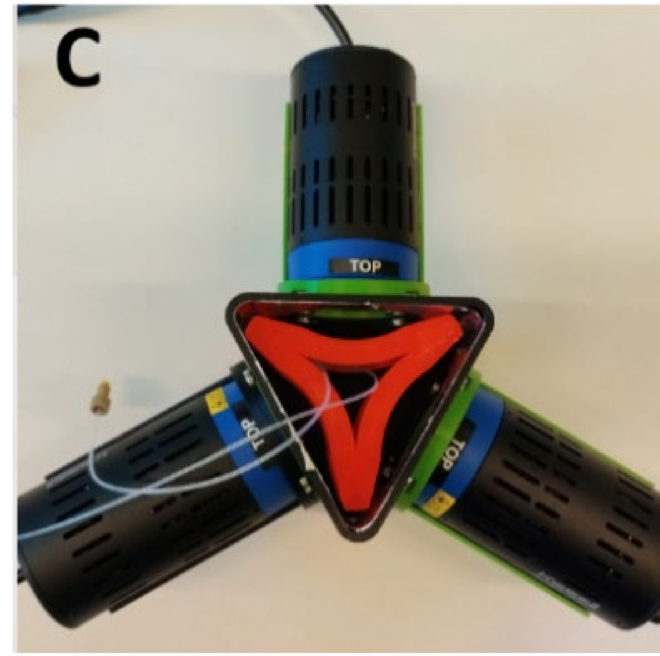
UFO – Batch



UFlow



Flow – Fidget Reactor



Fully characterized, standardized batch and flow setups that are affordable.

Designs available via: Masson, Zondag, Schuurmans, Noël, *React. Chem. Eng.* **2024**, *9*, 2218-2225.

For characterization procedure: Zondag, Schuurmans, Chaudhuri, Visser, Soares, Padoin, Kuijpers, Dorbec, van der Schaaf, Noël, *Nature Chemical Engineering* **2024**, *1*, 462–471.

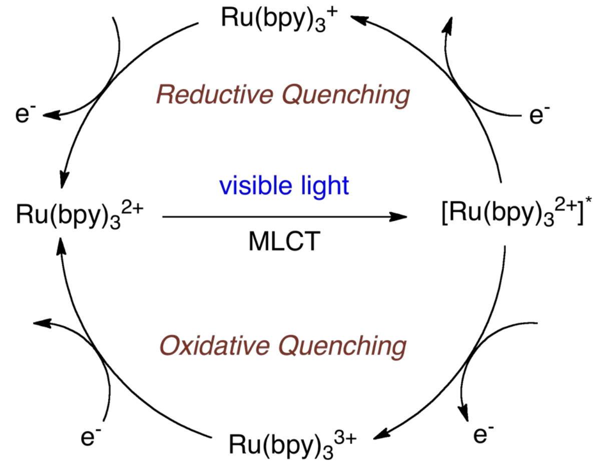
Photocatalysis

Photoredox Catalysis

photocatalysis allows for absorption of wavelengths of the UV-A and VIS

<u>Advantages:</u>
- cheap, energy-efficient and high intensity energy light sources (LEDs)
- mild reaction conditions (room temperature, functional group tolerance)
- new opportunities in organic synthesis

$Ru(bpy)_3Cl_2$ is the most studied one-electron photoredox catalyst.

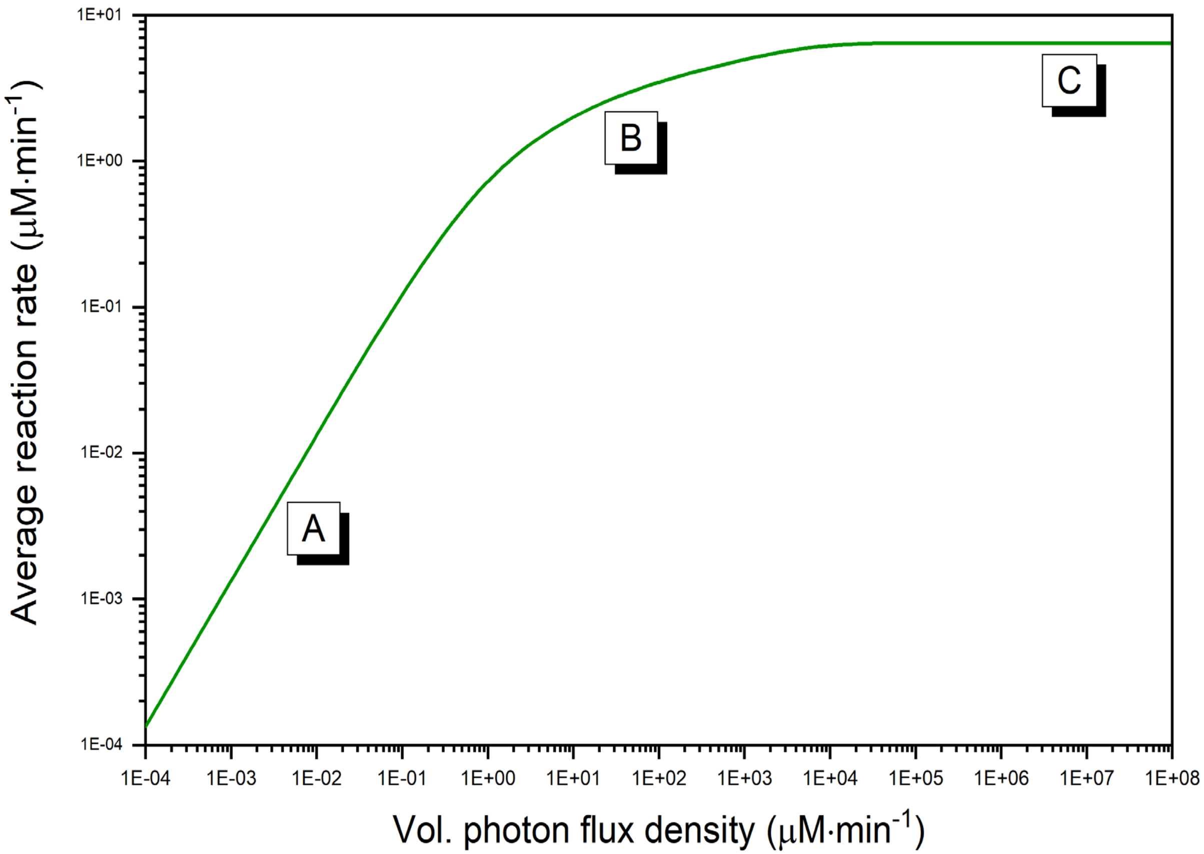


Special issue in *Chemical Reviews* on **Photochemical Catalytic Processes** (Paolo Melchiorre, Guest Editor), **2022**, *122*, 1483-2980.
For a perspective on PC: Noel, Zysman-Colman, *Chem Catalysis* **2022**, *2*, 468-476.

Light activation of molecules

Thermochemical activation: $k = A^{\left(-\frac{Ea}{RT}\right)}$

Photochemical activation: $k = \alpha \cdot I^{\beta}$



For comprehensive reviews: (i) Cambié, Bottecchia, Straathof, Hessel, Noël, *Chem. Rev.* **2016**, *116*, 10276-10341. (ii) Buglioni, Raymenants, Slattery, Zondag, Noël, *Chem. Rev.* **2022**, *122*, 2752-2906.

Industrial Importance of Photoredox Catalysis

Every single pharma- and agro-chemical company has initiated programs to implement Photoredox catalysis.

Noel, Zysman-Colman, *Chem Catalysis* **2022**, *2*, 468-476.

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Medicinal Chemistry:

- Goal: identify new chemical structures ASAP.
- Small amounts for bio-assays and ADME studies
- Well implemented

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- Scalable process for clinical trials and commercialization
- Challenging!

Noel, Zysman-Colman, *Chem Catalysis* **2022**, *2*, 468-476.

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Scale up: 50 kg product/day is a good estimate for what is required in pharma!

This requires about 1000 W of optical power per day.

Noel, Zysman-Colman, *Chem Catalysis* **2022**, *2*, 468-476.

Industrial Importance of Photoredox Catalysis

1000 W of optical power per day to produce 50kg/day

To put it in perspective:

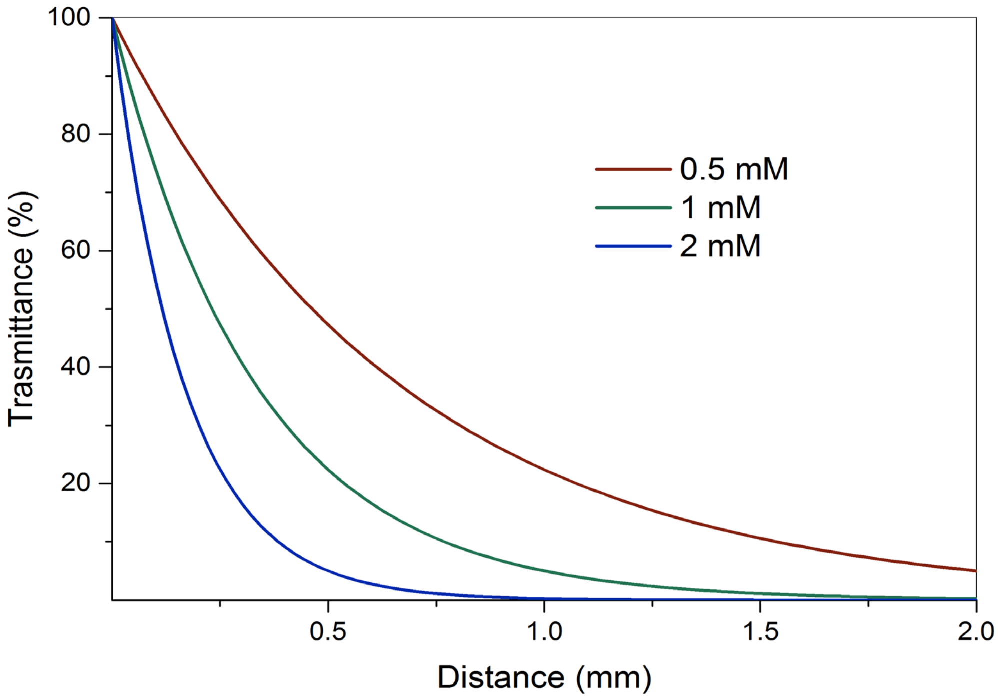
This amounts to the light delivered by 5000 CFL light bulbs !!!

Photocatalysis

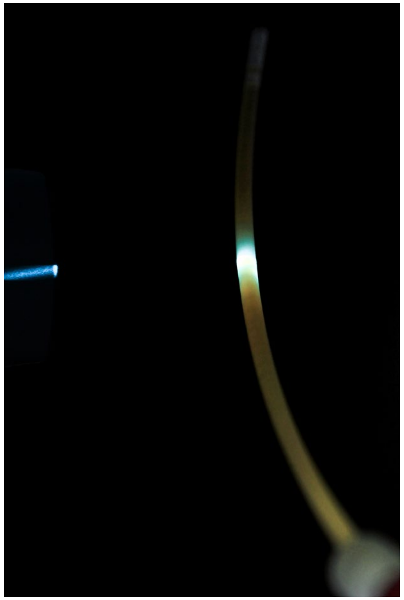
scale up problems

Batch : limited penetration depth of irradiation because of absorption results in longer reaction times, higher catalyst loadings and difficult scale-up

$$\log(T) = \log(I_0/I) = \varepsilon.l.c \qquad \text{(Bouguer-Lambert-Beer)}$$



Batch

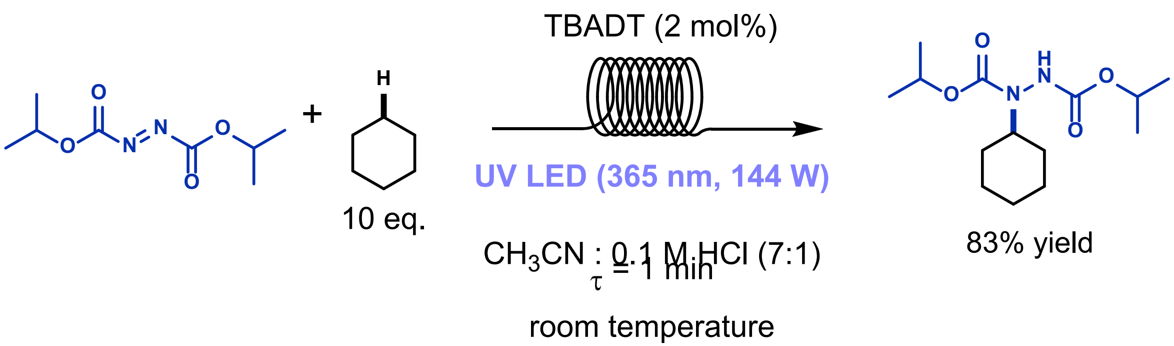


Flow

For comprehensive reviews: (i) Cambié, Bottecchia, Straathof, Hessel, Noël, *Chem. Rev.* **2016**, *116*, 10276-10341. (ii) Buglioni, Raymenants, Slattery, Zondag, Noël, *Chem. Rev.* **2022**, *122*, 2752-2906.

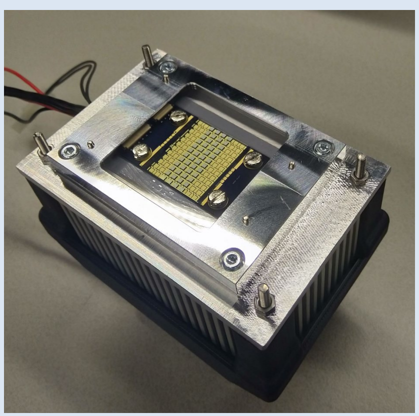
Scaling Photochemistry

Longer operation times + intensified reaction conditions:

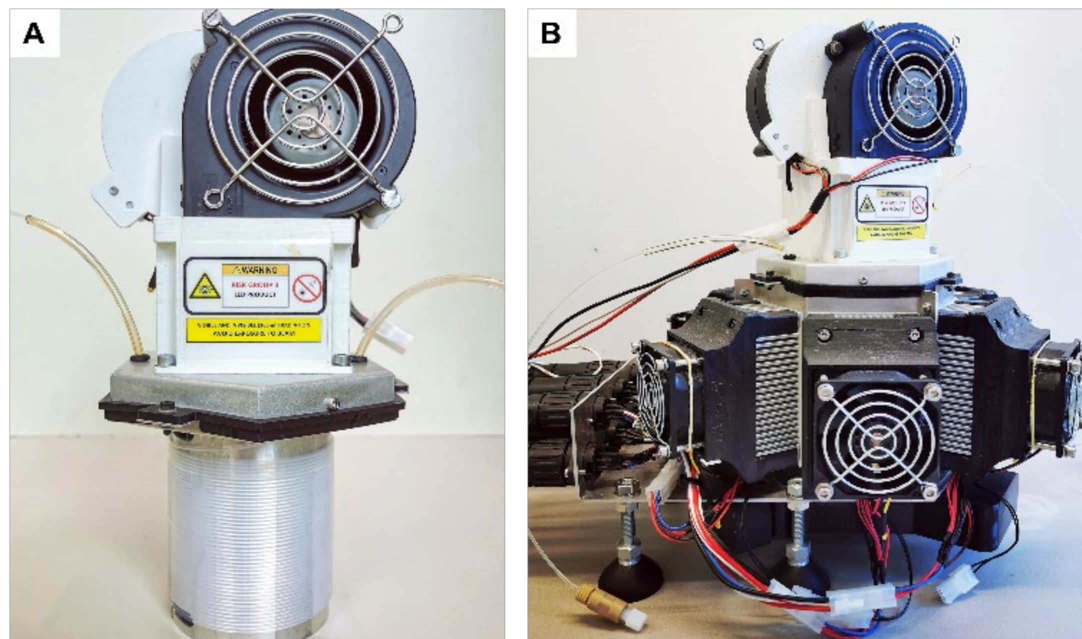


Reactor : 11 mL volume, ID 750 μm

Productivity : 314 mol/h (2.15 kg/day)



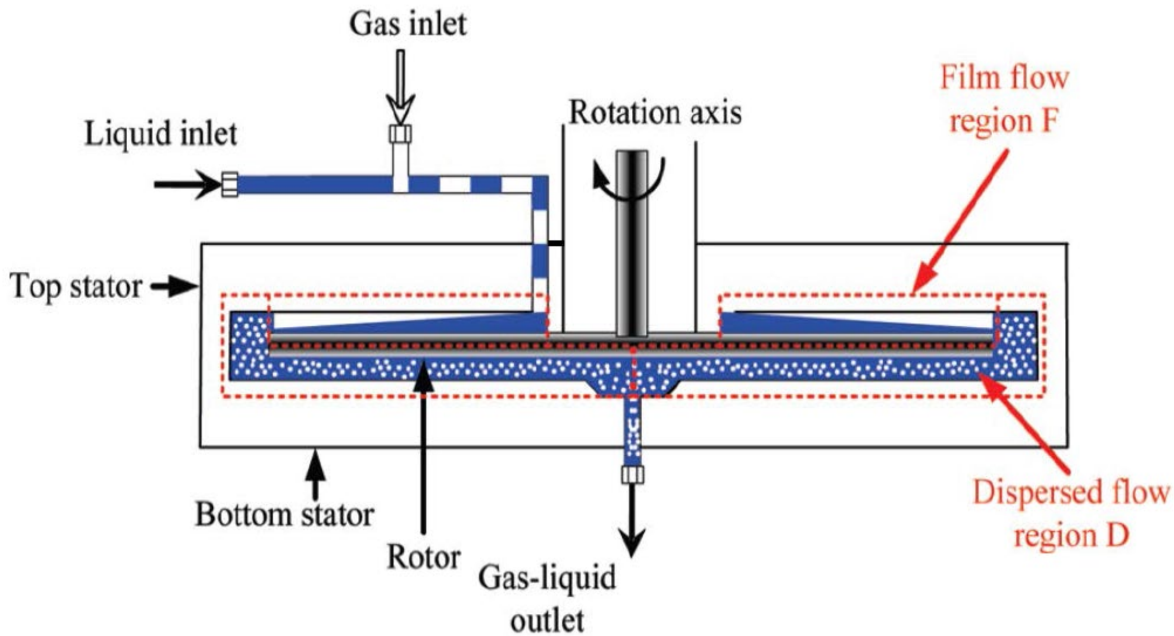
Chip-on-Board LEDs
(24 W optical power/unit)



Wan, Wen, Laudadio, Capaldo, Lammers, Rincon, Garcia-Losada, Mateos, O'Frederick, Broersma, Noel, *ACS Central Sci.* **2022**, *8*, 51-56.

Rotor-Stator Spinning Disk Technology

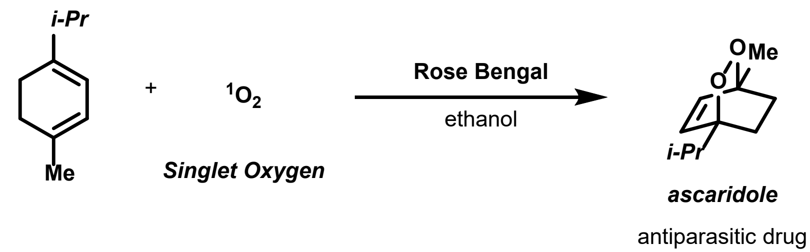
Scaling multiphase reaction conditions:

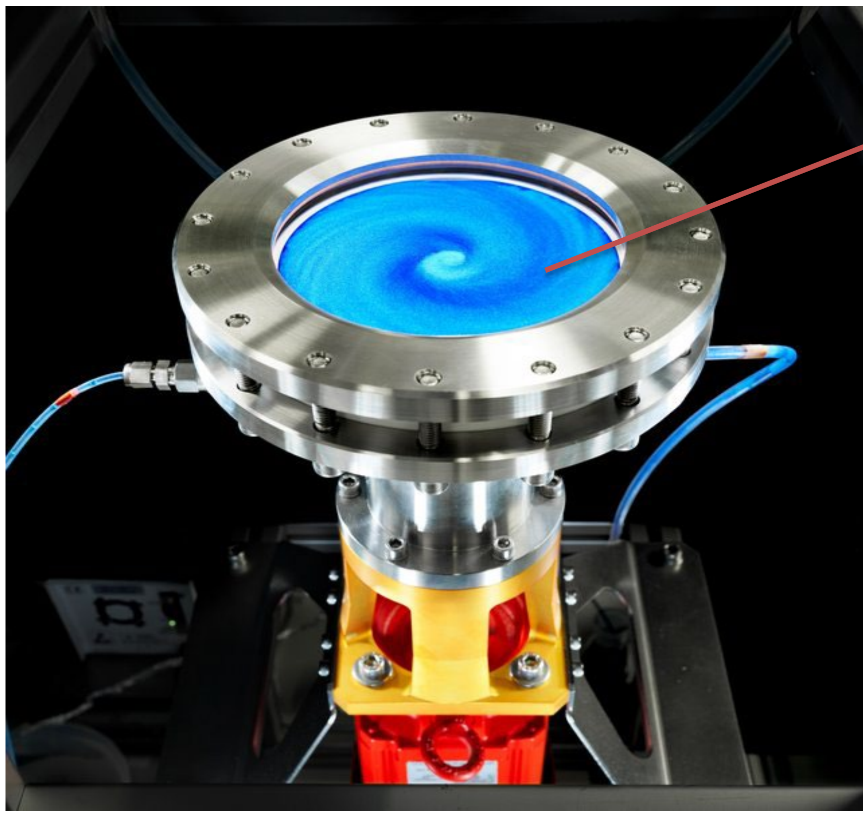


- Reactor = two stators and one rotating disc.
- Distance between rotor and stators is about 1-2 mm
- Rotational speed (1000-3000 rpm) induces high shear and thus provides high mass and heat transfer.

For a review: (i) F. Visscher, J. van der Schaaf, T. A. Nijhuis, J. C. Schouten, *Chem. Eng. Res. Des.* **2013**, *91*, 1923-1940. (ii) J. van der Schaaf, J. C. Schouten, *Curr. Opin. Chem. Eng.* **2011**, *1*, 84-88,

Rotor-Stator Spinning Disk Technology



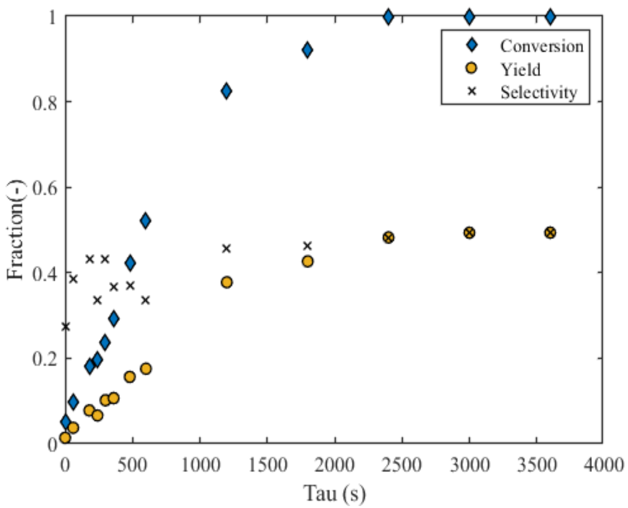


Quartz Window (Stator)

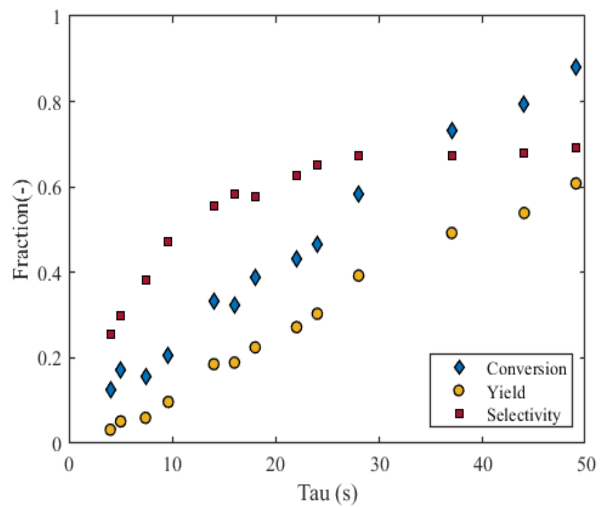
Chaudhuri, Kuijpers, Hendrix, Hacking, Shivaprasad, Emanuelsson, Noel, van der Schaaf, *Chem. Eng. J* **2020**, *100*, 125875.

Rotor-Stator Spinning Disk Technology

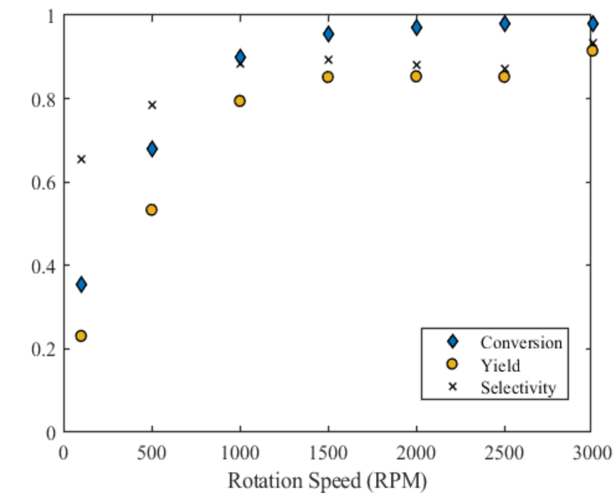
Batch (V_R = 5 mL)



Microflow (id = 0.76 mm, V_R = 1 mL)



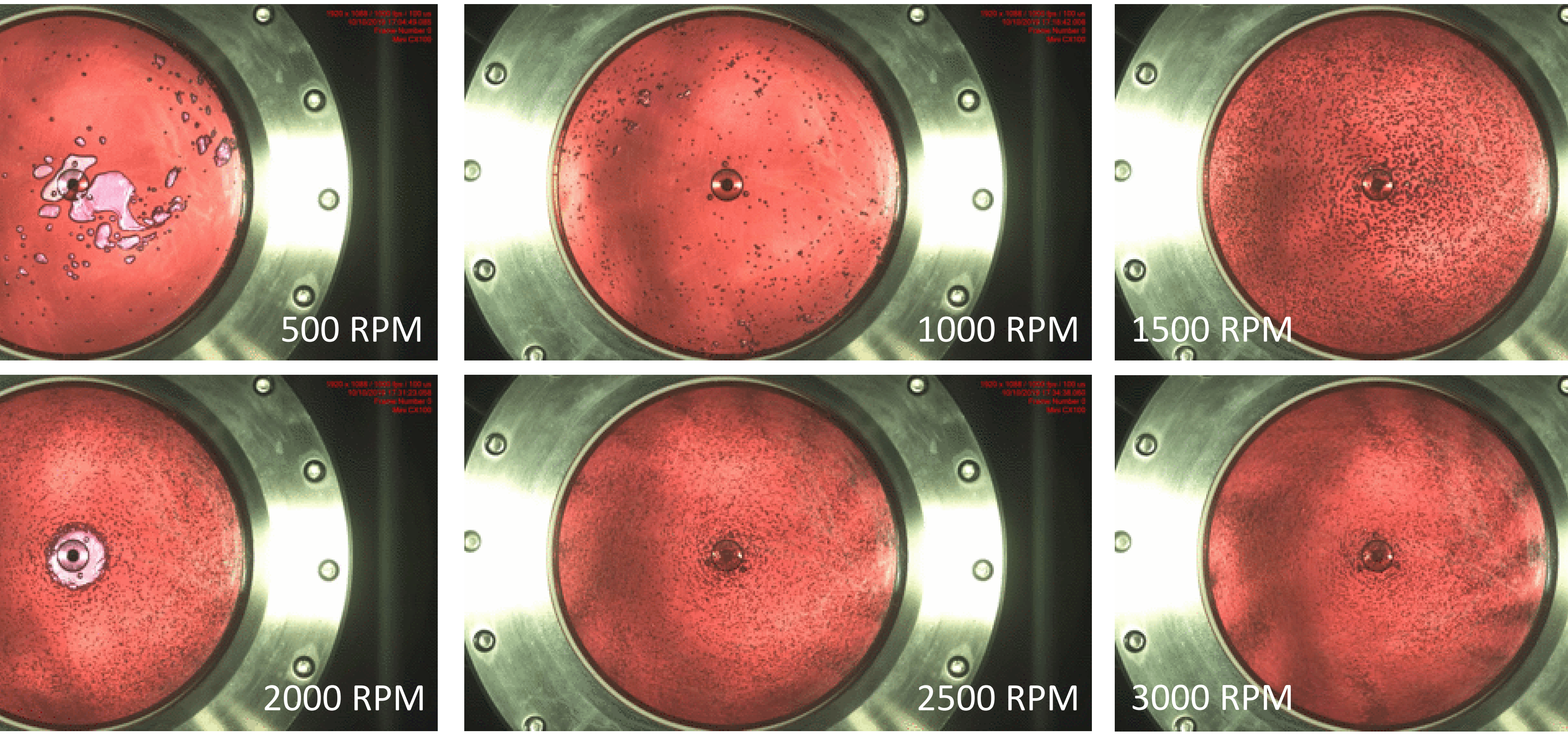
pSDR at 50 mL/min (V_R = 28 mL, h = 2 mm)



1. Selectivity goes up from 50% (batch) to 70% (flow) to 90-95% (pSDR).
2. Residence time is reduced from 40 minutes (batch) to 1 min (flow) to 27 seconds (pSDR)
3. Throughput increases from 0.375 mmol/h (batch) to 4.2 mmol/h (flow) to 270 mmol/h (pSDR)

Chaudhuri, Kuijpers, Hendrix, Hacking, Shivaprasad, Emanuelsson, Noel, van der Schaaf, *Chem. Eng. J* **2020**, *100*, 125875.

Rotor-Stator Spinning Disk Technology

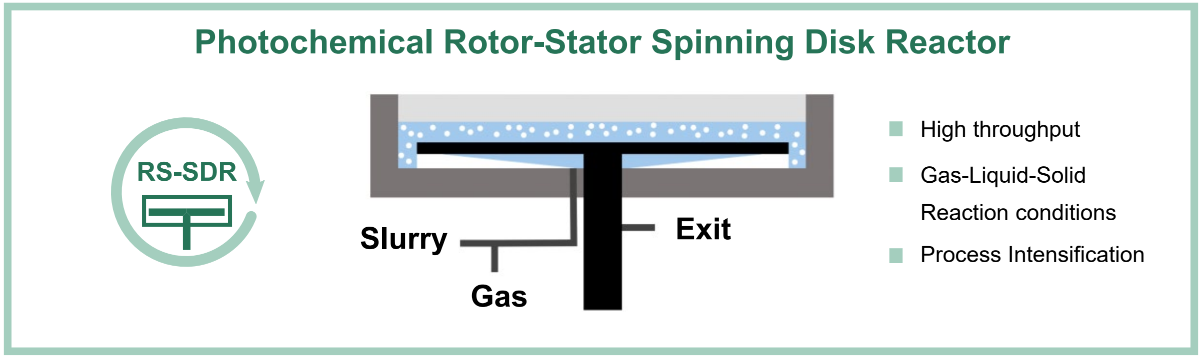


Chaudhuri, Kuijpers, Hendrix, Hacking, Shivaprasad, Emanuelsson, Noel, van der Schaaf, *Chem. Eng. J* **2020**, *100*, 125875.

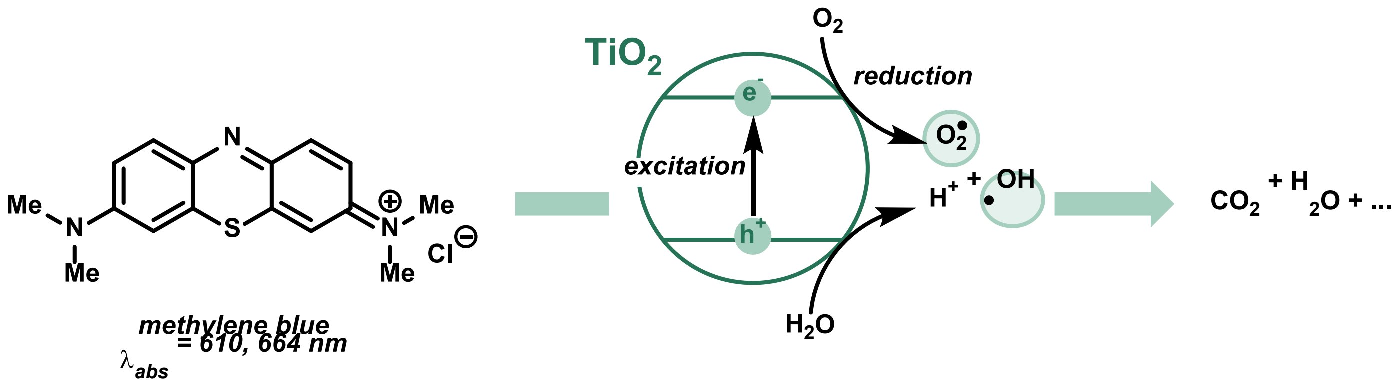
Photochemical Spinning Disk Reactor

Handling heterogeneous Photocatalysts

A Photochemical Rotor-Stator Spinning Disk Reactor enables scale up of complex heterogeneous photocatalytic reaction conditions



B Degradation of methylene blue enabled by titanium dioxide semiconductor photocatalysis

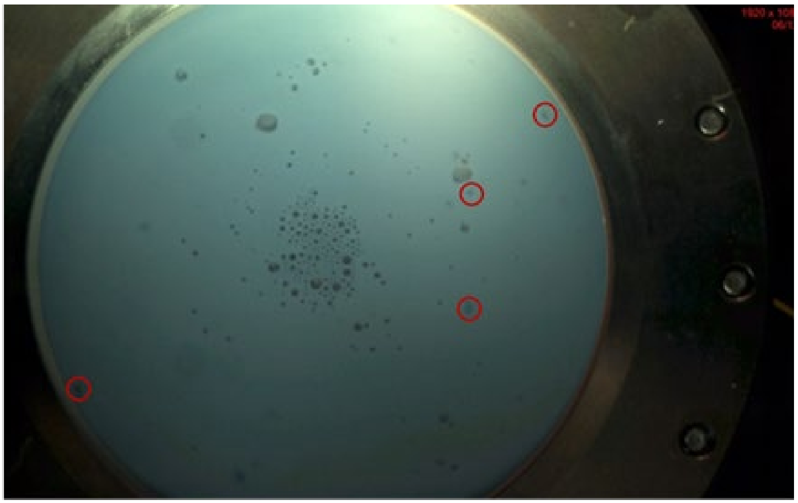


Chaudhuri, Zondag, Schuurmans, Van der Schaaf, Noel, *Org. Process Res. Dev.* **2022**, *26*, 1279-1288.

Photochemical Spinning Disk Reactor

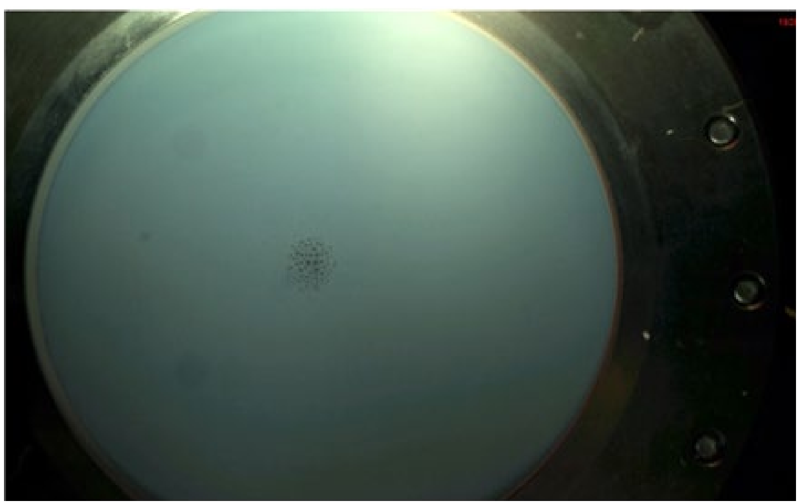
Handling heterogeneous Photocatalysts

A



500 RPM (red dots show particle agglomeration)

B



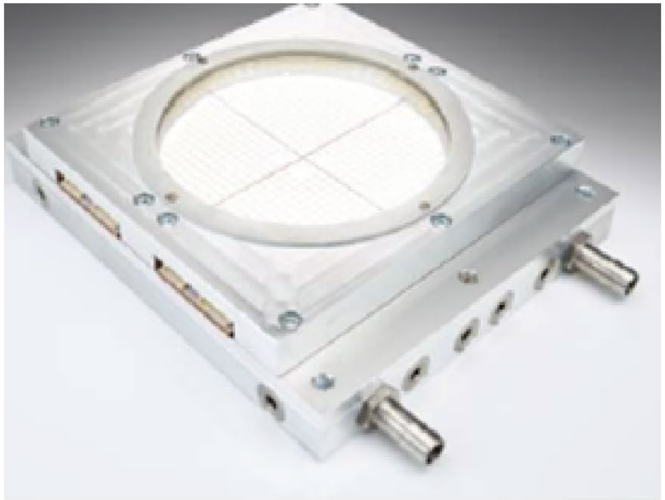
2000 RPM (10 mg/mL TiO_2)

Chaudhuri, Zondag, Schuurmans, Van der Schaaf, Noel, *Org. Process Res. Dev.* **2022**, *26*, 1279-1288.

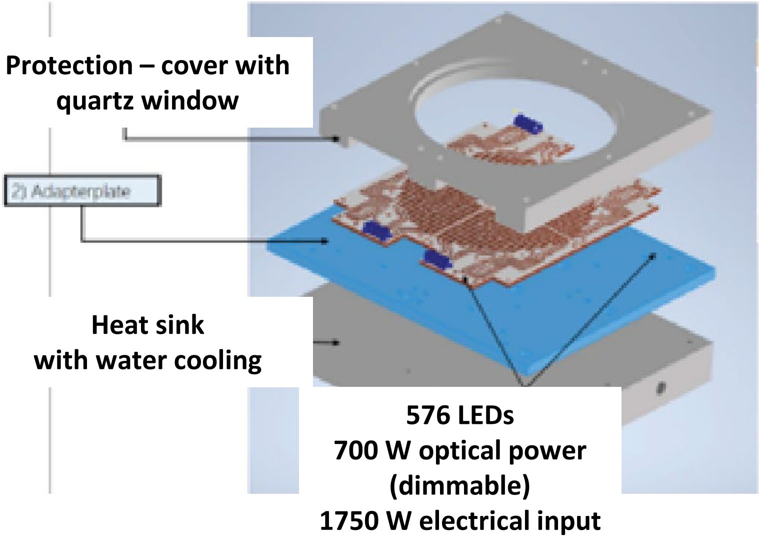
Photochemical Spinning Disk Reactor

Matching with high power LEDs

a



b



high light intensity enables to exploit excellent mass-transfer capacity of SDR

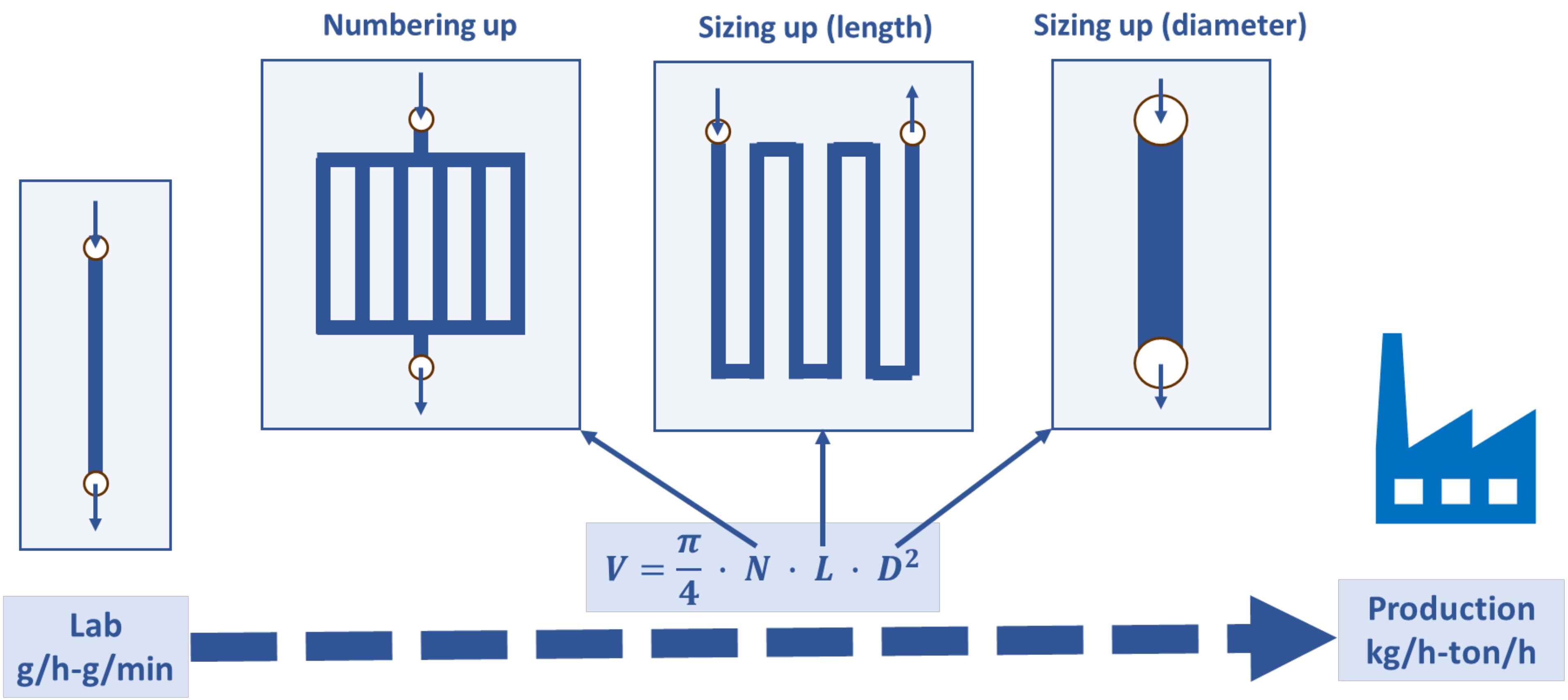
↓

18 kg/day productivity for α-terpinene photooxidation

Chaudhuri, de Groot, Schuurmans, Bianchi, Zondag, Kuijpers, Broersma, Dorbec, Van der Schaaf, Noel, *in preparation*.

Photoredox Catalysis

scaling via flow technology

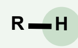


For reviews on scaling flow reactors: (i) Dong, Wen, Zhao, Kuhn, Noël, *Chem. Eng. Sci. X* **2021**, 100097. (ii) Donnelly, Baumann, *J. Flow Chem.* **2021**,*11*, 223-241. (iii) Berton, de Souza, Abdiaj, McQuade, Snead, *J. Flow Chem.* **2020**, *10*, 73-92.

Synthetic methodology enabled by flow

Expanding Chemical Space

Photocatalytic sp^3 C–H functionalization via HAT



- generally unreactive bond
- activated and non-activated C–H bonds
- untapped synthetic potential

For a review: (a) Capaldo, Ravelli, Fagnoni, *Chem. Rev.* **2022**, *122*, 1875-1924. (b) Capaldo, Quadri, Ravelli, *Green Chem.* **2020**, *22*, 3376–3396.

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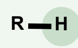

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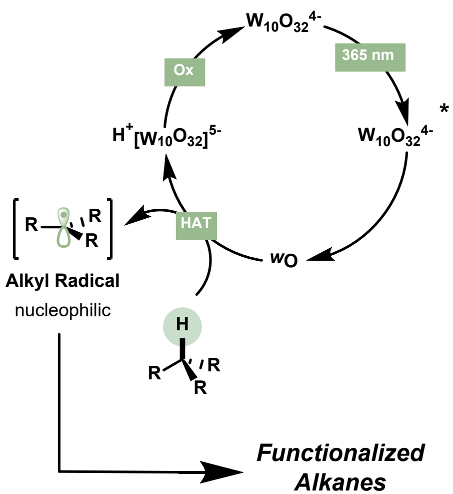
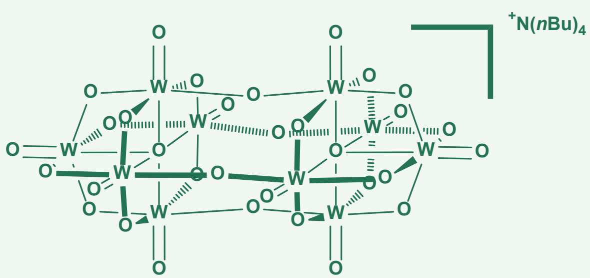
Generation of radical intermediates via Hydrogen Atom Transfer





TBADT ((Bu$_4$N)$_4$W$_{10}$O$_{32}$)

For a review: (a) Capaldo, Ravelli, Fagnoni, *Chem. Rev.* **2022**, *122*, 1875-1924. (b) Capaldo, Quadri, Ravelli, *Green Chem.* **2020**, *22*, 3376–3396.

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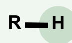

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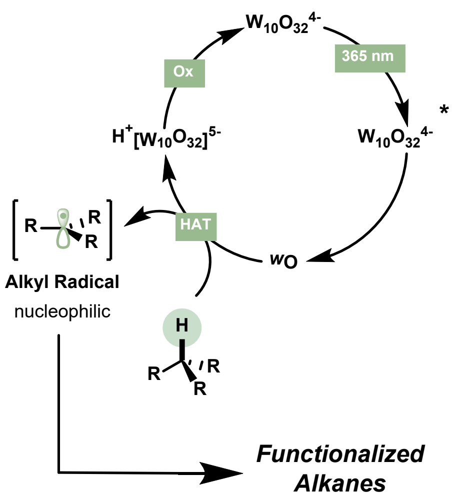
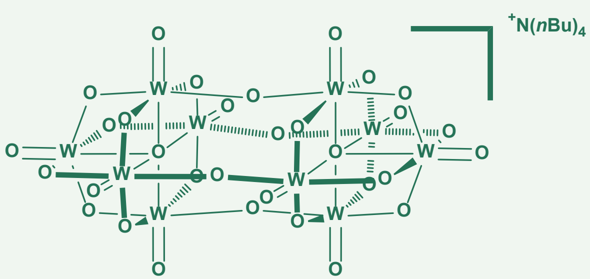


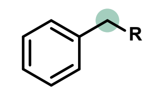


TBADT $((Bu_4N)_4W_{10}O_{32})$

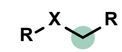
Selectivity of decatungstate HAT photocatalysis

increased reactivity at:

* allylic and benzylic positions

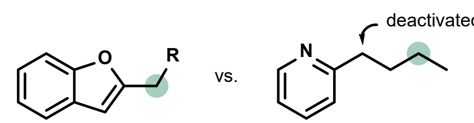


* α positions compared to amines and ethers:

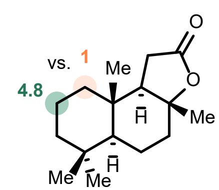


with X = O, N

* electron-rich heterocycles activate the benzylic position, vs.
electron-poor heterocycles deactivate the benzylic position



* Inherent radical stability: tertiary > secondary > primary
vs. sterical hindrance due to large size of decatungstate

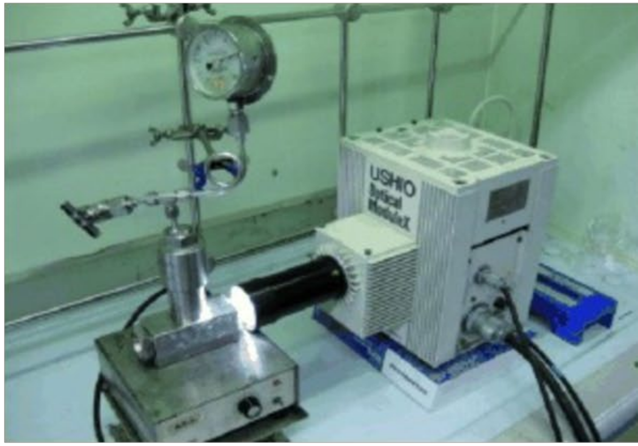


Allows for systematic structural tuning of biologically active molecules

This is an essential aspect of pharmaceutical research.

For a review: (a) Capaldo, Ravelli, Fagnoni, *Chem. Rev.* **2022**, *122*, 1875-1924. (b) Capaldo, Quadri, Ravelli, *Green Chem.* **2020**, *22*, 3376–3396.

Photocatalytic HAT using gasses in flow



For a review: (i) Laporte, Masson, Zondag, Noël, *Angew. Chem. Int. Ed.* **2024**, *63*, e20231610.

(ii) Mallia, Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327–360.

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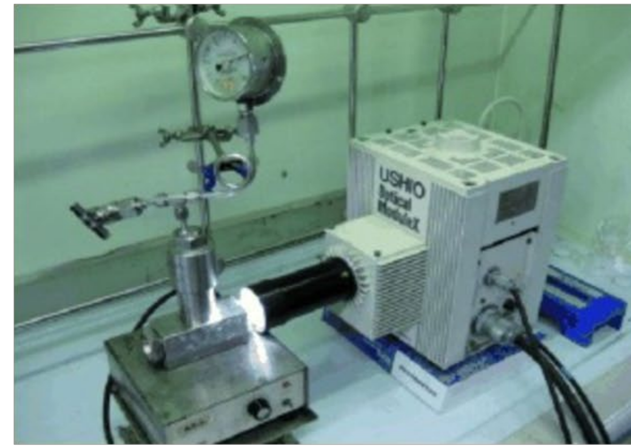

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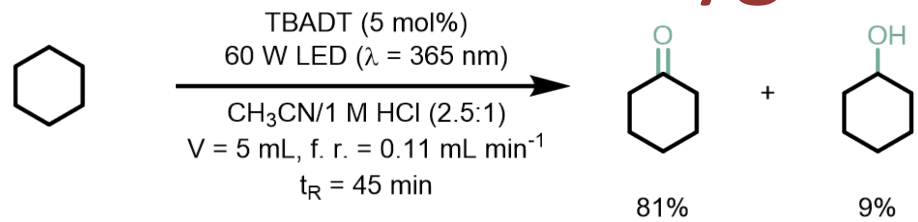
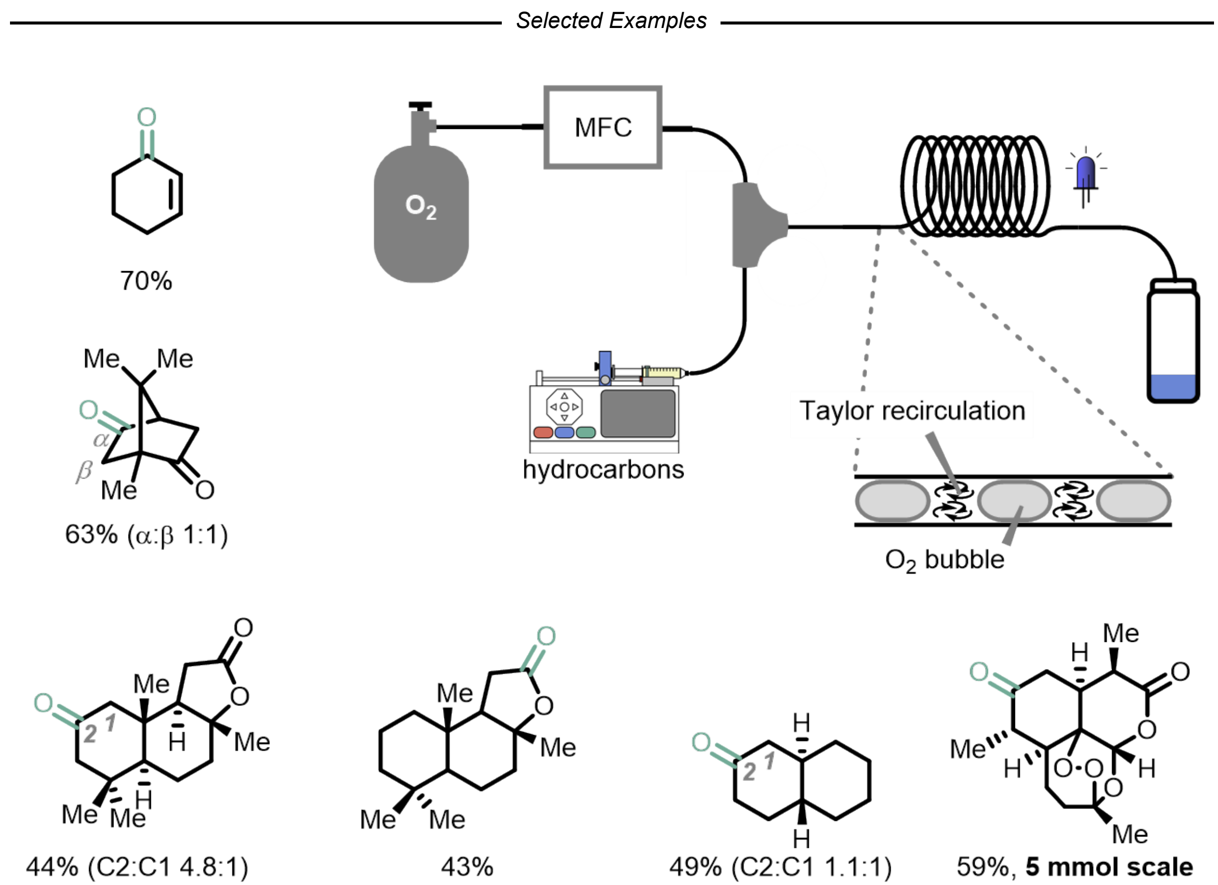
(ii) Mallia, Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327–360.

Photocatalytic sp^3 C–H oxidation

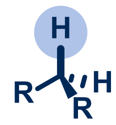
safe use of oxygen





Laudadio, Govaerts, Wang, Ravelli, Koolman, Fagnoni, Djuric, Noël, *Angew. Chem. Int. Ed.* **2018**, *57*, 4078-4082.

Most challenging problem in C–H functionalization



Gaseous Alkane

"Remaining unsolved, but increasingly important due to the production of shale gas, is the original goal: the mild and selective conversion of methane and light hydrocarbons to functionalized feedstocks"

John F. Hartwig*, JACS* **2016***, 138,* 2-24.

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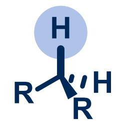

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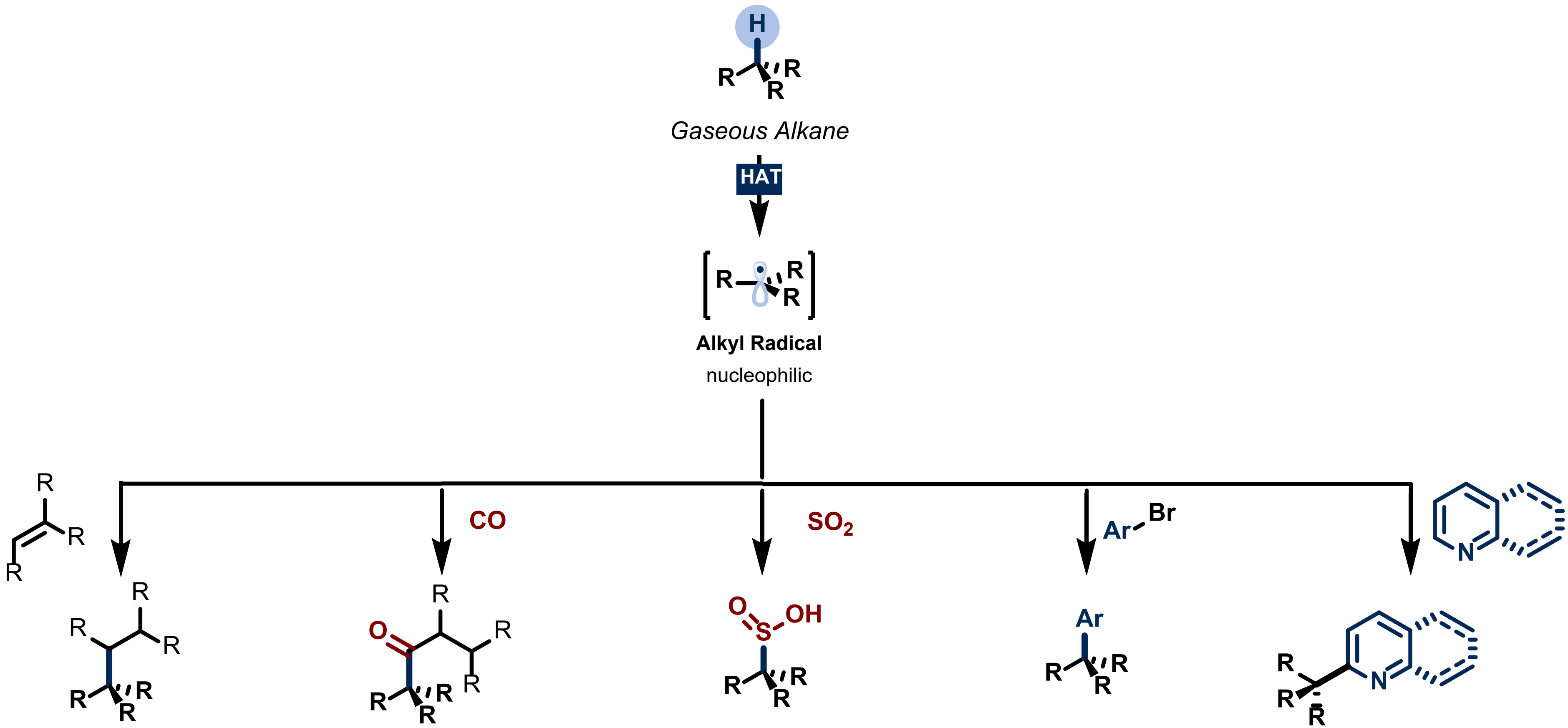
John F. Hartwig*, JACS* **2016***, 138,* 2-24*.*

"[Natural gas] is a vast, low-cost feedstock of hydrocarbons that remains untapped as a raw material, simply because there has been no easy way to turning it into synthetically useful compounds"

Robert G. Bergman*, Nature* **2007**, *138,* 391-392*.*

Photocatalytic sp³ C–H functionalization of light alkanes



Science **2020**, *369*, 92-96.

Angew. Chem. Int. Ed. **2023**, *62*, e202308563.

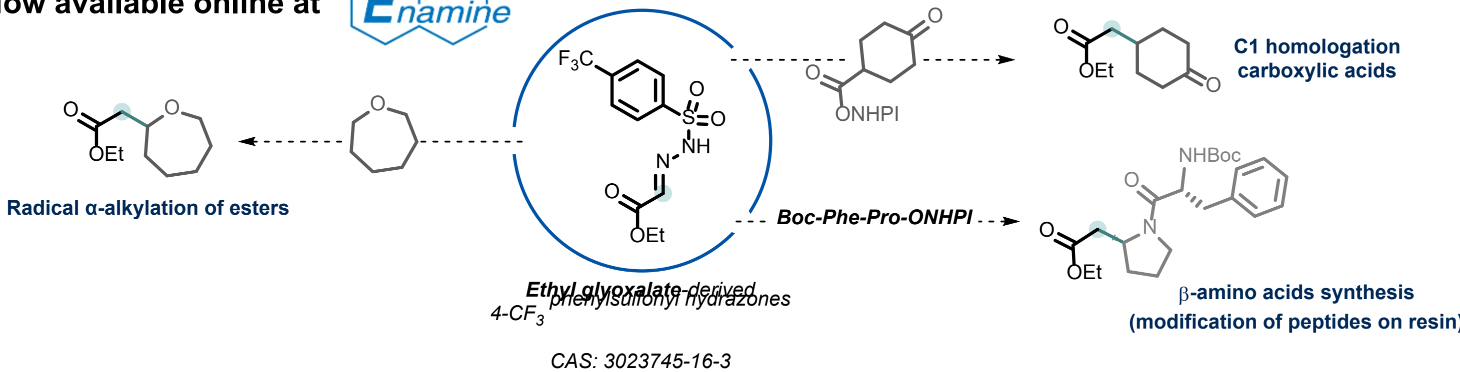
Nature Commun. **2024**, *15*, 5246.

Angew. Chem. Int. Ed. **2024**, *63, e202413846*.

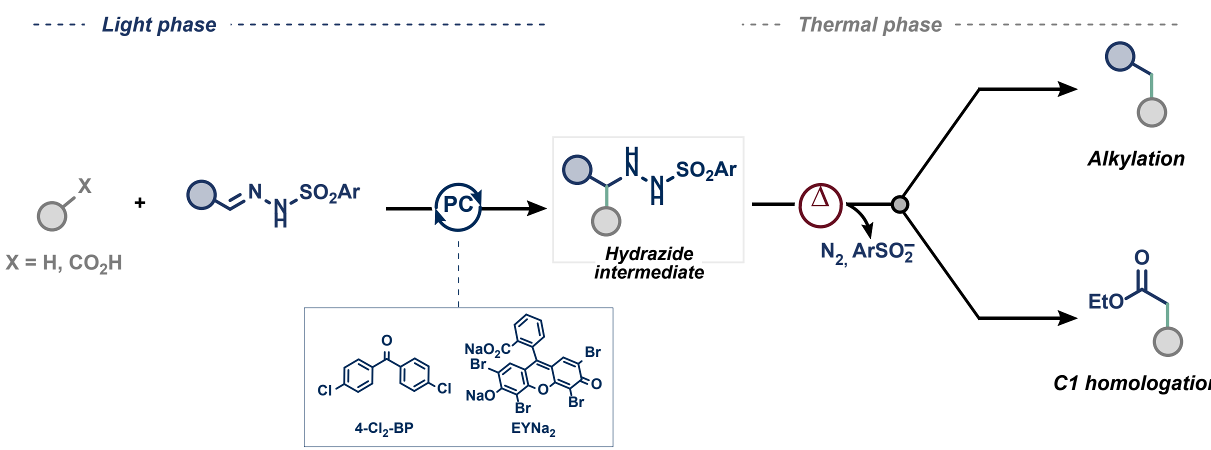
in preparation

Sulfonyl hydrazone, a versatile building block

Now available online at Enamine



Via a one-pot, two-step process:



For HAT: Pulcinella, Bonciolini, Lukas, Sorato, Noël, *Angew. Chemie Int. Ed.* **2023**, *62,* e202215374.

For decarboxylative coupling: Bonciolini, Pulcinella, Leone, Schiroli, Luguera Ruiz, Sorato, Dubois, Gopalakrishnan, Masson, Della Ca', Protti, Fagnoni, Zysman-Colman, Johansson, Noël, *Nature Commun.*, **2024**, *15*, 1509.

Reaction Optimization

Streamlining and optimizing a compound trace into a widely applicable synthetic method is both demanding and time-intensive.

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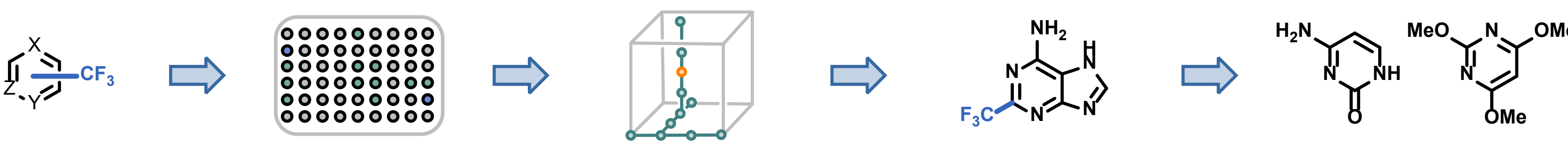
Typical strategy for synthetic methodology development:



Interesting Transformation → **Random Screening Reaction Conditions** → **HIT Optimization One-Factor-At-A-Time** → **Model Substrate with High Yield & Selectivity** → **Reaction Protocol for Entire Substrate Scope**

Reaction Optimization

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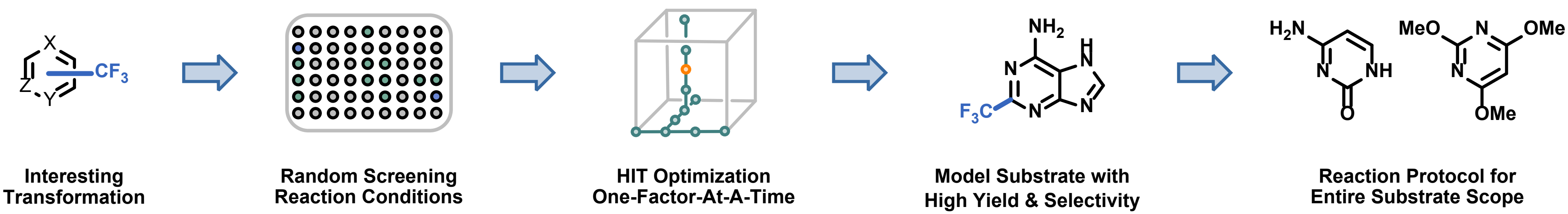


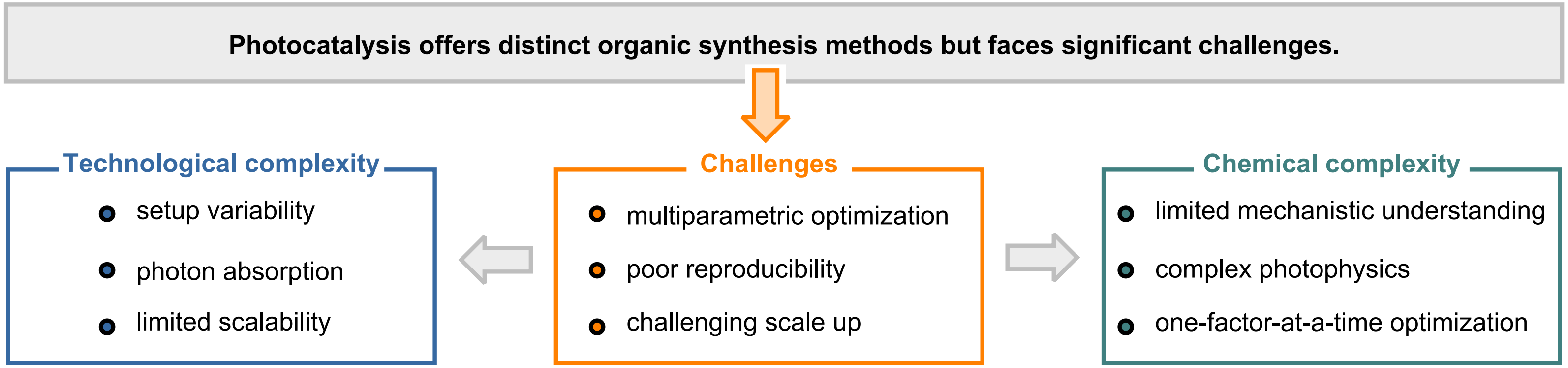
Most substrates have suboptimal yields.

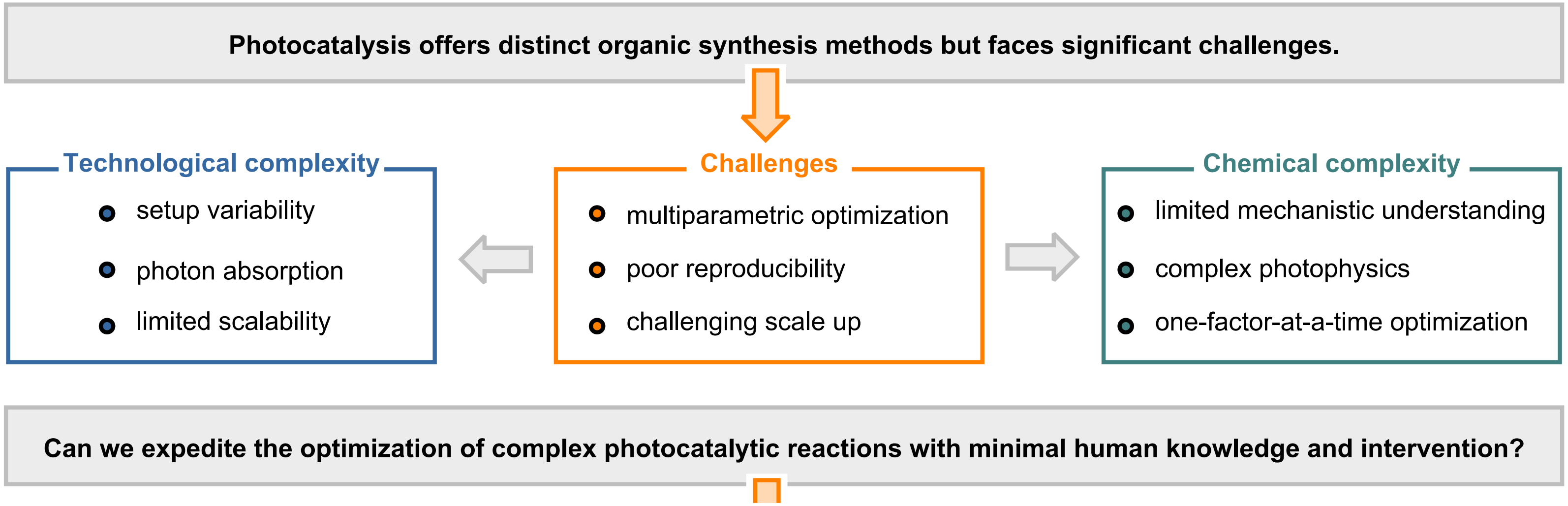
Reaction Optimization

If most substrates in a scope have suboptimal yields.

Why not let a machine do the work?

Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.


Photocatalysis offers distinct organic synthesis methods but faces significant challenges.
Technological complexity
setup variability
photon absorption
limited scalability
Challenges
multiparametric optimization
poor reproducibility
challenging scale up
Chemical complexity
limited mechanistic understanding
complex photophysics
one-factor-at-a-time optimization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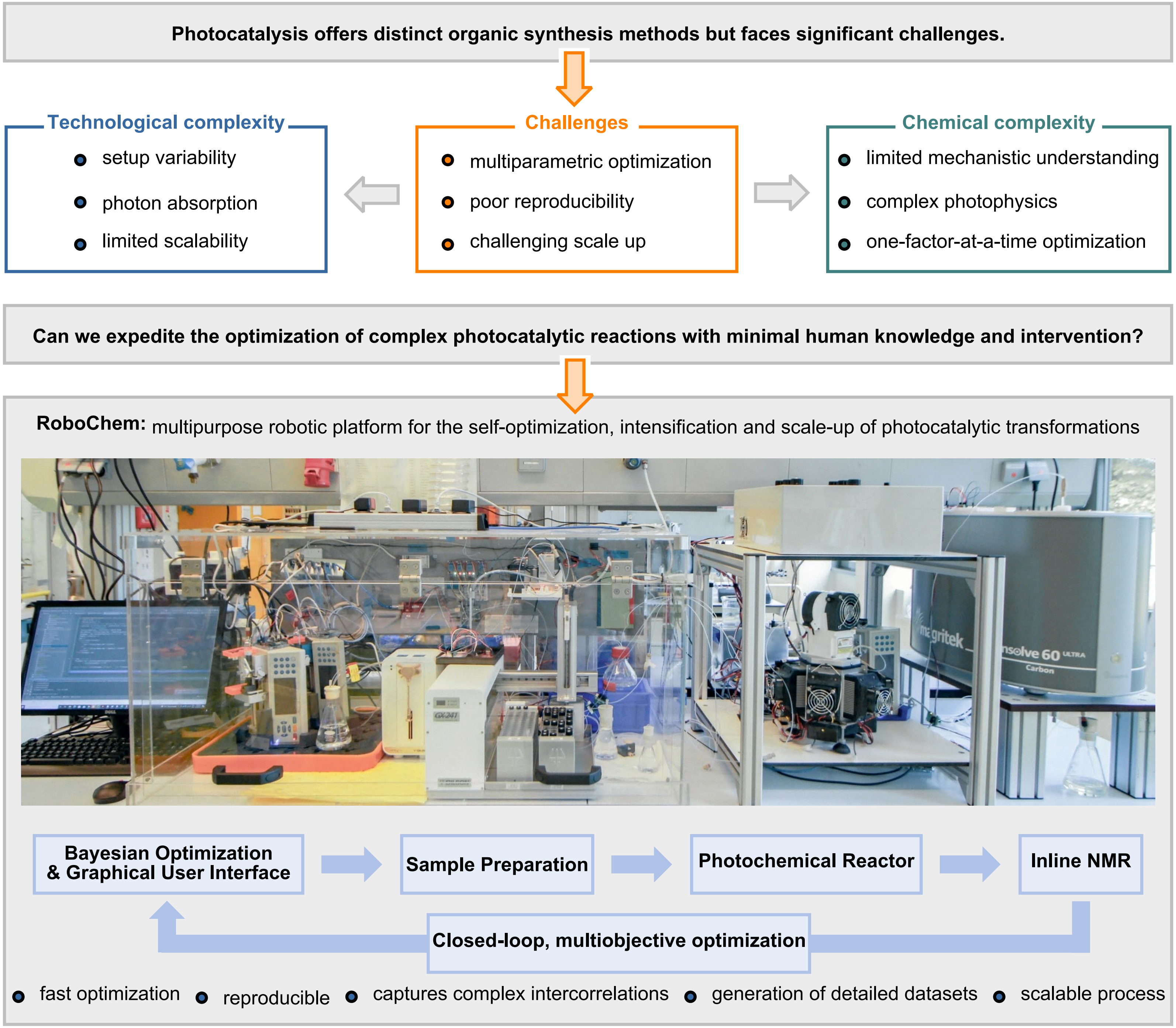
Can we expedite the optimization of complex photocatalytic reactions with minimal human knowledge and intervention?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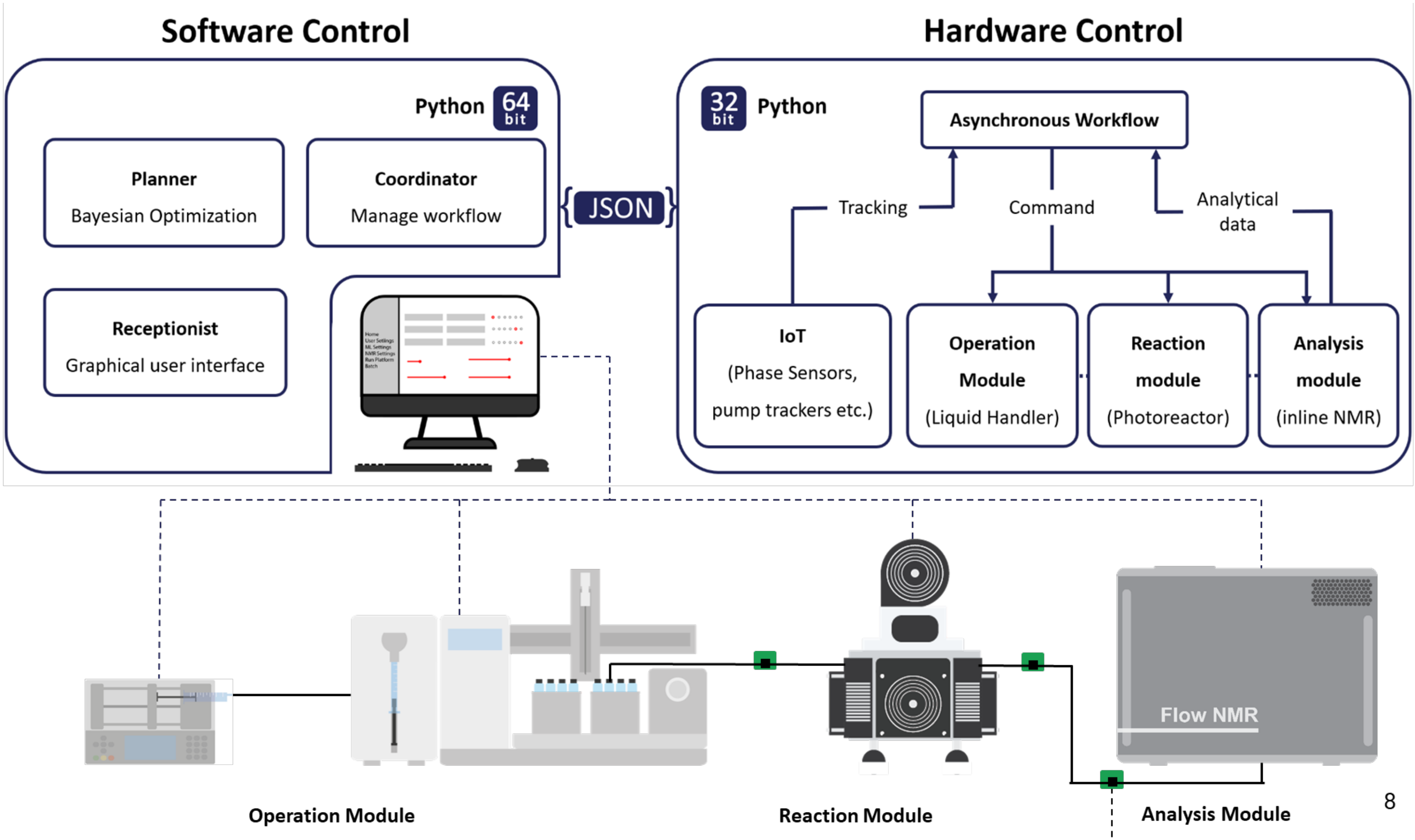
one-factor-at-a-time optimization
Can we expedite the optimization of complex photocatalytic reactions with minimal human knowledge and intervention?
RoboChem: multipurpose robotic platform for the self-optimization, intensification and scale-up of photocatalytic transformations
Bayesian Optimization & Graphical User Interface
Sample Preparation
Photochemical Reactor
Inline NMR
Closed-loop, multiobjective optimization
fast optimization
reproducible
captures complex intercorrelations
generation of detailed datasets
scalable process

RoboChem
An all-in-one robotic platform



Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

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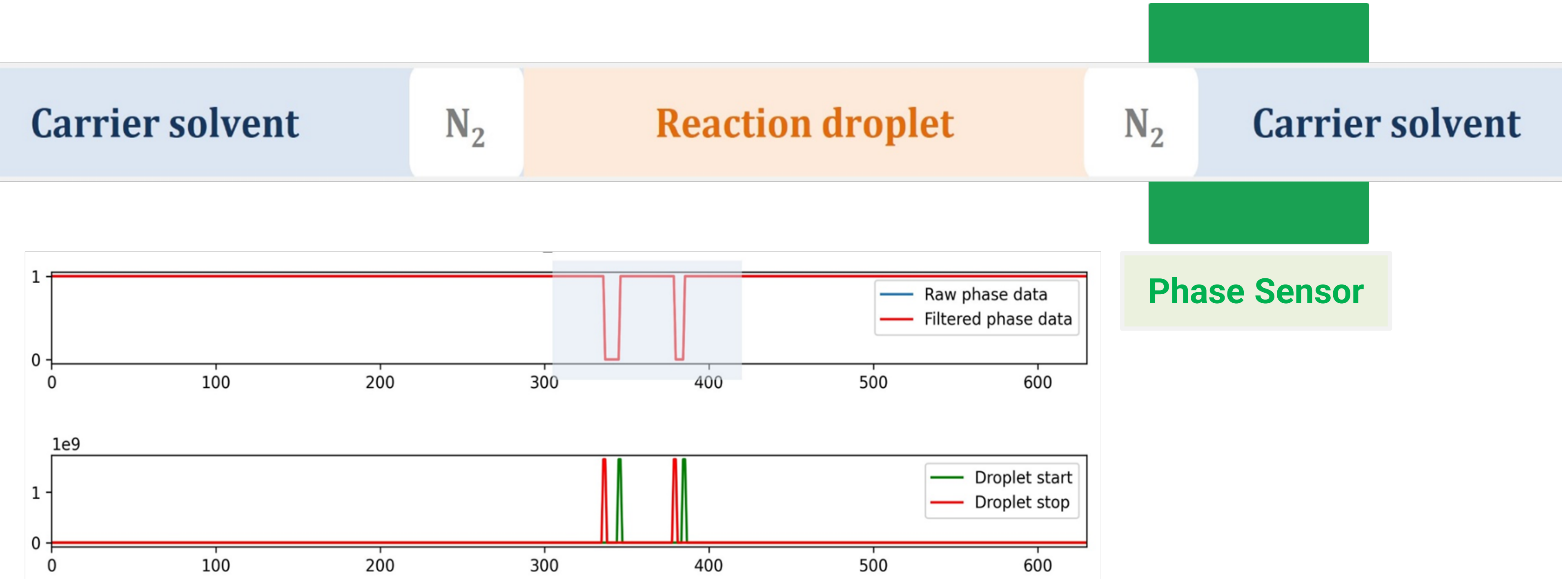

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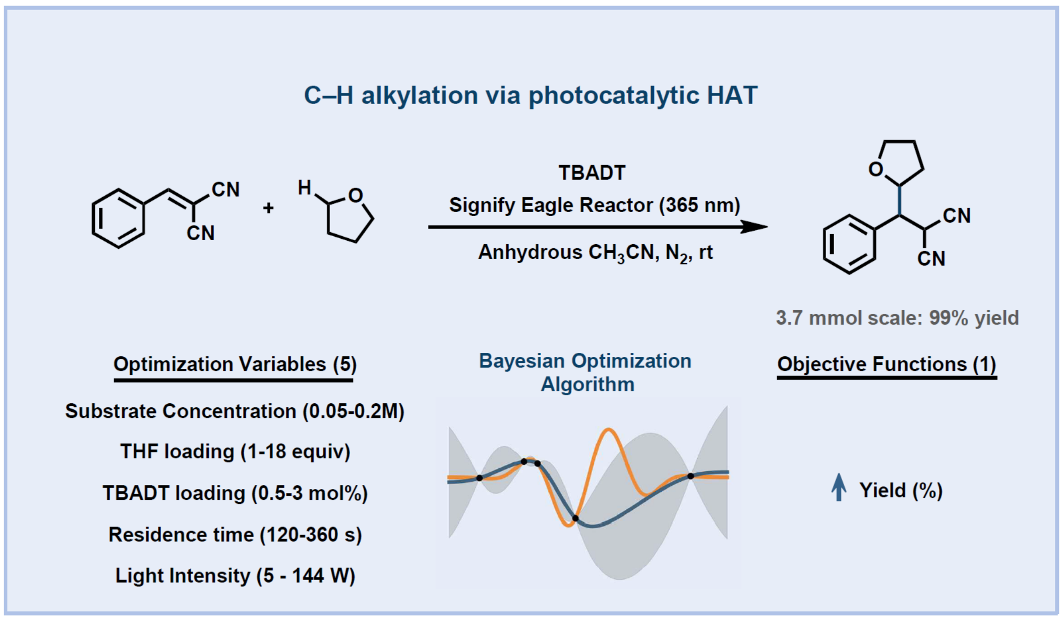
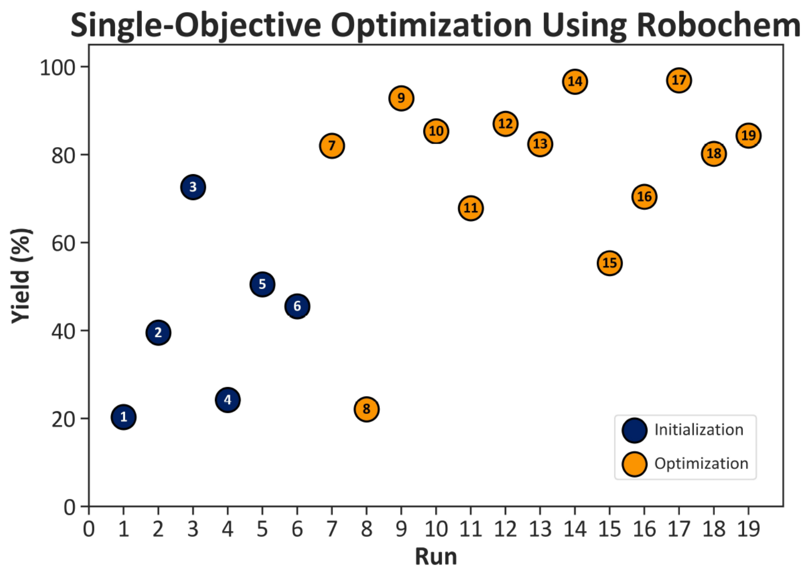


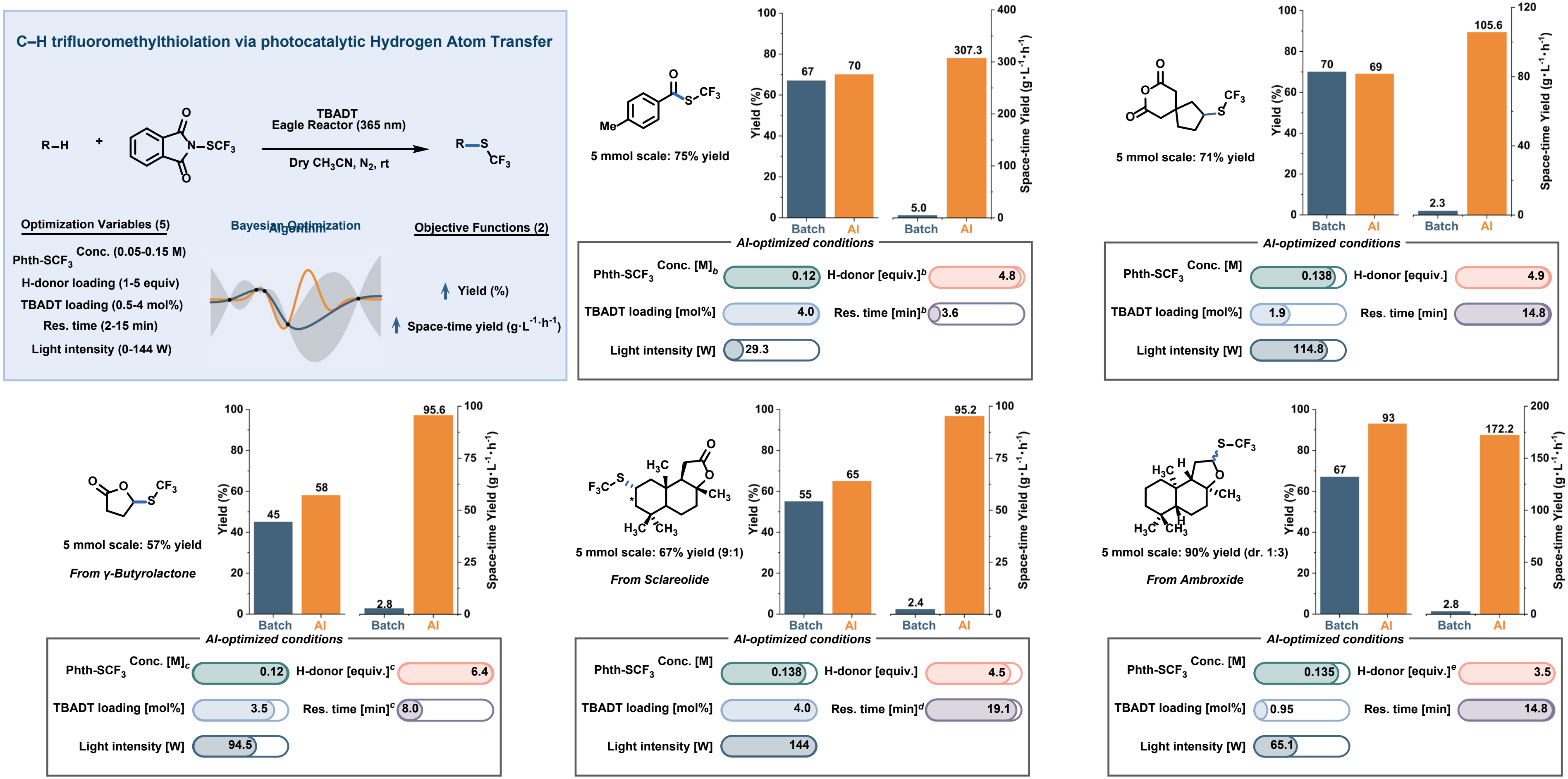


Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

RoboChem
An all-in-one robotic platf[illegible]m

Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

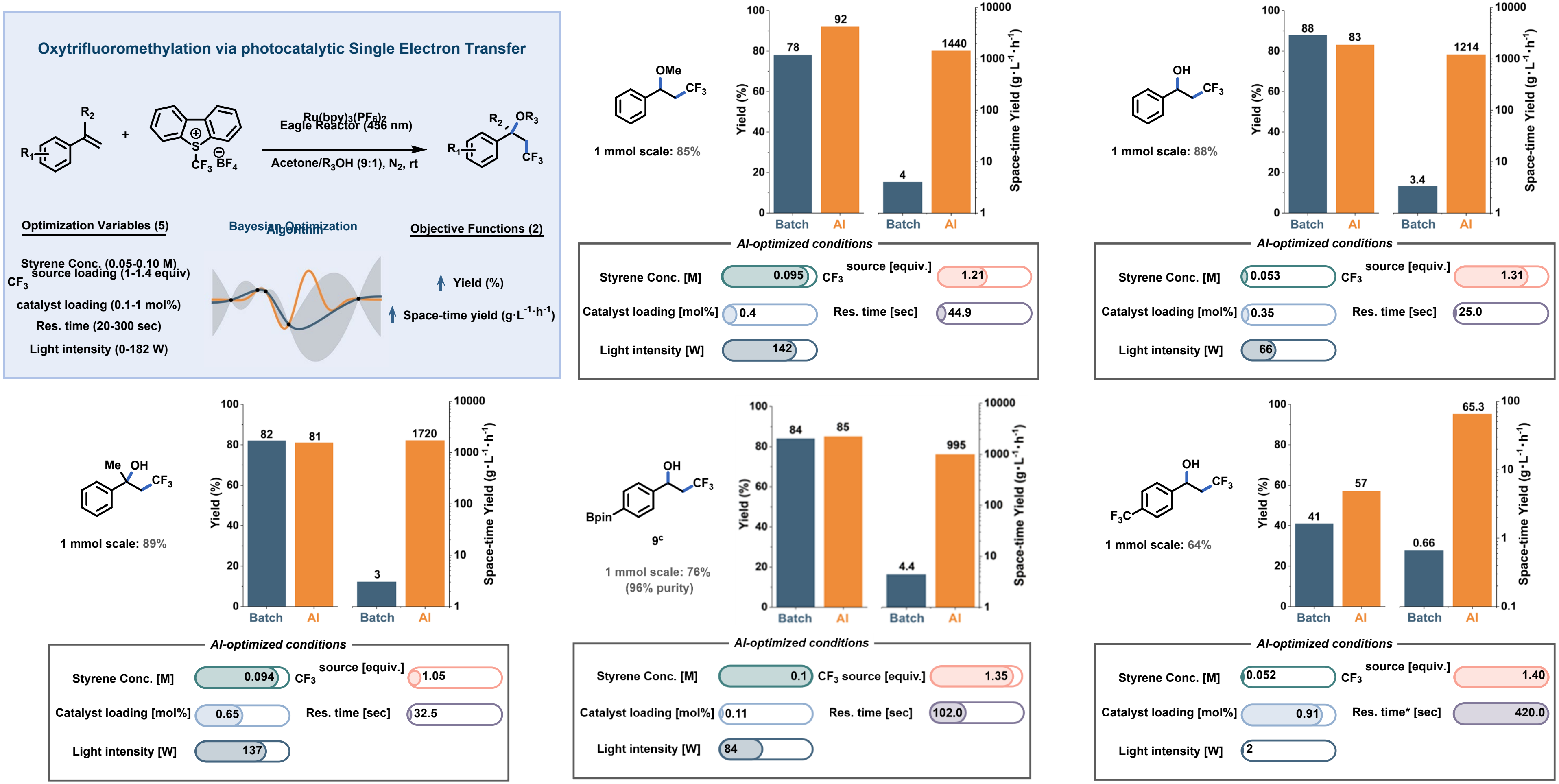
Trifluoromethylthiolation via HAT



Original work: Schirmer, Rolka, Karl, Holzhausen, König, *Org. Lett.* **2021**, *23*, 5729–5733.

Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

Oxytrifluoromethylation via SET



Original work: Yasu, Koike, Akita, *Angew. Chem. Int. Ed.* **2012**, *51*, 9567-9571.

Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

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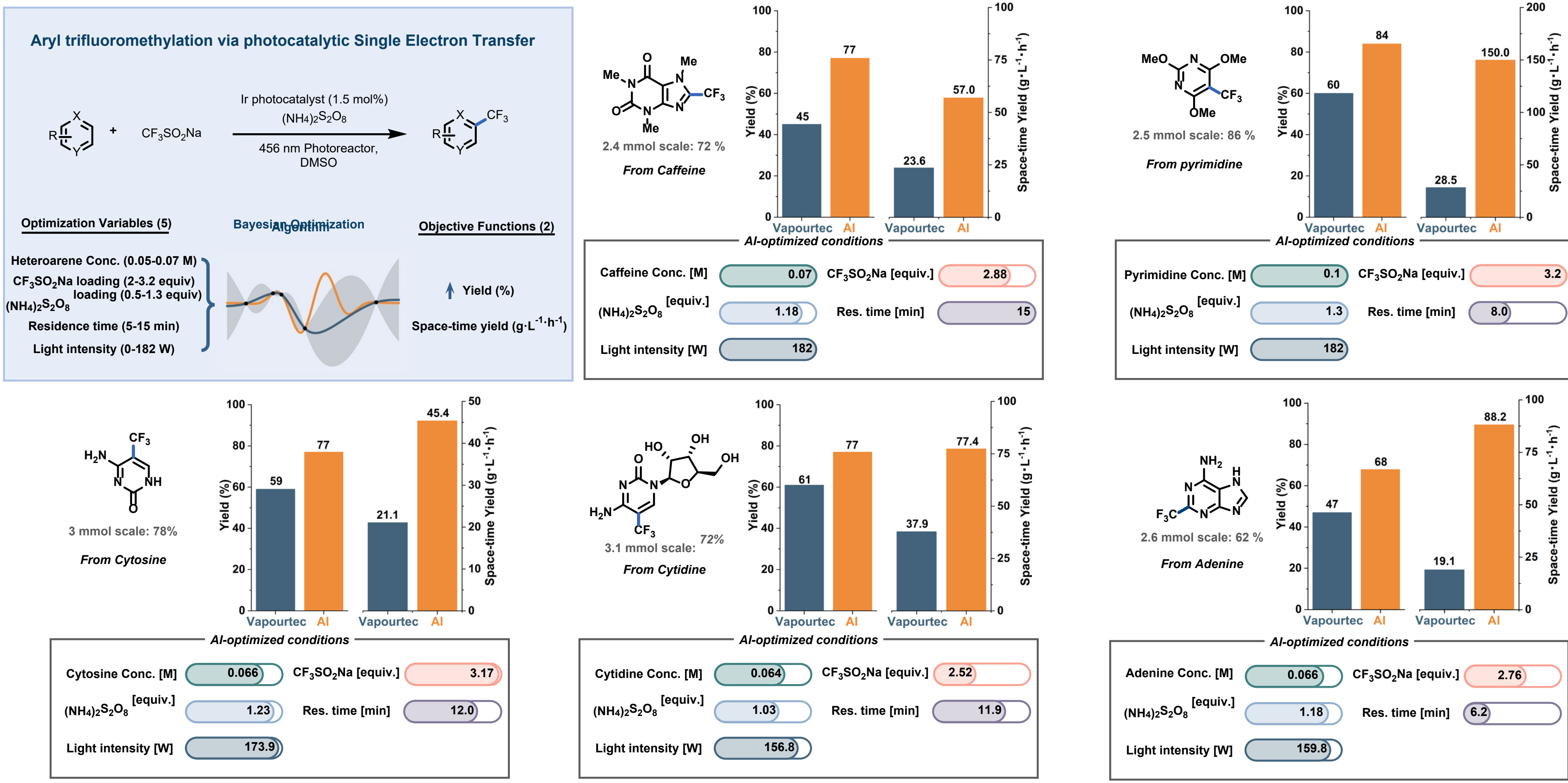
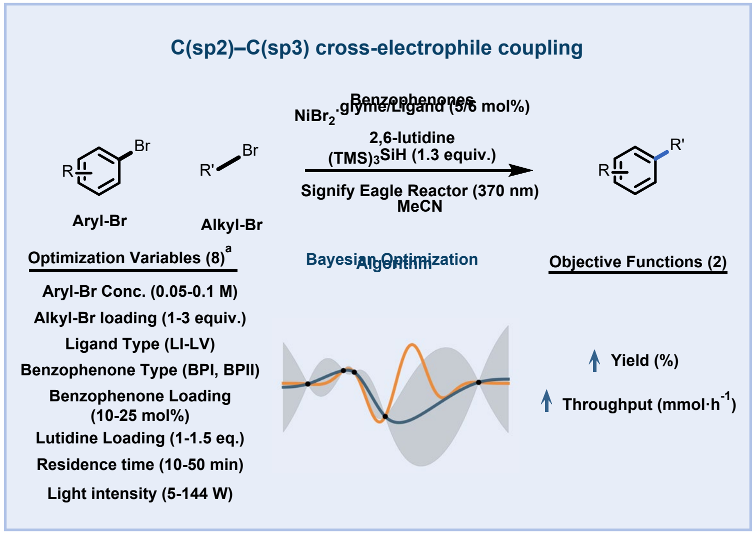
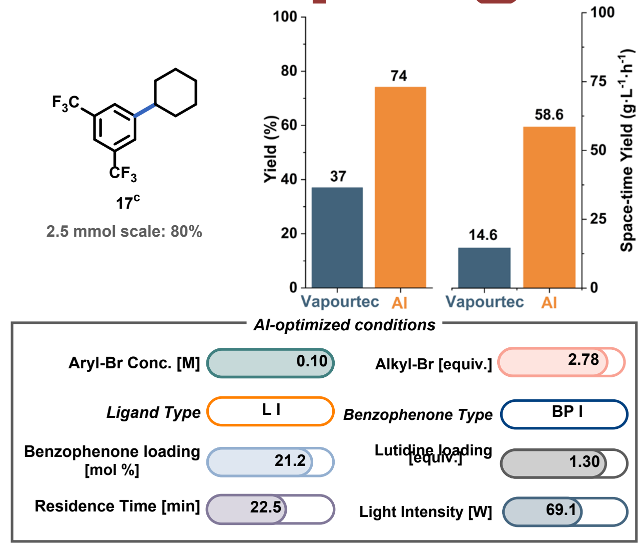


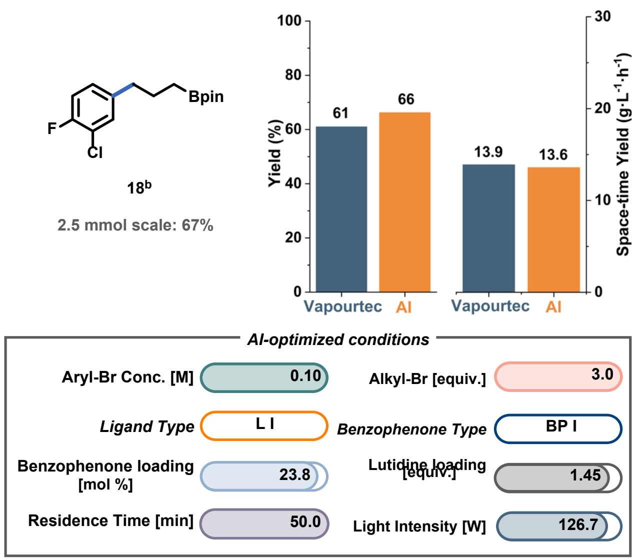
Original work: Abdiaj, Bottecchia, Alcazar, Noël, *Synthesis* **2017**, *49*, 4978-4985.

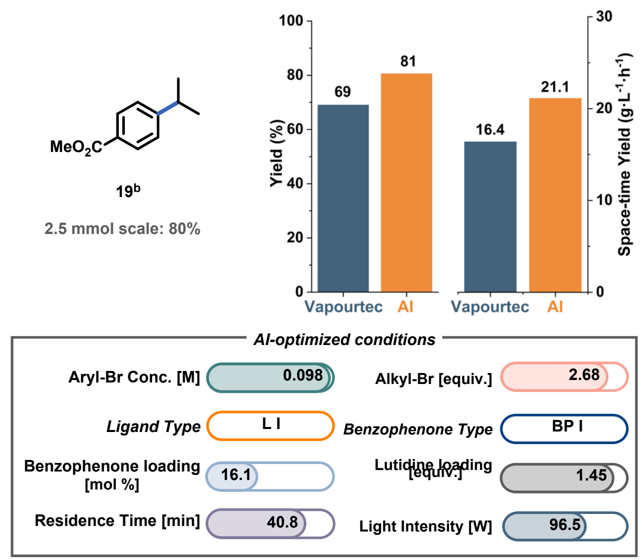
Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

Cross-Electrophile Coupling









Original work: Luridiana, Mazzarella, Capaldo, Rincon, Garcia-Losada, Mateos, Frederick, Nuno, Buma, Noël, *ACS Catal.* **2022**, *12*, 11216–11225.

Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

Is chemistry ready for an AI revolution?

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Wiktor Beker, Rafał Roszak, Agnieszka Wołos, Nicholas H. Angello, Vandana Rathore, Martin D. Burke,* and Bartosz A. Grzybowski*

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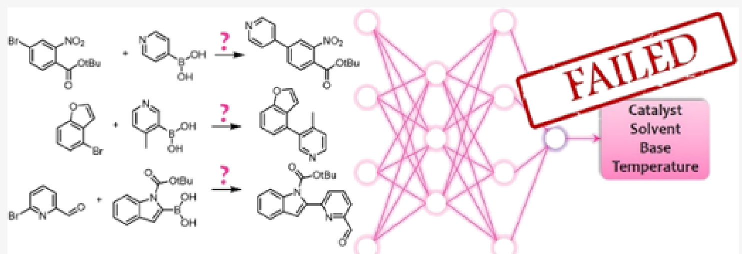

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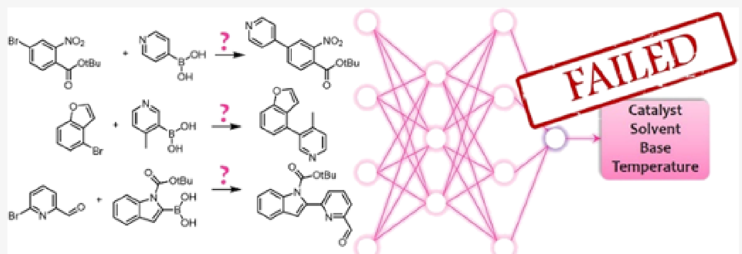

Caused by

- *Subjective preferences in selecting reaction conditions by chemists*
- *Lack of reliable and standardized data, including lack of negative data.*

Grzybowski *et al.*, *J. Am. Chem. Soc.* **2022**, *144*, 4819-4827.

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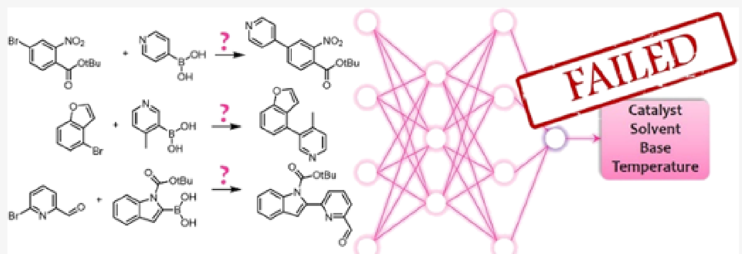

Caused by

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Fundamental flaw in the current synthetic literature (!)

Grzybowski *et al.*, *J. Am. Chem. Soc.* **2022**, *144*, 4819-4827.

Digitization of Chemistry

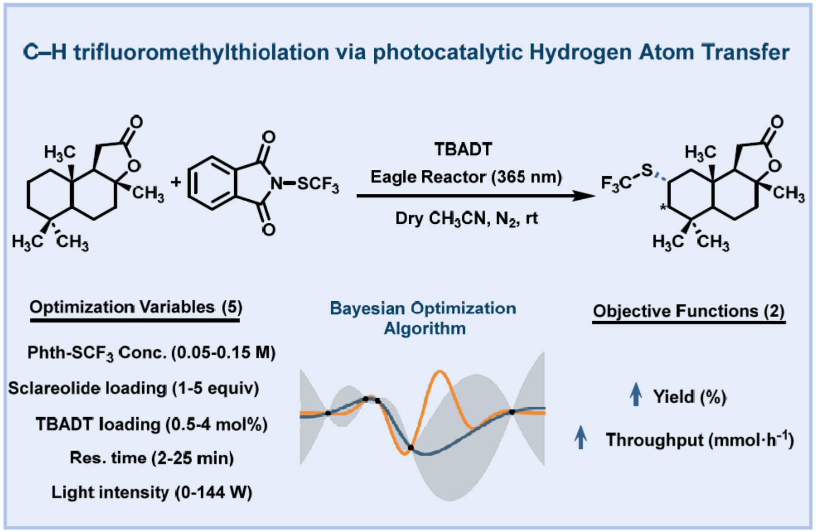


Table S15. Experimental conditions and results for trifluoromethylthiolation campaign of sclareolide.

run	Phth-SCF$_3$ Conc. (M)	Sclareolide loading (equiv.)	TBADT loading (mol%)	Residence time (min)	Light intensity (W)	Yield (%)	Throughput (mmol/hr)
1	0.100	4.00	4.00	15.0	144	58.6	0.668
2	0.064	4.42	1.75	5.1	117	21.2	0.457
3	0.132	1.95	3.35	8.8	104	50.4	1.282
4	0.125	1.88	1.38	9.0	108	51.6	1.226
5	0.062	1.63	2.44	12.3	1	1.8	0.015
6	0.100	2.75	2.25	9.0	108	57.1	1.084
7	0.065	3.77	3.18	10.9	84	51.5	0.523
8	0.138	4.06	3.56	4.5	36	5.4	0.282
9	0.075	1.88	3.13	9.0	36	4.2	0.059
10	0.100	3.42	2.72	6.0	32	3.5	0.100
11	0.141	2.68	0.90	11.2	135	32.2	0.690
12	0.149	4.47	3.97	19.1	92	47.1	0.630
13	0.093	1.38	2.79	9.0	144	25.8	0.456
14	0.100	4.28	3.94	13.4	122	50.1	0.641
15	0.138	4.50	4.00	19.8	144	65.3	0.776
16	0.138	2.31	2.69	9.4	108	4.7	0.119
17	0.145	3.21	4.00	19.1	97	60.7	0.789
18	0.131	4.45	3.93	13.6	105	58.4	0.961
19	0.128	1.68	1.22	17.2	61	31.7	0.403
20	0.072	3.26	1.87	4.5	142	11.2	0.304
21	0.121	2.00	3.13	7.3	36	8.7	0.248
22	0.091	5.00	1.37	8.9	0	0.0	0.000
23	0.092	4.75	0.72	18.9	63	23.0	0.190
24	0.115	4.24	3.94	13.7	64	52.0	0.750
25	0.082	4.53	1.21	15.8	85	36.6	0.327
26	0.119	4.88	2.69	13.4	132	52.3	0.791

Clean, detailed and reproducible datasets

- No mass, heat or photon transfer issues
- No human error
- Positive and negative data available

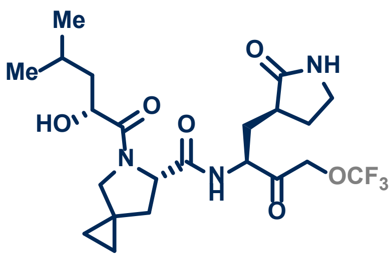
Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

For a review on self-driving labs, see: Bailey, Slattery, Savino, Noel, *Matter* **2024**, *7,* 2382–2398.

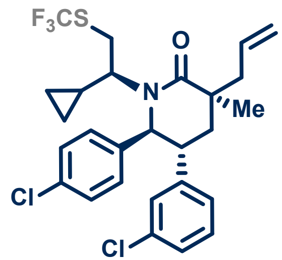
On-demand Generation Fluorinated Reagents

Emerging fluorinated moieties

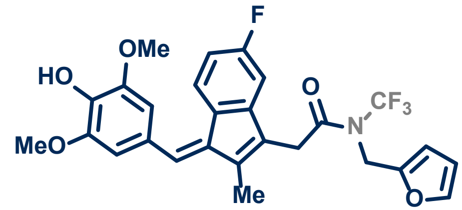
Growing interest into trifluoromethyl groups attached to heteroatoms



CMX990
SARS-CoV-2 protease inhibitor



WO2011153509
MDM2 inhibitor intermediate



WO2016100542
RAS Gtpase inhibitor

- *New chemical space by the XCF_3 motifs*
- *Fine tuning of the molecular properties*
- *XCF_3 are gaining momentum as an alternative to $C\text{-}CF_3$ fragments*

Emerging Fluorinated Motifs: Synthesis, Properties and Applications, Wiley-VCH **2020**

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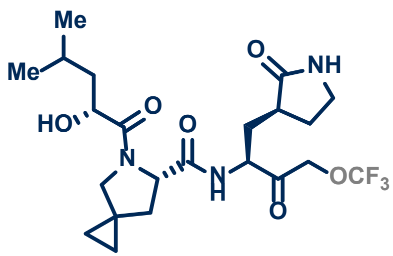
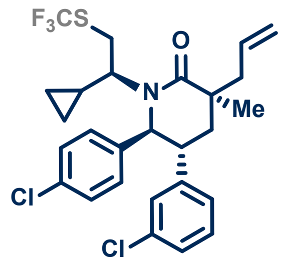


CMX990
SARS-CoV-2 protease inhibitor



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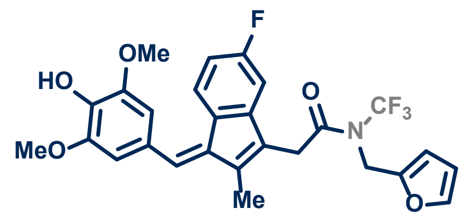

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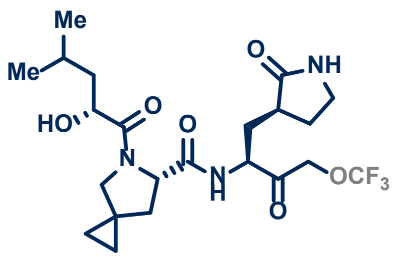

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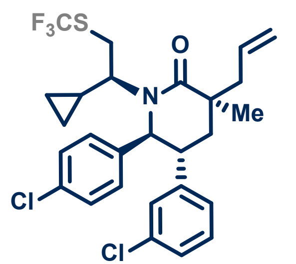

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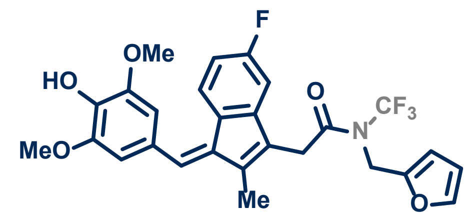

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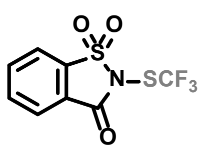
But how to make them?

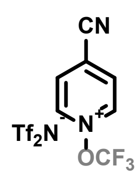
Trifluoromethylthiolation — **Trifluoromethoxylation** — **Trifluoromethylamination**

$[Me_4N][SCF_3]$

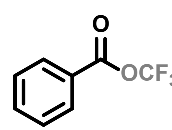
Yagupolskii, 2003



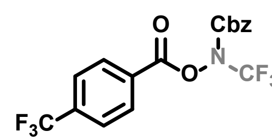
Shen, 2014



Togni, 2018



Hu, 2018



Huang & Xu, 2022

Emerging Fluorinated Motifs: Synthesis, Properties and Applications, Wiley-VCH **2020**

Proposed change in EU law

Potential ban on polyfluorinated alkyl substances (PFAS) in EU?

ECHA
EUROPEAN CHEMICALS AGENCY

ANNEX XV RESTRICTION REPORT

PROPOSAL FOR A RESTRICTION

SUBSTANCE NAME(S): Per- and polyfluoroalkyl substances (PFASs)

Tyrrell, *Org. Process Res. Dev.* **2023**, *27*, 1422-1426.

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EUROPEAN CHEMICALS AGENCY

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BUT

The ban could still involve reagents or even API intermediates…

Tyrrell, *Org. Process Res. Dev.* **2023**, *27*, 1422-1426.

Synthesis of CF_3X moieties

We need new synthetic methods that are:

- *Environmentally-friendly*
- *Starting from non-banned chemicals, e.g. alkali fluorides*
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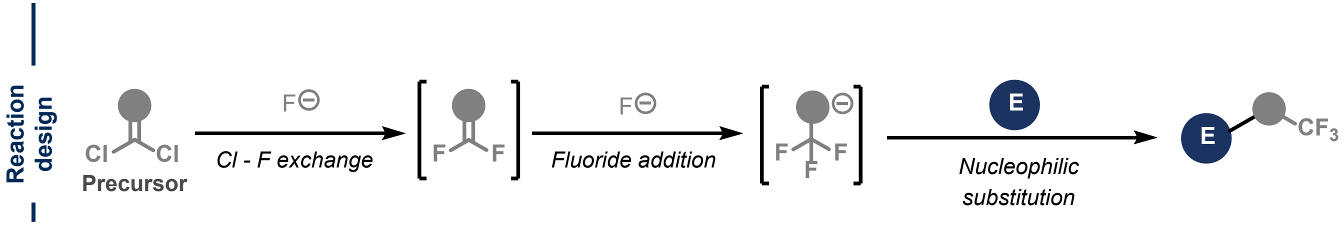

Spennacchio, Bernus, Stanic, Mazzarella, Colella, Douglas, Boutureira, Noel, *Science* **2024**, *385*, 991-996.

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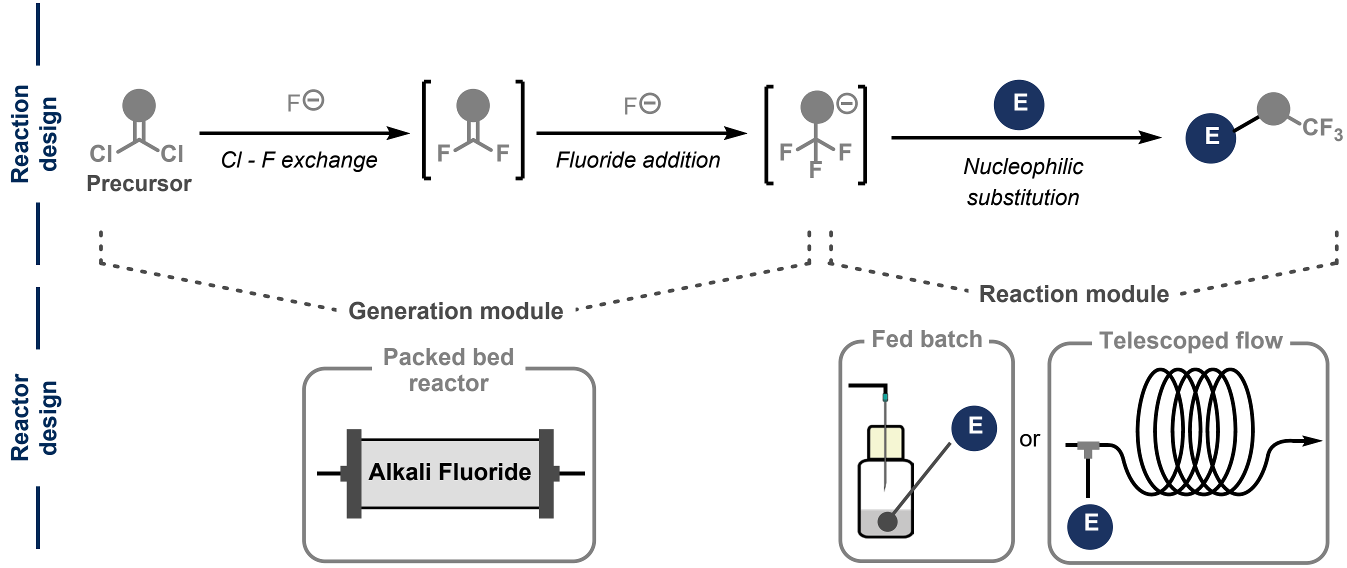

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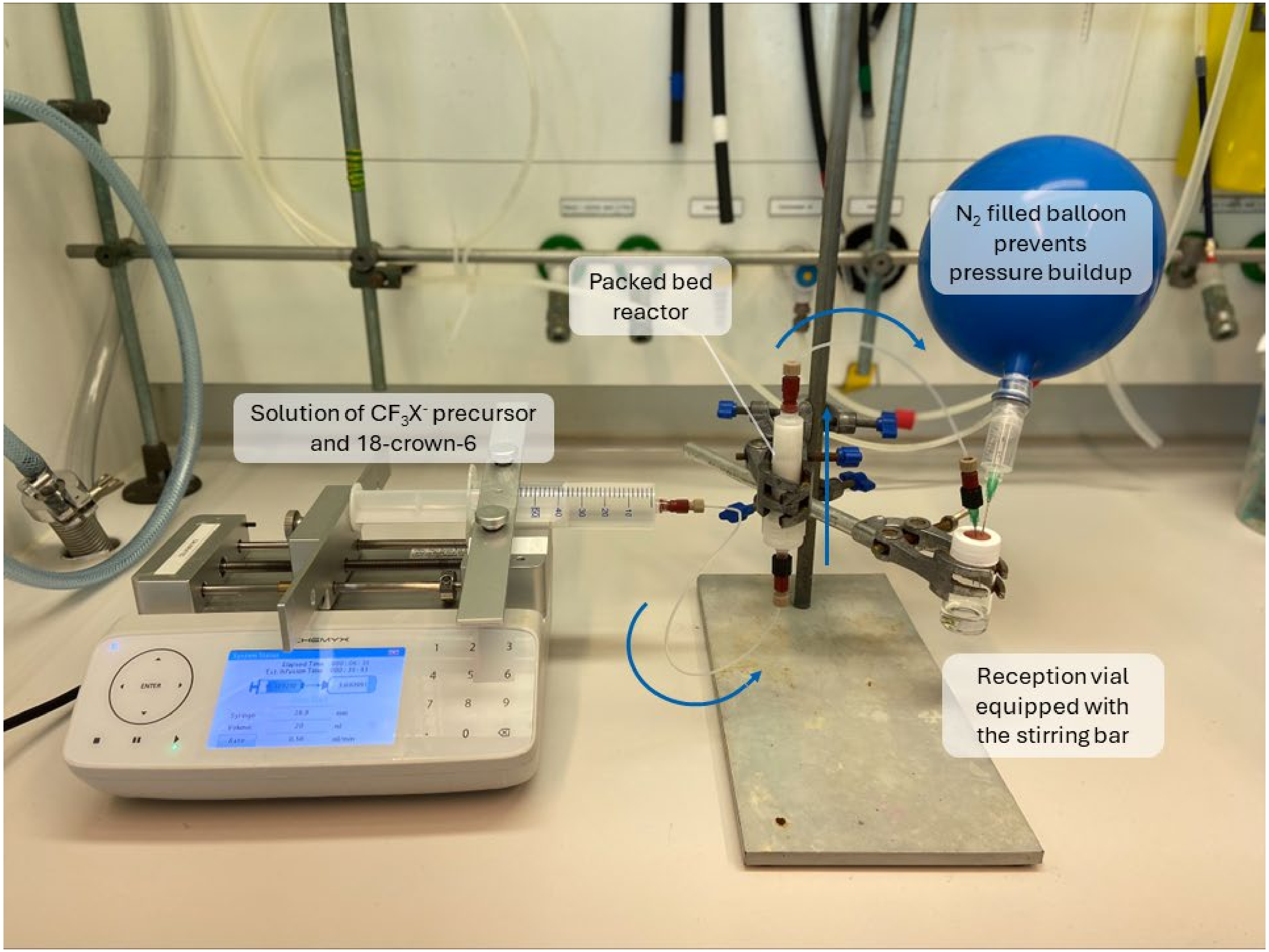

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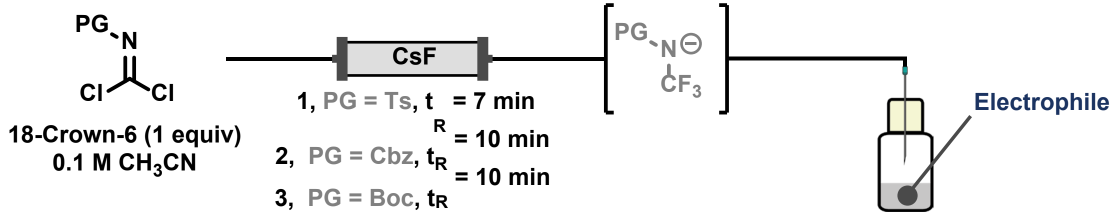
Synthesis of CF_3N anions on demand



Spennacchio, Bernus, Stanic, Mazzarella, Colella, Douglas, Boutureira, Noel, *Science* **2024***, 385*, 991-996.

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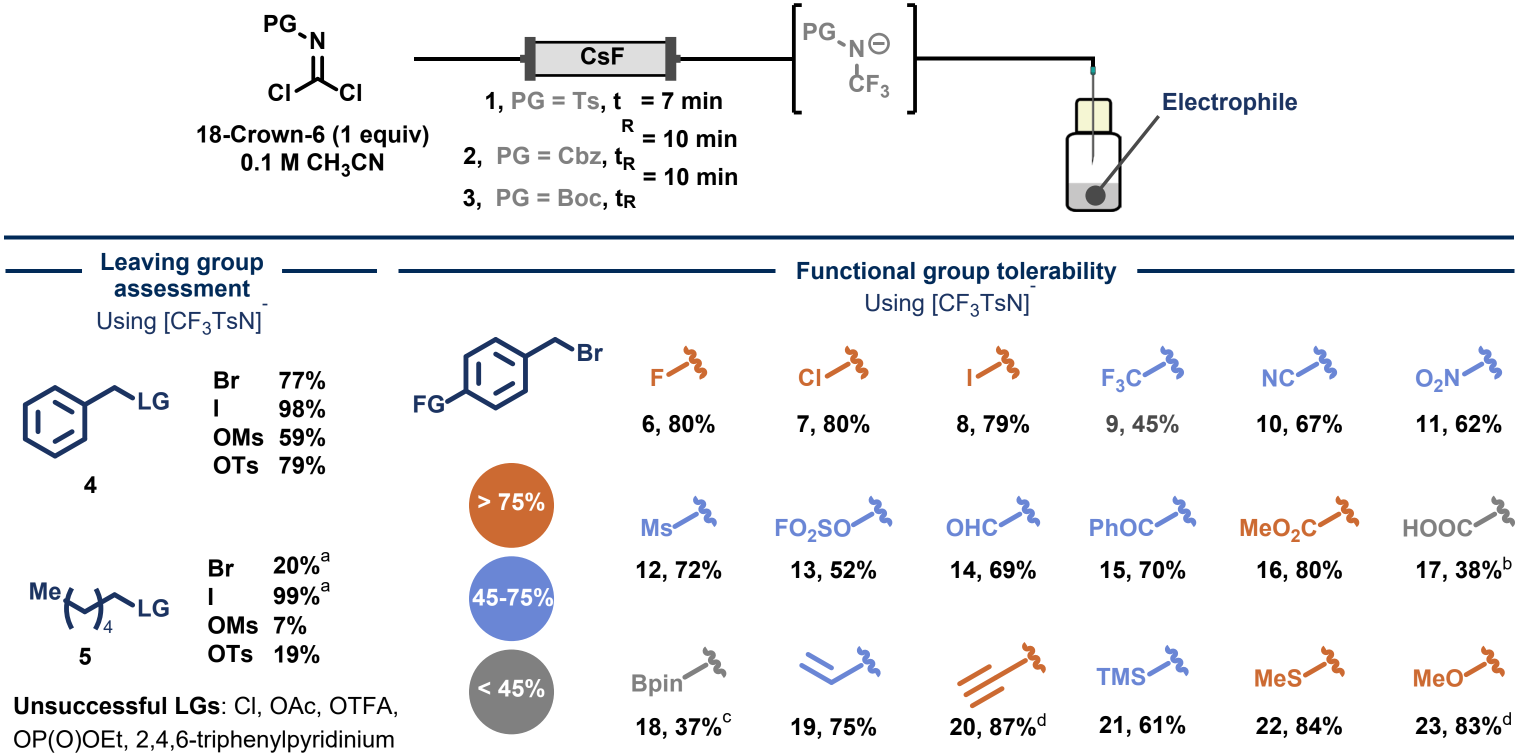

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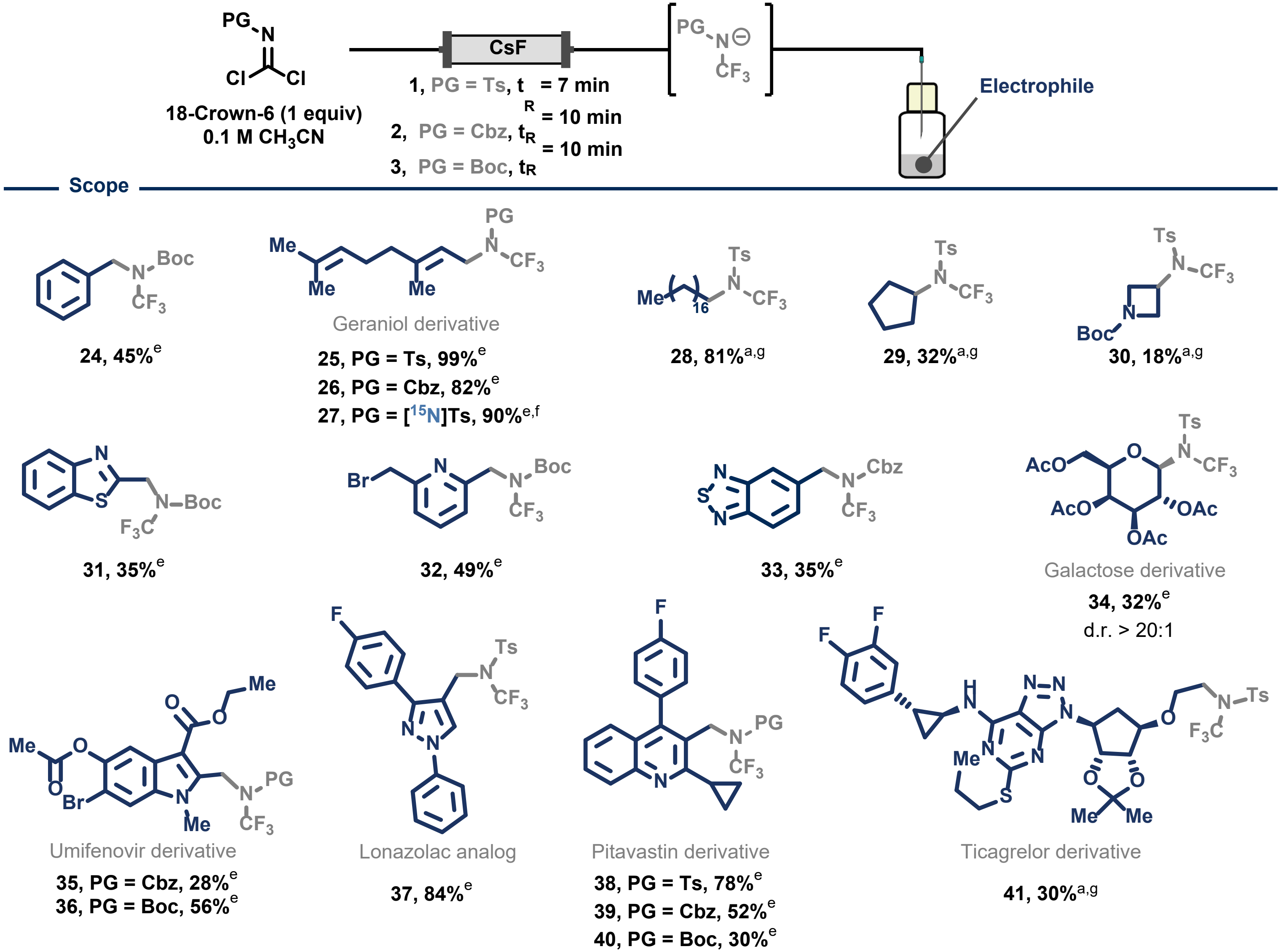
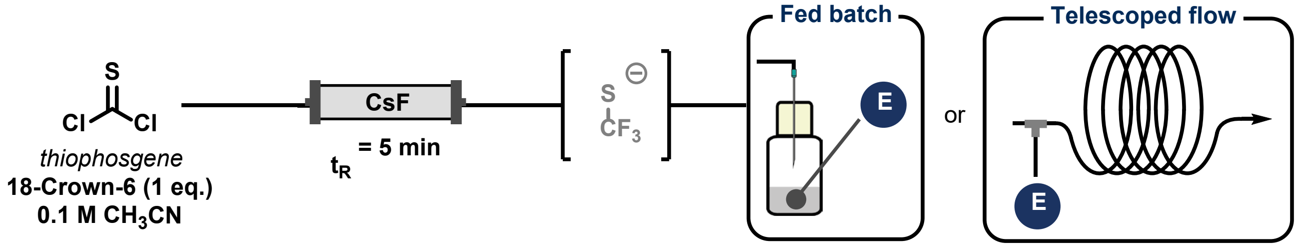


Spennacchio, Bernus, Stanic, Mazzarella, Colella, Douglas, Boutureira, Noel, *Science* **2024**, *385*, 991-996.

Synthesis of CF_3S anions on demand



Spennacchio, Bernus, Stanic, Mazzarella, Colella, Douglas, Boutureira, Noel, *Science* **2024**, *385*, 991-996.

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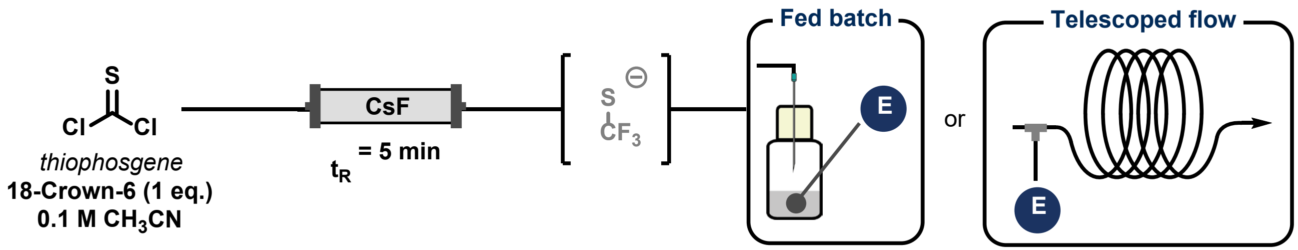
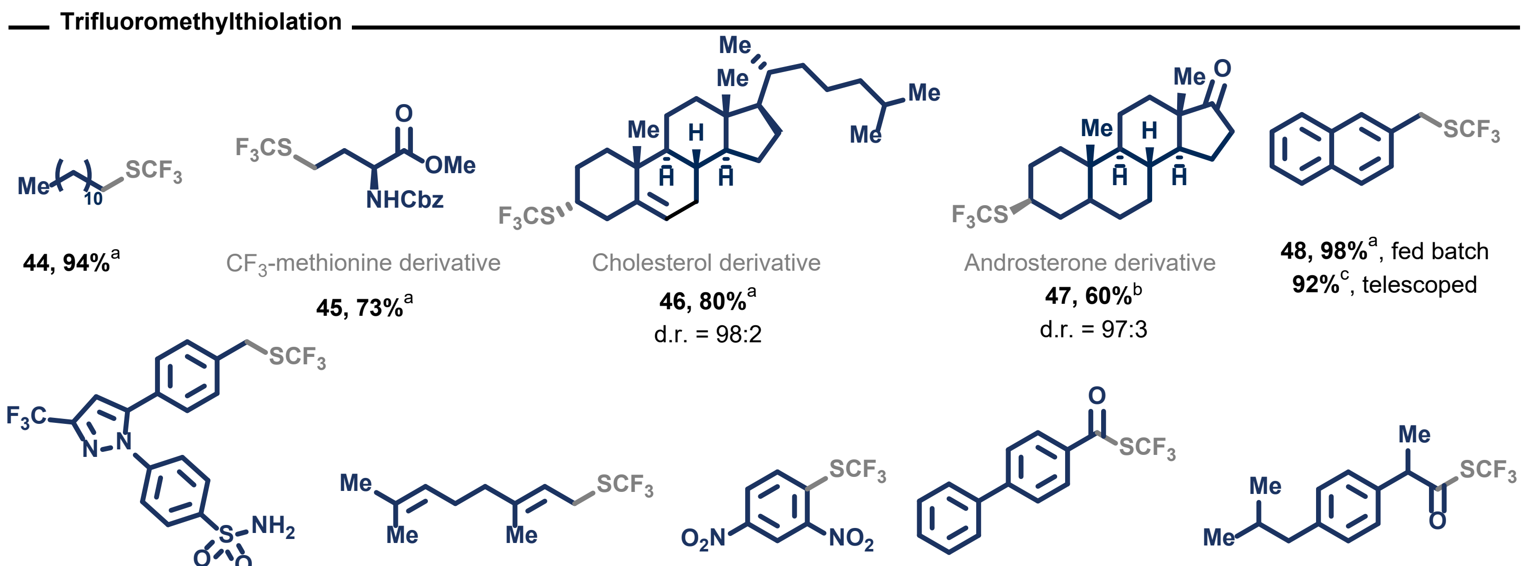




44, 94%[a]

CF3-methionine derivative
45, 73%[a]

Cholesterol derivative
46, 80%[a]
d.r. = 98:2

Androsterone derivative
47, 60%[b]
d.r. = 97:3

48, 98%[a], fed batch
92%[c], telescoped

Celecoxib derivative
49, 41%[a], fed batch
69%[c], telescoped

Geraniol derivative
50, 90%[a], fed batch
98%[c], telescoped

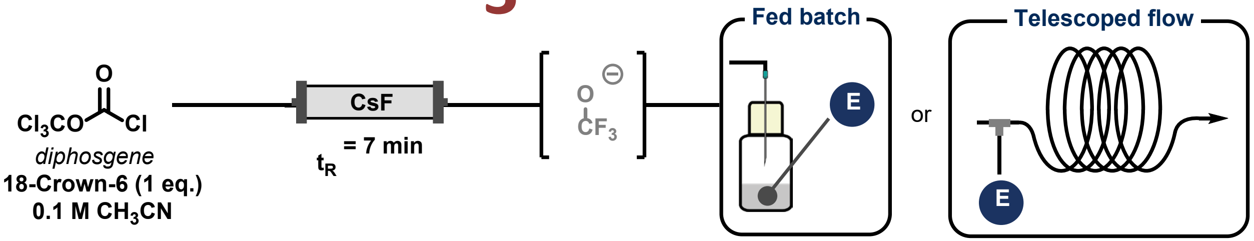
51, 61%[d]

52, 82%[e]

Ibuprofen derivative
53, 54%[e]

Spennacchio, Bernus, Stanic, Mazzarella, Colella, Douglas, Boutureira, Noel, *Science* **2024**, *385*, 991-996.

Synthesis of CF_3O anions on demand



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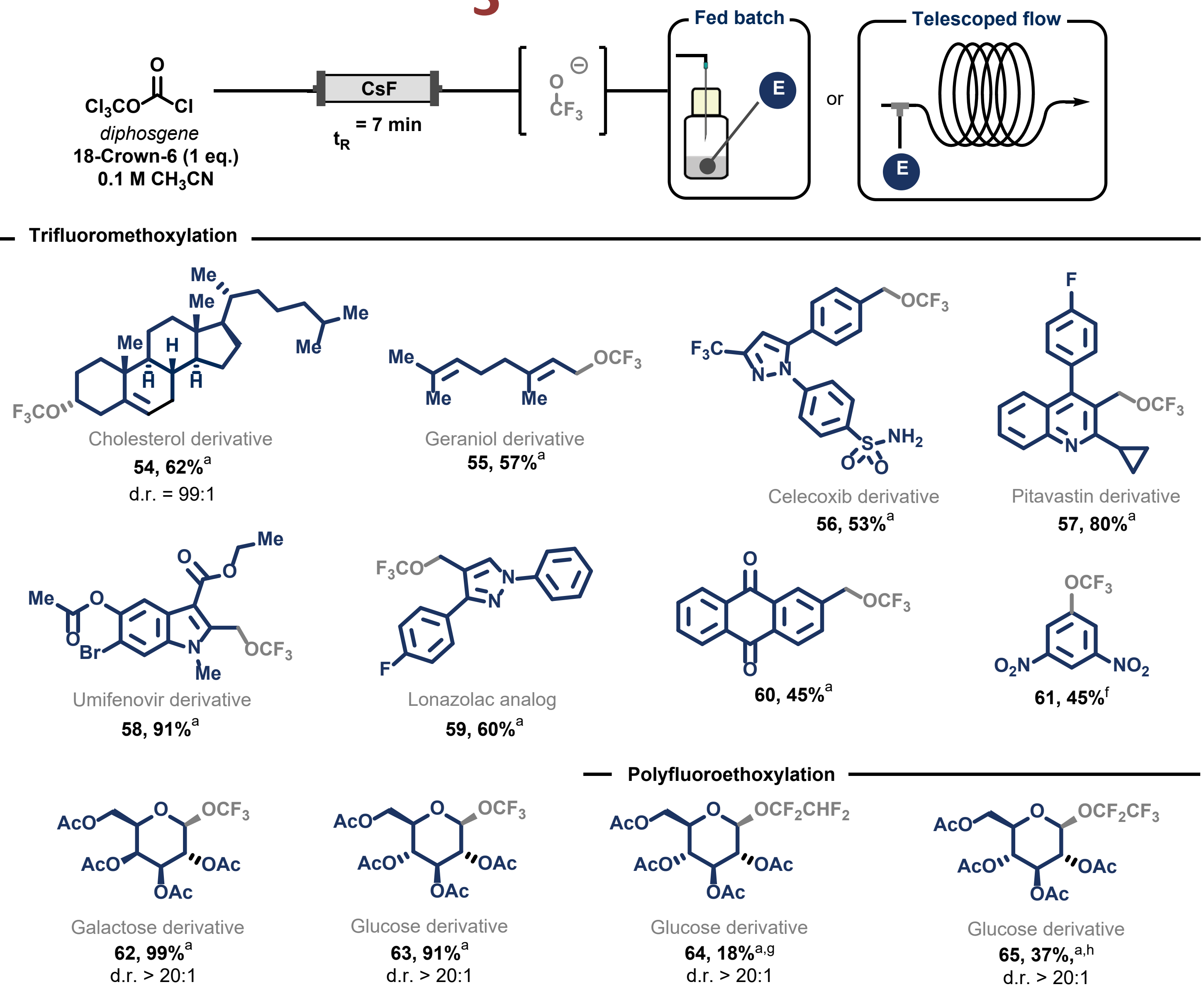

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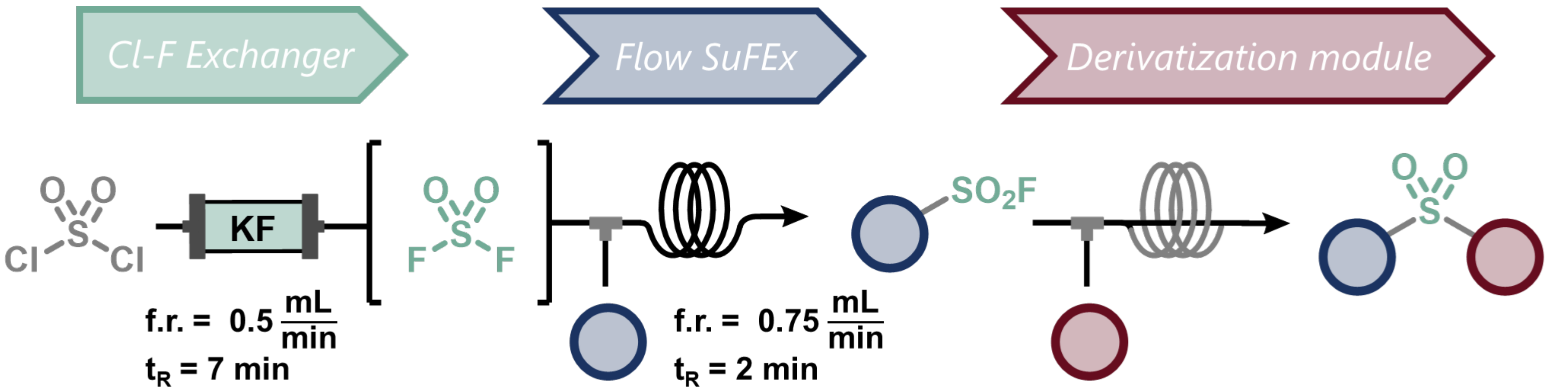
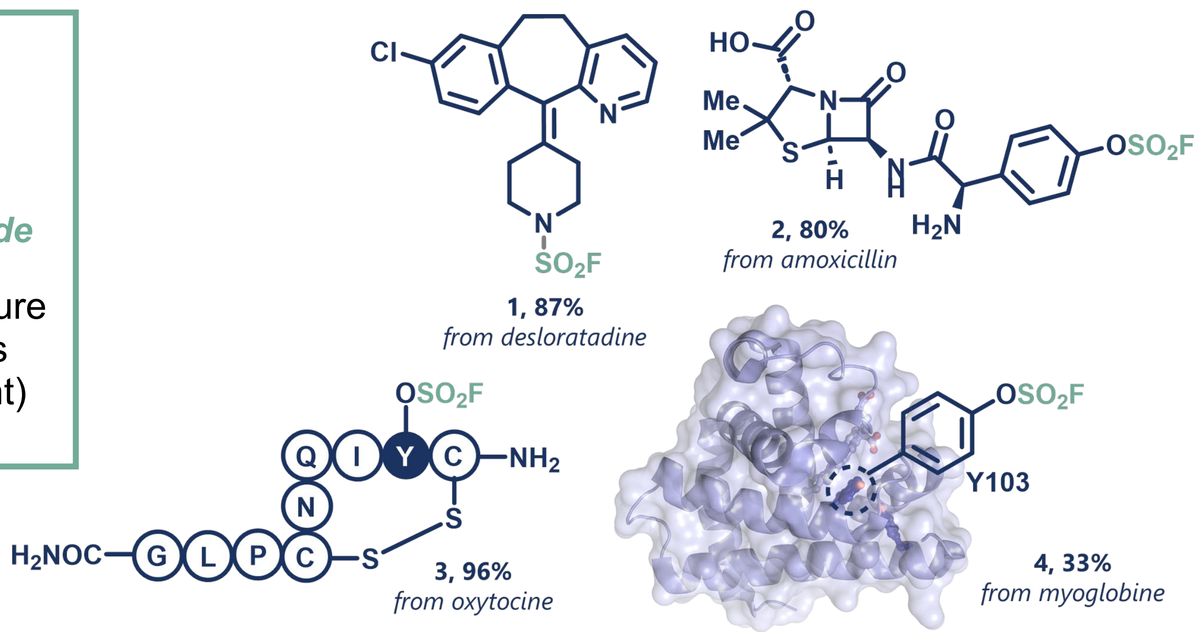
On-demand SO_2F_2 generation



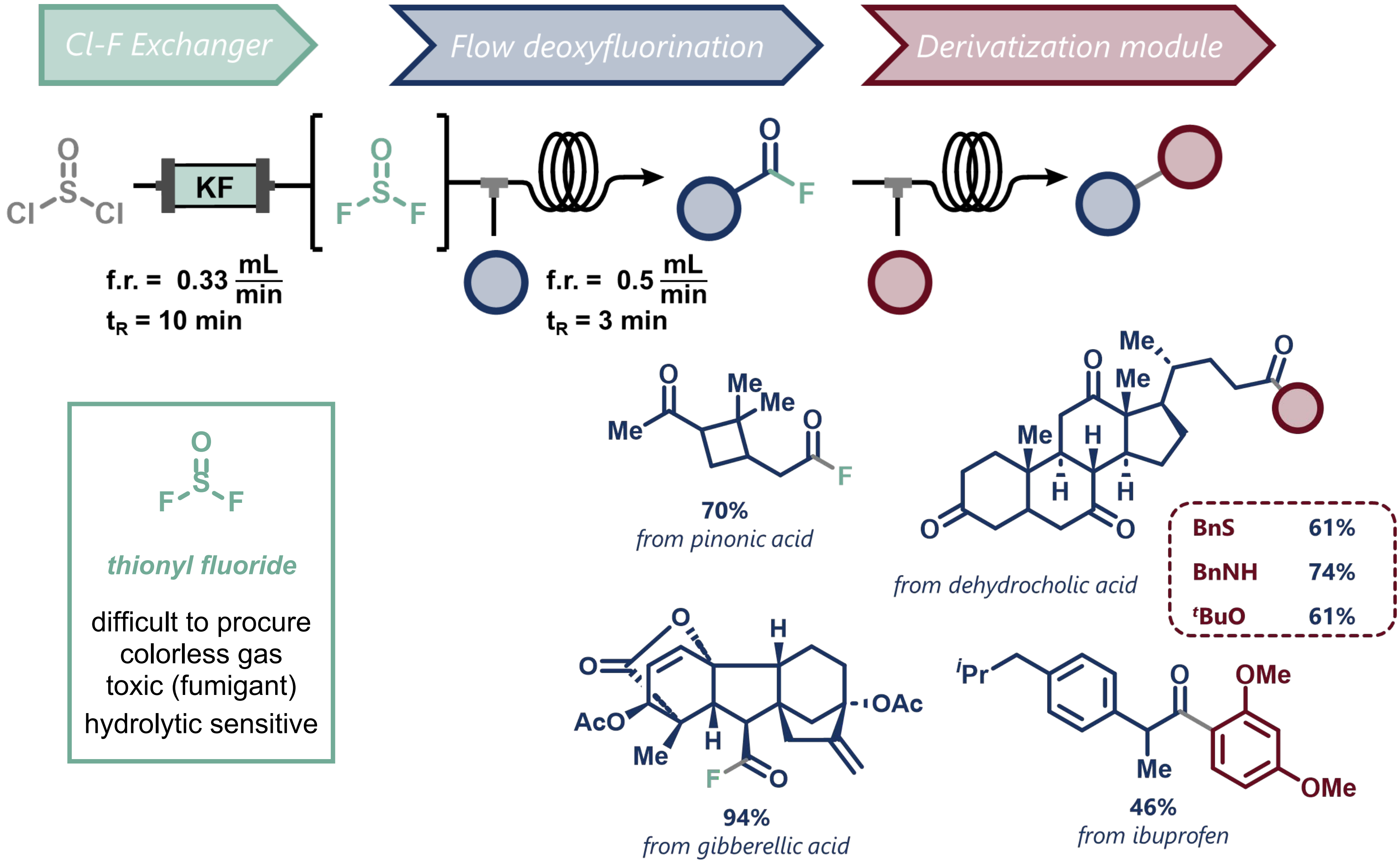
sulfuryl fluoride

difficult to procure
colorless gas
toxic (fumigant)



Bernus, Mazzarella, Stanic, Zhai, Vazquez, Boutureira, Gargano, Grossmann, Noel, *Nature Synth.* **2024**, *3,* 185-191.

On-demand SOF_2 generation



Mazzarella, Stanic, Bernus, Mehdi, Henderson, Boutureira, Noel, *JACS AU* **2024**, *4*, 2989–2994.

Conclusions

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- **Go with the Flow!**

Acknowledgements

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