Universiteit van Amsterdam

NRG Noël Research Group

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

Prof. Dr. ing. Timothy Noël

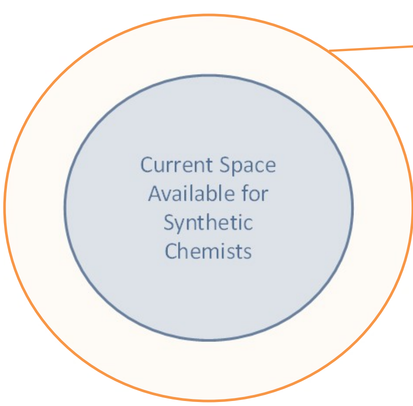
Van 't Hoff Institute for Molecular Sciences
University of Amsterdam
The Netherlands

t.noel@uva.nl
www.NoelResearchGroup.com

@NoelGroupUvA, @tnoel82

1

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

NRG Noël Research Group

2

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.

3

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

Problem: In general, people resist change.

4

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."

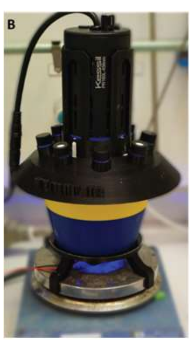
For an opinion article: Noël, *Chemistry World* **2019**, https://www.chemistryworld.com/opinion/flow-into-the-chemistry-curriculum/4010382.article .

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

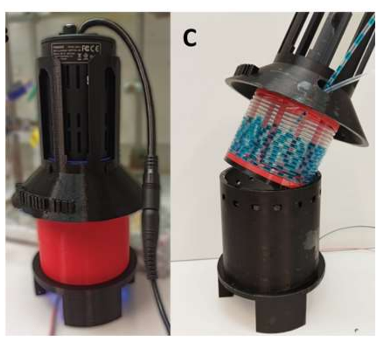
5

Democratization of Flow Chemistry

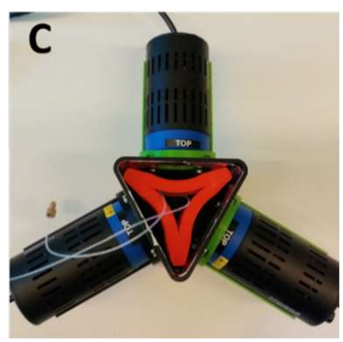
UFO – Batch



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.

6

Photocatalysis

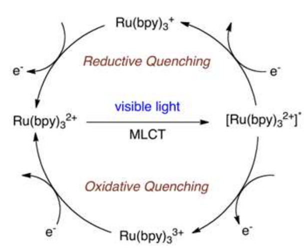
7

Photoredox Catalysis

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

Advantages:
- 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.



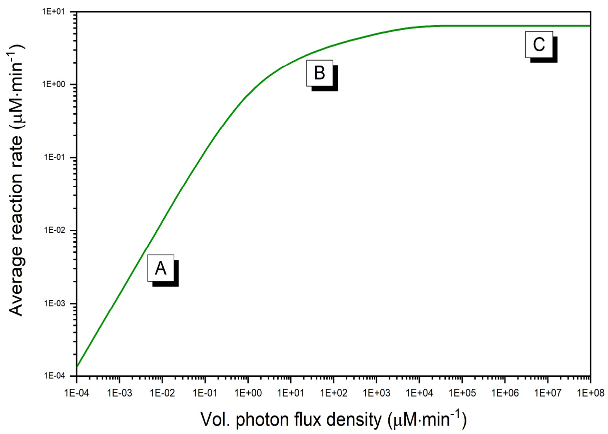
Special issue in *Chemical Reviews* on **Photochemical Catalytic Processes** (Paolo Melchiorre, Guest Editor), **2022**, *122*, 1483-2980.
For a perspective on PC: Noel, Zysman-Colman, *Chem Catalysis* **2022**, *2*, 468-476.

8

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.

9

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.

10

Industrial Importance of Photoredox Catalysis

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

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

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

11

Industrial Importance of Photoredox Catalysis

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

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

Process Chemistry:
- Goal: clean, cost-effective manufacturing process for new medicines
- Scalable process for clinical trials and commercialization
- Challenging!

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

12

Industrial Importance of Photoredox Catalysis

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

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

Process Chemistry:
- Goal: clean, cost-effective manufacturing process for new medicines
- Scalable process for clinical trials and commercialization
- Challenging!

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.

13

Industrial Importance of Photoredox Catalysis

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

To put it in perspective:

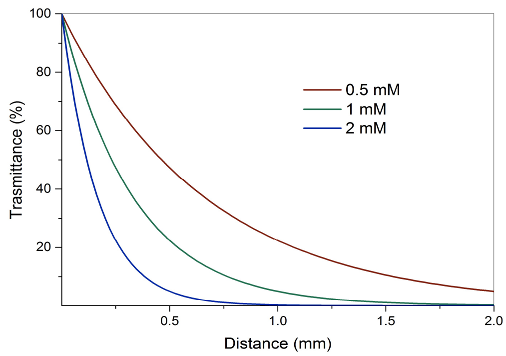
This amounts to the light delivered by 5000 CFL light bulbs !!!

14

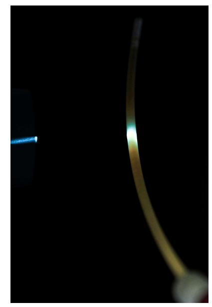
Photocatalysis
scale up problems

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

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




Batch

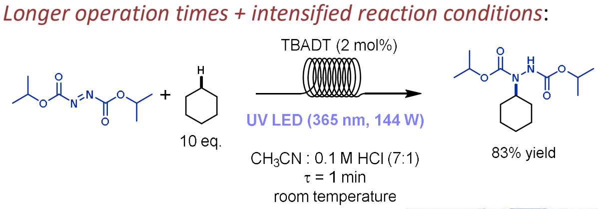

Flow

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.

15

Scaling Photochemistry

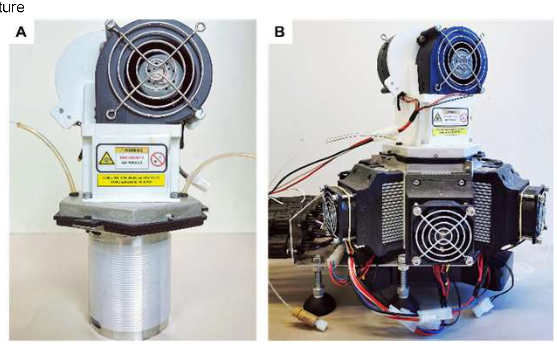
Longer operation times + intensified reaction conditions:



Reactor : 11 mL volume, ID 750 µm

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

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

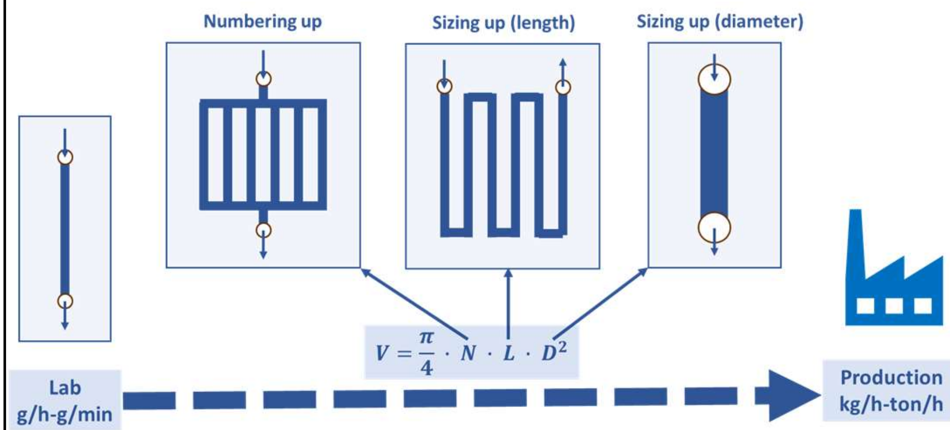


Wan, Wen, Laudadio, Capaldo, Lammers, Rincon, Garcia-Losada, Mateos, O'Frederick, Broersma, Noel, *ACS Central Sci.* **2022**, *8*, 51-56.

16

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.

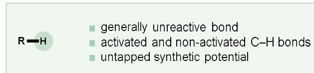
17

Synthetic methodology enabled by flow

Expanding Chemical Space

18

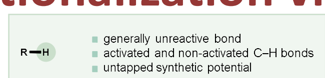
Photocatalytic sp^3 C–H functionalization via HAT

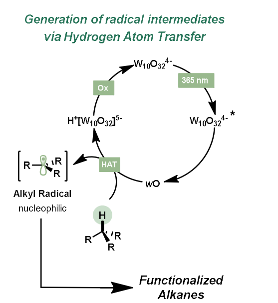


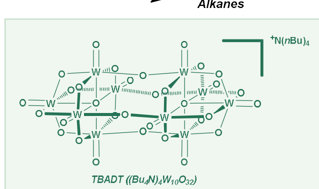
For a review: (a) Capaldo, Ravelli, Fagnoni, *Chem. Rev.* **2022**, *122*, 1875-1924. (b) Capaldo, Quadri, Ravelli, *Green Chem.* **2020**, *22*, 3376–3396.

19

Photocatalytic sp^3 C–H functionalization via HAT



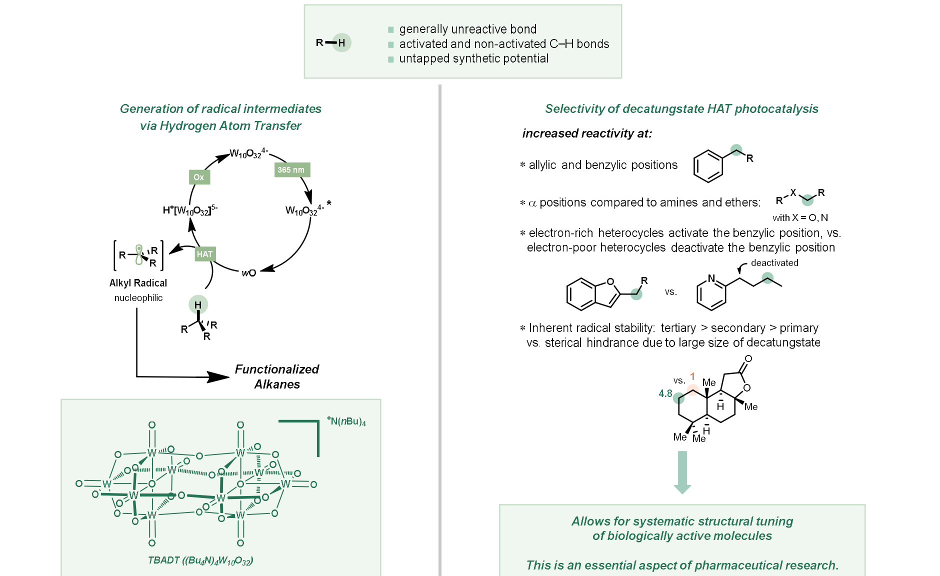




For a review: (a) Capaldo, Ravelli, Fagnoni, *Chem. Rev.* **2022**, *122*, 1875-1924. (b) Capaldo, Quadri, Ravelli, *Green Chem.* **2020**, *22*, 3376–3396.

20

Photocatalytic sp^3 C–H functionalization via HAT

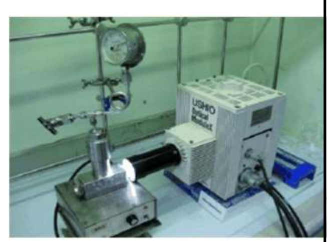


For a review: (a) Capaldo, Ravelli, Fagnoni, *Chem. Rev.* **2022**, *122*, 1875-1924. (b) Capaldo, Quadri, Ravelli, *Green Chem.* **2020**, *22*, 3376–3396.

21

Photocatalytic HAT using gasses in flow





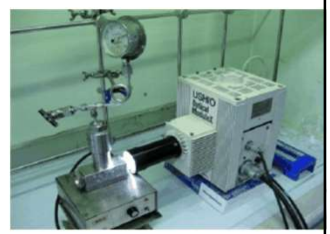
For a review: (i) Laporte, Masson, Zondag, Noël, *Angew. Chem. Int. Ed.* **2024**, *63*, e20231610.

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

22

Photocatalytic HAT using gasses in flow



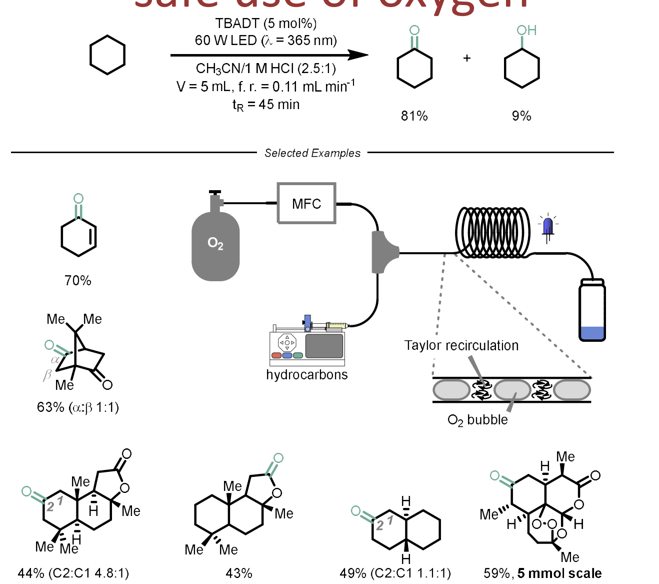



For a review: (i) Laporte, Masson, Zondag, Noël, *Angew. Chem. Int. Ed.* **2024**, *63*, e20231610.
(ii) Mallia, Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327–360.

23

Photocatalytic sp^3 C–H oxidation

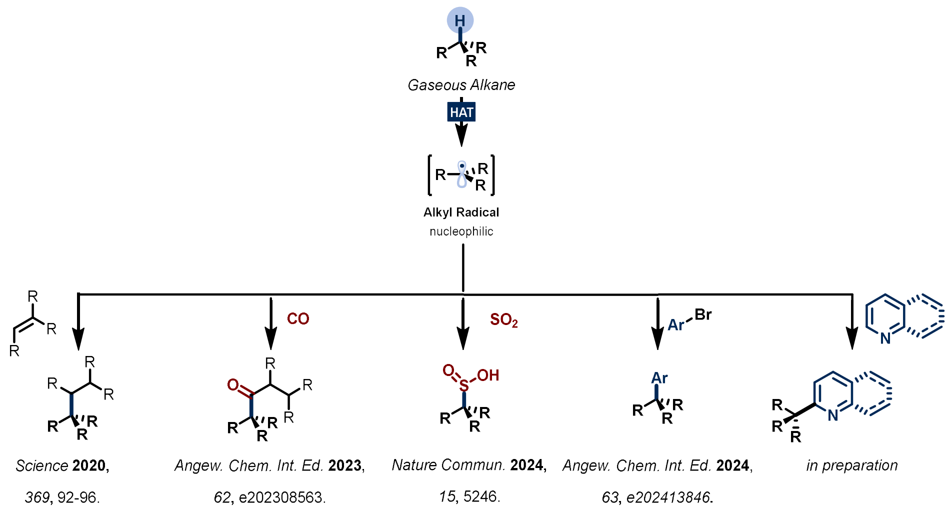
safe use of oxygen



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

24

Photocatalytic sp³ C–H functionalization of light alkanes



25

Reaction Optimization

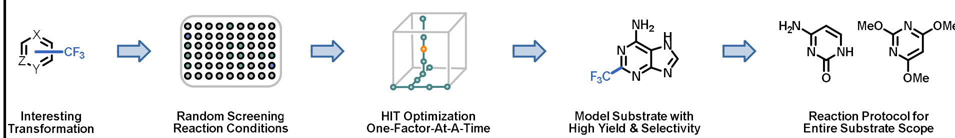
Streamlining and optimizing a compound trace into a widely applicable synthetic method is both demanding and time-intensive.

26

Reaction Optimization

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

Typical strategy for synthetic methodology development:

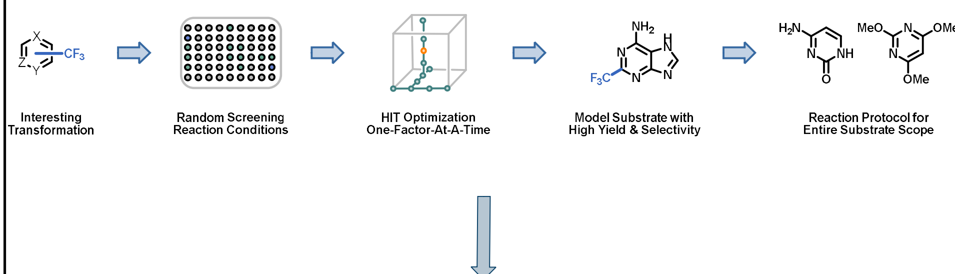


27

Reaction Optimization

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

Typical strategy for synthetic methodology development:



Most substrates have suboptimal yields.

28

Reaction Optimization

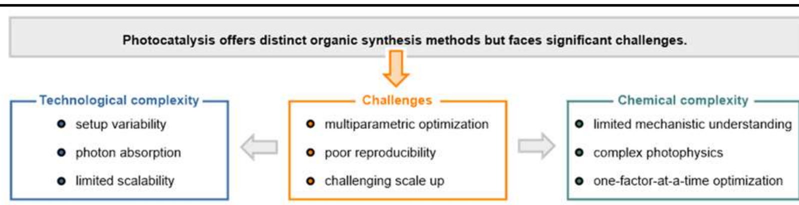
If most substrates in a scope have suboptimal yields.

↓

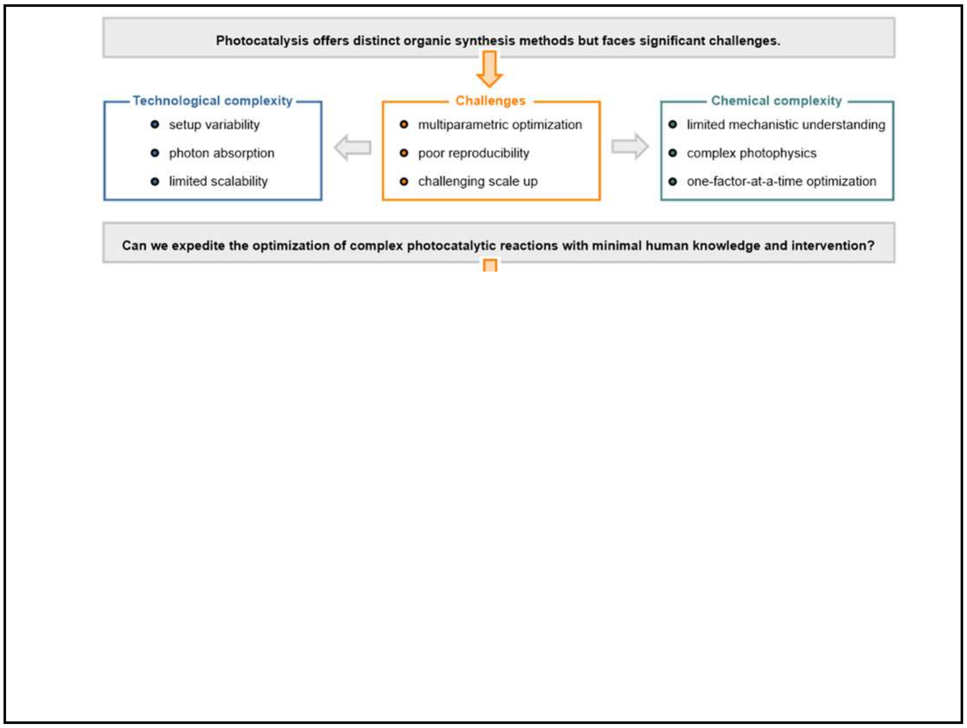
Why not let a machine do the work?

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

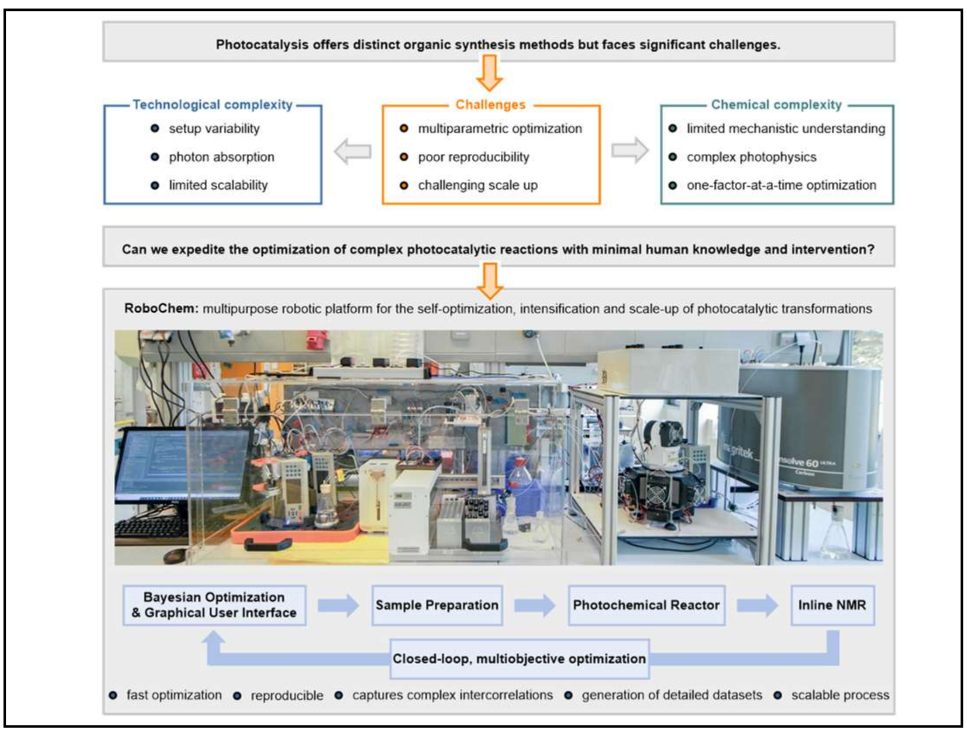
29



30

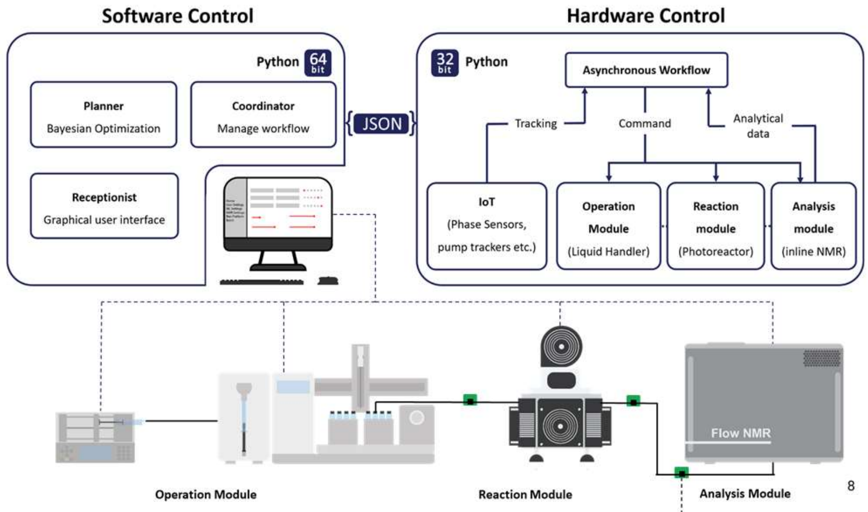

Photocatalysis offers distinct organic synthesis methods but faces significant challenges.
Technological complexity
setup variability
photon absorption
limited scalability
Challenges
multiparametric optimization
poor reproducibility
challenging scale up
Chemical complexity
limited mechanistic understanding
complex photophysics
one-factor-at-a-time optimization
Can we expedite the optimization of complex photocatalytic reactions with minimal human knowledge and intervention?

31


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
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

32

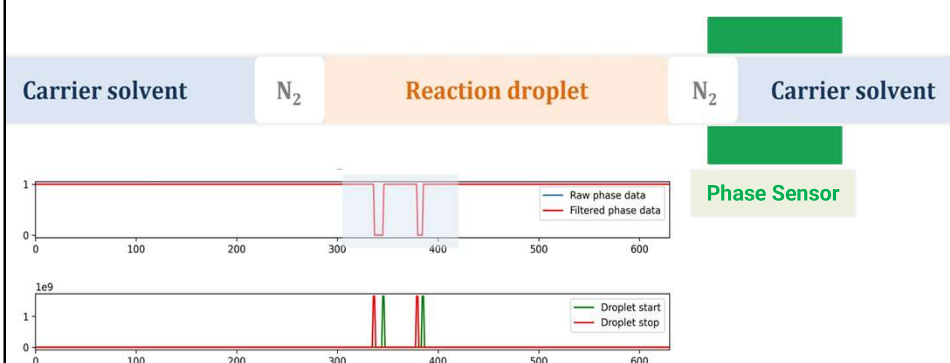
RoboChem
An all-in-one robotic platform



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

33

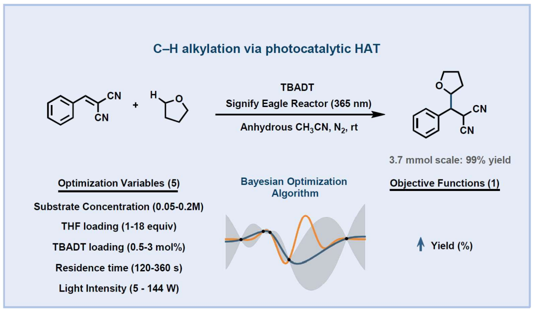
RoboChem
An all-in-one robotic platform

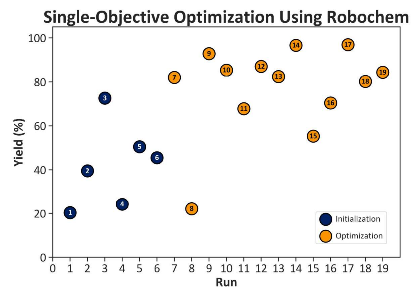


Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

34

RoboChem
An all-in-one robotic platform

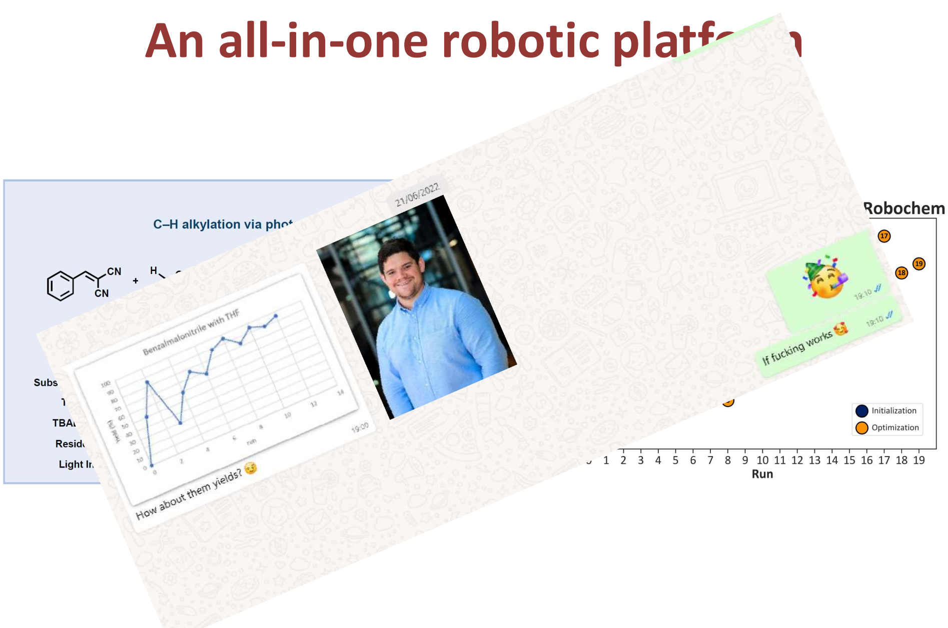




Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

35

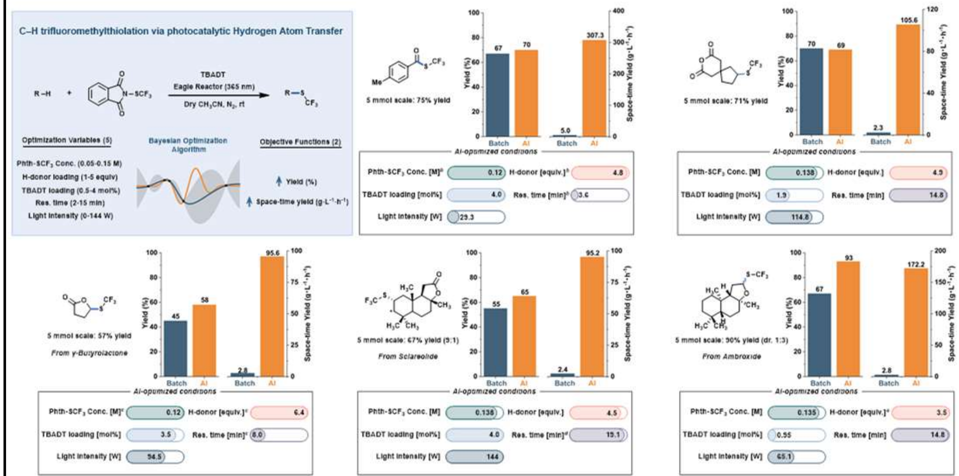
RoboChem
An all-in-one robotic platf



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

36

Trifluoromethylthiolation via HAT

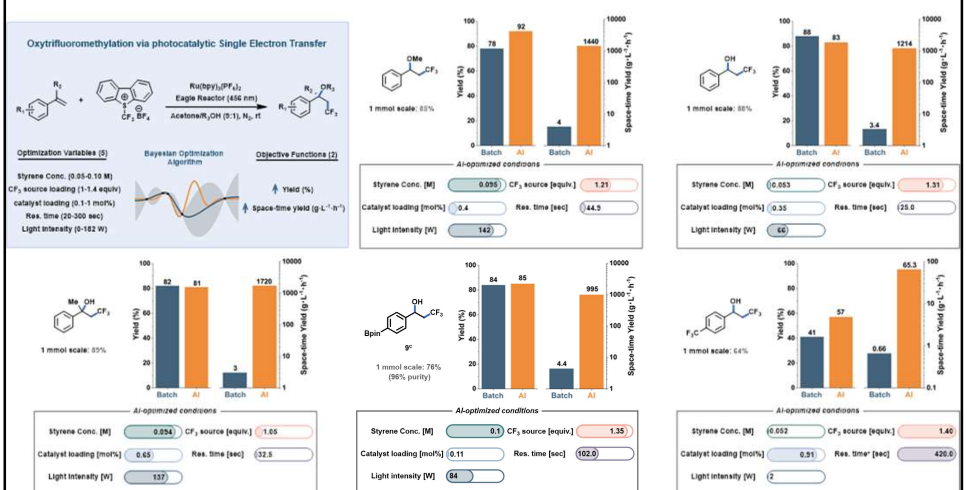


Original work: Schirmer, Rolka, Karl, Holzhausen, König, *Org. Lett.* **2021**, *23*, 5729–5733.

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

37

Oxytrifluoromethylation via SET

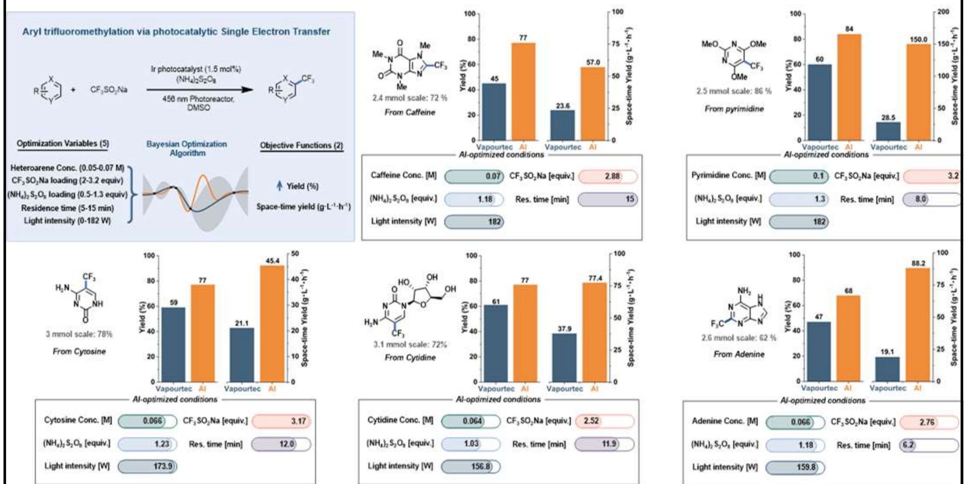


Original work: Yasu, Koike, Akita, *Angew. Chem. Int. Ed.* **2012**, *51*, 9567-9571.

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

38

Trifluoromethylation via SET



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

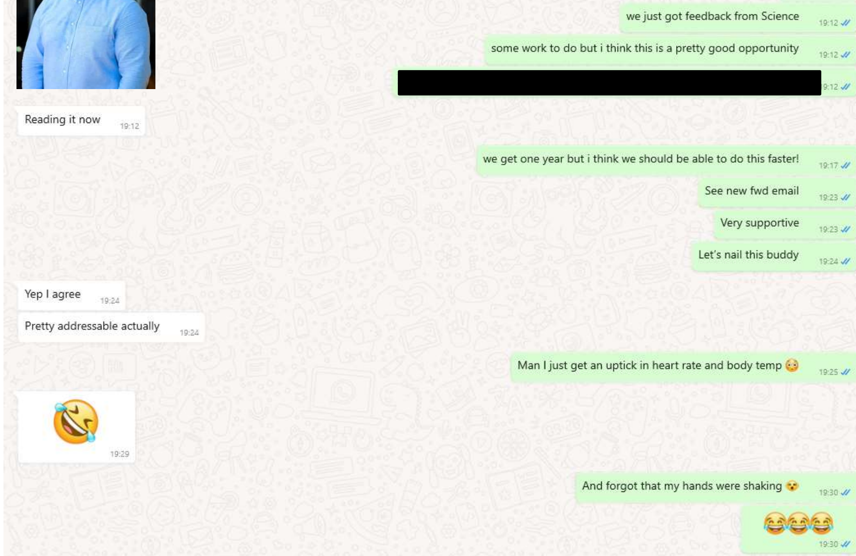
Slattery, Wen, Tenblad, Pintossi, Orduna, den Hartog, Noel, *Science* **2024**, *383*, eadj1817.

39

Submitted, then wait…

40

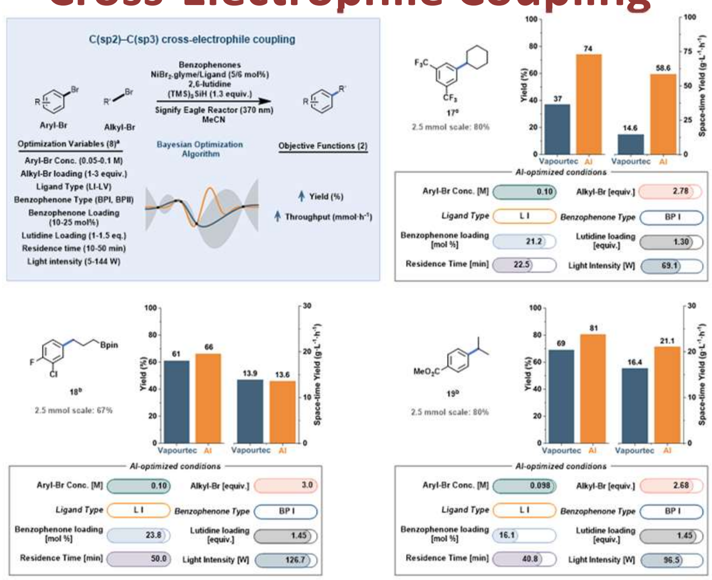
News from referees…



Read full account via: https://www.noelresearchgroup.com/category/blog/

41

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.

42

Is chemistry ready for an AI revolution?

43

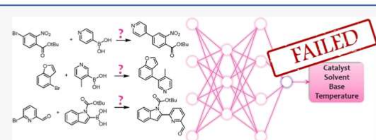
Is chemistry ready for an AI revolution?

Machine Learning May Sometimes Simply Capture Literature Popularity Trends: A Case Study of Heterocyclic Suzuki–Miyaura Coupling

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

Cite This: *J. Am. Chem. Soc.* 2022, 144, 4819–4827
Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



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

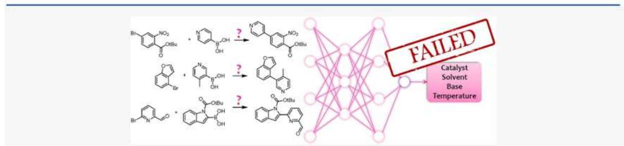
44

Is chemistry ready for an AI revolution?

Machine Learning May Sometimes Simply Capture Literature Popularity Trends: A Case Study of Heterocyclic Suzuki–Miyaura Coupling

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

Cite This: J. Am. Chem. Soc. 2022, 144, 4819–4827 Read Online



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.

45

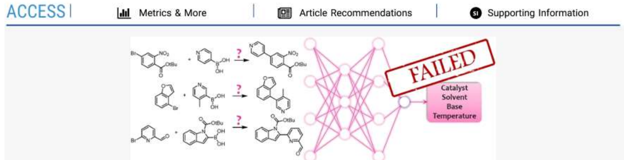
Is chemistry ready for an AI revolution?

Machine Learning May Sometimes Simply Capture Literature Popularity Trends: A Case Study of Heterocyclic Suzuki–Miyaura Coupling

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

Cite This: J. Am. Chem. Soc. 2022, 144, 4819–4827 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



Caused by

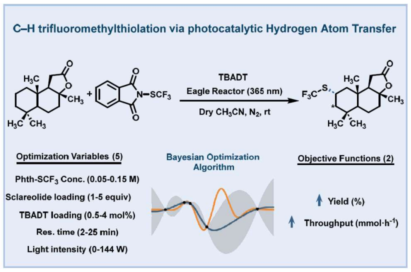
- *Subjective preferences in selecting reaction conditions by chemists*
- *Lack of reliable and standardized data, including lack of negative data.*

Fundamental flaw in the current synthetic literature (!)

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

46

Digitization of Chemistry



Clean, detailed and reproducible datasets

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

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

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.

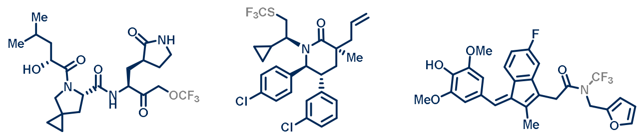
47

On-demand Generation Fluorinated Reagents

48

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

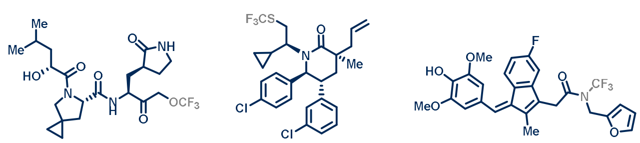
- *New chemical space by the XCF_3 motifs*
- *Fine tuning of the molecular properties*
- *XCF_3 are gaining momentum as an alternative to C-CF_3 fragments*

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

49

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-CF_3 fragments*

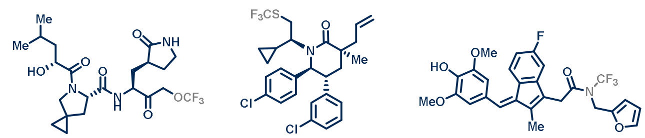
But how to make them?

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

50

Emerging fluorinated moieties

Growing interest into trifluoromethyl groups attached to heteroatoms

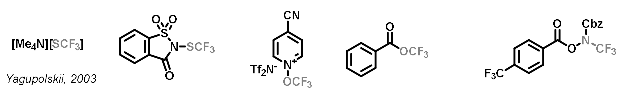


CMX990 SARS-CoV-2 protease inhibitor | WO2011153509 MDM2 inhibitor intermediate | WO2016100542 RAS Gtpase inhibitor

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

But how to make them?

Trifluoromethylthiolation — Trifluoromethoxylation — Trifluoromethylamination



Yagupolskii, 2003 | *Shen, 2014* | *Togni, 2018* | *Hu, 2018* | *Huang & Xu, 2022*

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

51

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.

52

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)

Exceptions are anticipated for pharmaceuticals and agrochemicals

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

53

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)

Exceptions are anticipated for pharmaceuticals and agrochemicals

BUT

The ban could still involve reagents or even API intermediates…

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

54

Synthesis of CF_3X moieties

We need new synthetic methods that are:

- *Environmentally-friendly*
- *Starting from non-banned chemicals, e.g. alkali fluorides*
- *Enable Late-stage Functionalization*

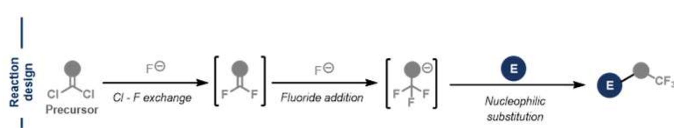
55

Synthesis of CF_3X moieties

We need new synthetic methods that are:

- *Environmentally-friendly*
- *Starting from non-banned chemicals, e.g. alkali fluorides*
- *Enable Late-stage Functionalization*

Our approach:



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

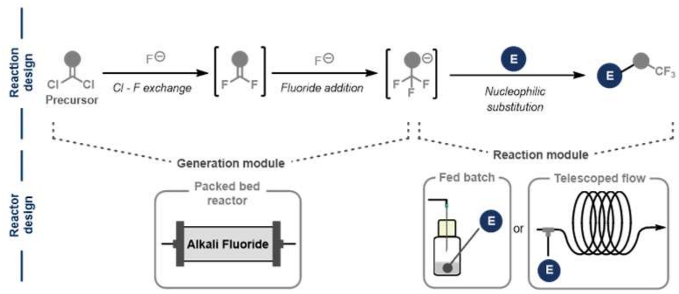
56

Synthesis of CF_3X moieties

We need new synthetic methods that are:

- *Environmentally-friendly*
- *Starting from non-banned chemicals, e.g. alkali fluorides*
- *Enable Late-stage Functionalization*

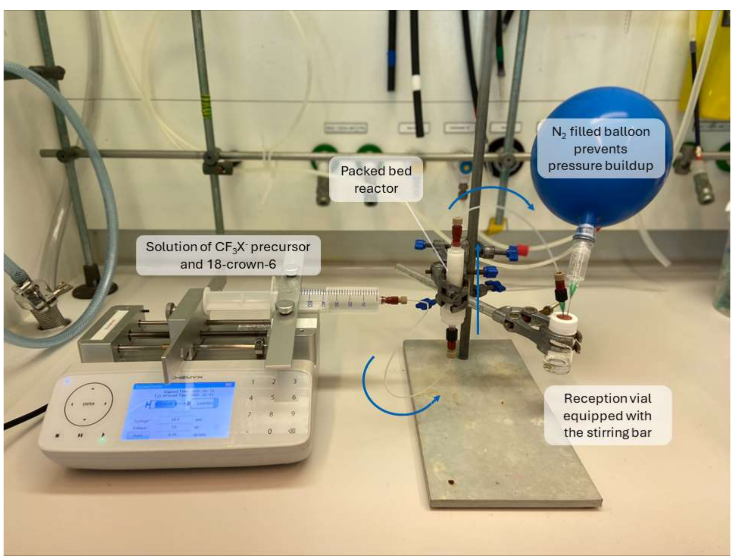
Our approach:



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

57

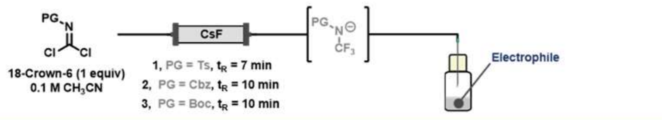
Synthesis of CF_3X moieties



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

58

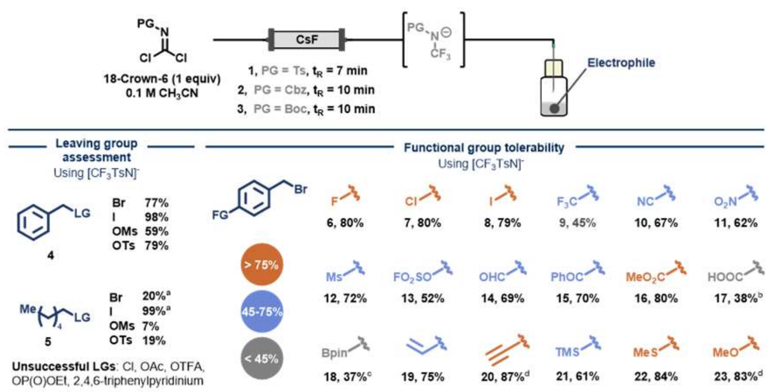
Synthesis of CF_3N anions on demand



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

59

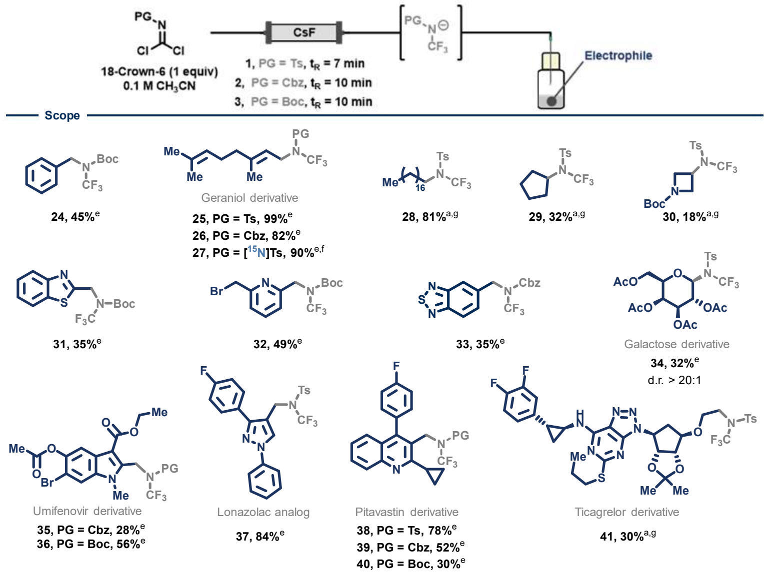
Synthesis of CF_3N anions on demand



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

60

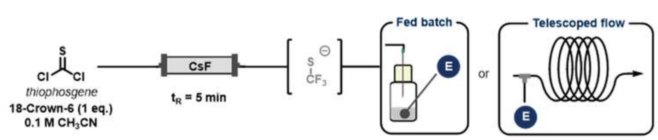
Synthesis of CF_3N anions on demand



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

61

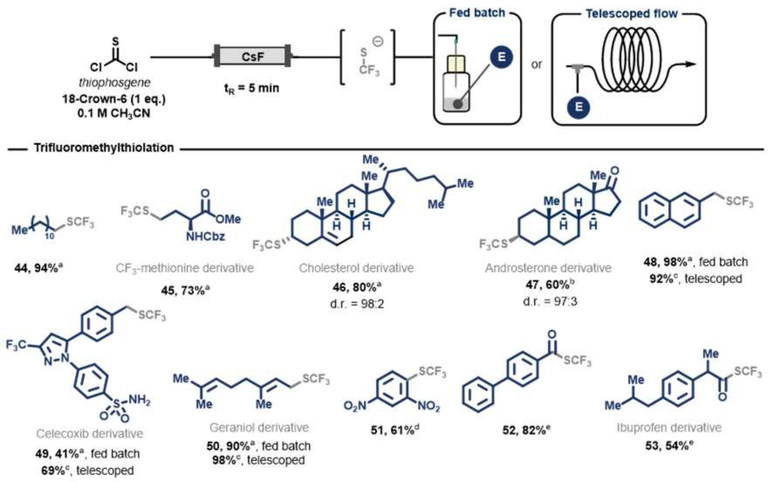
Synthesis of CF_3S anions on demand



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

62

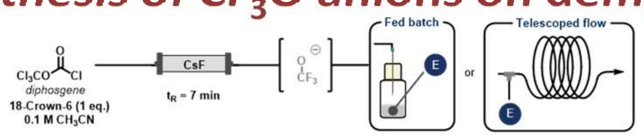
Synthesis of CF_3S anions on demand



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

63

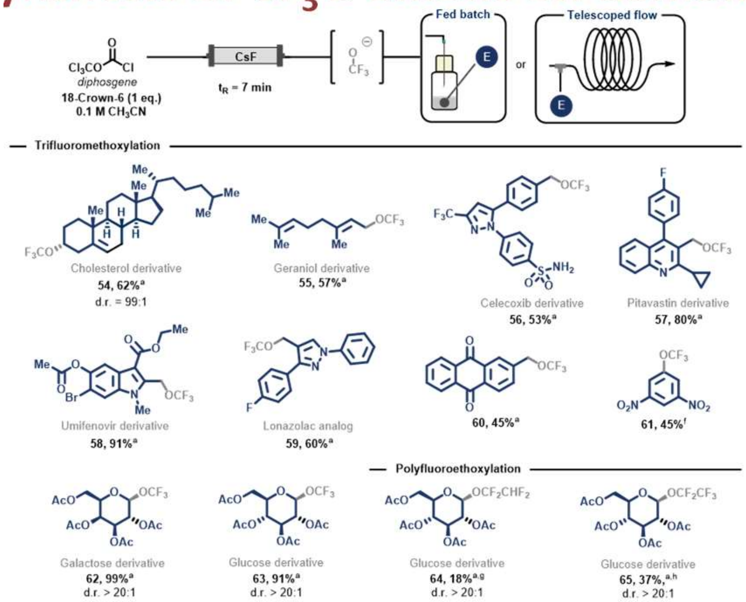
Synthesis of CF_3O anions on demand



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

64

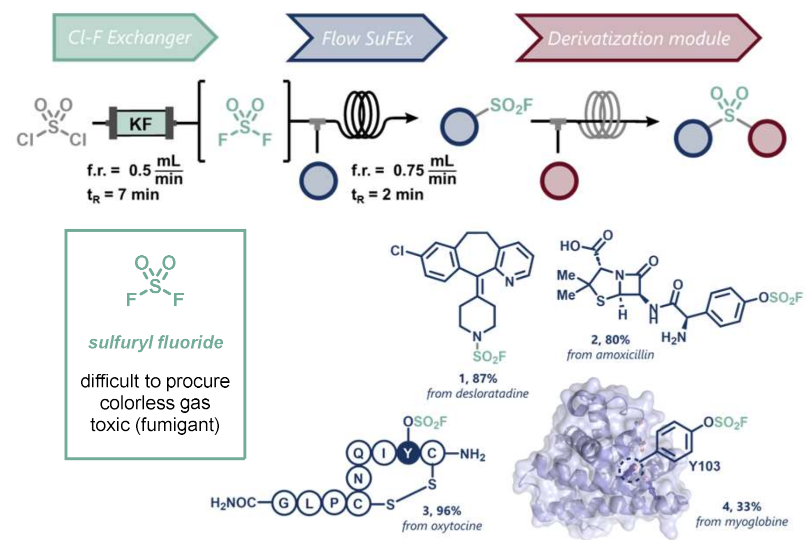
Synthesis of CF_3O anions on demand



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

65

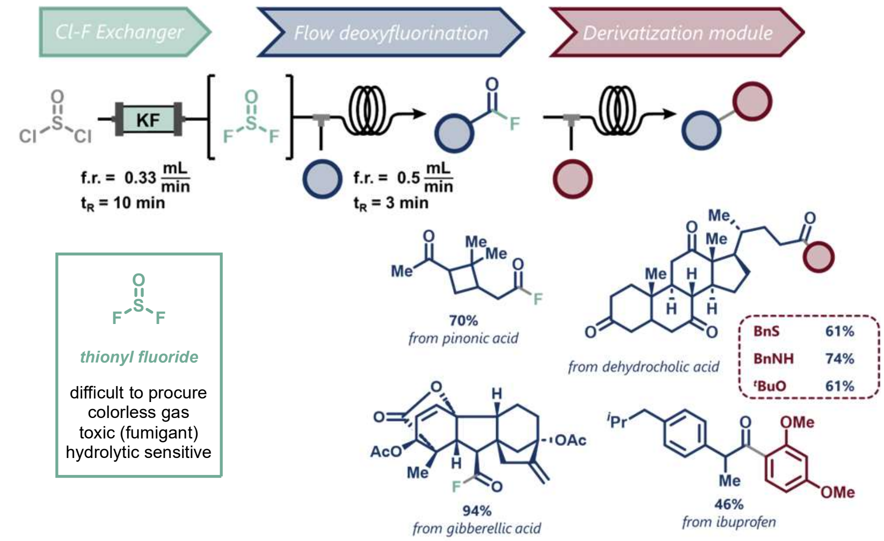
On-demand SO_2F_2 generation



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

66

On-demand SOF_2 generation



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

67

Conclusions

- **Use of microreactors for organic chemistry**:
  - Many advantages: intensified reaction conditions, scalability, safety, reduced reaction times, etc.

68

Conclusions

- **Use of microreactors for organic chemistry**:
  - Many advantages: intensified reaction conditions, scalability, safety, reduced reaction times, etc.
- **So what are you waiting for?**
  - But be careful, look for advantages of flow!
  - … and carry out only those reactions in flow which are worth pursuing.

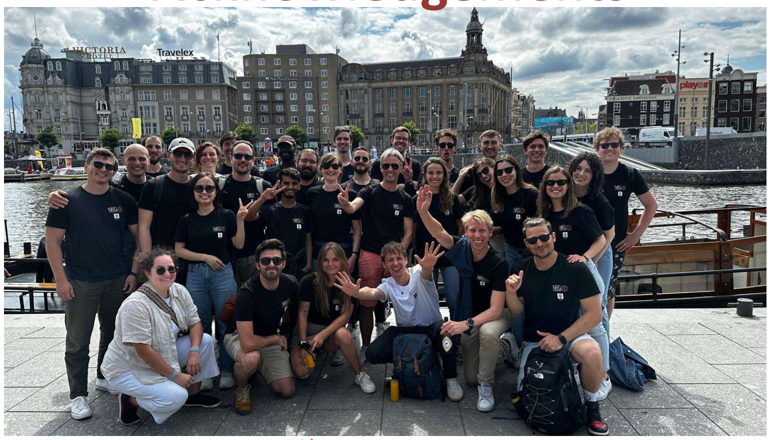
69

Conclusions

- **Use of microreactors for organic chemistry**:
  - Many advantages: intensified reaction conditions, scalability, safety, reduced reaction times, etc.
- **So what are you waiting for?**
  - But be careful, look for advantages of flow!
  - … and carry out only those reactions in flow which are worth pursuing.
- **Go with the Flow!**

70

Acknowledgements



71