A Unified Flow Strategy for the Preparation and Use of Trifluoromethyl-heteroatom Anions

Mauro Spennacchio,+[1,2] Miguel Bernús,+[1,3] Jelena Stanić,+[1] Daniele Mazzarella,[1,4] Marco Colella,[1,2] James J. Douglas,[5] Omar Boutureira,[3] Timothy Noël* [1]

[1] Flow Chemistry Group, Van 't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, Amsterdam, The Netherlands.

[2] FLAME-Lab, Flow Chemistry and Microreactor Technology Laboratory, Department of Pharmacy-Drug Sciences, University of Bari "A. Moro", Via E. Orabona 4, 70125, Bari, Italy.

[3] Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/ Marcel·lí Domingo 1, 43007 Tarragona, Spain.

[4] Department of Chemical Sciences, University of Padova, Via Francesco Marzolo 1, 35131, Padova, Italy.

[5] Early Chemical Development, Pharmaceutical Sciences R&D, AstraZeneca, Macclesfield U.K.

+ These authors contributed equally.

*Correspondence to: t.noel@uva.nl.

Abstract

The trifluoromethyl group (CF_3) is a key functionality in pharmaceutical and agrochemical development, greatly enhancing the efficacy and properties of resulting compounds. However, attaching the CF_3 group to heteroatoms such as sulfur, oxygen, and nitrogen poses challenges due to the lack of general synthetic methods and reliance on bespoke reagents. Here, we present a modular flow platform that streamlines the synthesis of heteroatom-CF_3 motifs. Our method uses readily available organic precursors in combination with cesium fluoride as the primary fluorine source, facilitating the rapid generation of $NCF_3(R)$, SCF_3, and OCF_3 anions on demand without reliance on perfluoroalkyl precursor reagents. This strategy offers a more environmentally friendly synthesis of trifluoromethyl(heteroatom)-containing molecules, with the potential for scalability in manufacturing processes facilitated by flow technology.

The trifluoromethyl group plays a fundamental role in medicinal chemistry and crop-protection science due to its remarkable impact on molecular properties. (*1,2*) The electron-withdrawing nature of the fluorine atoms induces a strong polarization of neighboring groups while increasing local hydrophobicity. (*3*) Furthermore, fluorinated functional groups increase the metabolic stability of the compounds, thus enhancing their efficacy. (*4*) These unique properties have prompted the chemical community to develop numerous methodologies for forging C–CF_3 bonds. (*5,6*) Consequently, the CF_3 group has become a well-established moiety in the toolbox of medicinal chemists for designing finely tuned APIs, and as such appears in approximately 5% of all FDA-approved drugs. (*1*)

Recently, there has been a growing interest in incorporating trifluoromethyl groups connected to heteroatoms, such as OCF_3, SCF_3, and NCF_3 moieties (Figure 1A). (*7*) These emerging fluorinated motifs further tune lipophilicity, oxidation resistance, and acid-base properties. (*8*) Despite their appeal, these moieties are greatly underrepresented in active pharmaceutical ingredients (APIs), comprising less than 10% of the total CF_3-containing drugs. (***Error! No s'ha definit el marcador.**,9*) The main hurdle lies in their integration into molecular scaffolds, as there is a notable scarcity of synthetic methods available. Typically, their introduction requires the use of expensive, moisture-sensitive, and atom-inefficient reagents (Figure 1B). (*10-14*) Furthermore, the preparation of these bespoke reagents often involves laborious processes spanning multiple steps, resulting in the generation of substantial amounts of fluorinated waste.

Notably, the persistent pollution from the synthesis and use of polyfluorinated alkyl substances (PFAS) has prompted a new restriction proposal in EU legislation. This proposal aims to tackle uncontrollable emissions at their source by banning a wide range of PFAS, including many CF_3-containing molecules and reagents. (*15*) While exceptions are expected for final pharmaceutical and agrochemical active ingredients, their synthesis often still depends on undesirable synthetic intermediates, reagents, or other CF_3-containing sources. (*16,17*) Therefore, it is crucial to develop methods for synthesizing these moieties at the late stage of synthesis from simple, non-fluorinated organic molecules. Ideally, this would involve using inexpensive and widely available alkali fluoride sources to avoid further pollution. Such an approach would reduce or eliminate the need for PFAS in synthesizing most current fluoroalkylating reagents, thereby minimizing waste generation and complying with proposed EU regulations.

To tackle these synthetic, legislative and environmental challenges, our strategy centered around the development of a versatile protocol capable of generating N–, S– and O–CF_3 anions on demand, and facilitating their immediate use as nucleophiles (Figure 1C, reaction design). This strategy entails the preparation of trifluoromethyl-heteroatom anions using alkali fluoride salts, as a fluorine source, in conjunction with appropriate precursors for each motif. In devising this reaction blueprint, certain criteria must be met: the precursors should be (i) bench-stable, (ii) commercially available or easily prepared, and (iii) operating with high atom economy. Conceptually, our envisioned mechanism involves the sequential preparation of the trifluoromethyl group from these precursors through two successive chlorine-fluorine exchange reactions, culminating in a final fluoride addition to yield the desired nucleophiles. These reactive species would then be primed for immediate reaction with suitable electrophiles to form new C–N, C–S or C–O bonds.

Based upon our previous research into chlorine-fluorine exchange in sulfur chlorides, (*18,19*) we decided to leverage flow technology for these transformations. We anticipated that a packed bed reactor filled with an alkali fluoride salt would be well-suited for generating the targeted trifluoromethyl-heteroatom anions (Figure 1C, reactor design). This design increases the efficiency of the multiple fluoride additions due to the increased surface area and improved mixing between the organic intermediates and the insoluble fluoride salt. (*20*) Importantly, this approach offers enhanced safety as all formed intermediates are contained within the microfluidic system. (*21,22*) Additionally, by integrating a reaction module downstream of the CF_3X anion generator, (*23*) we enable seamless reaction of the anion with electrophiles, thereby providing a divergent and streamlined platform for the derivatization of molecules bearing heteroatom–CF_3 motifs.

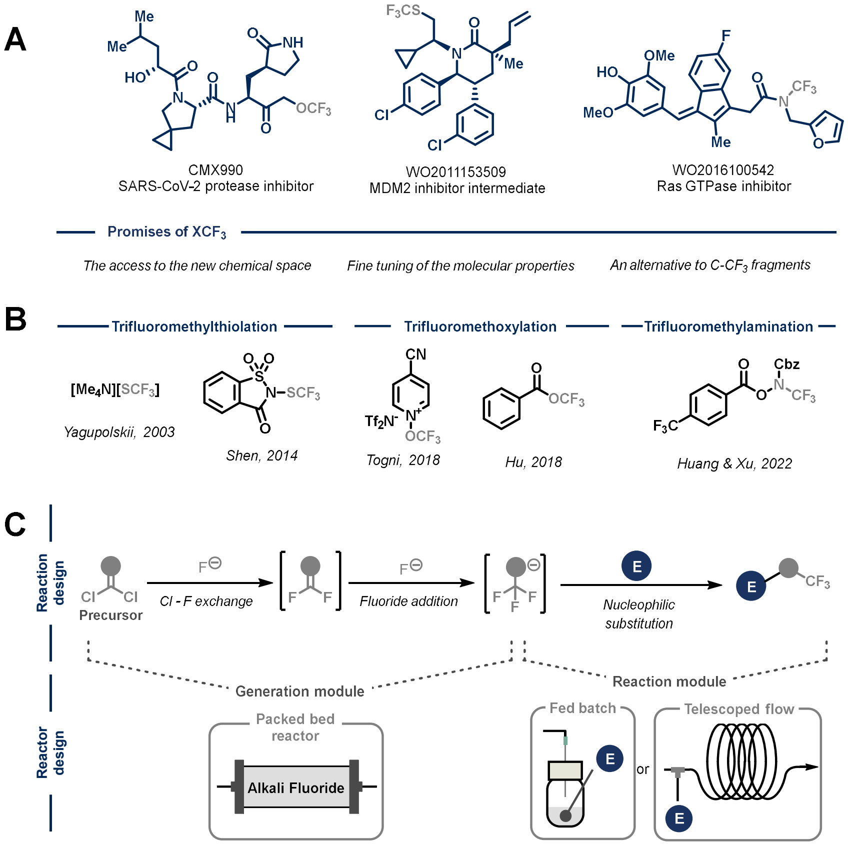

Figure 1. Background and concept. **A.** Examples of active pharmaceutical ingredients containing heteroatom–CF_3 fragments. **B.** Selection of reagents for the introduction of SCF_3, OCF_3 and NCF_3 motifs. **C.** Reaction and reactor design. Stepwise construction of the trifluoromethyl group to generate heteroatom-centered trifluoromethyl anions, and their subsequent reaction with electrophiles.

NCF_3 fragment incorporation. Our research began with a focus on introducing the NCF_3 fragment. This relatively unexplored moiety has recently garnered attention from the medicinal chemistry community as a valuable scaffold for modulating pharmacokinetic properties such as lipophilicity and amine basicity. (***Error! No s'ha definit el marcador.**,24*) Despite its potential, the widespread adoption of this fragment has been hindered by the limited availability of methodologies available for its installation. (*25*) In most cases, existing methodologies rely on the trifluoromethylation of amines, requiring the stoichiometric use of silver salts (*26-28*) or reagents with low atom economy. (*29-32*)

Based on our strategic approach, we reasoned that protected imidoyl dichlorides (Fig. 2, **1**–**3**) could serve as appropriate precursors for producing NCF_3(PG) anions through their reaction with a fluoride source, thus obtaining the nucleophilic species through three consecutive carbon-fluorine bond formations. These precursors can be obtained on a multigram scale bearing different protecting groups (> 30 g for Ts **1**, > 4 g for Cbz **2,** and 7 g for Boc **3**) from inexpensive and readily available starting materials (see Supplementary Materials for further details). Furthermore, ^{15}N-labelled imidoyl dichlorides can be readily synthesized as well (> 3 g for [^{15}N]Ts **1**), offering access to isotopically labeled $^{15}NCF_3$-containing products. The safety concerns arising from their structural similarity to phosgene are partly mitigated by their physical state, as reagent **1** is a solid while reagents **2** and **3** are liquids. Additionally, DSC and TGA analyses of reagent **1** indicate good thermal stability, with decomposition occurring only at temperatures above 180 ºC (See Supplementary Information).

Preliminary batch experiments revealed that upon mixing tosyl-protected imidoyl dichloride **1** with 9 equivalents of cesium fluoride (CsF) in acetonitrile, the targeted trifluoromethylamino anionic species could be observed by ^{19}F NMR after 2 hours (see Supplementary Materials). Subsequent addition of benzyl bromide to the crude reaction mixture afforded trifluoromethylamine **4** in 63% yield after 2 hours at 80 ºC.

Next, we transitioned this methodology to our engineered flow system. One crucial aspect of this strategy is the electronic density on the nitrogen atom. Trifluoromethylamino anions are prone to undergo α-defluorination when there is a significant electronic density on the nitrogen atom. (*33*) To mitigate this decomposition pathway while maintaining optimal nucleophilicity, we employed 18-crown-6 in conjunction with our precursor. This approach enables the complexation of the cesium cations, thereby preventing their interaction with fluorine atoms and stabilizing the desired anionic species. Thus, flowing a solution of the imidoyl dichloride **1** and 18-crown-6 ether (1 equiv) through a cartridge filled with CsF accelerated the generation of the NCF_3(Ts) anion to just 7 minutes.

Having confirmed promising results for our generator module, we proceeded to evaluate the reactivity of the anionic species through a leaving group assessment (Fig. 2 Leaving group assessment). The results indicated the need for effective nucleofuges for the reaction to proceed successfully. In the case of the benzyl benchmark substrate, chloride, acetate, trifluoroacetate, and Katrizky salt electrophiles failed to yield the desired product. However, bromide, iodide, mesylate, and tosylate derivatives proved to be competent substrates towards the formation of product **4** in good to excellent yields (59-98%). Regarding the *n*-hexyl substrate, iodide-bearing substrates underwent satisfactory substitution in the presence of silver triflate, resulting in the formation of alkyl amine **5**, while bromide, mesylate, and tosylate variants still provided the target product in quantities suitable for medicinal chemistry applications.

Subsequently, we set out to investigate the compatibility of the generated NCF_3(Ts) anions with the presence of different functional groups (Fig. 2, Functional group compatibility). To this end, we engaged the tosyl-protected anion, generated in the CsF-packed bed, in a reaction with an array of 4-substituted benzyl bromides. Derivatives featuring a halogen substituent and strongly electron-withdrawing groups such as trifluoromethyl, nitrile, and nitro, were efficiently converted into the corresponding products in good yields (Fig. 2, entries **6-13**). Carbonyl-derived functionalities such as aldehyde, phenyl ketone, and methyl ester proved largely compatible with the trifluoromethylamination reaction (Fig. 2, entries **6-12**). Despite its protic nature, the presence of a free carboxylic acid was also tolerated, albeit with moderate yield (Fig. 2, entry **17**). Also, the boronpinacolate-substituted arene reacted in a synthetically useful yield, whereas vinyl and acetylide derivates reacted in high yields (Fig. 2, entries **18-20**). Finally, electron-donating substituents such as trimethylsilyl, methoxy, and thiomethoxy were compatible, affording the substituted trifluoromethyl-amines in good to excellent yields (Figure 1, entries **21-23**).

Next, we explored the compatibility of our trifluoromethylamination protocol with various classes of electrophiles. The NCF_3 fragment, bearing different protecting groups, was successfully installed in benzylic and allylic motifs in only 2 hours at 80 ºC (Fig. 2, entries **24-26**). Our methodology proved further compatible with the direct introduction of isotopically labeled $^{15}NCF_3(PG)$ fragments by starting from a ^{15}N-labeled precursor (Fig. 2, entry **27**). For this transformation, both the generation of the anion and the substitution step were performed in batch, highlighting the generality of our approach, which extends beyond flow setups. Next, both primary and secondary alkyl iodides underwent efficient trifluoromethylamination, albeit with the use of silver triflate and extended reaction times (Fig. 2, entries **28**-**30**, see Supplementary Materials for detailed reaction conditions). Nitrogen-containing heterocycles and acetyl-protected galactosyl bromide (Fig. 2, entries **31**–**33**) were also obtained in moderate to good yields. Finally, we applied this protocol to various API intermediates, including those derived from densely functionalized Ticagrelor, a Lonazolac analogue, Pitavastatin, and Umifenovir (Fig. 2, entries **34**–**40**), demonstrating compatibility with complex molecular architectures and incorporation of different *N*-protecting groups.

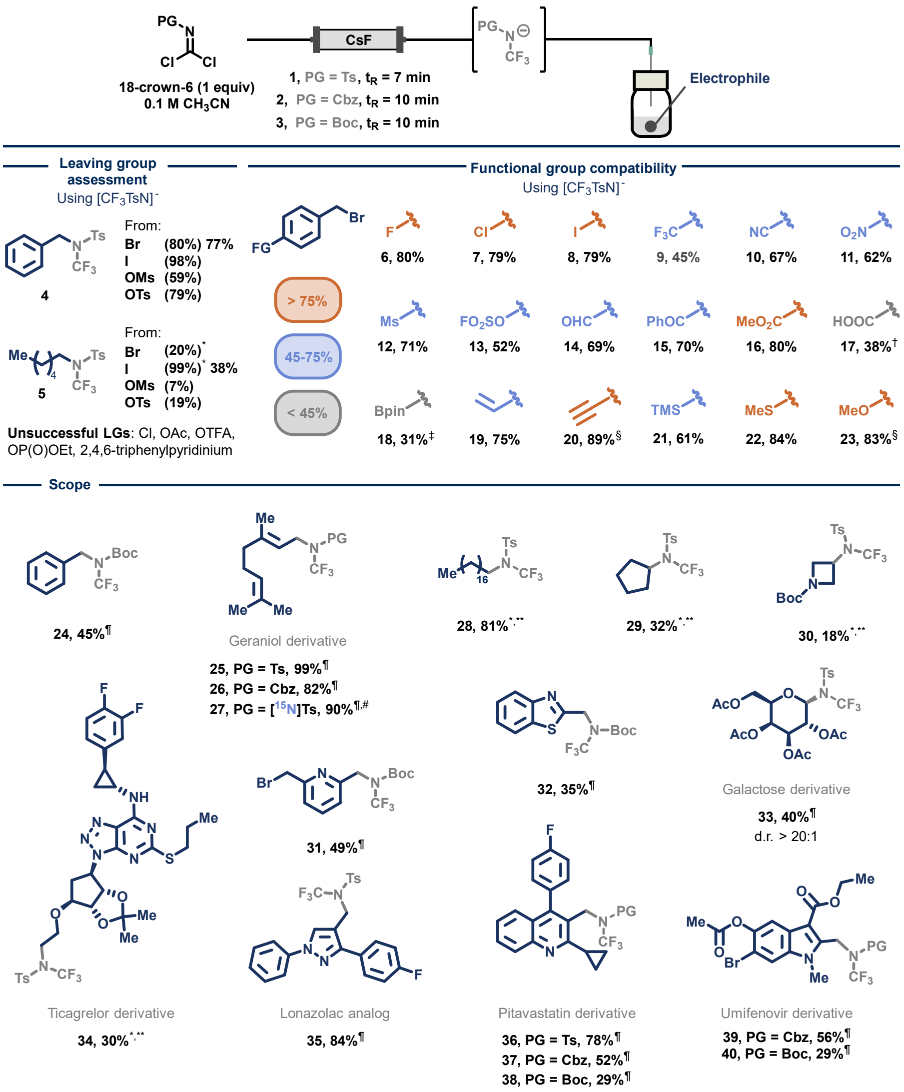

Figure 2. On demand generation of NCF3(PG) anions and their reaction with electrophiles. All yields are those of isolated compounds. Standard conditions for $[NCF_3(PG)]^-$ generation: imidoyl dichloride derivative (0.1 M in MeCN with 1 equiv of 18-crown-6) was passed through a 3.8 mL cartridge filled with a 7:3 w/w mixture of CsF and glass beads. Standard conditions for the substitution: electrophile (0.2 mmol) is added to the solution of the anion (from 2 to 4 equivalents) and heated at 80 ºC. For detailed reaction conditions of each substrate see S.M. *1.1 equiv of AgOTf were used. †Isolated after an esterification step. ‡Isolated after bromination of the Bpin moiety. §3-substituted benzyl bromide was used ¶From the bromide. #Reaction performed in batch. **From the iodide.

Extension to SCF3 and OCF3 fragment incorporation. Building upon the success of the flow system for the $NCF_3(PG)$ anion generation, we proceeded to investigate the incorporation of chalcogen-based trifluoromethyl fragments following our overarching on-demand generator strategy. The trifluoromethylthio (SCF_3) and trifluoromethoxy (OCF_3) groups are both of substantial interest due to their potential as lipophilic modulators for the fine-tuning of active pharmaceutical ingredients. (*34*)

For the on-demand flow generation of trifluoromethylthiolate anions ($[SCF_3]^-$), thiophosgene **41** was selected as the precursor owing to its commercial availability, cost-effectiveness, and extensive industrial application on the ton-scale. (*35*) In the case of the trifluoromethoxy anions

($[OCF_3]^-$) we opted for diphosgene **42** as the precursor, as it is widely used as a more convenient alternative to toxic and gaseous phosgene in various carbonylation reactions. (*36*) Analogous to the process with protected imidoyl dichlorides, the reaction with cesium fluoride and our selected precursors would initially produce gaseous thiocarbonyl or carbonyl fluoride intermediate, respectively. However, the enclosed flow system ensures that these intermediates rapidly undergo further reaction with another fluoride ion, leading to the rapid and complete formation of the desired trifluoromethyl-chalcogen anions, thus mitigating any potential safety risks. After a brief optimization (see the Supplementary Materials), we successfully generated both chalcogen-trifluoromethyl nucleophiles in our system with a residence time as short as 5 minutes for the trifluoromethylthiolate anion, and 7 minutes for the trifluoromethoxy anion. With these results in hand, we proceeded to evaluate a diverse scope of electrophilic partners.

The trifluoromethylthio fragment was successfully incorporated into both primary (Fig. 3, entries **43** and **44**) and secondary alkyl electrophiles (Fig. 3, entries **45** and **46**), furnishing natural product derivatives such as SCF_3-modified methionine, cholesterol and androsterone in good to excellent yields (up to 94%). Nucleophilic substitution reactions with benzylic and allylic substrates, including a celecoxib derivative, resulted in trifluoromethylthiolated products with excellent yields (Fig. 3, entries **47-49**). Notably, these transformations could be efficiently carried out in a telescoped flow fashion resulting in a remarkable acceleration of the reaction time from 2 hours to just 5 minutes, while maintaining practically similar yields. The generated anions were also subjected to an aromatic nucleophilic substitution reaction, yielding a Csp^2-SCF_3 product (Fig. 3, entry **50**), as well as a nucleophilic acyl substitution, resulting in the formation of the desired thioesters (Fig. 3, entries **51** and **52**).

In our nucleophilic trifluoromethoxylation protocol, a secondary alkyl bromide was swiftly converted into the corresponding product in good yields (Fig. 3, entry **53**). The reaction proved to be versatile by delivering products in good to excellent yields for allylic and benzylic substrates bearing multiple functionalities and heterocyclic scaffolds. These were also represented by API intermediate derivatives, such as Celecoxib, Pitavastatin, Umifenovir, and a Lonazolac analog (Fig. 3, entries **54-59**). Moreover, the trifluoromethoxy anion also reacted in a S_NAr manifold (Fig. 3, entry **60**) and could modify glycosyl substrates (Fig. 3, entries **61** and **62**).

Furthermore, our methodology could be extended to incorporate longer polyfluoroethoxy chains. By flowing fluoroalkyl anhydrides as anion precursors through the CsF-packed bed, these substrates can initially undergo acyl fluoride formation, followed by alkoxy anion formation upon a second fluoride addition. We employed this strategy to obtain tetra- and pentafluoroethoxy-derived glycosyl products (Fig. 3, entries **63** and **64**).

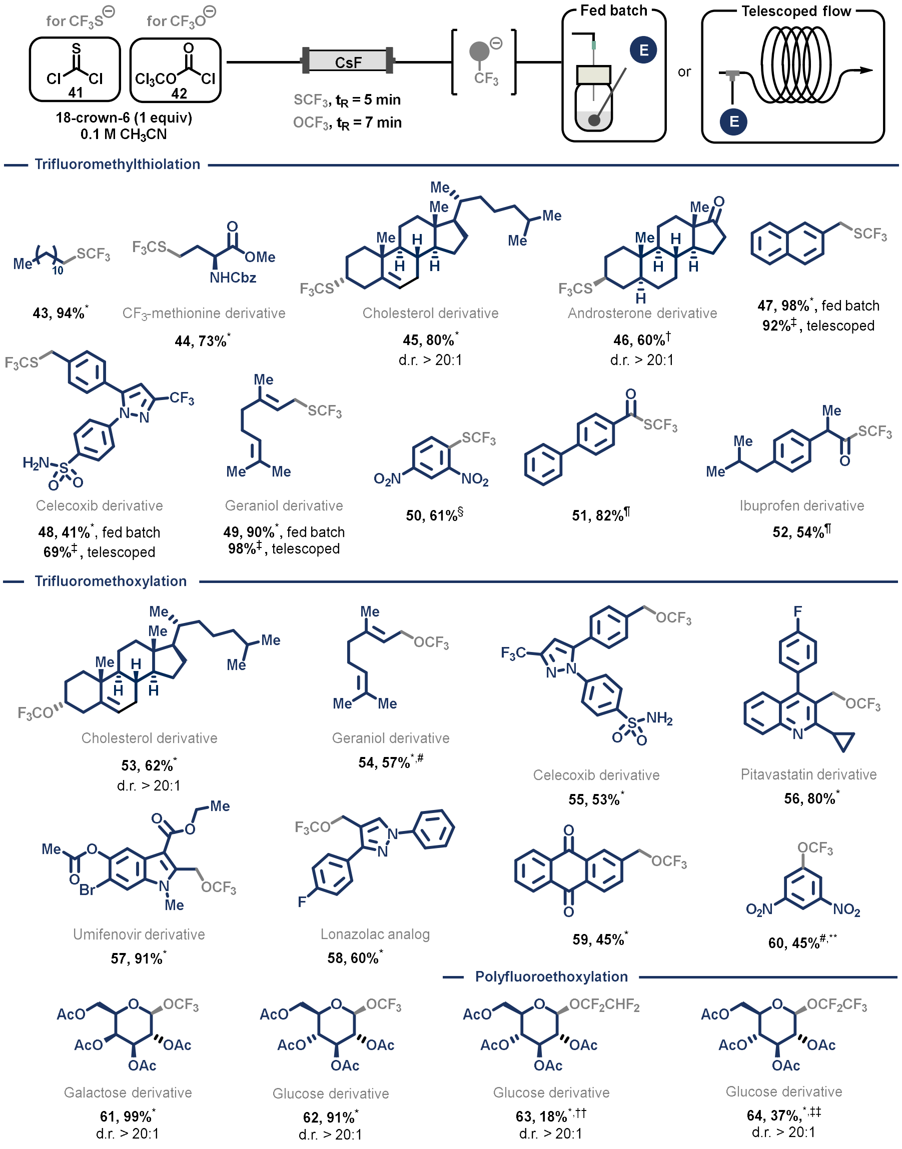

Figure 3. On demand generation of SCF_3 and OCF_3 anions and their reaction with electrophiles. All yields are those of isolated compounds unless otherwise noted. Standard conditions for anion generation: thiophosgene or diphosgene (0.1 M in MeCN with 1 equiv of 18-crown-6) was passed through a 3.8 mL cartridge filled with a 7:3 w/w mixture of CsF and glass beads. Standard conditions for the fed batch substitution: electrophile (0.2 mmol) is added to the solution of the anion (from 2.5 to 7 equiv) and stirred at room temperature. For the fluoralkoxylation reactions 1 equiv of AgOTf was used. For detailed reaction conditions of each substrate see the S.M. *From the bromide. †From the mesylate. ‡See S.M. for telescoped-flow conditions. §From fluoride. ¶From the acyl chloride using 3 equiv. of TMSCl. #NMR yield reported due to the volatility of the product. **From the [$N_2 \cdot BF_4$]. ††Difluoroacetic anhydride was used as anion precursor. ‡‡Trifluoroacetic anhydride was used as anion precursor.

Conclusion

The presented flow strategy enables the generation of reactive $NCF_3(PG)$, SCF_3, and OCF_3 anions from bench stable organic precursors using cesium fluoride as the sole fluorine source. These nucleophilic species are generated on-demand and subsequently reacted with a wide variety of electrophiles under different substitution pathways, including natural-derived products and advanced API intermediates. Based on our findings, we anticipate that this system will be useful for the divergent preparation of heteroatom trifluoromethyl molecules in both academic and industrial contexts. Importantly, our strategy avoids the use of environmentally threatening perfluoroalkyl materials, thereby opening the door to a more sustainable synthesis of fluorochemicals.

Acknowledgements

We express our gratitude to Prof. Renzo Luisi from the University of Bari for his invaluable suggestions and unwavering support during the execution of this work. We also thank Dr. Adrian Moreno from the University Rovira i Virgili for the DSC and TGA analysis of reagent 1.

Funding: We acknowledge financial support from the European Union H2020 research and innovation program for an ERC CoG grant for T.N. (FlowHAT, No. 101044355) and a Marie S. Curie Grant fellowship for D. M. (ELECTRORGANO, No. 101022144), the Spanish Government-MICIU, the national agency of investigation-AEI/10.13039/501100011033, and the European Regional Development Fund-ERDF for project PID2020-120584RB-I00 to O.B. and FPU Fellowship (FPU19/01969 and EST22/00303) to M.B.. M.C. also expresses gratitude to MUR Action IV.6 PON R&I 2014-2020 – DM 1062.

Author contributions

M.B. conceived the initial idea for the project. M.S., M.B., J.S., D.M., M.C., performed and analyzed the experiments. J. J. D. provided input for the selection of complex substrates. T.N. and O.B. were responsible for funding acquisition. T.N. directed and supervised the project, with regular scientific input from all authors. M.B and T.N wrote the manuscript with comments from all the other authors.

Competing interests

No competing interests are declared.

Data and materials availability

All experimental data, including detailed procedures, optimization tables, description of the setup and characterization data is available in supplementary materials.

References

1. M. Inoue, Y. Sumii, N. Shibata, Contribution of organofluorine compounds to pharmaceuticals, *ACS Omega*, **5**, 10633–10640 (2020).

2. Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, Current contributions of organofluorine compounds to the agrochemical industry. *iScience*. **23**, 101467 (2020).
3. E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, Applications of fluorine in medicinal chemistry. *Journal of Medicinal Chemistry*. **58**, 8315–8359 (2015).
4. V. Gouverneur, K. Muller, in *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications* (Imperial College Press, 2012)
5. V. P. Reddy, in *Organofluorine chemistry Synthesis and Applications*, J. Hayton, Ed. (Elsevier, 2021).
6. R. Britton, V. Gouverneur, J.-H. Lin, M. Meanwell, C. Ni, G. Pupo, J.-C. Xiao, J. Hu. Contemporary synthetic strategies in organofluorine chemistry. *Nat Rev Methods Primers* **1**, 47 (2021).
7. J.-A. Ma, D. Cahard in *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*, (Wiley-VCH Verlag GmbH & Co. KGaA, 2020).
8. N. A. Meanwell, Fluorine and fluorinated motifs in the design and application of Bioisosteres for Drug Design. *Journal of Medicinal Chemistry*. **61**, 5822–5880 (2018).
9. B. Zdrazil *et al.*, The CHEMBL database in 2023: A drug discovery platform spanning multiple bioactivity data types and time periods. *Nucleic Acids Res.* **52**, D1180–D1192 (2023).
10. W. Tyrra, D. Naumann, B. Hoge, Y. L. Yagupolskii, A new synthesis of trifluoromethanethiolates—characterization and properties of tetramethylammonium, Cesium and di(benzo-15-crown-5)cesium trifluoromethanethiolates. *J. Fluor. Chem.* **119**, 101–107 (2003).
11. C. Xu, B. Ma, Q. Shen, N-trifluoromethylthiosaccharin: An easily accessible, shelf-stable, broadly applicable trifluoromethylthiolating reagent. *Angew. Chem. Int. Ed.* **53**, 9316–9320 (2014).
12. B. J. Jelier, P. F. Tripet, E. Pietrasiak, I. Franzoni, G. Jeschke, A. Togni, Radical trifluoromethoxylation of Arenes triggered by a visible-light-mediated N−O bond redox fragmentation. *Angew. Chem. Int. Ed.* **57**, 13784–13789 (2018).
13. M. Zhou, C. Ni, Y. Zeng, J. Hu, Trifluoromethyl benzoate: A versatile trifluoromethoxylation reagent. *J. Am. Chem. Soc.* **140**, 6801–6805 (2018).
14. S. Liu, Y. Huang, J. Wang, F.-L. Qing, X.-H. Xu, General Synthesis of *N*-Trifluoromethyl Compounds with *N*-Trifluoromethyl Hydroxylamine Reagents. *J. Am. Chem. Soc.* **144**, 1962–1970 (2022).
15. European Chemicals Agency (ECHA), https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas (accessed 13th April, 2023)
16. European Chemicals Agency (ECHA), Annex XV Restriction Report, Proposal for a restriction https://echa.europa.eu/documents/10162/f605d4b5-7c17-7414-8823-b49b9fd43aea (accessed 13th April, 2023)
17. N. D. Tyrrell, A proposal that would ban manufacture, supply, and use of all fluoropolymers and most fluorinated reagents within the entire EU. *Org. Process Res. Dev.* **27**, 1422–1426 (2023).
18. M. Bernús, D. Mazzarella, J. Stanić, Z. Zhai, A. Yeste-Vázquez, O. Boutureira, A. F. G. Gargano, T. N. Grossmann, T. Noël, A modular flow platform for sulfur(VI) fluoride exchange ligation of small molecules, peptides and proteins. *Nat. Synth.* **3**, 185–191 (2023).

19. D. Mazzarella, J. Stanic, M. Bernús, A. Seyed-Mehdi, C. Henderson, O. Boutureira, T. Noël In-flow generation of thionyl fluoride (SOF2) enables the rapid and efficient synthesis of acyl fluorides from carboxylic acids. *JACS Au* doi: 10.1021/jacsau.4c00318 (2024).
20. T. Noël, T. J. Maimone, S. L. Buchwald, Accelerating palladium-catalyzed C-F bond formation: Use of a microflow packed-bed reactor. *Angew. Chem. Int. Ed.* **50**, 8900–8903 (2011).
21. M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, Taming hazardous chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **45**, 4892–4928 (2016).
22. L. Capaldo, Z. Wen, T. Noël, A field guide to flow chemistry for Synthetic Organic Chemists. *Chem. Sci.* **14**, 4230–4247 (2023).
23. D. Dallinger, B. Gutmann, C. O. Kappe, The concept of chemical generators: On-site on-demand production of hazardous reagents in Continuous Flow. *Acc. Chem. Res.* **53**, 1330–1341 (2020).
24. S. Schiesser, H. Chepliaka, J. Kollback, T. Quennesson, W. Czechtizky, R. J. Cox, *N*-trifluoromethyl amines and azoles: An underexplored functional group in the medicinal chemist's toolbox. *J. Med. Chem.* **63**, 13076–13089 (2020).
25. S. Liu, Y. Huang, J. Wang, F.-L. Qing, X.-H. Xu, General synthesis of *N*-trifluoromethyl compounds with *N*-trifluoromethyl hydroxylamine reagents. *J. Am. Chem. Soc.* **144**, 1962–1970 (2022).
26. T. Scattolin, K. Deckers, F. Schoenebeck, Efficient synthesis of trifluoromethyl amines through a formal umpolung strategy from the bench-Stable Precursor (Me4N)SCF3. *Angew. Chem. Int. Ed.* **56,** 221–224 (2016).
27. J. Yu, J.-H. Lin, J.-C. Xiao, Reaction of thiocarbonyl fluoride generated from Difluorocarbene with amines. *Angew. Chem. Int. Ed.* **56**, 16669–16673 (2017).
28. T. Scattolin, S. Bouayad-Gervais, F. Schoenebeck, Straightforward access to *N*-trifluoromethyl amides, carbamates, thiocarbamates and Ureas. *Nature* **573**, 102–107 (2019).
29. T. Umemoto, K. Adachi, S. Ishihara, CF3 Oxonium Salts, O-(Trifluoromethyl) dibenzofuranium Salts: In Situ Synthesis, Properties, and Application as a Real CF3+ Species Reagent. *J. Org. Chem.* **72,** 6905–6917 (2007).
30. K. Niedermann, N. Früh, E. Vinogradova, M. S. Wiehn, A. Moreno, A. Togni, A ritter-type reaction: Direct electrophilic trifluoromethylation at nitrogen atoms using hypervalent iodine reagents. *Angew. Chem. Int. Ed.* **50**, 1059–1063 (2010).
31. F. Teng, J. Cheng, C. Bolm, Silver-mediated *N*-trifluoromethylation of sulfoximines. *Org. Lett.* **17**, 3166–3169 (2015).
32. T. Cao, P. Retailleau, T. Milcent, B. Crousse, Synthesis of *N*-CF3 hydrazines through radical trifluoromethylation of azodicarboxylates. *Chem. Comm.* **57**, 10351–10354 (2021).
33. Y. Pan, The Dark Side of fluorine. *ACS Med. Chem. Lett.* **10**, 1016–1019 (2019).
34. G. Landelle, A. Panossian, F. Leroux, Trifluoromethyl ethers and –thioethers as tools for medicinal chemistry and Drug Discovery. *Curr. Top. Med. Chem.* **14**, 941–951 (2014).
35. C. J. O'Donell, M. J. Cloninger, Thiophosgene in Encyclopedia of Reagents for Organic Synthesis (EROS), (Wiley-VCH Verlag GmbH & Co. KGaA, 2008).
36. K. Kurita, Trichloromethyl Chloroformate in Encyclopedia of Reagents for Organic Synthesis (EROS), (Wiley-VCH Verlag GmbH & Co. KGaA, 2001).
37. R. Kaur *et al.*, Selenocoxib-3, a novel anti-inflammatory therapeutic effectively resolves colitis. *Mol. Cell. Biochem.* **478**, 621–636 (2022).

38. X. Gu *et al.*, Steroid compound 3-site hydroxyl configuration inversion method, CN108864237A (2018).
39. E. Napolitano *et al.*, A process for resolving racemic mixtures and a diastereoisomeric complex of a resolving agent and an enantiomer of interest, WO2007088571A2 (2009).
40. 1. R. D. Larsen, E. G. Corley, P. Davis, P. J. Reider, E. J. Grabowski, α-hydroxy esters as chiral reagents: Asymmetric synthesis of 2-arylpropionic acids. *J. Am. Chem. Soc.* **111**, 7650–7651 (1989).
41. H. Wu *et al.*, Glutamine side chain 13C=18O as a nonperturbative IR probe of amyloid fibril hydration and assembly. *J. Am. Chem. Soc.* **141**, 7320–7326 (2019).
42. T. Hiyama, T. Minami, K. Takahashi, Synthesis of artificial HMG-COA reductase inhibitors based on the olefination strategy. *Bull. Chem. Soc. Jpn.* ***68**, 364–372 (1995).*
43. Y.-M. Yang, J.-F. Yao, W. Yan, Z. Luo, Z.-Y. Tang, Silver-mediated trifluoromethoxylation of (hetero)aryldiazonium tetrafluoroborates. *Org. Lett.* **21**, 8003–8007 (2019).
44. A. Buchanan *et al.*, Antibodies to ticagrelor and methods of use, WO2016050867A1 (2016).
45. N. Weidmann, J. H. Harenberg, P. Knochel, Continuous flow preparation of (hetero)benzylic lithiums via iodine–lithium exchange reaction under Barbier conditions. *Org. Lett.* **22**, 5895–5899 (2020).
46. C. Yu, R. Huang, F. W. Patureau, Direct dehydrogenative access to Unsymmetrical Phenones. *Angew. Chem. Int. Ed.* **61** (2022), doi:10.1002/anie.202201142.
47. M. E. Sergeev, F. Morgia, M. Lazari, C. Wang, R. M. van Dam, Titania-catalyzed radiofluorination of tosylated precursors in highly aqueous medium. *J. Am. Chem. Soc.* **137**, 5686–5694 (2015).
48. Z. Yang, J. (Steve) Zhou, Palladium-catalyzed, asymmetric mizoroki–heck reaction of benzylic electrophiles using phosphoramidites as chiral ligands. *J. Am. Chem. Soc.* **134**, 11833–11835 (2012).
49. Q. Dai, L. Liu, J. Zhang, Palladium/xiao-phos-catalyzed kinetic resolution of *sec*-phosphine oxides by *p*-benzylation. *Angew. Chem. Int. Ed.* **60**, 27247–27252 (2021).
50. S.-Z. Sun, C. Romano, R. Martin, Site-selective catalytic Deaminative alkylation of unactivated olefins. *J. Am. Chem. Soc.* **141**, 16197–16201 (2019).
51. P. L. Robinson, C. N. Barry, J. W. Kelly, S. A. Evans, Diethoxytriphenylphosphorane: A mild, regioselective cyclodehydrating reagent for conversion of diols to cyclic ethers: Stereochemistry, synthetic utility, and Scope. *J. Am. Chem. Soc.* **107**, 5210–5219 (1985).
52. J. Su *et al.*, Design, synthesis, and biological evaluation of largazole derivatives: Alteration of the zinc-binding domain. *Tetrahedron*. **70**, 7763–7769 (2014).
53. P. Gajewski *et al.*, Expanding the catalytic scope of (cyclopentadienone)iron complexes to the hydrogenation of activated esters to alcohols. *ChemCatChem*. **8**, 3431–3435 (2016).
54. I. Mosiagin *et al.*, Catalytic *ipso*-nitration of organosilanes enabled by electrophilic *n*-nitrosaccharin reagent. *Angew. Chem. Int. Ed.* **62** (2023), doi:10.1002/anie.202310851.
55. K. S. Bloome, *et al.* Palladium-Catalyzed Heck-Type Reactions of Alkyl Iodides *J. Am. Chem. Soc.* **133**, 20146-20148 (2018).

56. Z.-D. Huang, R. Ding, P. Wang, Y.-H. Xu, T.-P. Loh, Palladium-catalyzed silylation reaction between benzylic halides and silylboronate. *Chem. Comm.* **52**, 5609–5612 (2016).
57. J.-S. Cui *et al.* Directional Shuttling of a Stimuli-Responsive Cone-Like Macrocycle on a Single-State Symmetric Dumbbel Axle *Angew. Chem. Int. Ed.* **57**, 7809-7814 (2018).
58. J. Burkhardt, K. Hamann, Reaktion von *n*-dichlormethylen-carbonsäureamiden, II. kondensation mit aminoalkoholen, Aminothioalkoholen und Diaminen. *Chem. Ber.* **100**, 2569–2576 (1967).
59. J. D. Walker, J. S. Madalengoitia, Optimization of methods for the generation of carbodiimides for zwitterionic 1,3-Diaza-Claisen rearrangements. *Tetrahedron Lett.* **56**, 3786–3789 (2015).
60. J. Mestre, M. Bernús, S. Castillón, O. Boutureira, Electrophilic reagents for the direct incorporation of uncommon SCF2CF2H and SCF2CF3 motifs. *J. Org. Chem.* **87**, 10791–10806 (2022).
61. M. J. Tanga, W. W. Bradford, J. E. Bupp, J. A. Kozocas, Syntheses of two potential food mutagens. *J. Heterocycl. Chem.* **40**, 569–573 (2003).
62. A. Das, A. G. Maher, J. Telser, D. C. Powers, Observation of a photogenerated rh2 nitrenoid intermediate in C–H amination. *J. Am. Chem. Soc.* **140**, 10412–10415 (2018).
63. J. A. Pollock, S. H. Kim, J. A. Katzenellenbogen, Imidoyl dichlorides as new reagents for the rapid formation of 2-aminobenzimidazoles and related azoles. *Tetrahedron Lett.* **56**, 6097–6099 (2015).
64. R.-P. Bao, X. Chen, C. Li, D.-H. Wang, Ir(III)-Catalyzed Mono-Olefination of Aryl C–H Bonds Using −SCF3 as a Weak Directing Group, *Org. Lett.* **21** 8116-8121 (2019).
65. G. Duran-Camacho, D. M. Ferguson, J. W. Kampf, D. C. Bland, M. S. Sanford, Isolable Pyridinium Trifluoromethoxide Salt for Nucleophilic Trifluoromethoxylation, *Org. Lett.* **23**, 5138-5142 (2021).
66. C. I. Merrill, N.L. Madison (1970), *Haloethers* (US3549711).
67. C.-P. Zhang, Q.-Y. Chen, J.-C. Xiao, Y.-C. Gu, A mild hydrodehalogenation of fluoroalkyl halides, *J. Fluorine Chem.* **130**, 671-673 (2009).
68. Palladium-catalyzed synthesis of allylboronic acids and their reaction with ketones. *Synfacts.* **9**, 0314–0314 (2013).
69. C. Xu *et al.*, Synthesis of chloro(phenyl)trifluoromethyliodane and catalyst-free electrophilic trifluoromethylations. *Org. Lett.* **20**, 3933–3937 (2018).
70. X.-G. Yang, J.-J. Li, F.-H. Du, Y.-X. Cheng, C. Zhang, Stereospecific dehydroxytrifluoromethylthiolation of alcohols promoted by a combination of hypervalent trifluoromethylthio-iodine(III) reagent and N-heterocyclic carbene. *Org. Lett.* **25**, 2964–2969 (2023).
71. J. Liu, X. Xu, Z. Chen, F. Qing, Direct dehydroxytrifluoromethylthiolation of alcohols using silver(i) trifluoromethanethiolate and tetra-*n*-butylammonium iodide. *Angew. Chem. Int. Ed.* **54**, 897–900 (2014).
72. M. Hopkinson *et al.*, Compounds for use as nucleophilic reagents for transferring functional groups onto high value organic compounds, WO2020141195A1 (2020).
73. A. Kolomeitsev, M. Médebielle, P. Kirsch, E. Lork, G.-V. Röschenthaler, Synthesis, structure and reactivity of a trifluoromethyl sulfide anionic salt stabilized with tetrakis(dimethylamino)ethylene dication (TDAE2+). *J. Chem. Soc., Perkin Trans. 1, 2183–2185 (2000).*

74. X. Shan *et al.*, Visible-light-promoted trifluoromethylthiolation and trifluoromethylselenolation of 1,4-dihydropyridines. *J. Org. Chem.* ***88**, 319–328 (2022)*.

75. J.-B. Liu, X.-H. Xu, F.-L. Qing, Silver-mediated oxidative trifluoromethylation of alcohols to alkyl trifluoromethyl ethers. *Org. Lett.* **17**, 5048–5051 (2015).