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

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Abstract

The trifluoromethyl group (CF_3) is a key moiety 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 significant challenges due to the lack of general synthetic methods and reliance on bespoke reagents. In this study, we present a unified approach to address this issue by employing a modular flow platform that streamlines the synthesis of heteroatom-CF_3 motifs. Our method utilizes 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. Despite their reactivity and atom economy, the instability of these anions has previously hindered their widespread application. However, our platform overcomes this limitation, enabling the subsequent coupling of these nucleophiles with a diverse range of electrophiles. This capability allows for the late-stage modification of various drug intermediates, offering a versatile and efficient synthetic route. A notable advantage of our approach is its sustainability. Unlike traditional methods reliant on polyfluoroalkyl substances (PFAS) as reagents, our strategy bypasses their use, resulting in a more environmentally friendly synthesis of trifluoromethyl(heteroatom)-containing molecules. Furthermore, our method expands the chemical space available for the heteroatom-CF_3 group, with the potential for scalability in manufacturing processes facilitated by flow technology.

Introduction

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 the hydrophobic surface of the molecule.[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, being present 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 confer unique features to drug molecules, impacting their lipophilicity, oxidation resistance, and acid-base properties.[8] Despite their appeal, these moieties are significantly underrepresented in active pharmaceutical ingredients (APIs), comprising less than 10% of the total CF_3-containing drugs.[1,9] The main hurdle lies in their challenging 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).[10,11,12,13,14] Furthermore, the preparation of these bespoke reagents often involves laborious processes spanning multiple steps, resulting in the generation of significant amounts of fluorinated waste.

Recently, a proposed change in EU law has raised concerns about a potential ban on a broad range of polyfluorinated alkyl substances (PFAS), including many CF_3-containing molecules and reagents.[15] While legislation is yet to be finalized, exceptions are expected for final pharmaceutical and agrochemical active ingredients.[16] However, the ban could still impact their synthesis if synthetic intermediates, the required bespoke reagents or other CF_3-containing sources were to be prohibited.[17] Therefore, it becomes crucial to develop methods for synthesizing these moieties, at the late stage of a synthesis, from simple, non-fluorinated organic molecules, ideally utilizing cheap and widely available alkali fluoride sources for which no restrictions are foreseen. Such an approach would not only comply with the proposed EU law but also minimize or eliminate the need for perfluorinated materials in synthesizing most of the currently used fluoroalkylating reagents.

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 facilitate 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 in 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 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 its seamless incorporation into electrophiles, thereby providing a divergent and streamlined platform for the derivatization of molecules bearing heteroatom–CF_3 motifs.

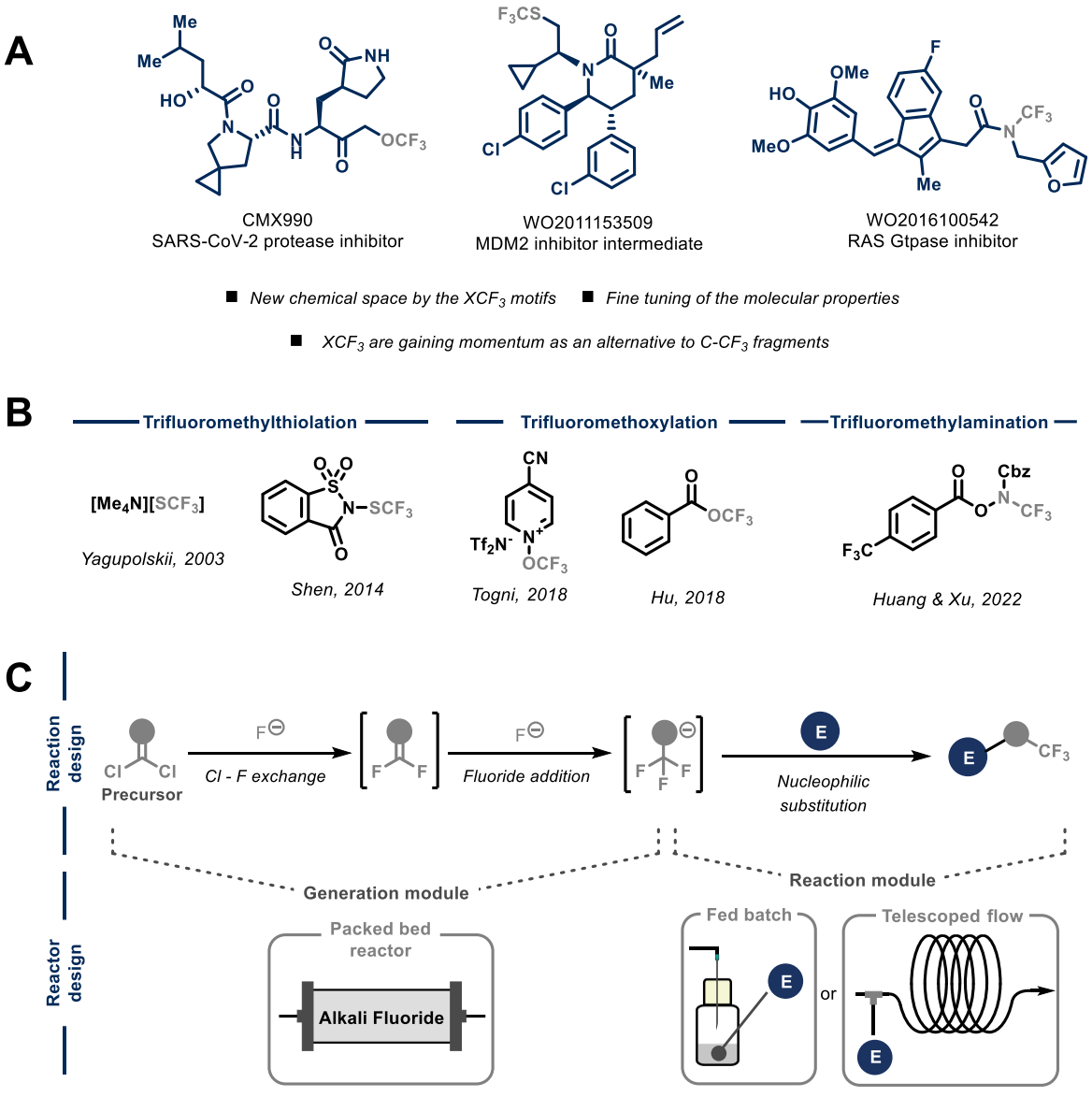


Figure 1. A. Examples of active pharmaceutical ingredients containing heteroatom–CF_3 fragments. **B.** Selection of reagents for the introduction of SCF_3, OCF_3 and NCF_3 motifs. **C.** Reaction and reactor design. Stepwise construction of the trifluoromethyl group to generate heteroatom-centered trifluoromethyl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

Results and discussion

Our research began with a focus on addressing the challenging task of introducing the elusive 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.[8,24] Despite its potential, the widespread adoption of this fragment has been hindered by the limited availability of methodologies available for its installation, especially the lack of methods for the direct incorporation of trifluoromethyl nitrogen fragments.[25] In most cases, existing methodologies rely on the trifluoromethylation of amines, requiring the stoichiometric use of silver salts[26,27,28] or reagents with low atom economy.[29,30,31,32] This limitation underscores the need for novel and more efficient approaches to overcome the challenges associated with introducing the NCF_3 motif.

Based on our strategic approach, we reasoned that protected imidoyl dichlorides (Scheme 1, **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. Notably, 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 Information 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.

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 Information). Subsequent addition of benzyl bromide to the reaction crude afforded trifluoromethylamine **4** in 63% yield after 2 hours at 80 ºC. To the best of our knowledge, this represents a new disconnection for the preparation of Csp^3–NCF_3 compounds.

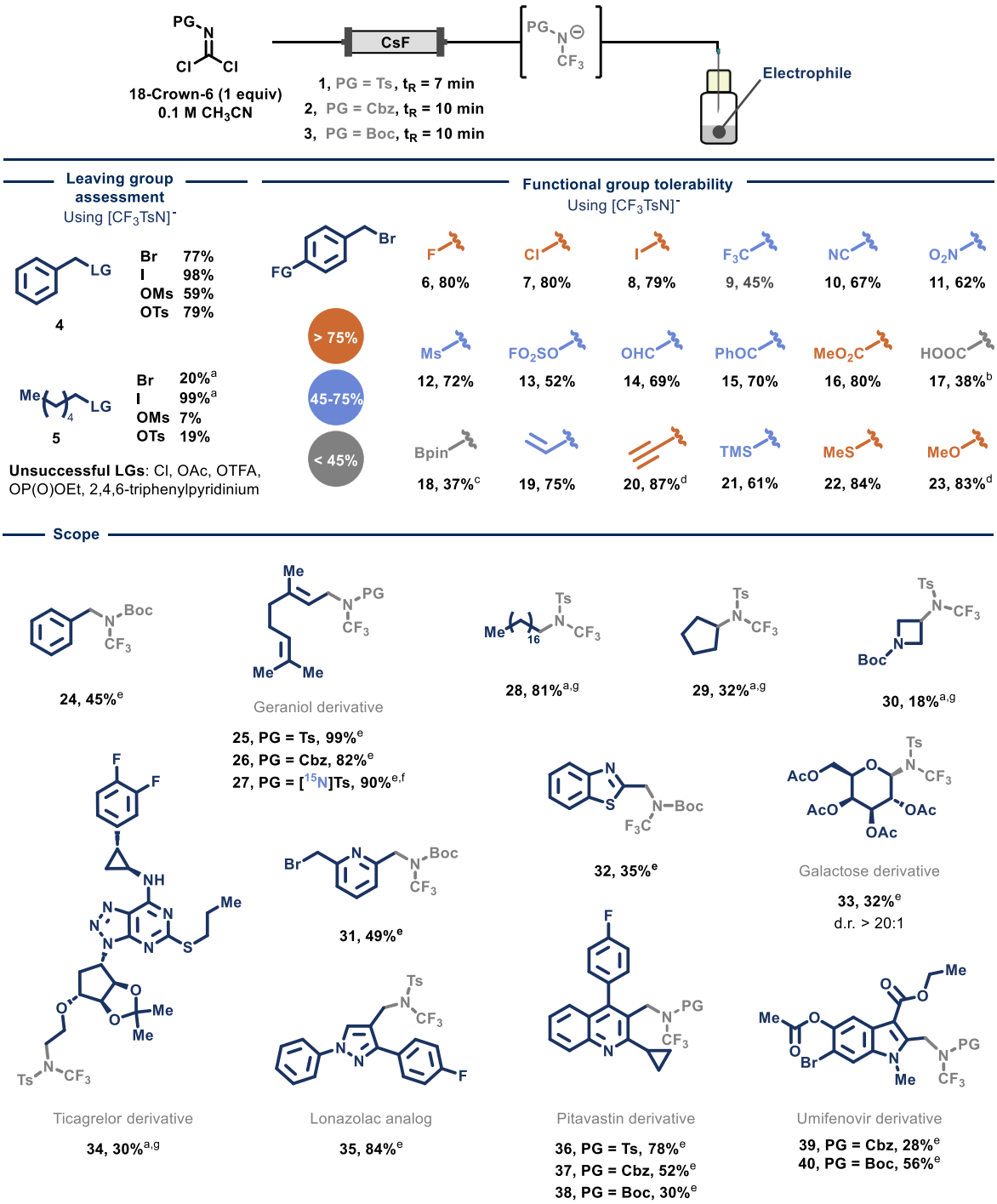
Next, we transitioned this methodology to our engineered flow system. One crucial aspect of this strategy is the electronic density on the nitrogen atom. Trifluoromethylamino anions are prone to undergo α-defluorination when there is an excessive electronic density on the nitrogen atom.[33] To mitigate 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 reduced 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 (Scheme 1, 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 (Scheme 1, Functional group tolerability). 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 (Scheme 1, entries **6**-**13**). Carbonyl-derived functionalities such as aldehyde, phenyl ketone, and methyl ester proved largely compatible with the trifluoromethylamination reaction (Scheme 1, entries **6**-**12**). Despite its protic nature, the presence of a free carboxylic acid was also tolerated, albeit yielding the product in moderate yield (Scheme 1, entry **17**). Also, the boronpinacolate-substituted arene reacted in a synthetically useful yield, whereas vinyl and acetylide derivates were rendered in high yields (Scheme 1, entries **18**-**20**). Finally, electron-donating substituents such as trimethylsilyl, methoxy, and thiomethoxy were well-tolerated, affording the substituted trifluoromethyl-amines in good to excellent yields (Scheme 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 (Scheme 1, entries **24**-**26**). Notably, our methodology proved also compatible with the direct introduction of isotopically labeled $^{15}NCF_3$(PG) fragments by starting from a ^{15}N-labeled precursor (Scheme 1, 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 requiring the use of silver triflate and extended reaction times (Scheme 1, entries **28**-**30**, see Supplementary Information for detailed reaction conditions). Nitrogen-containing heterocycles and acetyl-protected galactosyl bromide (Scheme 1, 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, Pitavastin, and Umifenovir (Scheme 1, entries **34**–**40**), demonstrating its compatibility with complex molecular architectures and its ability to incorporate different *N*-protecting groups.



Scheme 1. On demand generation of $NCF_3(PG)$ 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 the S.I. [a]1.1 equiv of AgOTf were used. [b]Isolated after an esterification step. [c]Isolated after bromination of the BPin moiety. [d]3-substituted benzyl bromide was used [e]From the bromide. [f]Reaction performed in batch. [g]From the iodide.

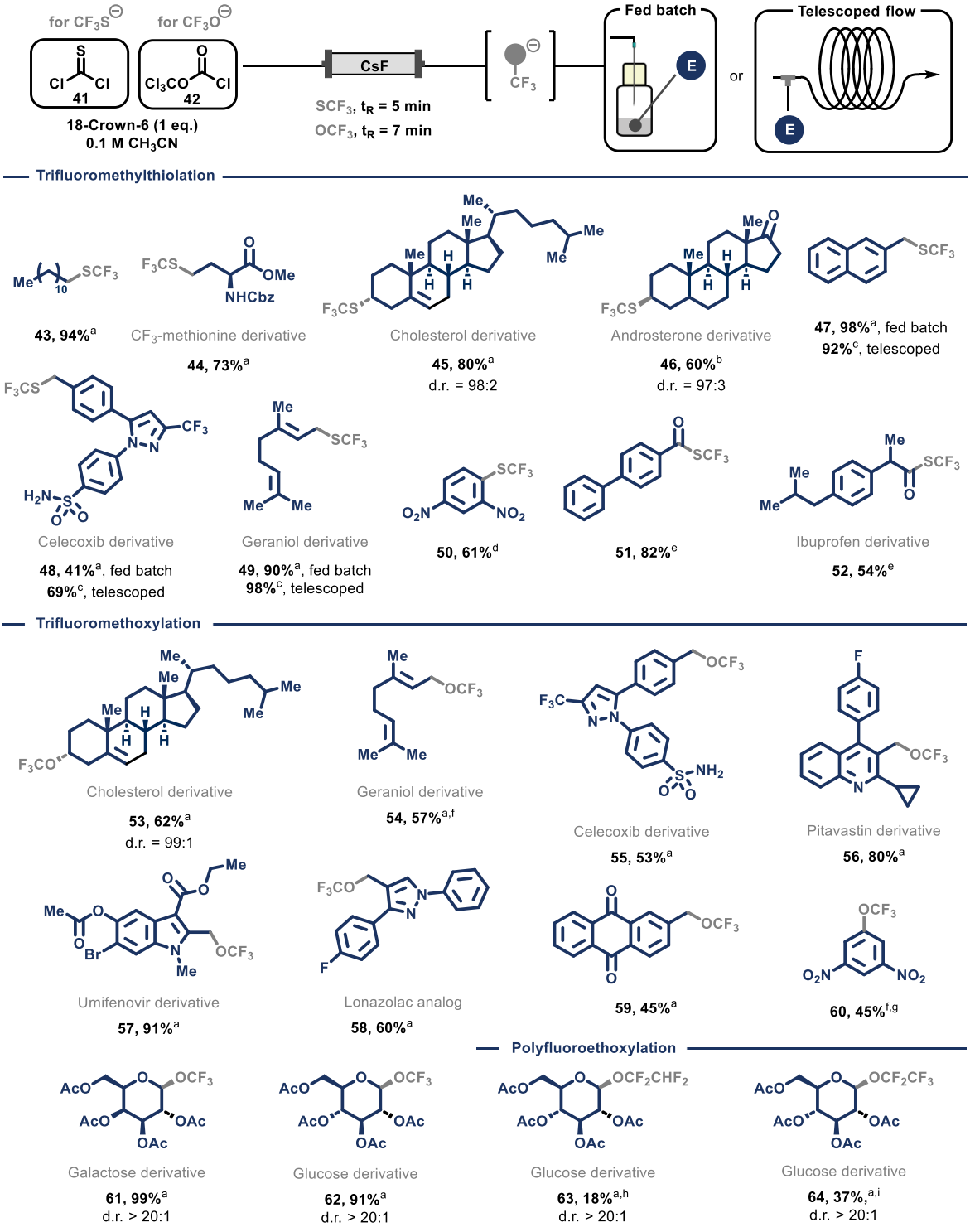
Building upon the success of the flow system for the NCF_3(PG) anion generation, we proceeded to investigate the incorporation of chalcogen-based trifluoromethyl fragments following our overarching on-demand generator strategy. The trifluoromethylthio (SCF_3) and trifluoromethoxy (OCF_3) groups are both of significant 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 Information), 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 one. With these results in hand, we proceeded to evaluate a diverse scope of electrophilic partners.

The trifluoromethylthio fragment was successfully incorporated into both primary (Scheme 2, entries **43** and **44**) and secondary alkyl electrophiles (Scheme 2, entries **45** and **46**), obtaining 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 trifluoromethythiolated products with excellent yields (Scheme 2, entries **47**-**49**). Notably, these transformations could be efficiently carried out in a telescoped flow fashion resulting in a remarkable reduction 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 (Scheme 2, entry **50**), as well as in a nucleophilic acyl substitution, resulting in the formation of the desired thioesters (Scheme 2, entries **51** and **52**).

In our nucleophilic trifluoromethoxylation protocol, a secondary alkyl bromide was swiftly converted into the corresponding product in good yields (Scheme 2, 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, Pitavastin, Umifenovir, and a Lonazolac analog (Scheme 2, entries **54**-**59**). Moreover, the trifluoromethoxy anion was also reacted in a S_NAr manifold (Scheme 2, entry **60**) and used to modify glycosyl substrates (Scheme 2, entries **61** and **62**).

Furthermore, our methodology can 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 (Scheme 2, entries **63** and **64**).



Scheme 2. On demand generation of SCF_3 and OCF_3 anions and its 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.I. [a]From the bromide. [b]From the mesylate. [c]See S.I. for telescoped-flow conditions. [d]From fluoride. [e]From the acyl chloride using 3 equiv. of TMSCl. [f]NMR yield reported due to the volatility of the product. [g]From the [$N_2 \cdot BF_4$]. [h]Difluoroacetic anhydride was used as anion precursor. [i]Trifluoroacetic anhydride was used as anion precursor.

Conclusions

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. In the case of the NCF_3 fragment, we disclose a new disconnection for the incorporation of this motif into Csp^3 electrophiles. Based on our findings, we anticipate that this system will be useful for the divergent preparation of heteroatom trifluoromethyl molecules in both academic and industry contexts. Importantly, our strategy avoids the use of environmentally threatening perfluoroalkyl materials, thereby opening the door to a more sustainable synthesis of fluorochemicals.

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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 need to be declared.

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