Shelf-Stable Electrophilic Reagents for the Direct Incorporation of SCF_2CF_2H and SCF_2CF_3 Motifs

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Abstract

The introduction of fluoroalkylthioether groups has attracted the attention of the drug discovery community given the special physicochemical and pharmacokinetic features they confer to bioactive compounds. Synthetic advances in the field have been capitalized by methods to incorporate SCF_3 and SCF_2H motifs, however, longer and synthetically more challenging polyfluoroethyl chains are still underdeveloped. Here, two saccharin-based electrophilic reagents have been disclosed for the efficient incorporation of SCF_2CF_2H and SCF_2CF_3 motifs. Their reactivity performance has been thoroughly investigated with a variety of nucleophiles such as thiols, alcohols, amines, alkenes, (hetero)aromatics, and organometallic species, including natural products and pharmaceuticals. Finally, multigram-scale preparation and divergent derivatization has been explored from SCF_2CF_2H derivatives.

Introduction

The introduction of fluoroalkyl motifs has been a cornerstone in synthetic, medicinal, and crop chemistry by virtue of the fine-tuning optimization of physicochemical properties of the modified compounds.[1] Over the last few years, the so-called *fluorinated emerging motifs*[2] have entered this arena to find structural alternatives to the most exploited CF_3 and F substituents. In this immense scenario, thiofluoroalkyl motifs (SR_F) occupy a privileged position since the association of fluoroalkyl chains with sulfur results in a powerful combination.[3] The high electronegativity induced by the fluorine atoms combined with the electronic density of the chalcogen, renders highly lipophilic fragments.[4] In medicinal chemistry, these attributes are interesting as they lead to more metabolically stable and higher cell-membrane/blood-brain-barrier permeable ingredients, thus, increasing the bioavailability of drug candidates.[5] Fluoroalkyl modified thioethers not only show outstanding Hansch lipophilicity (*e.g.* CF_3, 0.88 *vs.* SCF_3, 1.44)[6] but also serve as pivotal groups to access other appreciated derivatives, including fluorinated sulfones, sulfonamides, and sulfoximines.[7] Collectively, these groups exhibit unique properties and represent new avenues for the development of improved bioactive compounds (Fig. 1A). Classically, SR_F motifs have been prepared by fluoroalkylation of SH, S_2, SCl, or SCN moieties *via* S–R_F disconnection (Fig. 1B, right panel).[8]

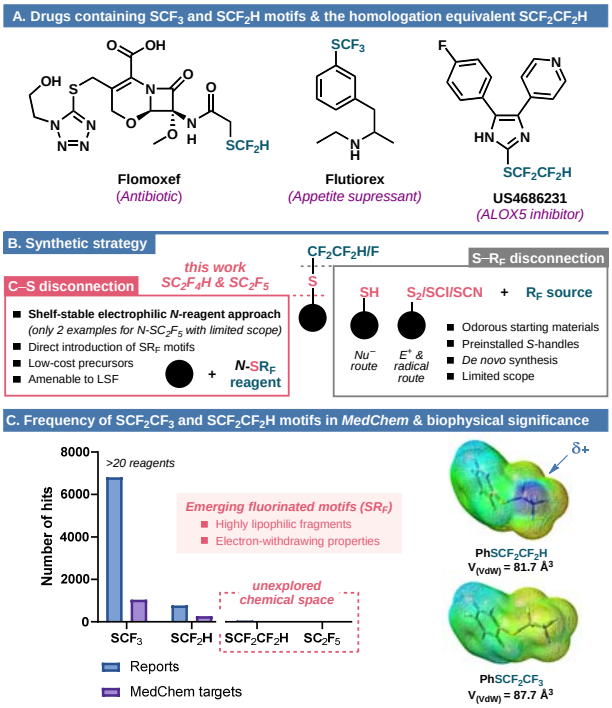


Fig. 1 Selected drugs containing SCF_3 and SCF_2H groups and the homologation equivalent SCF_2CF_2H (panel A). Synthetic strategy and disconnections to R–SR_F motifs (panel B). Reports on the installation of selected SR_F motifs and *MedChem* targets containing these fragments. Biophysical significance of SCF_2CF_3 and SCF_2CF_2H motifs (panel C). Hits obtained with Reaxys database. For Van der Waals (VdW) volume calculation see ref. 9. For electrostatic potential surface calculation see ref. 10.

However, this strategy is not amenable to late-stage functionalization as it requires a preinstalled sulfur handle in the parent molecule. For this reason, fluoroalkylthiolating reagents (and other direct, *one-pot* protocols) have emerged as a power alternative for the direct modification of target compounds *via* C–S disconnection (Fig. 1B, left panel).[11] In recent years, most of the vast number of reports describing nucleophilic, electrophilic, radical, or oxidative fluoroalkylthiolating agents/protocols are limited to the introduction of SCF_3,[12] followed in number by SCF_2H.[13,14] Despite recent advances in the field, drug development comprising other polyfluorinated ethyl congeners is virtually absent (Fig. 1C, right panel). Compared to the SCF_3 motif, SCF_2CF_2H and SCF_2CF_3 fragments confer a larger Van der Waals volume (81.7 $Å^3$ and 87.7 $Å^3$, respectively *vs.* 58.3 $Å^3$ for SCF_3).[¡Error! Marcador no definido.] Thus, higher lipophilicity is expected because of the increase in fluorination degree, although subtle differences in polarity may arise due to the uncommon fluorination patterns (Fig. 1C, right panel).[15] Alike the CF_2H group,[16] examination of the electrostatic potential surface of $PhSCF_2CF_2H$ indicates a terminal electropositive region, suggesting the capability of this group to act as a hydrogen bond donor (Figs. S5 and S6, ESI†). Besides a few *one-pot* nucleophilic/radical methods,[17] to the best of our knowledge, only two *N*-electrophilic sulfenamide reagents have been disclosed by Billard for the introduction of the SCF_2CF_3 motif. However, the electrophilic reactivity shown is limited to the modification of two examples of activated aromatics (phenol and 1,3-dimethoxybenzene), ethynyl lithium, and Grignard nucleophiles.[18] On the other hand, although mechanistically different to the prototypical *N*-electrophilic reagents, the *in situ* generated $^{-}SC_2F_5$ anion from either sulfenamide reagents by Billard[19] or from benzothiazolium reagents by Hopkinson[20]

enabled the formal incorporation of the SCF_2CF_3 motif *via* nucleophilic substitution of halides, tosylates/mesylates, or alcohols, respectively. Concerning the other potentially valuable SCF_2CF_2H fragment, and although recent efforts have been undertaken towards the development of tetrafluoroethylation protocols,[21,22] direct transfer of tetrafluoroethylthioether units still remains uncharted.

Results and discussion

Reagent Design and Development

Willing to develop electrophilic reagents able to transfer the aforementioned thiofluoroalkyl chains, we turned our attention to imide and sulfonamide-based scaffolds. Typically, the N–S–R_F triad in these reagents is constructed by a general nucleophilic approach from either thiolate salts and *N*-Cl compounds (for SCF_3)[23] or $AgCF_2H$ and *N*-SCl precursors (for SCF_2H).[13] However, longer fluoroalkyl thiols show very low stability due to α-fluoride elimination processes.[24] Thus, all our first attempts using the *in situ* generated $M^+ {}^-SC_2F_5$, ($M^+ = Ag^+$, Cu^+, NMe_4^+)[25] were unsuccessful (Fig. 2A). In view of these results, we decided to adjust the synthetic strategy using *electrophilic* ^+SR_F synthons for the preparation of the final electrophilic reagents (Fig. 2B).[26] Thus, chlorination of readily available 1,1,2,2-tetrafluoroethyl **1a** and pentafluoroethyl **1b** benzyl thioethers gave access to key sulfenyl chlorides,[27] which reacted with various imide, and sulfonamide salts to render a family of *N*-reagents **2a**–**8a**, **8b**, featuring succinimide, phthalimide, saccharine, and sulfonamides as representative leaving groups. Importantly, this synthetic protocol uses cheap and widely available starting materials, making it suitable for scaling-up reactions (up to 52 g of **8a** prepared). The choice of the optimal reagent was based on a balance between synthetic yield, reactivity, stability, and cost (Table S1, ESI†). Saccharine-SCF_2CF_2H **8a** and SCF_2CF_3 **8b** exhibited the best overall results (Fig. 2C).[§]

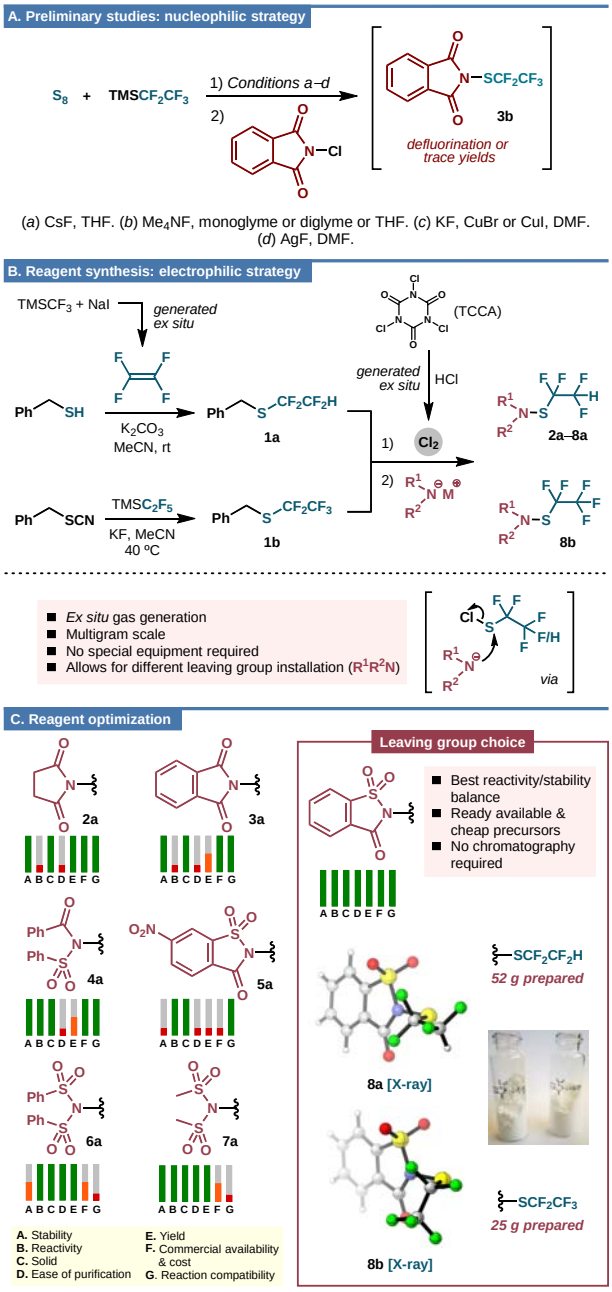
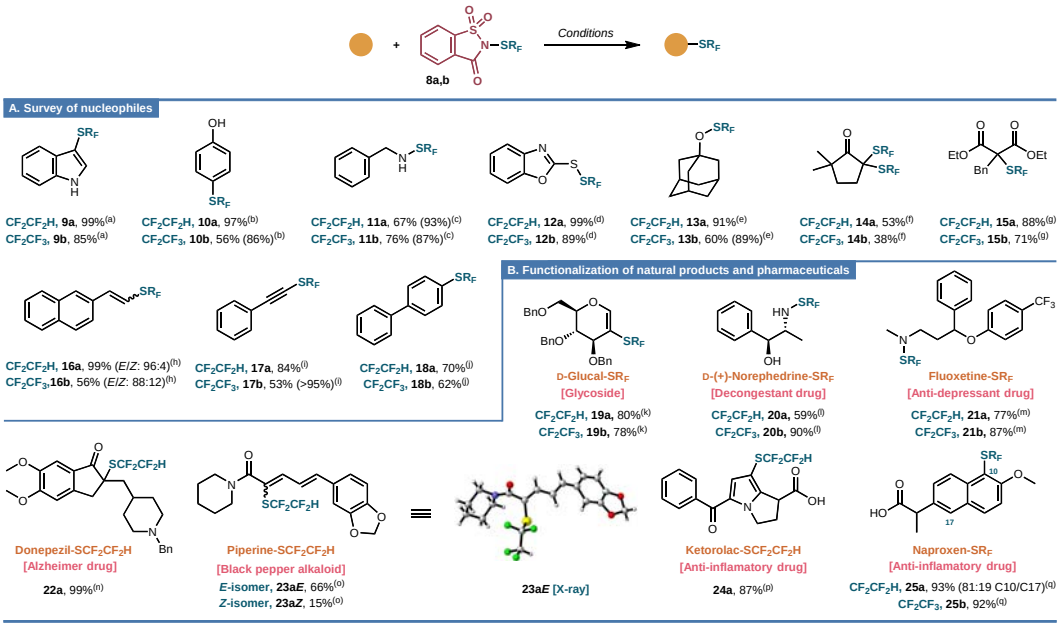


Fig. 2 Preliminary attempts for the preparation of SCF_2CF_3 reagent **3b** using the standard nucleophilic route (*panel A*). *Umpolung* (electrophilic) route to SCF_2CF_2H **2a–8a** and SCF_2CF_3 **8b** reagents (*panel B*). Reagent optimization (*panel C*). See the ESI† for details. TMS = trimethylsilyl, TCCA = trichloroisocyanuric acid.



Scheme 1 Scope of nucleophiles (*panel A*) and functionalization of natural products and pharmaceuticals (*panel B*). *Reagents and conditions*: (a) 1*H*-indole (1.0 equiv), **8a,b** (1.1 equiv), CH_2Cl_2, 40 ºC. (b) PhOH (1.0 equiv), **8a,b** (1.2 equiv), TfOH (1.0 equiv), CH_2Cl_2, rt. (c) $BnNH_2$ (1.0 equiv), **8a,b** (1.1 equiv), CH_2Cl_2, rt. (d) 2-Mercaptobenzoxazole (1.0 equiv), **8a,b** (1.1 equiv), CH_2Cl_2, rt. (e) Adamantol (1.0 equiv), **8a,b** (1.3 equiv), Et_3N (2.5 equiv), CH_2Cl_2, rt. (f) (*i*) 2,2-Dimethylcyclopentan-1-one (1.0 equiv), KHMDS (1.2); (*ii*) **8a,b** (2.5 equiv), THF, –78 ºC. (g) (*i*) Diethyl 2-benzylmalonate (1.0 equiv), NaH (3 equiv); (*ii*) **8a,b** (1.7 equiv), THF, rt. (h) (*i*) 2-Vinylnaphthalene (1.0 equiv), TMSCl (3 equiv), **8a,b** (2.2 equiv); (*ii*) DBU (6 equiv), MeCN, rt. (i) (*i*) Phenylacetlylene (1.0 equiv), *n*-BuLi (1.1 equiv); (*ii*) **8a,b** (1.2 equiv), THF, –78 ºC. (j) (*i*) 4-Bromo-1,1'-biphenyl (1.0 equiv), *n*-BuLi (1.1 equiv); (*ii*) **8a,b** (1.2 equiv), THF, –78 ºC. (k) (*i*) tri-*O*-Benzyl-D-glucal (1.0 equiv), 3 Å MS, TMSCl (3 equiv), **8a,b** (2.2 equiv); (ii) DBU (6 equiv), MeCN, rt. (l) (1*S*,2*R*)-(+)-Norephedrine (1.0 equiv), **8a,b** (3 equiv), CH_2Cl_2, rt. (m) Fluoxetine (1.0 equiv), **8a,b** (1.5 equiv), Et_3N (1.1 equiv), CH_2Cl_2, rt. (n) (*i*) Donepezil (1.0 equiv), KHMDS (1.3 equiv); (*ii*) **8a** (1.3 equiv), THF, –78 ºC. (o) Piperine (1.0 equiv), **8a** (2.2 equiv), TMSCl (1.2 equiv), CH_2Cl_2, rt. (p) Ketorolac (1.0 equiv), **8a** (2.0 equiv), TMSCl (2 equiv), CH_2Cl_2, rt. (q) *rac*-Naproxen (1.0 equiv), **8a,b** (1.5 equiv), TfOH (1.2 equiv), $CHCl_3$, 40 ºC (for **25a**) or 70 ºC (for **25b**). Isolated yields given. Yields in parenthesis were determined by ^{19}F NMR using 1,4-difluorobenzene (DFB) as internal standard (see the ESI† for details). MS = molecular sieves, TfOH = trifluoromethanesulfonic acid, HMDS = hexamethyldisilazane, THF = tetrahydrofuran, TMS = trimethylsilyl, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.

Both reagents showed robust stability not only in the solid state but also in solution. No detectable decomposition in non-polar solvents after heating up to 50 ºC for prolonged reaction times (> 1 week) was observed for **8a**. In contrast, some polar (DMF, THF) and protic (H_2O) solvents promote slight to high decomposition rates, which are accelerated by temperature (Fig. S1, ESI†). Moreover, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) demonstrated the thermal stability of reagents **8a,b** (Figs. S2 and S3, ESI†).

Reaction Scope

With the optimal reagents in hand, their applicability was first evaluated with representative nucleophiles (Scheme 1A). First, a preliminary solvent compatibility study of **8a** with *N*-H indole demonstrated that solvents of different nature

(chlorinated, aprotic polar, and aprotic non-polar solvents) do not substantially affect the performance of the reaction with yields of **9a** up to >95% (Fig. S4, ESI†). Thus, reaction of *N*-H indole in CH_2Cl_2 with **8a,b** afforded **9a** (99%) and **9b** (85%) after heating at 40 ºC for 1 h or 24 h, respectively. Reaction with phenol required the addition of TfOH as a promoter and afforded **10a** (97%) and **10b** (86%). Next, we assayed the suitability of other nucleophiles to afford N–, O–, and S–SR_F bonds.[28] Thus, reaction with benzylamine gave the desired products **11a** (93%) and **11b** (87%) after 1 h at room temperature, while reaction with 2-mercaptobenzoxazole afforded instantaneously disulfides **12a** (99%) and **12b** (89%). Unlike phenol, which required a protic acid that activates the electrophilic reagent, preliminary results with alcoholic nucleophiles indicate the necessity of an exogenous base (*e.g.*, Et_3N) to deprotonate the hydroxyl moiety and deliver the desired products. Thus, adamantol derivatives **13a** (91%) and **13b** (89%) were obtained after 1 h at room temperature, using Et_3N as a base. Reactions with the preformed enolate of 2,2-dimethylcyclopentanone afforded the double substitution products **14a** (53%) and **14b** (38%). Attempts to selectively obtain the monosubstituted product were unsuccessful due to the increased reactivity of the monosubstituted intermediate. Treatment of diethyl benzylmalonate with sodium hydride (NaH) and subsequent reaction with **8a,b** afforded **15a** and **15b** in 88% and 71% yield, respectively. Alkenes are also suitable nucleophiles as demonstrated with 2-vinylnaphthalene, using an addition/elimination sequence that afforded *E*/*Z* mixtures (up to 96:4) of vinylic SCF_2CF_2H **16a** (99%) and SCF_2CF_3 **16b** (56%). Whilst treatment of phenylacetylene with **8a** in the presence of CuBr failed to deliver the desired product,[18] reaction of the alkyne with *n*-BuLi and subsequent reaction with **8a,b** rendered **17a** (84%) and **17b** (>95%). Similarly, generation of the organolithium intermediate from 4-bromobiphenyl by lithium-bromine exchange afforded **18a** (70%) and **18b** (62%) after subsequent reaction with **8a,b**.

Next, having demonstrated the versatility of our reagents with model nucleophiles, we aimed to evaluate their efficiency for the direct/late-stage modification of natural products and pharmaceuticals (Scheme 1B).[29] First, the aforementioned addition/elimination protocol also worked well for the benzyl-protected D-glucal to afford **19a** (80%) and **19b** (78%).[30] Interestingly, despite the large volume of SCF_2CF_3 and SCF_2CF_2H groups, they have less impact on the conformation of 2-substituted-D-glucals than their alkyl (*e.g.*, CF_2CF_3, CF_3) counterparts as indicated by the analysis of diagnostic coupling constants $^3J_{3,4}$ = 4–4.6 Hz and $^3J_{4,5}$ = 5–5.8 Hz (intermediate conformation deformed towards the $^5H_4$) (Fig. S7, ESI†).[31,32] (+)-Norephedrine was chemoselectively *N*-modified to **20a** (59%) and **20b** (90%) under mild reaction conditions without competitive *O*-substitution. The secondary amine of fluoxetine (Prozac™) also reacted successfully to deliver **21a,b** in 77% and 87% yield, respectively. Donepezil, a drug used in the treatment of Alzheimer's disease, was reacted with potassium bis(trimethylsilyl)amide (KHMDS) to generate the enolate that subsequently reacted with **8a** to afford **22a** in an excellent 99% yield. Similarly to 2-vinylnaphthalene and D-glucal, the use of the same addition/elimination protocol with piperine (black pepper alkaloid) and **8a** in the presence of trimethylsilyl chloride (TMSCl) as a promoter, afforded **23a** as a separable mixture of *E*/*Z*-isomers **23a*E*** (66%) and **23a*Z*** (15%), resulting from the modification of the conjugated diene system as determined by NMR and X-ray (for the *E*-isomer)[§] analysis. Reaction of **8a** with ketorolac, an anti-inflammatory agent, afforded **24a** (87%) with the exclusive modification of the pyrrole moiety thus, demonstrating the compatibility of our reagent **8a** with carboxylic acids. Finally, when naproxen was reacted with **8a** and TfOH as a promoter, **25a** (93%) was obtained as an 81:19 mixture of C10/C17 regioisomers. In contrast, reaction with **8b** afforded **25b** (92%) as the sole C10-isomer.

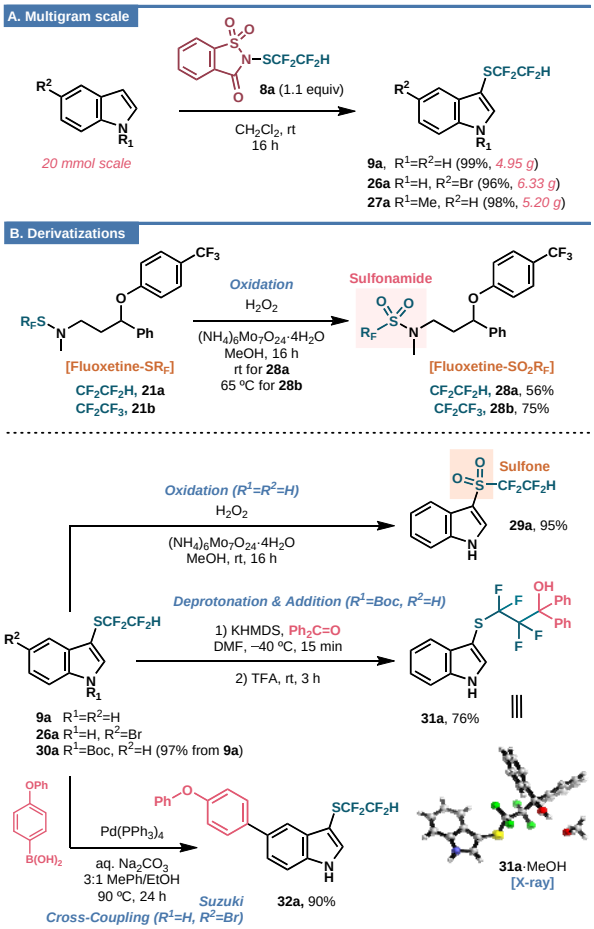


Fig. 3 Multigram-scale preparation of tetrafluoroethylthio indoles (*panel A*) and derivatization reactions (*panel B*). See the ESI† for details. Boc = *tert*-butoxycarbonyl, DMF = *N,N*-dimethylformamide, HMDS = hexamethyldisilazane, TFA = trifluoroacetic acid.

Large Scale and Derivatization

Next, multigram-scale reactions (20 mmol) with a series of unprotected and *N*-Me-protected indoles afforded gram amounts of the corresponding SCF_2CF_2H-analogues **9a**, **26a**, and **27a** with yields up to 99% (Fig. 3A). Notably, reaction crudes are substantially clean and only excess of **8a** and saccharine are observed, which indeed can be simply removed by sequential washings with aqueous Na_2CO_3. Because the 1,1,2,2-tetrafluoroethylthio moiety represents an interesting platform for accessing other compounds, various derivatization reactions were evaluated (Fig. 3B). First, sulfenamide fluoxetine derivatives **21a,b** were oxidized to sulfonamides **28a** (56%) and **28b** (75%) using H_2O_2 and a molybdenum catalyst. This methodology represents an overall workable strategy to obtain uncommon, fluorinated sulfonamides (Fig. 3B, upper panel). Noteworthy, the same oxidation conditions could be applied to the oxidation of thioether **9a** to the corresponding sulfone **29a** (95%) (Fig. 3B, lower panel). Next, after *N*-Boc protection of indole **9a** to **30a** (Boc_2O, Et_3N, CH_2Cl_2, rt, 16 h, 97%), the SCF_2CF_2H moiety of product **30a** was deprotonated with KHMDS and the resulting carbanion quenched with benzophenone. Finally, *N*-Boc removal with TFA gave access to CF_2CF_2-bridged **31a** in 76% yield (suitable for X-ray diffraction).[§] This strategy serves as a proof of concept for the functionalization with electrophiles of terminal SCF_2CF_2H-containing compounds.[22] Finally, Suzuki cross-coupling of 5-bromoindole **26a** with an aryl boronic

acid partner smoothly afforded **32a** in an excellent 90% yield, thus demonstrating group compatibility with Pd-catalyzed transformations.

Conclusions

In summary, two new reagents for the direct introduction of SCF_2CF_2H and SCF_2CF_3 motifs have been disclosed. These electrophilic agents are synthetized in three steps from simple and readily available starting materials and can be obtained in a multigram scale. Electrophilic introduction has proven successful in a range of different nucleophiles, including amines, alcohols, thiols, electron-rich (hetero)aromatics, phenols, ketones, 1,3-diesters, and alkenes as well as organolithium alkyne and arene derivatives. The robustness of the transformation, including its operational/purification simplicity has been further demonstrated with a range of complex structures, including blockbuster drugs and natural products. Gram-scale reactions and product derivatization to sulfones, sulfonamides, and deprotonation of SCF_2CF_2H-addition to electrophiles as well as orthogonal metal-mediated reactions have also been demonstrated. We expect our findings will provide new opportunities in drug and agrochemical discovery by expanding the toolbox of reagents for the introduction of new fluorinated motifs into natural products and active ingredients.

Author Contributions

J.M and M.B. performed all the experiments. O.B. supervised the project. O.B. and S.C. were responsible for funding acquisition. All the authors contributed to the preparation of the manuscript.

Conflicts of interest

The authors are co-inventors on a patent application (PCT/EP2021/067690) that incorporates discoveries described in this manuscript.

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Notes and references

§ CCDC deposition numbers 2099949 (**8a**), 2099951 (**8b**), 2099950 (**23a*E***), and 2099948 (**31a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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