Bifluoride Ion Mediated SuFEx Trifluoromethylation of Sulfonyl Fluorides and Iminosulfur Oxydifluorides

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Abstract: Sulfur-Fluoride Exchange (SuFEx) is the new generation click chemistry transformation exploiting the unique properties of S-F bonds and their ability to undergo near-perfect reactions with nucleophiles. We report here the first SuFEx based protocol for the efficient synthesis of pharmaceutically important triflones and bis(trifluoromethyl)sulfur oxyimines from the corresponding sulfonyl fluorides and iminosulfur oxydifluorides, respectively. The new protocol involves the rapid exchange of the S-F bond with trifluoromethyltrimethylsilane ($TMSCF_3$) upon activation with potassium bifluoride in anhydrous DMSO. The reaction tolerates a wide selection of substrates and proceeds under mild conditions without need for chromatographic purification. A tentative catalytic mechanism is proposed supported by DFT calculations, involving formation of the free trifluoromethyl anion followed by nucleophilic displacement of the S-F through a five-coordinate intermediate. The preparation of a benzothiazole derived bis(trifluoromethyl)sulfur oxyimine with cytotoxic selectivity for MCF7 breast cancer cells demonstrates the utility of this methodology for the late-stage functionalization of bioactive molecules.

Click chemistry is a synthesis technology designed to support the ever-growing need for reliable reactions to create functional molecules.[1] Since first described in 2001, it has had a profound impact on modern science and is a significant development in enabling the building of chemical libraries. The Sulfur-Fluoride Exchange (SuFEx) reaction developed by the Sharpless group in 2014 represents a new generation of near-perfect metal-free click chemistry transformations.[2] SuFEx exploits the unique balance between stability and reactivity of high oxidation state sulfur-fluoride functionalities (e.g. sulfonyl fluorides), which unlike their S-Cl counterparts are resilient to reductive collapse, leaving a clear pathway for S-F exchange.

Key to SuFEx reactivity is the special ability of fluoride ion to transit from a strong covalent bond to a leaving group, which is assisted by interactions with "H^+" or "R_3Si^+" in close under strict kinetic and spatial constraints catalyzed by suitable nitrogen Lewis bases (e.g. Et_3N, DBU)[2,3] and also thought to involve bifluoride counterion species.[4] These conditions promote S-F exchange with nucleophiles such as aryl silyl ethers and amines to give the corresponding S-O and S-N bonds, respectively. As with all click reactions, SuFEx exhibits a combination of strong thermodynamic driving forces and consistent well-controlled reaction pathways, rendering them robust and reliable for a wide range of applications.[5]

A unique feature of SuFEx is the availability of SuFExable building blocks, which serve as connective hubs for creating new linkages. These include the connective gases: sulfuryl fluoride (SO_2F_2)[2] and thionyl tetrafluoride ($O{=}SF_4$),[6] which allow modules to be united through a single sulfur hub by nucleophilic exchange; and the sulfonyl fluoride based connectors ethenesulfonyl fluoride (ESF)[2,7] and 1-bromoethene-1-sulfonyl fluoride (BESF),[8] which offer additional connective pathways through 1,4-addition and cycloaddition chemistry (Figure 1A).

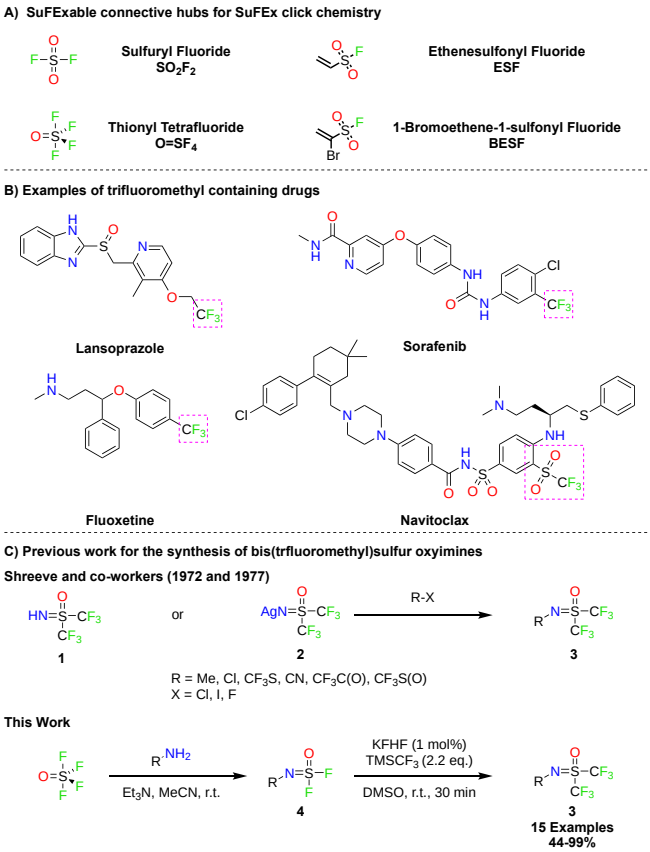


Figure 1. A) Examples of connective SuFEx hubs; B) A selection of drugs containing the trifluoromethyl functionality; C) Synthesis of a selection of simple inorganic bis(trifluoromethyl)sulfur oxyimines by Shreeve and co-workers, an overview of this work.

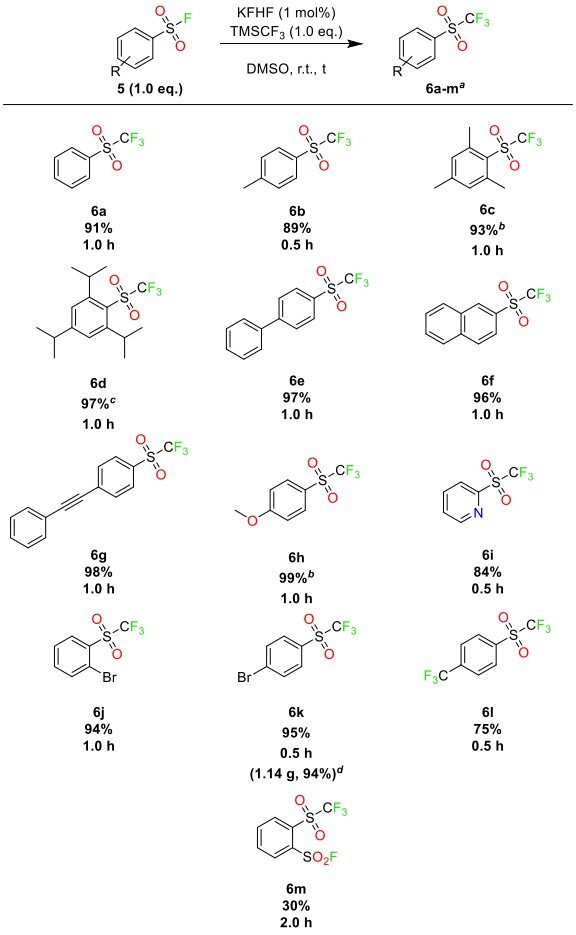
Expanding the repertoire of available SuFEx transformations, we report here the development of a straightforward and efficient SuFEx trifluoromethylation protocol for the incorporation of trifluoromethyl group into biologically relevant molecules. The method exploits the stability and tolerance of SuFExable sulfonyl fluorides and iminosulfur oxydifluorides to late-stage S-F exchange. Using a combination of the

silyl-capped carbon nucleophile trifluoromethyltrimethylsilane (Ruppert's reagent, $TMSCF_3$) and bifluoride, the new SuFEx protocol delivers pharmaceutically relevant trifluoromethyl sulfones and bis(trifluoromethyl)sulfur oxyimines in excellent yield. This is significant because fluorine is an important hydrogen bioisostere, and the selective incorporation of fluorine rich functionality into therapeutic or diagnostic small molecules can impart many desirable pharmacokinetic and physicochemical properties. These include metabolic stability, increased lipophilicity, enhanced binding interaction (due to electrostatic interactions) and efficacy, whilst also changing physical and metabolic properties.[9,10] Several major pharmaceutical drugs contain a $-CF_3$ group, including the proton-pump inhibitor lansoprazole; the anti-cancer drug sorafenib and the blockbuster antidepressant fluoxetine (Figure 1B). As such, there has been increasing interest in the development of novel trifluoromethylation protocols, including through direct nucleophilic or electrophilic addition, radical and organometallic methodologies.[9]

The development of a reliable and robust SuFEx protocol for incorporating $-CF_3$ groups into molecules through the formation of S(VI)-CF_3 bonds was therefore considered highly desirable for a number of reasons: 1) sulfur bound-CF_3 has much potential in drug development, as exemplified by the experimental anti-cancer drug navitoclax (Figure 1B),[11] which comprises an aryl triflone moiety; 2) compared to the more common S-Cl functionality, S-F bonds are stable and allow for late-stage functionalization;[12] and 3) it would allow access and exploration of new and unprecedented sulfur bound-CF_3 functionality like bis(trifluoromethyl)sulfur oxyimines, which themselves represent a novel class of fluorine-rich substrate that have scarcely been reported (Figure 1C).

To investigate the SuFEx chemistry of $TMSCF_3$ we first explored the conversion of sulfonyl fluorides to the corresponding trifluoromethyl sulfones. This transformation, and related,[13] had been reported with moderate success using $TMSCF_3$ and TBAF, although due to the inevitable presence of water in the reagent mixture, the nature of the fluoride is uncertain because TBAF samples are almost always hydrated. This results in the formation of bifluoride (HF_2^-), hydroxide (OH^-) as well as fluoride ions; hence an excess of $TMSCF_3$ is often required to compensate for reagent decomposition.[14] We anticipated that under anhydrous conditions and with a pure source of a bifluoride ion catalyst, the SuFEx trifluoromethylation would be significantly improved. Thus, a reaction screen was performed using 4-toluenesulfonyl fluoride and potassium bifluoride (KFHF) salt as the SuFEx catalyst (SI, T1). A low catalyst loading (1 mol%) of KFHF was found to be satisfactory when used in combination with 1 equivalent of $TMSCF_3$ in anhydrous DMSO.[15] We observed that anhydrous polar aprotic solvents were critical for the reaction, presumably due to improved solubility of the catalyst, with DMSO identified as the solvent of choice to ensure full conversion to the target products in under 30 min (SI, T1).[16] Attempts to perform the reaction using potassium fluoride in DMSO were unsuccessful. The use of the KFHF salt offers many advantages as it is cost effective, less-hygroscopic and can be easily removed through aqueous workup compared to organic onium bifluorides which require extra purification steps.

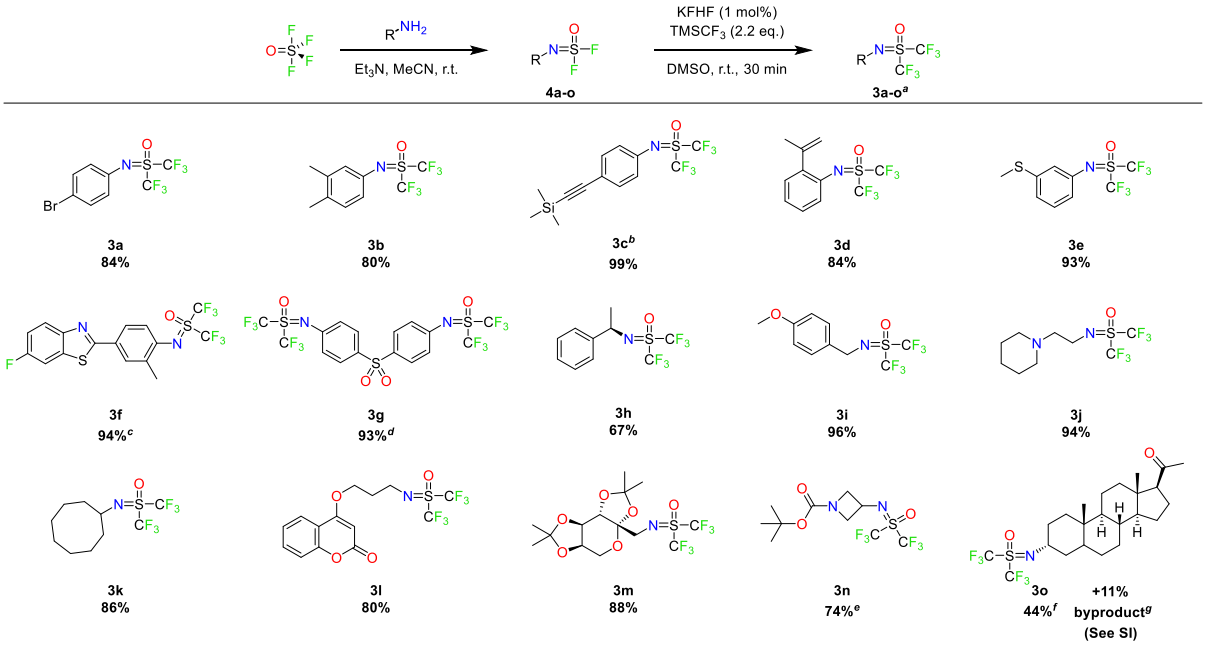
The optimal reaction conditions were compatible with a wide range of substrates (Scheme 1, **6a**-**6m**),[17] resulting in good yields (30-98%), including sterically hindered (**6c** and **6d**) and electron-rich substrates (**6h**), which required longer reaction times and increased loadings of KFHF (5-20 mol%). The protocol is also amenable to gram scale synthesis (**6k**) without compromising yield.[18]



Scheme 1. Synthesis of triflones; [a] Isolated yields, reactions performed on 1.3 mmol of the sulfonyl fluoride; [b] 5 mol% KFHF used; [c] 20 mol% KFHF and 1.2 eq. $TMSCF_3$ used; [d] Reaction performed on 3.5 mmol of the sulfonyl fluoride, 1.0 h reaction time.

We next explored the new SuFEx trifluoromethylation protocol to access the scarcely known bis(trifluoromethyl)sulfuroxyimines **3**, from the corresponding iminosulfur oxydifluorides. This particular conversion had no prior precedence, presumably due to the limited availability of the iminosulfur oxydifluoride starting materials.[6] We find only 9 examples of related bis(trifluoromethyl)sulfur oxyimine (**3**) compounds in the literature,[19] themselves synthesized primarily by the alkylation of bis(trifluoromethyl)sulfur oxyimine ($(CF_3)_2S(O)=NH$ (**1**), or the corresponding silver salt $(CF_3)_2S(O)=NAg$ (**2**) with alkyl halides, trifluoromethylsulfinyl fluoride, cyanogen chloride, trimethylsilyl chloride and trifluoromethylsulfenyl chloride (Figure 1C).[19a]

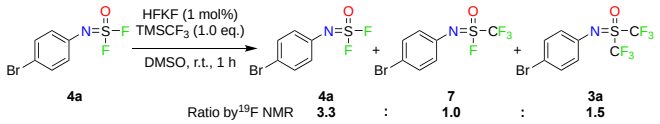
To further develop the family of bis(trifluoromethyl)sulfur oxyimine compounds, a selection of iminosulfur oxydifluorides (**4a**-**o**) were prepared from the reaction of $O{=}SF_4$ gas with the corresponding primary amines using previously reported SuFEx conditions.[6] Using a modified protocol with a slight excess of $TMSCF_3$ (2.2 equivalents), full consumption of the iminosulfur oxydifluoride starting materials was observed (determined by ^{19}F NMR), giving rise to the target bis(trifluoromethyl)sulfur oxyimine products **3a**-**o** in excellent yield (Scheme 2). The new SuFEx protocol is compatible with a wide array of iminosulfur oxydifluorides, including aromatic (**3a**-**g**) and benzyl (**3h**-**i**), while in the case of 4-ethynylbenzeneiminosulfur oxydifluoride, trimethylsilylation of the terminal alkyne also occurred to give the bis-trifluoromethylated product **3c**. Finally, we observed that the method could be applied to a set of aliphatic substrates (**3h**-**o**), with the target products isolated in excellent yield; including compounds containing a high density of heteroatoms (**3l**-**o**).[20] Applying the conditions to the steroid based iminosulfur oxydifluoride **4o** required increased equivalents of $TMSCF_3$ (6.6 eq.) and KFHF (21 mol%) to facilitate full conversion of the starting material due to the electrophilic ketone group present. In this case, the bis(trifluoromethyl)sulfur oxyimine **3o** was isolated in 44% yield along with a byproduct (See SI).[21] The inclusion of the CF_3 group through the bis(trifluoromethyl)sulfur oxyimine may offer significant potential in cases where the modifying of lipophilic properties (CLogP) are required, for example the CLogP of **3a** is 3.13 a dramatic increase compared to the parent 4-bromoaniline and **4a** with CLogP values of 1.78 and 1.43 respectively.[22]



Scheme 2. Synthesis of bis(trifluoromethyl)sulfur oxyimines; [a] Isolated yields from the conversion of iminosulfur oxydifluorides **4** to the bis(trifluoromethyl)sulfur oxyimine products **3**, reactions performed on 0.25 mmol of the iminosulfur oxydifluoride; [b] Terminal alkyne of iminosulfur oxydifluoride used; [c] Total of 11% KFHF used, 2 h reaction time; [d] 4.4 eq. $TMSCF_3$ used; [e] Total of 21 mol% KFHF and 4.4 eq. $TMSCF_3$ used, 3.0 h reaction time; [f] Total of 21 mol% KFHF and 6.6 eq. $TMSCF_3$, 5.0 h reaction time; [g] 11% of by product observed (See SI).

Limiting the amount of trifluoromethylation reagent $TMSCF_3$ to 1 eq. led to a complex and inseparable mixture of the fluorosulfonimidoyl triflone **7** and bis(trifluoromethyl)sulfur oxyimine **3a** products, along

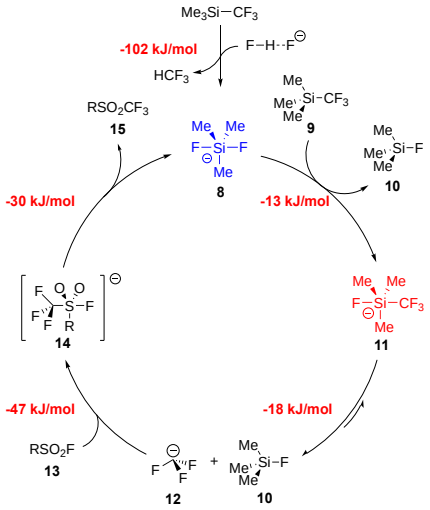
with unreacted starting material (Scheme 3). Unlike introducing an amino or aryloxy group leading to higher inertness over the iminosulfur oxydifluoride precursor, the mono-trifluoromethylated product is more activated to exchange than its parent compound.



Scheme 3. The reaction of **4a** with 1 eq. of $TMSCF_3$ under SuFEx conditions (ratio estimated from the integration of ^{19}F NMR).

Until very recently the mechanism of anion-initiated trifluoromethylation remained unclear, with previous mechanistic proposals suggesting the involvement of both siliconate and carbanion pathways.[23] A comprehensive mechanistic study by Lloyd-Jones and co-workers of the trifluoromethylation of ketones and aldehydes with $TMSCF_3$ has helped resolve the siliconate-carbanion dichotomy.[24] They used a combination of stopped-flow NMR/IR studies and DFT calculations to discern that the direct transfer of CF_3 from siliconate species to carbonyl electrophiles is kinetically prohibited due to the very high barrier of inversion for the CF_3 anion, which subsequently necessitates involvement of "free" CF_3 anion rather than a CF_3-siliconate species. Their calculations also indicated that reactions with ketones and aldehydes proceeded *via* a lower-barrier process involving attack of the electrophile by a "free" CF_3 anion arising from rapid and reversible CF_3 dissociation from the siliconate.[24]

To date, the pathways empowering SuFEx catalysis remain a matter of conjecture, although interactions with "H^+" or "R_3Si^+" in the SuFEx transition state have been suggested.[2] Here we tentatively propose a bifluoride initiated pathway (Scheme 4) on the basis of theoretical calculations.[25] Initial formation of a siliconate complex (**8**) occurs through the reaction of bifluoride and $TMSCF_3$ to release fluoroform (ΔG = -102 kJ/mol). The siliconate complex can then react with a second $TMSCF_3$ molecule to form the readily reported siliconate species (**11**) and TMSF (**10**) with ΔG of -12 kJ/mol. Reversible dissociation of CF_3 from the siliconate (**11**) gives the necessary "free" CF_3 anion (**12**) and TMSF (**10**), followed by nucleophilic attack of **12** at the activated electrophilic sulfur center to yield a five-coordinate sulfur intermediate (**14**)[25] with ΔG of -47 kJ/mol. Dissociation of the fluoride reforms the siliconate complex (**8**), releasing the triflone product (**15**) and regenerating the possible catalytically active species, difluorotrimethylsilicate with ΔG of -30 kJ/mol.



Scheme 4. Proposed mechanism for the bifluoride catalyzed transformation of sulfonyl fluorides to triflones, including calculated free energies (ΔG).

Finally, to demonstrate the utility of SuFEx trifluoromethylation to a functional, biologically relevant compound, and to probe the biocompatibility of the underexplored bis(trifluoromethyl)sulfur oxyimine functional group, the benzothiazole derived bis(trifluoromethyl)sulfur oxyimine **3f** was synthesized from the corresponding iminosulfur oxydifluoride **4f** (Scheme 2). Benzothiazole compounds have been shown to possess significant anticancer activity, operating via a complex mechanism that culminates in the formation of reactive nitrenium species, which themselves form DNA adducts ultimately leading to cell death.[26] The in vitro bioactivity of the bis(trifluoromethyl)sulfur oxyimine **3f** was examined against MCF7 breast cancer and MCF10A mammary epithelial cells, revealing a significant degree of selectivity towards the cancerous cells with an IC_{50} of 0.60 μM against MCF7 (Figure 2A). In contrast, at the concentration range utilized, only 57% cell death was observed for MCF10A and therefore the IC_{50} would exceed 50 μM when higher concentrations are administered (Figure 2A). Fluorescence imaging clearly shows uptake of compound **3f** in both MCF7 and MCF10A cells (Figure 2B). Collectively, for the first time, these results demonstrate the potential of the bis(trifluoromethyl)sulfur oxyimine functional group in a biological setting, which may offer significant benefits in future drug discovery and optimization studies where biocompatible fluorine rich functionalities are desired.

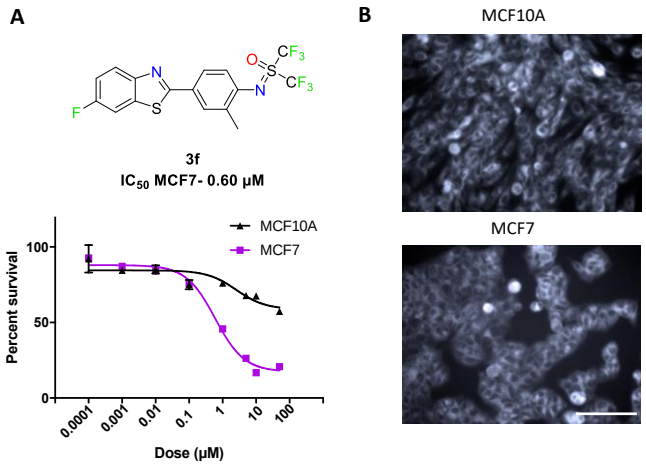


Figure 2. A) Benzothiazole compound **3f** synthesized by the method in Scheme 2 and tested against MCF7 and MCF10A. MCF7 breast cancer cells and MCF10A breast cells, seeded at $4x10^3$ cells/well were treated for 72 h with **3f**. Cell viability was assessed by an MTT assay. Readings from experimental duplicates with technical triplicates were averaged and calculated as percentage survival compared to DMSO control, error bars indicate SEM; B) **3f** was dosed to breast normal (MCF10A) or cancer (MCF7) cells following 24 h of growth. Fifty minutes after compound addition images were acquired using the LionHeart FX live imaging system. Scale bar represents 100 µm.

In conclusion, we have developed an efficient and robust bifluoride ion catalyzed SuFEx click chemistry protocol for the synthesis of trifluoromethyl sulfones, and previously underrepresented bis(trifluoromethyl)sulfur oxyimines. The reactions are fast, high yielding and require only sub-stoichiometric amounts of the bifluoride catalyst KFHF. We tentatively propose a mechanism involving bifluoride activation of $TMSCF_3$ to produce the necessary free CF_3 anion, yielding a five-coordinate sulfur intermediate that weakens the S-F bond allowing dissociation of fluoride to reform the siliconate intermediate (**8**). With increasing interest into methods for installing trifluoromethyl functionality into drugs and drug candidates, we believe that this new SuFEx click chemistry protocol will find wide application in drug discovery, as demonstrated by the synthesis of the bis(trifluoromethyl)sulfur oxyimine **3f**—a benzothiazole derived compound with selective cytotoxicity activity against MCF7 breast cancer cells.

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Keywords: SuFEx • click chemistry • fluorine • trifluoromethylation • bis(trifluoromethyl)sulfur oxyimine • bifluoride mediated •

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[14] a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *57*, 757-786; b) Moderately improved yields have been achieved by Yagupolski and co-workers (see reference 11a) using catalytic quantities of anhydrous TASF (10 mol%) and 2 equivalents of $TMSCF_3$, although with only a very small substrate scope.

[15] When reagent grade DMSO was used no conversion to the desired product was observed (SI, T1).

[16] The use of DMF as the reaction solvent during optimisation (see SI) led to full consumption of the starting material under the reaction conditions however, an unknown by-product was observed by ^{19}F NMR.

[17] The optimal conditions for the procedure were found to be: 1 eq. sulfonyl fluoride, 1 eq. $TMSCF_3$, 1 mol% KFHF in anhydrous DMSO for 30 min.

[18] The bis-trifluoromethylated analogue of **6m** was not observed.

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[20] For some substrates (**4f**, **4n** and **4o**) separate conditions were required to obtain full conversion to the corresponding products, which included increasing the amount of KFHF and $TMSCF_3$.

[21] A by-product was also formed through the nucleophilic addition of CF_3 to the carbonyl moiety followed by TMS protection of the resultant alcohol in an 11% yield.

[22] CLogP was calculated using ChemDraw Professional 16.0, **2016** PerkinElmer Infomatics, Inc.

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[25] DSDPBEP86/def2-TZVPP//B3LYP-D3(BJ)/6-31+G(d) all with implicit DMSO solvent (see SI). All species in Scheme 4 are minima. While the five-coordinate sulfur intermediate (**14**) resembles an S_N2 transition state, **14** is a minima; the calculated S_N2 barrier for CF_3 replacing F is *ca*. 80 kJ/mol, which is higher than is expected for the true TS.

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