Bifluoride Ion Catalyzed Late-Stage SuFEx Trifluoromethylation of Sulfonyl Fluorides and Iminosulfur Oxydifluorides

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Abstract: Sulfur-Fluoride Exchange (SuFEx) is a new generation click chemistry transformation that exploits 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 late-stage synthesis of pharmaceutically important trifluoromethyl sulfones 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 ($TMSCF_3$, Ruppert's reagent), upon activation with catalytic potassium bifluoride in anhydrous DMSO. The reaction tolerates a wide selection of substrates and proceeds under mild conditions without need for chromatographic purification. DFT calculations provide the first reported mechanism of anhydrous SuFEx reactivity, which confirms catalytic bifluoride behaviour with a five-coordinate sulfur 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 a 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) and also thought to involve bifluoride counterion species. 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.[3]

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 (SOF_4),[4] which allow modules to be united through a single sulfur hub by nucleophilic exchange; and the sulfonyl fluoride based connectors ethenesulfonyl fluoride (ESF)[2,5] and 1-bromoethene-1-sulfonyl fluoride (BESF),[6] which offer additional connective pathways through 1,4-addition and cycloaddition chemistry (Figure 1A).

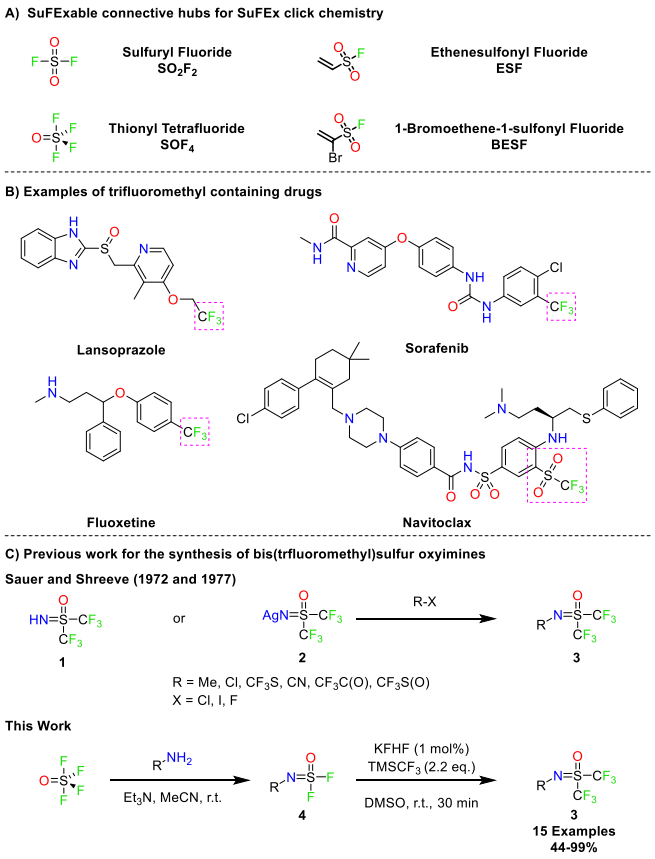


Figure 1. A) Examples of connective SuFEx hubs; B) A selection of drugs comprising the trifluoromethyl functionality; C) Synthesis of a selection of simple bis(trifluoromethyl)sulfur oxyimines by Sauer and Shreeve, an overview of this work.

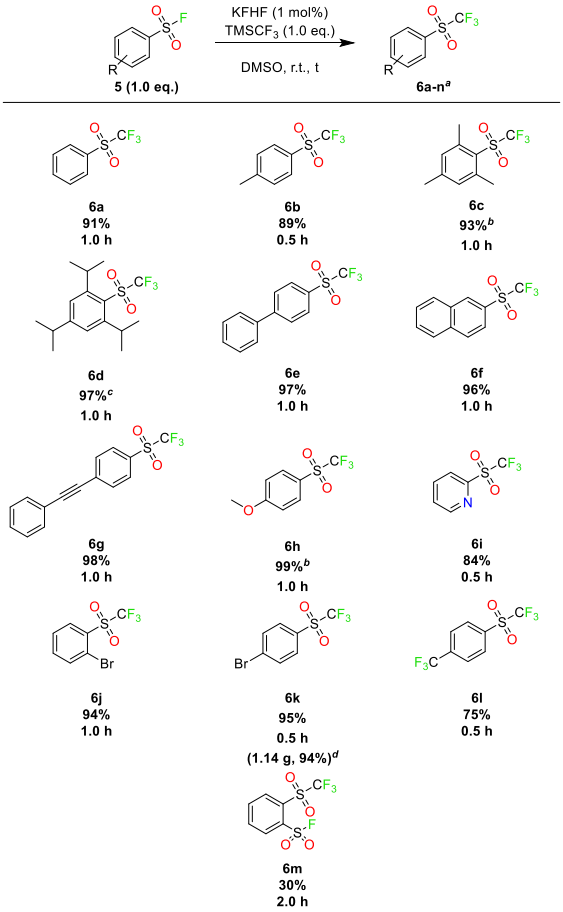
Expanding the repertoire of available SuFEx transformations, we report here the development of a straightforward and efficient SuFEx trifluoromethylation protocol for the incorporation of fluorine into biologically relevant molecules. The method exploits the stability and tolerance of SuFExable sulfonyl

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 ion catalysis, 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 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.[7,8] Several major pharmaceutical drugs incorporate 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 a dramatic increase in trifluoromethylation protocols for incorporating the trifluoromethyl group through direct nucleophilic or electrophilic addition, radical and organometallic methodologies.[7c].

The development of a reliable and robust SuFEx protocol for incorporating $-CF_3$ groups into molecules through the formation of $S-CF_3$ 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)[9] which contains an aryl trifluoromethyl sulfone moiety. However, due to a lack of convenient and suitable trifluoromethylation protocols of high oxidation sulfur-fluoride compounds there are limited drugs which contain $S-CF_3$ functionalities; 2) compared to the more common S-Cl functionality, S-F bonds are stable and allow for late stage functionalization;[10] 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 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 a large excess of $TMSCF_3$ is often required to compensate for reagent decomposition.[11] We anticipated that under anhydrous conditions and with a clean source of a bifluoride ion catalyst, the SuFEx trifluoromethylation would be dramatically 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.[12] We observed that anhydrous polar aprotic solvents were critical for the reaction, presumably due to improved solubility of the catalyst; DMSO was identified as optimal for ensuring full conversion to the target products in 30 min (SI, T1).[13] Attempts to perform the reaction using an alternative fluoride salt, such as potassium fluoride, was unsuccessful, with only trace amounts of product observed (SI, T1).

The optimal reaction conditions were compatible with a wide range of substrates (Scheme 1, **6a**-**6m**), resulting in excellent 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.[14]

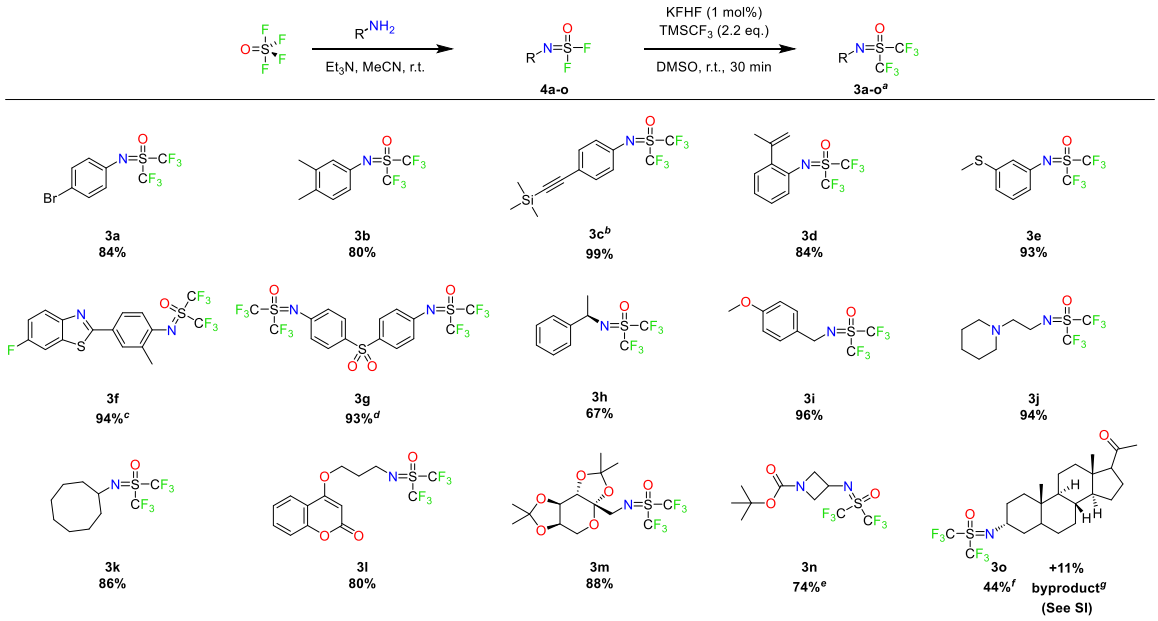


Scheme 1. Synthesis of trifluoromethyl sulfones; [a] Isolated yields, reactions performed on 1.3 mmol of the sulfonyl fluoride; [b] 5 mol% KFHF used; [c] 20 mol% KFHF and 1.2 eq. $TMSCF_3$ used; [d] Reaction performed on 3.5 mmol of the sulfonyl fluoride, 1.0 h reaction time.

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, until now, limited availability of the iminosulfur oxydifluorides starting materials.[4] We find only 9 examples of related bis(trifluoromethyl)sulfur oxyimine (**3**) compounds in the literature;[15] synthesized primarily by the alkylation of bis(trifluoromethyl)sulfur oxyimine (or its silver salt) with alkyl halides, trifluoromethylsulfinyl fluoride, cyanogen chloride, trimethylsilyl chloride and trifluoromethylsulfenyl chloride.[15a]

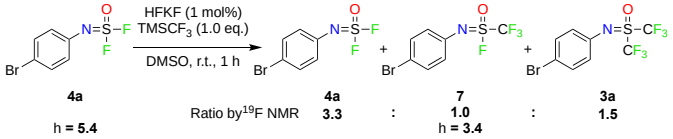
To further develop this novel family of bis(trifluoromethyl)sulfur oxyimine compounds, a selection of iminosulfur oxydifluorides (**4a**-**o**) were prepared from the reaction of SOF_4 with the corresponding

primary amines.[4] 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**).[16] 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. In this event, the bis(trifluoromethyl)sulfur oxyimine **3o** was isolated in 44% yield along with a byproduct (See SI).[17]



Scheme 2. Synthesis of bis(trifluoromethyl)sulfur oxyimines; [a] Isolated yields, 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).

The attempted mono-trifluoromethylation of **4a** using 1 eq. of $TMSCF_3$ led to a complex and inseparable mixture of the mono- **7** and bis-trifluoromethylated **3a** products, along with unreacted starting material (Scheme 3). This is consistent with the calculated chemical hardness (**η**) values for **4a** (**η** = 5.4) and **7** (**η** = 3.4), which indicate that the mono-trifluoromethylation product **7** is more activated to exchange than the starting material **4a** (lower **η** values suggest increased reactivity).



Scheme 3. Attempted mono-trifluoromethylation of **4a**, (ratio estimated from the integration of ^{19}F NMR) and the calculated chemical hardness (**η**) values of **4a** and **7**.

To discern the role of bifluoride ion in the SuFEx trifluoromethylation, DFT studies were performed at the DSDPBEP86/def2-TZVPP//B3LYP-D3(BJ)/6-31G(d,p) level of theory with a DMSO solvent. The results provide the first reported insight into the mechanism of anhydrous SuFEx reactivity (Figure 2A). It has previously been proposed that a hypervalent silicon intermediate acts as a fluoride source and is responsible for nucleophilic addition to sulfonyl fluorides,[2,18] with numerous examples of such silicon intermediates being reported.[19] Nucleophilic fluorination of $TMSCF_3$ (**9**) was modelled for both $[FHF]^-$ (**8**) and F^-, with low barriers of $\Delta G^{\ddagger}$= 47.4 and 28.3 kJ mol^{-1}, respectively, which indicates that both processes readily occur. The reaction with bifluoride additionally yields HF (Figure 2B), which is determined to be important in later steps in the mechanism. Loss of F^- or $-CF_3^-$ anions from $TMSCF_3F^-$ (**10**) is calculated to be -6.9 and -12.4 kJ mol^{-1}, respectively, confirming that $-CF_3^-$ is the most likely leaving group. Subsequently, $TMSCF_3F^-$ with a hypervalent silicon readily initiates trifluoromethylation of the sulfur center ($\Delta G^{\ddagger}$= 58.1 kJ mol^{-1}) to yield a five-coordinate sulfur intermediate (Int1). The loss of F^- and $-CF_3^-$ from Int1 is calculated to be -108 and -131 kJ mol^{-1}, respectively, which favours $-CF_3^-$ as the leaving group (leading back to the starting reactant). However, the presence of HF (by employing $[FHF]^-$ to fluorinate $TMSCF_3$) enables homoassociation (the association between a base and its conjugate acid through a hydrogen bond) that facilitates the defluorination of the sulfonyl intermediate (TS2, $\Delta G^{\ddagger}$= 32.4 kJ mol^{-1} from Int1) and yields the required product and a reconstituted bifluoride (confirming catalytic behavior). In comparison, in the absence of HF (by employing F^- to fluorinate $TMSCF_3$), the spontaneous 'S_N1-like' defluorination (TS2-a) yields a substantially higher barrier of 56.0 kJ mol^{-1} (from Int1) with products that are also less thermodynamically stable than with bifluoride. Although fluoride addition from KF to $TMSCF_3$ to produce $TMSCF_3F^-$ is kinetically favoured, the subsequent spontaneous defluorination of the five-coordinate sulfonyl group requires considerable energy. The liberation of HF from $[FHF]^-$ following fluorination of $TMSCF_3$ affords a powerful conjugate base for later defluorination of the sulfonyl fluoride (Int1) in preference to the loss of $-CF_3^-$. We propose that a powerful hydrogen bond acceptor is necessary for non-aqueous SuFEx reactions with silicon mediators. The proposed mechanism is consistent with the need for anhydrous DMSO,[12] with the effect of homoassociation typically being higher in non-aqueous solutions.

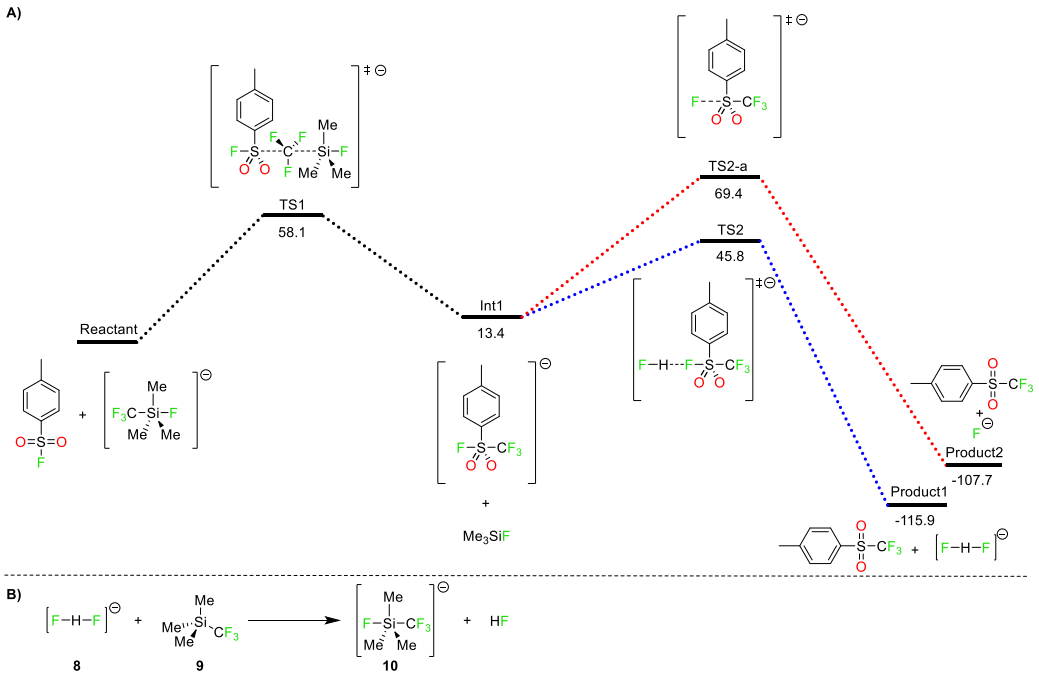


Figure 2. A) Calculated free energy diagram for the SuFEx mediated trifluoromethylation of tosyl-fluoride. Relative free energies (ΔG) are given in kJ mol^{-1}. All data calculated at the DSDPBEP86/def2-TZVPP//B3LYP-D3(BJ)/6-31+G(d,p) DMSO level of theory; B) Bifluoride anion addition to trifluoromethyltrimethylsilane to give the hypervalent ate complex with loss of HF.

Finally, to demonstrate the utility of late-stage 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.[20] 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 3A). 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 3A). Fluorescence imaging clearly shows uptake of compound **3f** in both MCF7 and MCF10A cells (Figure 3B). 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.

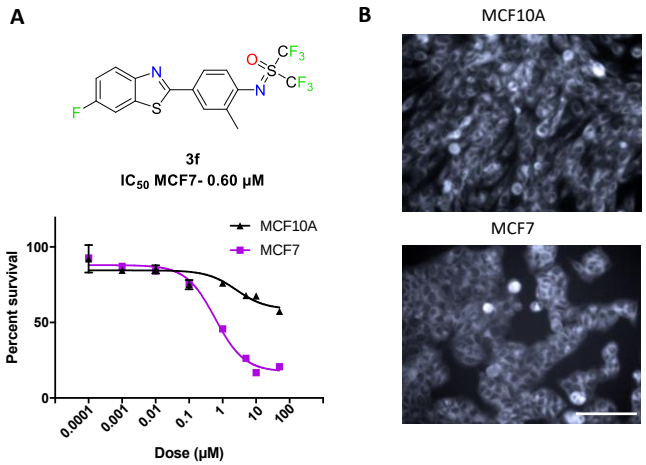


Figure 3. A) Benzothiazole compound **3f** synthesized by the method in Scheme 2 and tested against MCF7 and MCF10A. MCF7 breast cancer cells and MCF10A breast cells, seeded at $4x10^3$ cells/well were treated for 72 h with **3f**. Cell viability was assessed by an MTT assay. Readings from experimental duplicates with technical triplicates were averaged and calculated as percentage survival compared to DMSO control, error bars indicate SEM; B) **3f** was added 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 late-stage 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. Extensive DFT calculations support the theory of bifluoride catalysis in the reaction mechanism, acting through a key five-coordinate sulfur intermediate which hydrogen fluoride homoassociates to the fluoride weakening the S-F bond, creating a superior leaving group and reforming the catalyst. With the vast amount of fluorine, in particular the trifluoromethyl functionality in drugs and drug candidates, we believe that this new 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 catalysis • DFT mechanism

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

[13] The use of DMF as the reaction solvent led to full consumption of the starting material under the reaction conditions however, a by-product was observed by ^{19}F NMR.

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

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[16] It is noteworthy that for a few substrates separate conditions were required, which included increasing the amount of KFHF and $TMSCF_3$, individually or combinatorial.

[17] 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.

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