SuFEx Activation with $Ca(NTf_2)_2$: A Unified Strategy to Access Sulfamides, Sulfamates and Sulfonamides from S(VI) Fluorides

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Supporting Information Placeholder

ABSTRACT: A method to activate sulfamoyl fluorides, fluorosulfates, and sulfonyl fluorides with calcium triflimide and DABCO for SuFEx with amines is described. The reaction was applied to a diverse set of sulfamides, sulfamates, and sulfonamides at room temperature under mild conditions. Additionally, we highlight the application of this transformation to parallel medicinal chemistry to generate a broad array of nitrogen-based S(VI) compounds.

Interest in sulfur(VI) fluorides has grown immensely since Sharpless and coworkers introduced the concept of sulfur-fluoride exchange (SuFEx) chemistry in 2014.[1, 2] For example, SuFEx has been applied extensively in chemical biology and medicinal chemistry with application toward protein labeling, protease inhibition, and drug target discovery.[3] In polymer chemistry, sulfur(VI) fluorides have been employed to generate novel polysulfates and polysulfonates, materials that have unique properties with promising applications.[1,4-5] Furthermore, advancements in fluorosulfurylation chemistry and the development of new reagents to install the $–SO_2F$ group have spurred additional exploration into these functional groups.[6-11,12] However, employment of sulfur(VI) fluorides as synthetic precursors toward nitrogen-based sulfonylated compounds is underdeveloped.[1,13-18]

Nitrogenous sulfur(VI) compounds are well represented among small molecule drugs. For example, sulfonamides make up 25% of all sulfur-based FDA approved drugs, with therapeutic applications for multiple indications such as bacterial infections, cardiovascular diseases, and cancer (Figure 1A).[19]

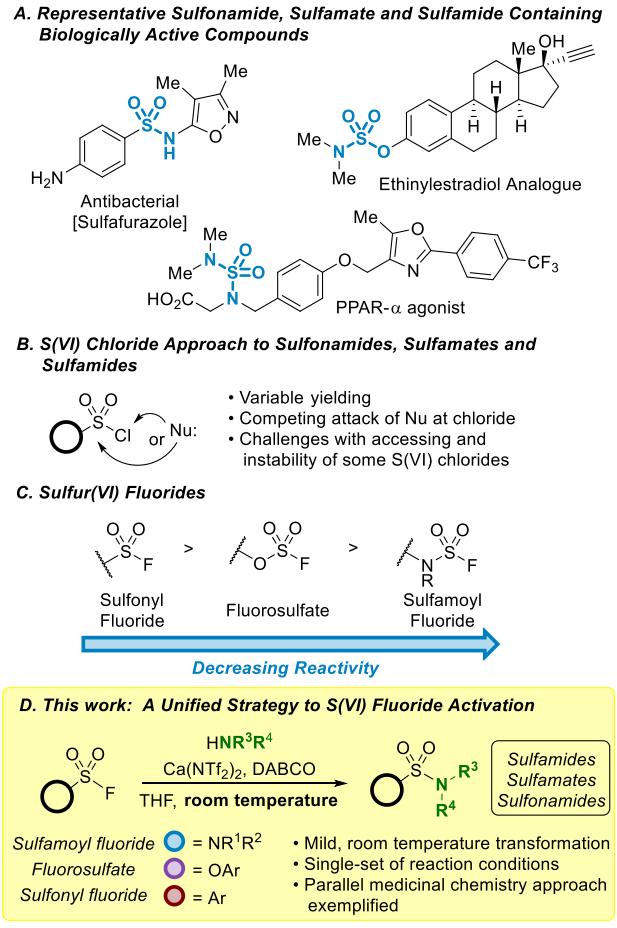


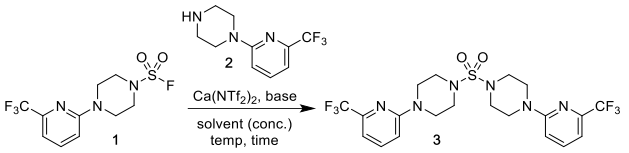
Figure 1. (A) Relative reactivities of key S(VI) fluorides; (B) S(VI) chloride-based approach to synthesize sulfonamides, sulfamates and sulfamides; (C) biologically active nitrogen-based S(VI) compounds; (D) our room temperature method using $Ca(NTf_2)_2$ and DABCO to synthesize sulfamides, sulfamates, and sulfonamides from S(VI) fluorides.

Sulfamides and sulfamates are also valuable motifs; however, they are comparatively underexplored, despite application across a variety of disease areas.[20] The most common approach to nitrogen-based sulfur(VI) compounds relies on the isolation or in situ generation of sulfur(VI) chlorides, such as sulfonyl chlorides (–SO_2Cl), chlorosulfates (–OSO_2Cl) and sulfamoyl chlorides (–NSO_2Cl).[1,21] Although widely used, there are several key challenges with their application. While some sulfonyl chlorides are commercially available, the synthesis of sulfonyl chlorides with more complex architectures can be challenging due to the harsh synthetic conditions required to access these compounds, and their inherent instability.[21b] In the presence of nucleophiles, sulfonyl chlorides can undergo competing addition to the chlorine or sulfur atom, dehydrochlorination, and hydrolysis.[1, 21-22] While less explored, the synthesis of chlorosulfates and sulfamoyl chlorides are beset by similar challenges (Figure 1B).[23]

In contrast, the corresponding S(VI) fluorides have remarkable hydrolytic, redox and thermal stability, rendering them attractive alternatives to S(VI) chlorides.[21] Despite innovation in their synthesis, there are still barriers to the broader application of S(VI) fluorides in organic chemistry. A key challenge is the reduced reactivity at the sulfur center compared to other S(VI) halides.[1] Furthermore, the canonical S(VI) fluorides – sulfonyl fluorides (–SO_2F), fluorosulfates (–OSO_2F), and sulfamoyl fluorides (–NSO_2F) – have considerably different reactivity at the sulfur center due to the reduced electrophilicity of the sulfur atom as the C–S bond is replaced with more resonance-donating atoms (Figure 1C). Notably, disubstituted sulfamoyl fluorides require forcing conditions to undergo sulfur-fluoride exchange,[24] limiting a common method toward their application in SuFEx chemistry.[25]

Our groups recently reported a $Ca(NTf_2)_2$-mediated activation of sulfonyl fluorides to generate sulfonamides.[13] We envisioned a similar Lewis-acid approach could be employed to activate less reactive sulfamoyl fluorides and fluorosulfates to access sulfamides and sulfamates, respectively. To date, a unified approach to enable SuFEx chemistry across a broader array of S(VI) fluorides does not exist, limiting adoption as synthetic precursors. Herein, we report a high yielding, unified method to access sulfamides, sulfamates and sulfonamides through the activation of sulfamoyl fluorides, fluorosulfates and sulfonyl fluorides with calcium triflimide and DABCO at room temperature.

Table 1. Optimization studies[a]



Entry	Amine equiv.	$Ca(NTf_2)_2$ equiv.	Base (equiv.)	Solvent (conc.)	Temp. °C	Time h	Yield
1	2	1	-	*t*-amylOH (0.2 M)	60	24	70%
2	2	1	-	*t*-amylOH (0.2 M)	90	24	89%
3	2	2	-	*t*-amylOH (0.2 M)	100	24	92%
4	2	1.1	-	*t*-amylOH (1.0 M)	90	2	96%
5	1.05	1.1	-	*t*-amylOH (1.0 M)	90	2	52%
6	1.05	1.1	DIPEA (1.5 eq.)	*t*-amylOH (1.0 M)	90	2	95% (54%)[b]
7	1.05	1.1	DABCO (1.5 eq.)	*t*-amylOH (1.0 M)	90	2	96% (88%)[b]
8	1.05	1.1	DABCO (1.5 eq.)	THF (0.5 M)	rt	24	93%
9	1.05	0	DABCO (1.5 eq.)	THF (0.5 M)	rt	24	NR[c]

[a]Reaction Scale: sulfamoyl fluoride **1** (0.35 mmol, 1.0 equiv). [b]Reaction was performed in the presence of 5% water by volume. [c]No reaction

Applying our previously reported method utilizing excess amine in *t*-amylOH generated sulfamide **3** in 70% yield (Table 1, Entry 1); however, sulfamoyl fluoride **1** was not fully consumed in the reaction and additional heating at 60 °C for 48 hours did not further improve the conversion. Increasing the temperature and equivalents of $Ca(NTf_2)_2$ did improve the yield, although the reactions still did not fully consume sulfamoyl fluoride **1** (Entries 2 and 3). We identified that increasing the concentration to 1 M had a marked effect, affording a 96% yield of sulfamide **3**, with full consumption of starting material (**1**) in only 2 hours (Entry 4).

We next explored the amine nucleophile and found that decreasing the equivalents (2 equiv → 1.05 equiv of amine **2**, Entry 5) required the addition of a base to drive the reaction to completion (e.g. DIPEA or DABCO, Entry 6 and 7). With DIPEA, the yield varied depending on the bottle of *t*-amylOH employed. We surmised that this could be a result of varying amounts of water present in the solvent. Indeed, the addition of 5% water (by volume) significantly decreased the yield from 95% to 54% (Entry 6). Notably, when DABCO was employed, the inclusion of 5% water in the reaction had minimal effect, yielding 88% yield of the desired sulfamide **3** (Entry 7). This result led us to hypothesize that DABCO may have an expanded role, beyond acting solely as a base in the reaction, and led us to investigate additional reaction parameters.[1, 26-27]

Toward this end, we explored the effect of various bases, solvents and Lewis acids on the transformation (see SI for details). DABCO proved exceptional as compared to other bases explored. With DABCO, we no longer observed a preference for an alcoholic solvent, the requirement for high concentration was less

pronounced, and the reaction proceeded at room temperature when using THF as a solvent (Entry 8). Evaluating a selected set of Lewis acids further established $Ca(NTf_2)_2$ as particularly effective across a variety of substrates (*vide infra*). It is noteworthy that in the absence of calcium, the reaction does not proceed (Entry 9).

We next investigated the generality of the sulfamide preparation by exploring a diverse set of amine nucleophiles with sulfamoyl fluoride **1** (Scheme 1A). Primary and secondary amines, as well as weaker amine nucleophiles such as aniline, methylimidazole and tetramethyl guanidine, readily underwent SuFEx to produce the desired sulfamides (**3-7**). Ammonia was also a competent nucleophile, generating sulfamide **8** with a free amino group. In addition, amine salts (i.e. HCl, TFA and MsOH) of morpholine were also tolerated, giving sulfamide **9**, albeit with a reduction in yield compared to the free-base. To further evaluate the versatility of the reaction, we paired a diverse array of sulfamoyl fluorides with various amines (Scheme 1B, **10-18**). The reaction was compatible with a broad range of functional groups (e.g. primary amide, halides, alkyne, etc.) and acid sensitive functionality (e.g. Boc and acetal protecting groups), as well as multiple heterocyclic motifs.

Fluorosulfates pose additional challenges, as multiple reaction pathways can be envisioned upon reaction with amine nucleophiles (Figure 2).[3b] Indeed, 4-cyanophenyl fluorosulfate in the presence of DABCO and amine **2** (excluding $Ca(NTf_2)_2$) resulted in significant side-product formation, including products outlined in Figure 2 (see SI for details). Remarkably, inclusion of $Ca(NTf_2)_2$ into the reaction mixture completely rescued the transformation, affording sulfamate **19** in 98% yield. A structurally diverse set of sulfamates were synthesized with secondary amines and phenolic fluorosulfates in excellent yield (Scheme 1C, **19-29**). Utilizing a primary amine with the electron poor 4-benzoylphenyl fluorosulfate, resulted in elimination of the phenol (see SI for details);[24] however, on a more electron-rich substrate (i.e. 4-methoxyfluorosulfate) desired product **28** could be isolated, with only a minor amount of side product formation.

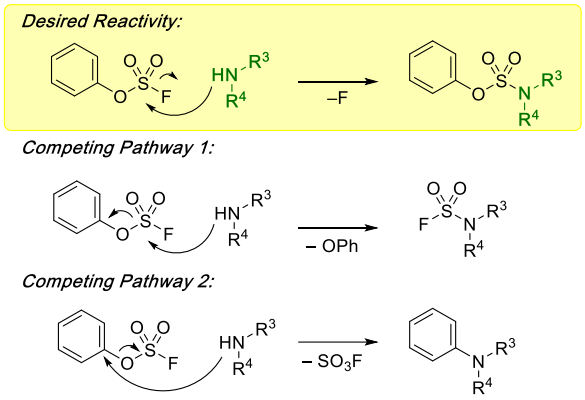
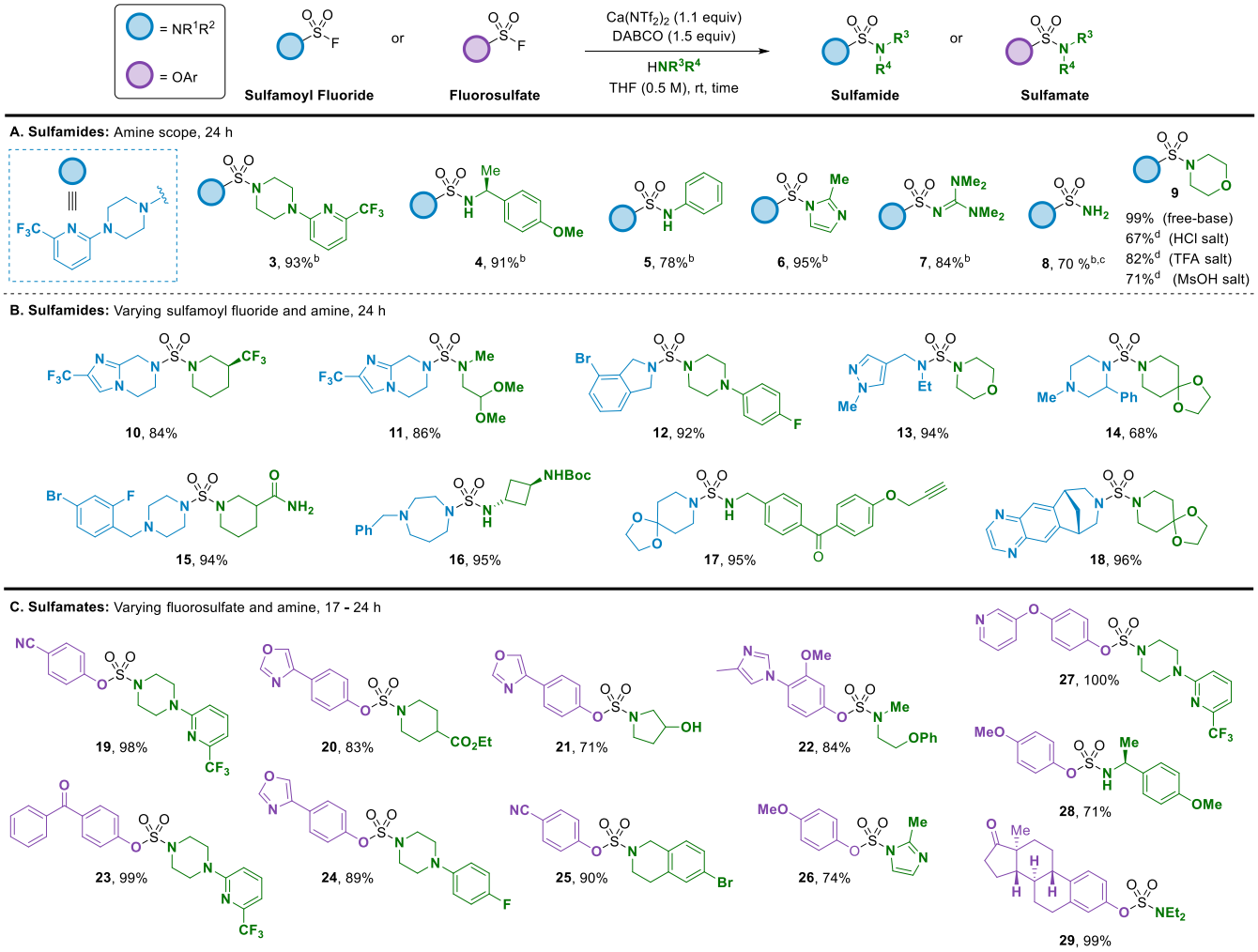


Figure 2. Possible Modes of Fluorosulfate Reactivity with Amines

Our previous work demonstrated the conversion of sulfonyl fluorides to sulfonamides using $Ca(NTf_2)_2$ with various amines; however, the reaction required elevated temperature (60 °C) and long reaction time (24 h). Applying the new $Ca(NTf_2)_2$/DABCO combination had an exceptional effect: phenylsulfonyl fluoride undergoes the SuFEx reaction to form sulfonamide **30** in 94% yield *in less than 30 minutes at room temperature* (Scheme 2). Encouraged by these

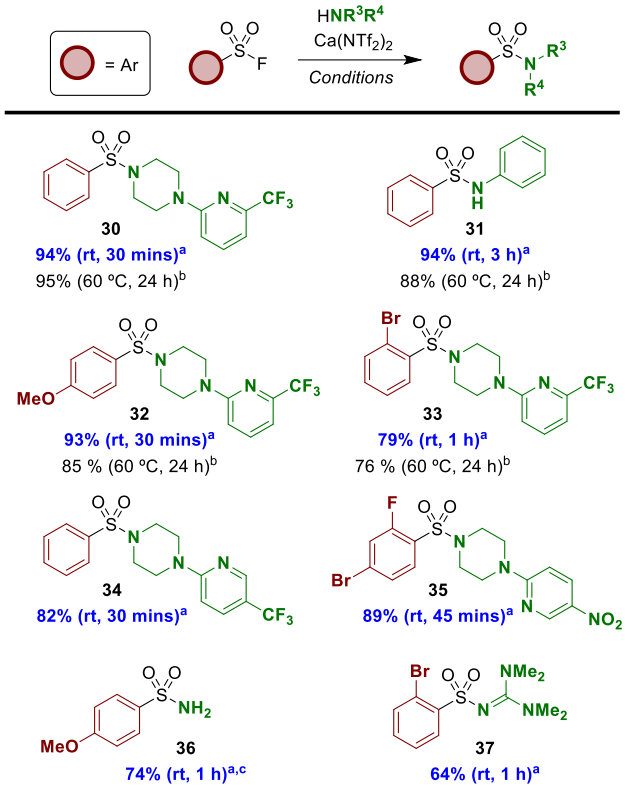


Scheme 1. Scope of Sulfamide and Sulfamate Formation

Reaction conditions: S(VI) fluoride (0.25 mmol, 1.0 equiv), amine (0.261 mmol, 1.05 equiv), $Ca(NTf_2)_2$ (170 mg, 0.27 mmol, 1.1 equiv), DABCO (0.37 mmol, 1.5 equiv) in THF (0.5 mL, 0.5 M) at room temperature for time indicated. [b]No reaction in the absence of $Ca(NTf_2)_2$ [c]2.0 equiv of 7 N NH_3 in MeOH was used as the amine source (0.5 mL, 0.5 M). [d]The corresponding amine salt of morpholine was used, along with 3.0 equiv. of DABCO.

results, we revisited a series of amine nucleophiles and sulfonyl fluorides for comparison. In all cases, comparable or improved yields were obtained, along with a dramatic increase in reaction rate, at a lower reaction temperature (i.e. sulfonamides **30**-**33**). Further scope was exemplified by varying the electronics on the sulfonyl fluoride, amine, and highlighting the use of both ammonia and tetramethyl guanidine nucleophiles (**34**-**37**).

Parallel medicinal chemistry (PMC) is frequently used in drug discovery to rapidly expand SAR and optimize lead compound properties. PMC-enabled chemistry should be tolerant of a wide-range of functional groups and have relatively simple reaction set-up and purification. This is to facilitate the use of a plate-based (e.g. 96-well or greater) format, automated liquid handling equipment and HPLC purification of final products, with the goal of generating numerous compounds in a more efficient manner than in singleton or batch format. To explore the utility of our $Ca(NTf_2)_2$/DABCO reaction conditions in PMC, we selected three S(VI) fluoride templates (sulfonyl fluoride **38**, fluorosulfate **39**, and sulfamoyl fluoride **1**) and a diverse set of amine monomers (Scheme 3, see SI for the full set of amines). Our protocol successfully translated to PMC format, generating >100 unique nitrogen-based S(VI) compounds with high overall success rate and purity across three classes of nitrogen-based S(VI) compounds (i.e. sulfonamide 40/44, sulfamate 27/31 and sulfamides 35/44 compounds). These results highlight the application of this robust transformation to a diverse set of functional groups and heterocycles.



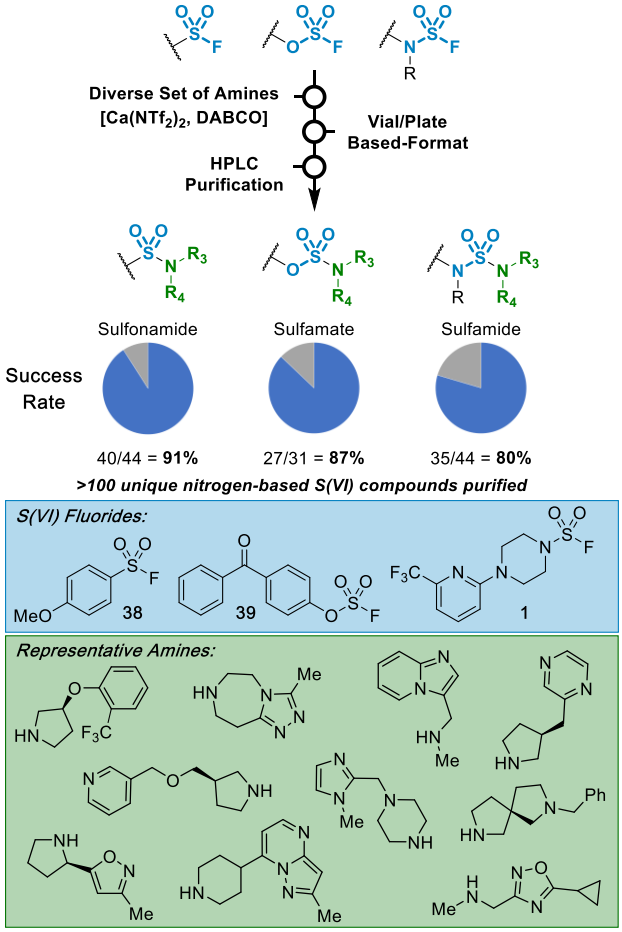
Scheme 2. SuFEx of Sulfonyl Fluorides toward Sulfonamides.

Reaction conditions: all reactions were conducted on a 0.4 mmol scale (sulfonyl fluoride) for indicated time. [a] amine (1.05 equiv), DABCO (1.5 equiv), $Ca(NTf_2)_2$ (1.1 equiv), THF (0.5 M), rt. [b] amine (2.0 equiv), $Ca(NTf_2)_2$ (1.0 equiv), *t*-amylOH (0.2 M), 90 °C, [c] 2 M solution of NH_3 in *i*PrOH was used. [d] 1.1 equiv of TMG was used.

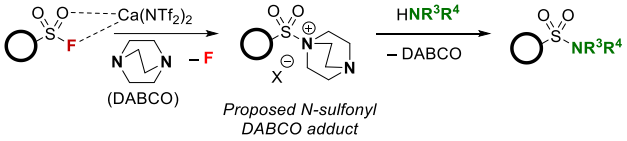
To probe the mechanism of this reaction, we conducted NMR (^1H and ^{19}F) and LCMS studies (see SI for details). Nucleophilic Lewis bases have been demonstrated to undergo halogen exchange with S(VI) chlorides and fluorides, activating the sulfur atom toward nucleophilic addition.[1, 26-27] Our hypothesis was that a similar addition of Lewis basic DABCO to the S(VI) center was promoting the SuFEx reaction.

Addition of DABCO to phenylsulfonyl fluoride ($PhSO_2F$) in deuterated THF, did not result in any change to the ^1H or ^{19}F NMR spectra of $PhSO_2F$. However, upon addition of $Ca(NTF_2)_2$, the ^{19}F signal from $PhSO_2F$ is significantly diminished, and the proton chemical shifts of the phenyl group and DABCO move downfield, suggesting deshielding of the protons. Subsequent addition of an amine nucleophile (**2**) to the mixture affords the desired sulfonamide product (**30**). These results, coupled with the fact that SuFEx does not occur in our reactions without $Ca(NTf_2)_2$, we propose a SuFEx mechanism that first involves Ca/DABCO activation of the S(VI) fluoride to form an activated *N*-sulfonyl-DABCO salt, that in the presence of an amine undergoes product formation (Scheme 4).[28]

Scheme 3. PMC of S(VI) Fluorides with Amines.



Scheme 4. Proposed mechanism of the SuFEx reaction.



In conclusion, we have developed a unified $Ca(NTf_2)_2$/DABCO-mediated method that activates S(VI) fluorides, with considerably different reactivity, toward SuFEx with amines. The reaction proceeds at room temperature and a diverse array of sulfamides, sulfamates and sulfonamides can be readily prepared. Parallel medicinal chemistry resulted in the isolation and purification of >100 structurally diverse nitrogen-based S(VI) compounds, exemplifying the utility of this chemistry toward a broad range of heterocyclic targets. Mechanistic studies to further understand the dual role of calcium and DABCO are currently underway. We anticipate the introduction of this $Ca(NTf_2)_2$/DABCO SuFEx method will further

solidify S(VI) fluorides as privileged S(VI) synthons in synthetic chemistry.

ASSOCIATED CONTENT

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Author Contributions

This work was performed in collaboration between the Ball laboratory at Pomona College and Pfizer Inc. #S.M. and C.W.P are co-first authors. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

S.M., T.W.B., J.K.D., B.C.V., J.B. and C.W.A., are employees at Pfizer.

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REFERENCES

1) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry. *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448

2) For representative reviews on sulfur-fluoride exchange see: (a) Fattah, T. A.; Saeed, A.; Albericio, F. Recent advances towards sulfur (VI) fluoride exchange (SuFEx) click chemistry. *Journal of Fluorine Chemistry* **2018**, *213*, 87–112. (b) Revathi, L.; Ravindar, L.; Leng, J.; Rakesh, K. P.; Qin, H.-L. Synthesis and Chemical Transformations of Fluorosulfates. *Asian J. Org. Chem*. **2018**, *7*, 662-682. (c) Chinthakindi, P. K.; Arvidsson, P. I. More Than Click Reagents? *Eur. J. Org. Chem.* **2018,** 3648-3666. (d) Barrow, A. S.; Smedley, C. J.; Zheng, Q.; Li, S.; Dong, J.; Moses, J. E. The growing applications of SuFEx click chemistry. *Chem. Soc. Rev.* **2019**, *40*, 2004-2028.

3) (a) Narayanan, A.; Jones, L. H. Sulfonyl fluorides as privileged warheads in chemical biology. *Chem. Sci.* **2015**, *6*, 2650-2659. (b) Jones, L. H. Emerging Utility of Fluorosulfate Chemical Probes. *ACS Med. Chem. Lett.* **2018**, *9*, 584-586.

4) Wang, H.; Zhou, F.; Ren, G.; Zheng, Q.; Chen, H.; Gao, B.; Klivansky, L.; Liu, Y.; Wu, B.; Xu, Q.; Lu, J.; Sharpless, K. B.; Wu, P. SuFEx-Based Polysulfonate Formation from Ethenesulfonyl Fluoride-Amine Adducts. *Angew. Chem. Int. Ed*. **2017**, *56*, 11203-11208.

5) Gao, B.; Zhang, L.; Zheng, Q.; Zhou, F.; Klivansky, L. M.; Lu, J.; Liu, Y.; Dong, J.; Wu, P.; Sharpless, K. B. Bifluoride-catalysed sulfur(VI) fluoride exchange reaction for the synthesis of polysulfates and polysulfonates. *Nat. Chem.* **2017**, 9, 1083-1088.

6) Veryser, C.; Demaerel, J.; Bieliūnas, V.; Gilles, P.; De Borggraeve, W. M. Ex-Situ Generation of Sulfuryl Fluoride for the Synthesis of Aryl Fluorosulfates. *Org. Lett.* **2017**, *19*, 5244-5247.

7) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. One-pot palladium-catalyzed synthesis of sulfonyl fluorides from aryl bromides. *Chem. Sci.* **2017**, *8*, 1233-1237.

8) Tribby, A. L.; Rodríguez, I.; Shariffudin, S.; Ball, N. D. Pd-Catalyzed Conversion of Aryl Iodides to Sulfonyl Fluorides Using SO_2 Surrogate DABSO and Selectfluor. *J. Org. Chem.* **2017**, *82*, 2294-2299.

9) Zhou, H.; Mukherjee, P.; Liu, R.; Evrard, E.; Wang, D.; Humphrey, J. M.; Butler, T. W.; Hoth, L. R.; Sperry, J. B.; Sakata, S. K.; Helal, C. J.; am Ende, C. W. Introduction of a Crystalline, Shelf-Stable Reagent for the Synthesis of Sulfur(VI) Fluorides. *Org. Lett.* **2018**, *20*, 812-815.

10) Laudadio, G.; de A Bartolomeu, A.; Verwijlen, L. M. H. M.; Cao, Y.; de Oliveira, K. T.; Noël, T. Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride. *J. Am. Chem. Soc*. **2019**, *141*, 11832-11836.

11) Lee, C.; Ball, N. D.; Sammis, G. M. One-pot fluorosulfurylation of Grignard reagents using sulfuryl fluoride. *Chem. Commun.* **2019**, *55*, 14753-14756.

12) Pérez-Palau, M.; Cornella, J. Synthesis of Sulfonyl Fluorides from Sulfonamides. *Eur. J. Org. Chem.* **2020**, ASAP.

13) Mukherjee, P.; Woroch, C. P.; Cleary, L.; Rusznak, M.; Franzese, R. W.; Reese, M. R.; Tucker, J. W.; Humphrey, J. M.; Etuk, S. M.; Kwan, S. C.; am Ende, C. W.; Ball, N. D. Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides. *Org. Lett.* **2018**, *20*, 3943-3947.

14) Guo T., Meng G., Zhan X., Yang Q., Ma T., Xu L., Sharpless, K.B., Dong, J. A New Portal to SuFEx Click Chemistry: A Stable Fluorosulfuryl Imidazolium Salt Emerging as an "F−SO_2^+" Donor of Unprecedented Reactivity, Selectivity, and Scope. *Angew. Chem. Int. Ed*. **2018,** *57*, 2605–10.

15) Thomas, J.; Fokin, V. V. Regioselective Synthesis of Fluorosulfonyl 1,2,3-Triazoles from Bromovinylsulfonyl Fluoride. *Org. Lett*. **2018**, *20*, 3749-3752.

16) Liu, J.; Wang, S.-M.; Qin, H.-L. Installation of sulfonyl fluorides onto primary amides. *Beilstein J. Org. Chem.* **2019**, *15*, 1907-1912.

17) Liu, F.; Wang, H.; Li, S.; Bare, G. A. L.; Chen, X.; Wang, C.; Moses, J. E.; Wu, P.; Sharpless, K. B. Biocompatible SuFEx Click Chemistry: Thionyl Tetrafluoride (SOF_4)-Derived Connective Hubs for Bioconjugation to DNA and Proteins. *Angew. Chem. Int. Ed.* **2019**, *58*, 8029-8033.

18) Zhang, S.; Xiong, H.; Lu F.; Ma, F.; Gu, Y.; Ma, P.; Xu, H.; Yang, G. Synthesis of *N*-Acyl Sulfamates from Fluorosulfonates and Potassium Trimethylsilyloxyl Imidates *J. Org. Chem.* **2019**, *84*, 15380-15388.

19) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. Topics in Current Chemistry *Topics in Curr. Chem.* **2018**, *376*, 1-34.

20) (a) Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. Sulfamates and their therapeutic potential. *Med. Res. Rev.* **2004**, *25*, 186-228. (b) Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. Therapeutic applications of sulfamates. *Expert Opin. Ther. Pat.* **2005**, *14*, 1273-1308. (c) Spillane, W.; Malaubier, J.-B. Sulfamic Acid and Its *N*- and *O*-Substituted Derivatives. *Chem. Rev*. **2013**, *114*, 2507-2586.

21) (a) Wright, S.W.; Hallstrom, K. N. Sulfonamides and Sulfonyl Fluorides from Heteroaryl Thiols. *J. Org. Chem.* **2006**, *71*, 1080-1084. (b) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Pipko, S. E.; Konovets, A. I.; Sadkova, I. V.; Tolmachev, A. Sulfonyl Fluorides as Alternative to Sulfonyl Chlorides in Parallel Synthesis of Aliphatic Sulfonamides. *ACS Comb. Sci.* **2014**, *16*, 192-197.

22) Gaulton, A.; Bellis, L. J.; Bento, A. P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.;

Al-Lazikani, B.; Overington, J. P. ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* **2011**, *40* , D1100-D1107.
23) Spillane, W. J.; McHugh, F. A.; Burke, P. O. Elimination mechanisms in the anilinolysis of sulfamoyl chlorides in chloroform and acetonitrile. *J. Chem. Soc., Perkin Trans.* **1998**, *2,* 13-18.
24) Mono substituted sulfamoyl fluorides are more reactive due to the ability to go through the sulfenium intermediate (see SI for details and the following reference): Edwards, D.R.; Wolfenden, R. Proton-in-Flight Mechanism for the Spontaneous Hydrolysis of *N*-Methyl *O*-Phenyl Sulfamate: Implications for the Design of Steroid Sulfatase Inhibitors. *J. Org. Chem.* **2012,** *77*, 4450-4453.
25) Employing the Sharpless MgO conditions (ref 1) with sulfamoyl fluoride **1** and amine **2** gave sulfamide **3** in 45% yield (see SI for details).
26) Gembus, V.; Marsais, F.; Levacher, V. An Efficient Organocatalyzed Interconversion of Silyl Ethers to Tosylates Using DBU and *p*-Toluenesulfonyl Fluoride. *Synlett* **2008**, 1463-1466.
27) For examples of DABCO addition to sulfonyl chlorides see: (a) Hartung, J.; Hünig, S.; Kneuer, R.; Schwarz, M.; Wenner. 1,4-Diazabicyclo[2.2.2]octance (DABCO) – an Efficient Reagent in the Synthesis of Alkyl Tosylates or Sulfenates. *Synthesis*, **1997**, 1433-1438. (b) Fu, Y.; Xu, Q.-S.; Li, Q.-Z.; Li, M.-P.; Shi, C.-Z.; Du, Z. Sulfonylation of 1,4-Diazabicyclo[2.2.2]octane: Charge-Transfer Complex Triggered C−N Bond Cleavage. *ChemistryOpen* **2019**, *8*, 127-131.
28) An alternative mechanism where coordination of DABCO to Ca could also be operational see: (a) Causero, A.; Ballmann, G.; Pahl, J.; Färber, C.; Intemann, J.; Harder, S. β-Diketiminate Calcium Hydride Complexes: The Importance of Solvent Effects. *Dalton Trans.* **2017**, *46*, 1822-1831. (b) Shi X.; Qin, G.; Wang, Y.; Zhao, L.; Liu, Z.; Cheng, J. Super-Bulky Penta-arylcyclopentadienyl Ligands: Isolation of the Full Range of Half Sandwich Heavy Alkaline-Earth Metal Hydrides. *Angew. Chem. Int. Ed.* **2019**, *58*, 4356-4360.