Ex situ Generation of Thiazyl Trifluoride (NSF_3) as a Gaseous SuFEx Hub

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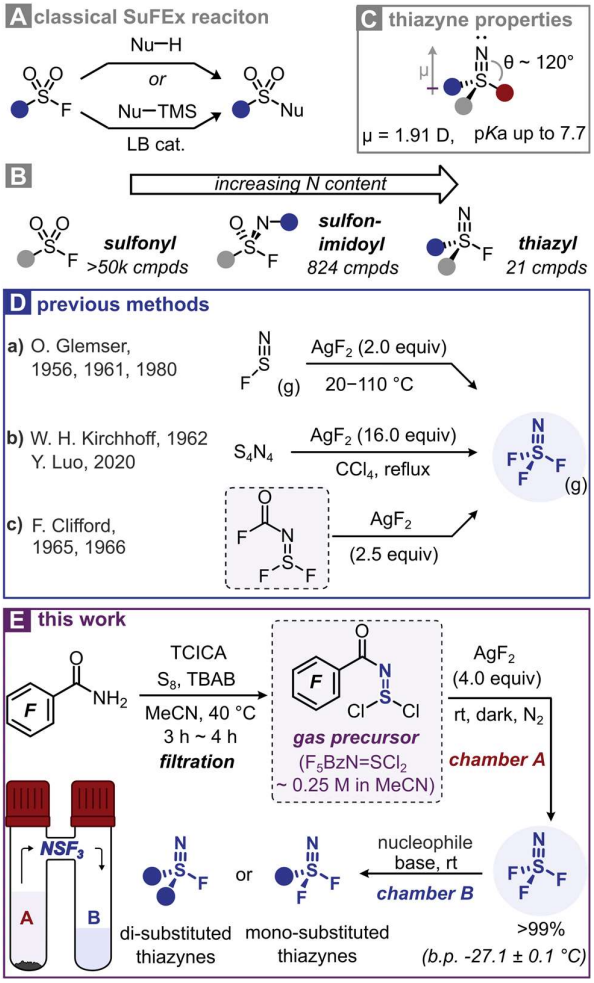
Abstract: Sulfur(VI)-fluoride exchange (SuFEx) chemistry, an all-encompassing term for substitution events that replace fluoride at an electrophilic sulfur(VI), enables the rapid and flexible assembly of linkages around a S^{VI} core. Although a myriad of nucleophiles and applications works very well with the SuFEx concept, the electrophile design has remained largely SO_2-based. Here, we introduce S≡N-based fluorosulfur(VI) reagents to the realm of SuFEx chemistry. Thiazyl trifluoride (NSF_3) gas is shown to serve as an excellent parent compound and SuFEx hub to efficiently synthesize mono- and disubstituted fluorothiazynes in an *ex situ* generation workflow. Gaseous NSF_3 was evolved from commercial reagents in a nearly quantitative fashion at ambient conditions. Moreover, the mono-substituted thiazynes could be extended further as SuFEx handles and be engaged in the synthesis of unsymmetrically disubstituted thiazynes. These results provide valuable insights into the versatility of these understudied sulphur functionalities paving the way for future applications.

Connective hubs with S^{VI}–F bonds are becoming more prevalent as a result of recent interest in high-valent sulfur species. Within the context of Sulfur(VI)−Fluoride Exchange (SuFEx) chemistry—a general term for substitution events replacing fluoride at the electrophilic sulfur center—these "*molecular plugins*" enable linkages to be created around the S^{VI} core in a selective and efficient way (Scheme 1**A**).[1] In 2014, Sharpless inaugurated sulfonyl fluorides ($R-SO_2F$) and fluorosulfates ($R-OSO_2F$) as click-type reagents.[2] This foundational work was followed by a surge in research related to S^{VI}–F bond participation in various transformations, particularly as covalent warheads in protein environments.[1, 3] In recent years, important advances have demonstrated that sulfonimidoyl fluorides, in which one S=O is replaced by S=NR, can undergo the same chemical transformations.[4]



Scheme 1. A) Classical SuFEx reaction; B) Number of compounds was determined via a SciFinder substructure search on the given fragment, accessed on 05/04/2023; C) Physicochemical properties of thiazyne; D) Previous approaches to the generation of thiazyl trifluoride; E) This work: The *ex situ* generation of thiazyl trifluoride (NSF_3) as gaseous SuFEx hub.

No fundamental constraint dictates a maximum bond order of 2 between sulfur and nitrogen. This notion led us to consider the thiazyl unit,[5][6] with its S≡N triple bond at the tetrahedral core, as a new SuFEx hub with room for three single-bonded substituents. Compared to the sulfonimidoyl and the especially well-studied sulfonyl units, reports on the thiazyl centerpiece as the 'third sulfur(VI) core' are sparse. (Scheme 1**B**). Its parent compound, thiazyl trifluoride (NSF_3) was first reported by Glemser in 1956.[7] This gaseous molecule (b.p. -27.1 ± 0.1 °C[8]) with a dipole moment of 1.91 D,[9] is significantly more polar than its sulfonyl counterpart SO_2F_2 (1.11 D).[10] The lone pair electron density focuses the highest HOMO orbital coefficient at the thiazyl nitrogen and endows it with several distinct features, such as a nucleophilic character and a p*K*a of up to 7.7 (Scheme 1**C**).[11] In addition, the insulating strength of NSF_3 is 1.35 times that of SF_6, and its Global Warming Potential (GWP) is about one-twentieth that of SF_6, making it an attractive alternative to SF_6.[12]

Building on these features and their Lewis-basic nature, fluorinated thiazynes are expected to exhibit unique reactivity compared with their sulfonyl counterparts. However contrasting to the number of reports related to the sulfonyl group, literature on the thiazyl group has remained virtually absent since the 1980s.[11, 13], [14] This discrepancy may be related to the unavailability of the NSF_3 gas. Existing routes for generation of NSF_3 are marked by prohibitive limitations, such as the use of gaseous (NSF) [6a, 7-8] or explosive (S_4N_4) [9] starting materials, the use of a high excess of reagents,[15] the need for high temperatures,[7, 9, 16] or the generation of various by-products requiring further purification of the gas stream[6a, 9, 16-17] (Scheme 1**D**). To enable exploration of NSF_3 as a SuFEx hub, it is, therefore, crucial to improving its synthesis, ideally making use of standard laboratory equipment.

In this work, we set out to address the availability issue of NSF_3 gas. We envisioned that an efficient lab-scale synthesis from commercially available materials would overcome the barrier for exploring this part of the SuFEx chemistry. Based on our previous work on sulfuryl fluoride[18] and triflyl fluoride gas,[19] we propose that an *ex situ* strategy from a gas precursor is an attractive strategy to work with fluorinated gases in a safe and near-stoichiometric manner.[20] Inspired by the work of Clifford[16] (method **c**), we found that iminosulfur dichloride $F_5BzN{=}SCl_2$ could serve as suitable precursor (Scheme 1**E**). Here, we demonstrate a gas generation workflow which starts from commercially available materials, and quantitatively produces NSF_3 at room temperature. We subsequently show that the SuFEx reaction between NSF_3 and oxygen and nitrogen nucleophiles results in a variety of disubstituted derivatives whose structures are reported.

Results and discussion

We envisioned that the production of NSF_3 in a two-chamber reactor would be the most practical way to use this gas safely on a lab scale.[21] Inspired by Clifford and Glemser's reports on *N*-acyliminothionyl fluoride as a gas precursor (Scheme 1**D, c**), we set out to redesign this approach by using a $RN{=}SX_2$ motif that was more synthetically accessible. *N*,*N*-dichloro(sulfon)amides ($RNCl_2$) are known to react with elemental sulphur to produce imidothionyl chlorides ($RN{=}SCl_2$).[22] Contact with AgF_2 would initially lead to a halogen exchange and formation of the corresponding imidothionyl fluorides ($RN{=}SF_2$), which we hypothesised could undergo the same oxidative cleavage as Clifford's precursor to furnish $N{\equiv}SF_3$ gas. A sulfonyl-based imidothionyl chloride (R = Ts) was elected as the first candidate, but only led to trace amounts of NSF_3, possibly due to the strong N–Ts bond. The more cleavable trifluoroacetyl variant (R = CF_3CO), produced higher amounts of NSF_3, but its parent dichloramine proved unstable (see SI sections 3.1-3.2).

Gratifyingly, when changing the *N*-protecting group to pentafluorobenzoyl (R = F_5Bz) an optimum was reached between reactivity and stability (Scheme 1**E**). A highly effective gas precursor acyliminosulfurdichloride ($F_5BzN{=}SCl_2$) could be obtained from pentafluorobenzamide (F_5BzNH_2). The optimal conditions involved trichloroisocyanuric acid (TCICA) as a chlorinating agent[23] with catalytic tetrabutylammonium bromide (TBAB) in a single step,[24] either at room temperature overnight or at 40 °C for only 3-4 hours. Conveniently, filtering off the solid cyanuric acid produced a sufficiently pure MeCN solution of the gas precursor, which was used as such for the gas generation. Finally, in a tube already containing 4.0 equiv of AgF_2, the precursor solution reacted efficiently to form the NSF_3 gas at room temperature with >99% ^{19}F NMR yield, consistently over several experiments (for optimization, see SI section 3.4).

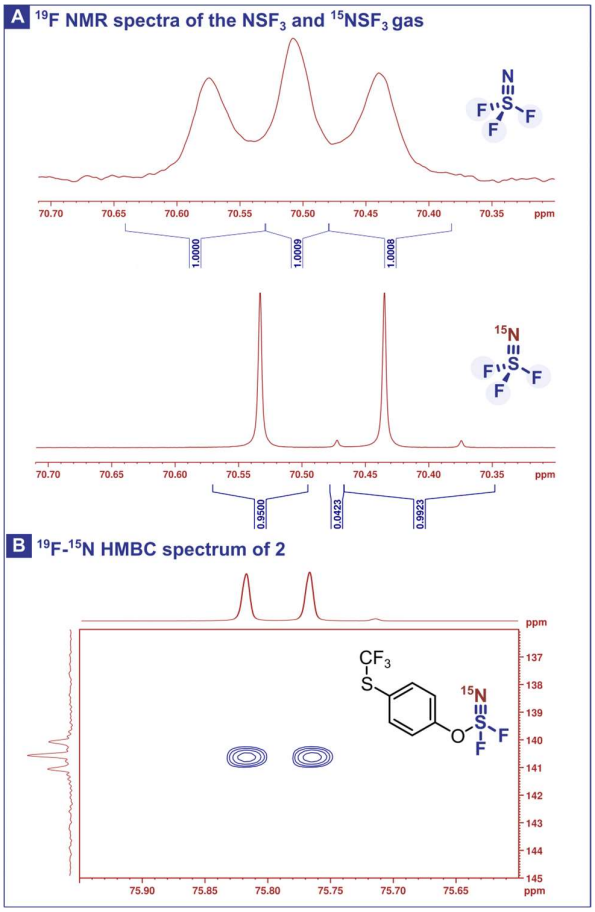


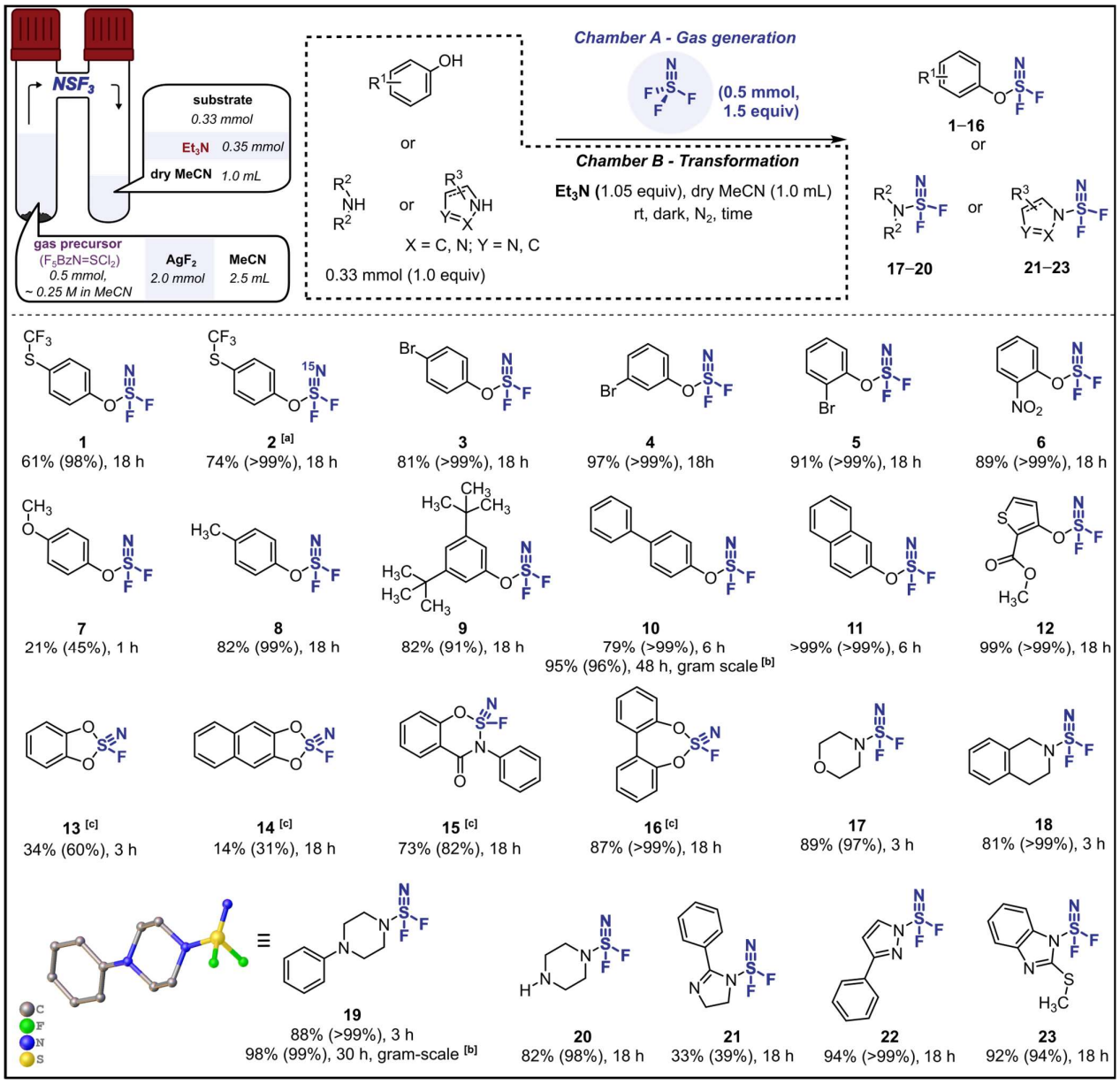
Figure 1. A) ^{19}F NMR spectra of solutions of $^{14}NSF_3$ (top) and $^{15}NSF_3$ (middle) gas dissolved in MeCN. The small peaks which are shifted by 0.06 ppm correspond to the ^{34}S isotopomers (abundance about 4%). B) ^{19}F-^{15}N HMBC spectrum of **2**; the left ^{15}N NMR spectrum is an external projection.

During the optimization of NSF_3 gas generation, we noticed that the ^{19}F NMR spectrum of NSF_3 appears as a 1:1:1 triplet (Figure 1**A**, top), a phenomenon that had been observed before.[25] While somehow unusual for quadrupolar nuclei such as ^{14}N, *J*-coupling can be seen in case of highly symmetric molecules as is the case for NSF_3. Indeed, we here observed a ^2J-coupling constant between ^{19}F-^{14}N of 25.3 Hz is found. To further elaborate on this, $^{15}NSF_3$ was synthesized from the ^{15}N isotope labeled pentafluorobenzamide. Its ^{19}F NMR spectrum now shows a distinct peak consisting of a doublet ($^2J_{^{15}N-F}$ = 36.9 Hz), owing to coupling wih spin ½ ^{15}N (Figure 1**A**, bottom). In addition, a lower-intensity doublet with the same coupling constant was observed which could be attributed to the ^{34}S isotopomer; the 95.0:4.22 integration ratio for both doublets matches the ^{32}S:^{34}S natural abundance ratio.[26] When, $^{15}NSF_3$ was used as the SuFEx hub to produce the ^{15}N labeled thiazyne **2** (details, see SI section 4.8), its ^{19}F-^{15}N HMBC spectrum clearly shows correlations between fluorine and nitrogen due to this ^2J coupling constant (Figure 1**B**).

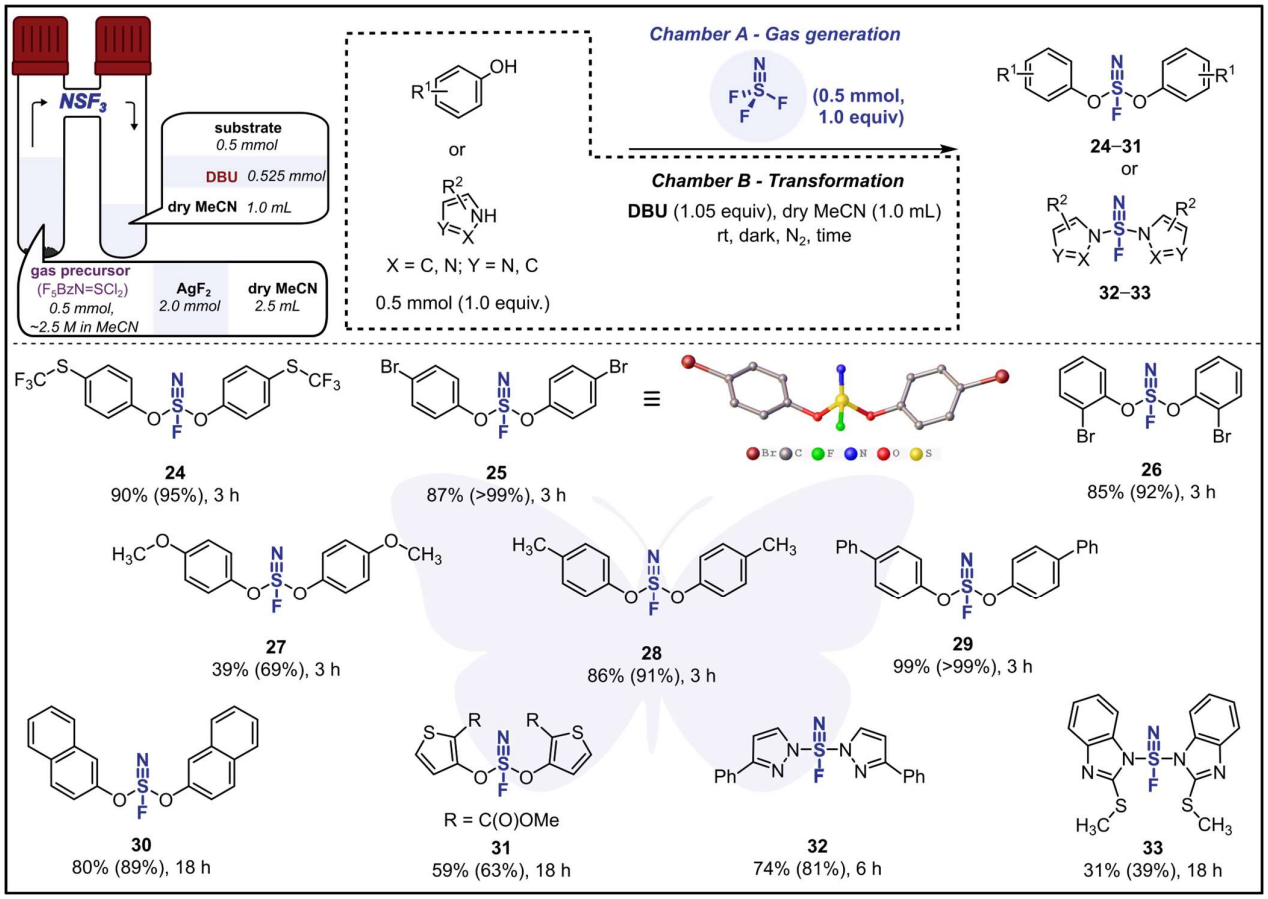
With our newly developed NSF_3 generation protocol in hand, we set out to develop the *ex situ* generation of thiazyl trifluoride (NSF_3) as a gaseous SuFEx hub in a two-chamber reactor. In our SuFEx set-up, the acetonitrile solution of the $F_5BzN{=}SCl_2$ as NSF_3 gas precursor was filtered into chamber A of the two-chamber reactor (the gas generation chamber), which was pre-filled with 4.0 equiv of AgF_2. Here, the Ag(II) salt consumed the precursor within a few hours to evolve the NSF_3 gas, which diffuses into chamber B (the reaction chamber) to react with a solution of the selected nucleophile.

The SuFEx reaction in chamber B was first investigated with aromatic alcohols (Scheme 2). The combination of Et_3N and MeCN proved to be optimal to obtain a high yield of mono-substituted thiazynes (for optimization, see SI section 3.5). While anhydrous MeCN provided the best results, the SuFEx reaction still proceeded efficiently in MeCN/H_2O (3:1). To our delight, the final reaction conditions allowed the formation of thiazyne **1** in 98% ^{19}F NMR yield at room temperature (Scheme 2).

Under optimized conditions, a variety of readily accessible phenol, secondary amine, and azole derivates was examined to further explore the scope of this methodology. Firstly, electron-deficient substituted phenols were successfully transformed into their corresponding thiazynes in good to excellent yield (**1**−**6**). Likewise, electron-rich and electron-neutral building blocks were smoothly converted into the corresponding thiazynes in very good to excellent yield (**8**−**11**), except compound **7**, whichlikely degraded over time. Interestingly, cyclized products **13**−**16** were obtained when two adjacent SuFExable groups were present in the starting material.[2, 27] After the transformation of various oxygen nucleophiles into reactive handles with NSF_3, a range of nitrogen nucleophiles such as aliphatic amines and azoles were engaged in a SuFEx reaction (Scheme 2, **17**−**23**). NSF_3 gas reacted rapidly with cyclic secondary amines to deliver the corresponding products; some even in 3 hours, such as **17**, **18**, and **19**. Finally, a large-scale experiment was performed to prepare the SuFExable thiazynes **10** and **19** in excellent isolated yields.

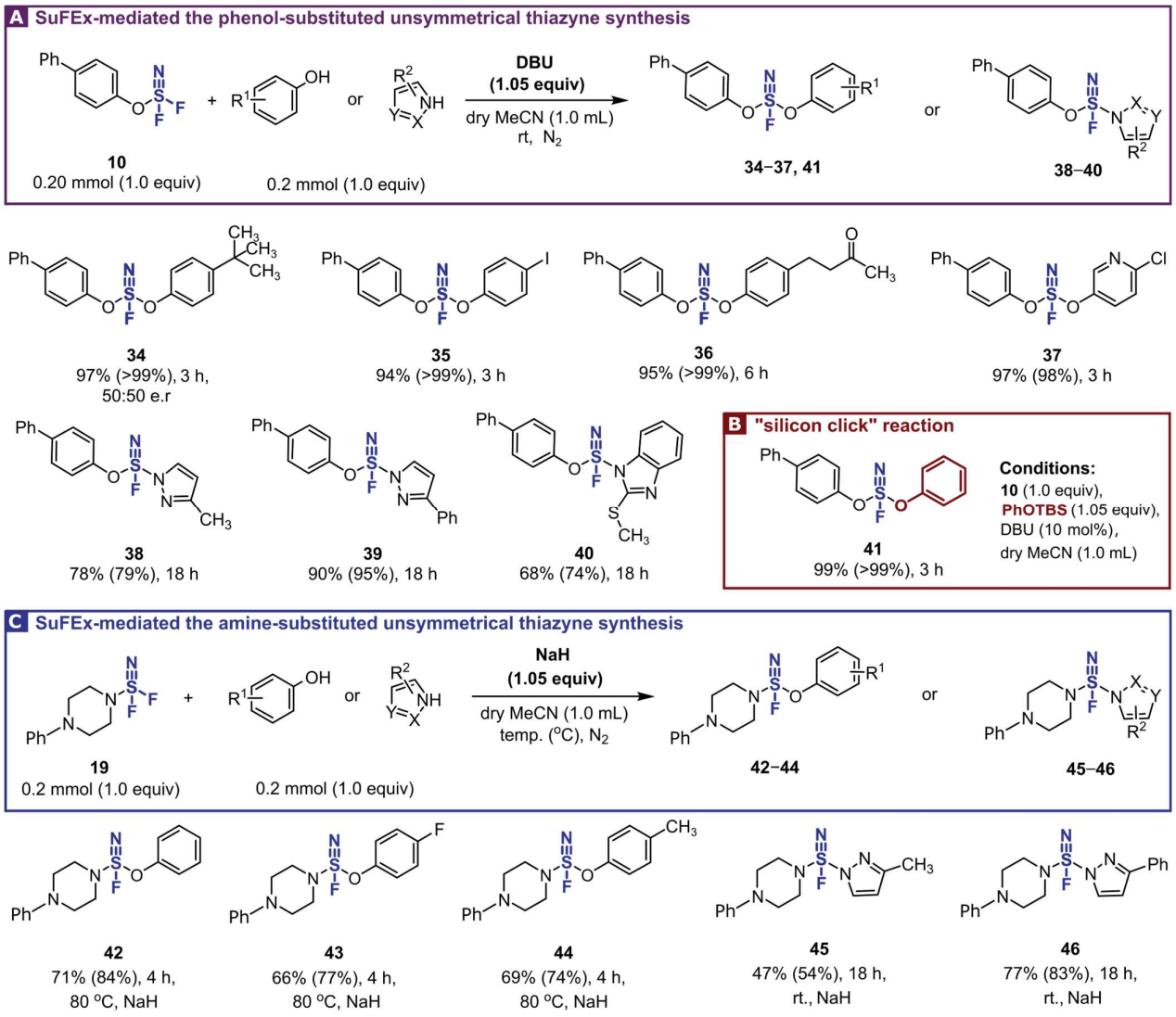


Scheme 2. Synthesis of monosubstituted thiazynes through *ex situ* generation of thiazyl trifluoride (NSF_3) gas in a two-chamber reactor. Unless stated otherwise, conditions were as follows: Chamber A: AgF_2 (2.0 mmol), dry MeCN, 2.5 mL and freshly made gas precursor solution ($F_5BzN{=}SCl_2$, 0.5 mmol,0.25 M in MeCN) at room temperature. Chamber B: substrate (0.33 mmol, 1.0 equiv), Et_3N (0.35 mmol, 1.05 equiv) in 1.0 mL of dry MeCN. All reactions were set up dry, under inert atmosphere and kept away from light. Experimental details, see SI, section 4.2. Isolated yield after column chromatography unless stated otherwise (between parentheses is given the ^{19}F NMR yield using $PhCF_3$ as the internal standard). [a] This ^{15}N labeled thiazyne **2** was prepared from the $^{15}NSF_3$ which was obtained from self-made isotopically labeled pentafluorobenzamide (details, see SI section 4.8). [b] The gram-scale reactions were set up using 10 mmol of pentafluorobenzamide to produce the gas precursor and 6.6 mmol nucleophiles as the starting material. For reaction, details see SI, section 4.4. Crystal structure of the mono-substituted thiazyne **19** (bottom left).[28] Mono-substituted thiazine **19** crystallizes in the triclinic space group *P*1 with two molecules in the asymmetric unit (r.m.s. deviation 0.180 Å after inversion). The S≡N distances are 1.411(6) and 1.403(6) Å. In the crystal, tetramers are formed by weak C–H···N and C–H···F interactions (Fig. S9). [c] The reaction used 2.05 equivalent of triethylamine (0.677 mmol).



Scheme 3. Synthesis of symmetric di-substituted thiazynes through *ex situ* generation of thiazyl trifluoride (NSF_3) gas in a two-chamber reactor. Gas generation chamber A: AgF_2 (2.0 mmol) and anhydrous MeCN (2.5 mL) and filtered freshly made gas precursor solution ($F_5BzN{=}SCl_2$, 0.5 mmol, 0.25 M in MeCN) at room temperature. Chamber B: substrate (0.5 mmol, 1.0 equiv), DBU (0.525 mmol, 1.05 equiv) in 1.0 mL of anhydrous MeCN. All reactions were set up dry, under inert atmosphere and kept away from light. Experimental details, see SI, section 4.3. Isolated yield after column chromatography unless stated otherwise. Between brackets is given the ^{19}F NMR yield using $PhCF_3$ as the internal standard, followed by the reaction time. Crystal structure of the di-substituted thiazyne **25** (top center).[28] Di-substituted thiazine **25** crystallizes in the orthorhombic space group *P*bca. The S≡N distance is 1.411(5) Å. The symmetry of the butterfly shape can be described with point group C_s. The dihedral angle between both phenyl planes is 32.5(3)°. One of the phenyl rings is involved in an S–F···π interaction (F···centroid distance is 3.156(5) Å), resulting in columns of molecules running in the *b*-direction (Fig. S10).

During the optimization of the SuFEx reaction we noticed that the use of DBU instead of Et_3N led to the exchange of two fluorides to access the "butterfly-shaped" symmetric di-substituted thiazynes selectively and efficiently (Scheme 3; for optimization, see SI 3.5). To explore the scope tolerance, a variety of phenols, secondary amines and azoles were examined. First, phenols including electron-rich (**28**, **29**), electron-deficient (**24**–**26**), and 2-naphthol (**30**) were successfully transformed into their corresponding thiazynes in very good to excellent isolated yield, most of them requesting only a short reaction time. Lower yields were obtained for the bis-(4-methoxyphenyl) derivative (**27**) which degraded over time and the bis(thiophenyl) derivative (**31**) due to the lower conversion of starting material. However, The azoles were less effective (<80% yields) than phenols, possibly an effect of the higher p*K*a values of azoles. Secondary amines could not be transformed into diaminothiazynes under these conditions.



Scheme 4. A) SuFEx-mediated phenol-substituted unsymmetrical thiazyne synthesis. Reaction conditions: **10** (0.2 mmol, 1.0 equiv), substrate (0.2 mmol, 1.0 equiv), DBU (0.21 mmol, 1.05 equiv), MeCN (1.0 mL). All reactions were set up dry, under inert atmosphere. Experimental details, see SI, section 4.5. The enantiomeric ratio was determined by HPLC analysis. B) "Silicon click" reaction: SuFEx-mediated unsymmetrical thiazyne synthesis through silyl-protected phenol. Reaction conditions: **10** (0.2 mmol, 1.0 equiv), tert-butyldimethyl(phenoxy)silane (0.21 mmol, 1.05 equiv), dry MeCN (1.0 mL), DBU (0.02 mmol, 10 mol%). All reactions were set up dry, under inert atmosphere. Experimental details, see SI, section 4.7. C) SuFEx-mediated the amine-substituted unsymmetrical thiazyne synthesis. Reaction conditions: **19** (0.2 mmol, 1.0 equiv), substrate (0.2 mmol, 1.0 equiv), sodium hydride (NaH, 60% disp., 0.21 mmol, 1.05 equiv), MeCN (1.0 mL). All reactions were set up dry, under inert atmosphere. Experimental details, see SI, section 4.6. Isolated yield after column chromatography unless stated otherwise. Between brackets is given the ^{19}F NMR yield using $PhCF_3$ as the internal standard, followed by the reaction time.

Observing that disubstitution occurs with a stronger base (DBU) but not with 'milder' conditions (Et_3N), we reasoned that the attenuated reactivity of the remaining S–F bonds in monosubstituted derivatives could be exploited to prepare unsymmetrically disubstituted thiazynes. To this end, aryloxythiazyne **10** as the S^{VI}–F electrophile was engaged in SuFEx reactions with various phenols or azoles to generate a small library of unsymmetrically disubstituted thiazynes. As before, DBU proved an efficient base for the second fluoride substitution, and different types of phenols (**34**–**37**) as well as azoles (**38**–**40**) all underwent the reaction smoothly (Scheme 4**B**). Intriguingly, the reaction with TBS-protected phenol and catalytic DBU furnished the desired product **41** quantitatively, in line with earlier work on the powerful 'silicon click' variety of SuFEx chemistry.[2, 29] Aminothiazyne **19** as a starting material was noticeably less electrophilic, and required sodium hydride (NaH) as a base to stoichiometrically deprotonate nucleophile reaction partners (Scheme 4**C**). SuFEx reactions with phenols succeeded at an elevated reaction temperature of 80 °C (**42**–**44**), while the S–F bond substitution by azoles occurred at room temperature (**45**, **46**).

In summary, we developed a two-chamber procedure for the efficient and safe *ex situ* processing of thiazyl trifluoride gas (NSF_3) as a new type of SuFEx hub. Herewith, a variety of mono- and di-substituted derivatives was built selectively, using tailored conditions for each consecutive substitution step. Furthermore,

phenolic and amine substituents were installed at will to obtain several unsymmetrical disubstituted thiazynes. To confirm the structures, two of the thiazynes were analyzed via X-ray. Moreover, the ability to perform the SuFEx reaction in the presence of water opens the possibility for future applications in chemical biology. Overall, we expect that the *ex situ* gas production approach will expand the usage of NSF_3 in the lab-scale synthesis, especially in producing the mono-substituted thiazynes that can then be explored as SuFEx electrophiles in diverse transformations, most notably as covalent warheads in chemical biology.

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Keywords: Click chemistry • SuFEx chemistry • Synthetic methods • Thiazyl trifluoride • Thiazyne

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[28] Deposition Numbers 2240276 (for **19**), and 2240277 (for **25**) 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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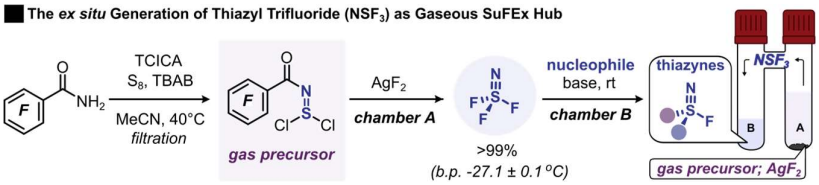

Here we report a synthetic procedure for the efficient *ex situ* generation of thiazyl trifluoride gas ($N{\equiv}SF_3$) as a new Sulfur(VI)-Fluoride Exchange hub. In typical SuFEx fashion, this triple-bonded azasulfur(VI) fluoride reagent and its mono-substituted derivatives react highly effectively with various nucleophiles to deliver a library of unreported thiazynes.

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