Click Chemistry

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Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry

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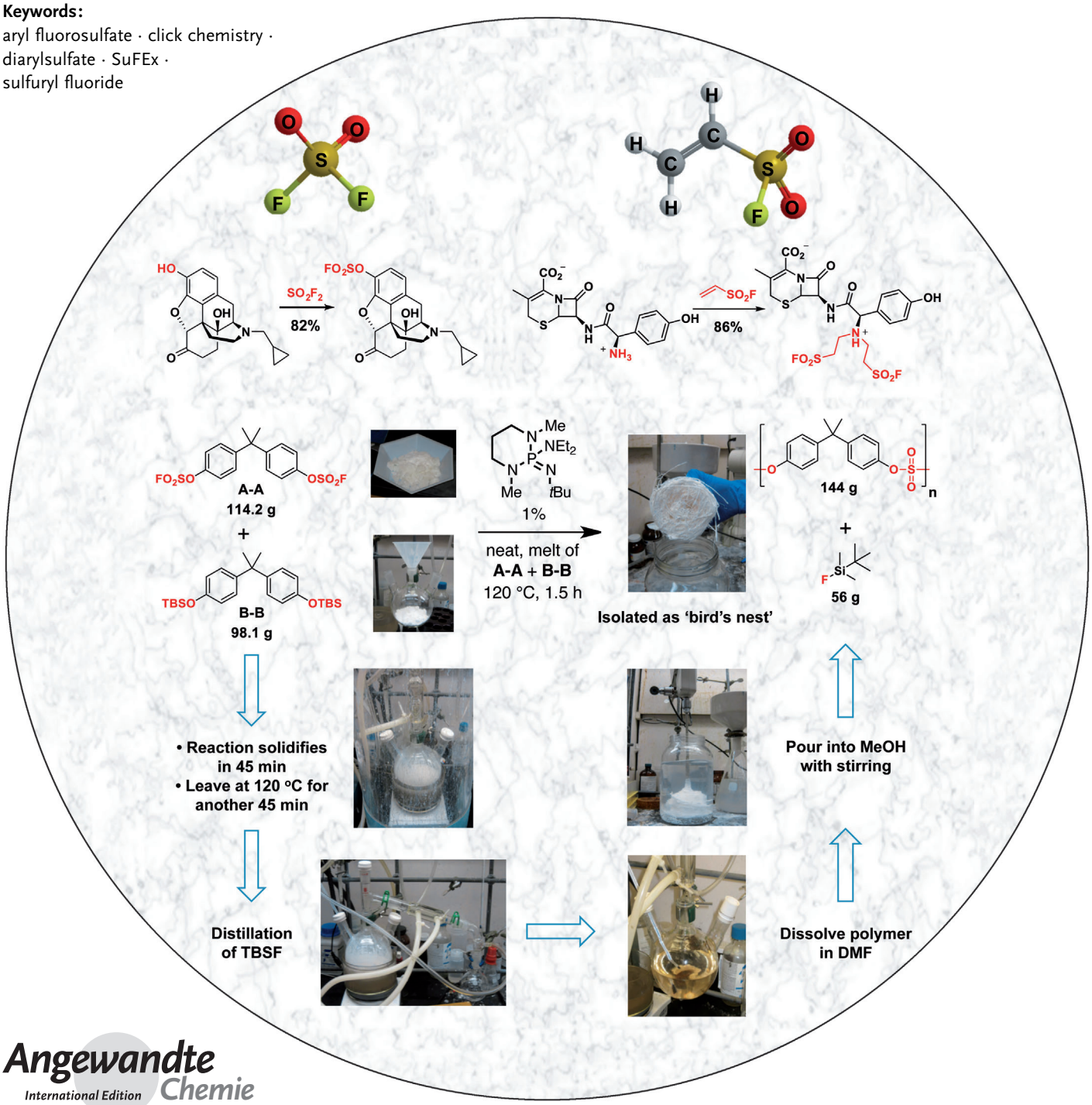

Aryl sulfonyl chlorides (e.g. Ts-Cl) are beloved of organic chemists as the most commonly used S^{VI} electrophiles, and the parent sulfuryl chloride, $O_2S^{VI}Cl_2$, has also been relied on to create sulfates and sulfamides. However, the desired halide substitution event is often defeated by destruction of the sulfur electrophile because the S^{VI}–Cl bond is exceedingly sensitive to reductive collapse yielding S^{IV} species and Cl^-. Fortunately, the use of sulfur(VI) fluorides (e.g., R-SO_2-F and SO_2F_2) leaves only the substitution pathway open. As with most of click chemistry, many essential features of sulfur(VI) fluoride reactivity were discovered long ago in Germany.[6a] Surprisingly, this extraordinary work faded from view rather abruptly in the mid-20th century. Here we seek to revive it, along with John Hyatt's unnoticed 1979 full paper exposition on CH_2=CH-SO_2-F, the most perfect Michael acceptor ever found.[98] To this history we add several new observations, including that the otherwise very stable gas SO_2F_2 has excellent reactivity under the right circumstances. We also show that proton or silicon centers can activate the exchange of S–F bonds for S–O bonds to make functional products, and that the sulfate connector is surprisingly stable toward hydrolysis. Applications of this controllable ligation chemistry to small molecules, polymers, and biomolecules are discussed.

From the Contents

1. Introduction

Click chemistry was introduced as a conceptual framework for functional molecular assembly 15 years ago, emphasizing the importance of carbon–heteroatom linkages in joining modular building blocks.[1] Taking inspiration from nature, click reactions were identified as processes that work under operationally simple, oxygen- and water-tolerant conditions, and generate products in high yields with minimal requirements for product purification. Such reactions invariably have an unusual combination of strong thermodynamic driving forces and consistent, well-controlled reaction pathways. In tandem, these two features allow the use of widely varying substrates with great reliability.

The azide–alkyne cycloaddition reaction[2] is especially useful because of the unobtrusive nature of its participating functional groups and the ability to turn on their ligating ability (to different extents, and for different purposes) by Cu^I catalysts,[3] installing strain in the alkyne component,[4] or holding them in close spatial proximity.[5] Thus, this click reaction emerged by finding ways to induce two functional groups to react with each other that otherwise have little propensity to do so, in spite of their highly energetic nature. In contrast, most other click reactions find a useful window of activity by moderating the properties of at least one highly reactive partner. We describe in this Review an example of the latter type—dubbed sulfur(VI) fluoride exchange (SuFEx)—made possible by the interplay between the unique hydrogen-bonding requirements of the fluoride ion and the thermodynamic and kinetic properties of fluoride bonds to sulfur(VI) and silicon centers.

The promiscuous nature of acid–base chemistry, characterized by fast exchange of protons and conjugate bases, usually makes it unsuitable for click chemistry, but SuFEx transformations are an exception. The special requirements for fluoride to transit from a strong covalent bond to a leaving group provide the key, requiring assistance by "H^+" or

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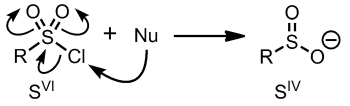
"R_3Si^+" under strict spatial and kinetic constraints. Conversely, since it is difficult to provide what this tiny anion needs to escape from the S^{VI} bond, the $-SO_2$-F unit is remarkably stable in typical acidic and basic environments. It thereby attains a hallmark of click reaction function, remaining "invisible" under most conditions and coming to life only when desired, in this case on a far fringe of acid–base territory.

The fine points of the catalysis which sparks the nearly moribund S^{VI}-F group to life remain a challenge for the future. For now, it is best to note the many practical outcomes of the unique acid–base guidance of sulfur(VI)-fluoride reactivity. Among them are an appreciation that different reaction conditions are appropriate for different desired applications: interfacial (aqueous/organic) reactions are advantageous in the nucleophilic side of fluoride reactivity dominated by the bifluoride (FHF^-) anion; homogeneous conditions are appropriate when silyl groups mediate very fast reactions of sulfonyl fluorides as electrophiles.

While the development of this chemistry is described in this Review around mechanistic themes, it derives from a continuing desire to identify the very best connective chemistries, those which proceed almost perfectly regardless of environment. The value of a connecting methodology depends on the ease and generality of the installation of the reactive partners, the stability of the linkage under useful conditions, and the properties of the linkage such as its conformation and polarity. Among nature's most important connectors are amide and phosphate diester groups, for proteins and nucleic acids, respectively. Neither linkage can presently be made in the laboratory by a click chemistry procedure—the building blocks are either too inert or too promiscuous in their reactivity. Instead, we focus on sulfur(VI) fluoride bonds as very demanding electrophiles, only reacting easily when the F^- ion is properly solvated or activated. The S^{VI}-F group can thereby serve as a key entry point to sulfuryl/sulfonyl connections, -Z-SO_2-Z′- (Z, Z′ = C, O, N), analogous to phosphonyl/phosphoryl connections but unburdened by charge. Its muted polarity allows the properties of the molecules built with SO_2 linkages to be influenced to a great degree by the motifs being connected. The resulting connector toolbox is also powerfully enhanced by another click reaction, the conjugate (Michael) addition of nucleophiles to the special electrophile ethenesulfonyl fluoride.

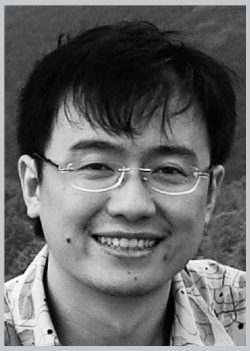
2. Sulfonyl Fluorides vs. Other Sulfonyl Halides

Sulfonyl chlorides are beloved of organic chemists as the most commonly used S^{VI} electrophiles. The interest of one of us (K.B.S.) in the chemistry of S^{VI} began about 30 years ago when RSO_2Cl and $ClSO_2Cl$ failed to serve as reliable connective units because of the facile reductive failure of the bond between sulfur(VI) and chlorine [Eq. (1)]. This



(1)

emerges most vexingly in the attempted formation of inorganic sulfate, sulfamide, and sulfamate linkages such as RO-SO_2-OR′, RNH-SO_2-NHR′, and ArO-SO_2-NRR′. Our attempts to develop quick and robust inorganic connectors for the fast assembly of sophisticated molecules was thereby delayed. Having now returned to the subject, we believe that sulfonyl fluoride and related groups constitute components of



Jiajia Dong was born in China and received his BA from Xiamen University in 2000. Prof. Biao Jiang supervised his 2006 PhD in organic chemistry from Shanghai Institute of Organic Chemistry (SIOC). He was a senior scientific researcher at Egret Pharma, Shanghai, before becoming a postdoctoral associate in 2009 with Prof. K. Barry Sharpless' group at The Scripps Research Institute. He is currently a research associate at The Scripps Research Institute with Prof. Jeffrey Kelly and Prof. K. Barry Sharpless.

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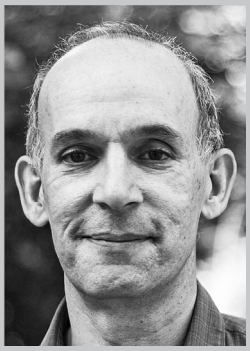
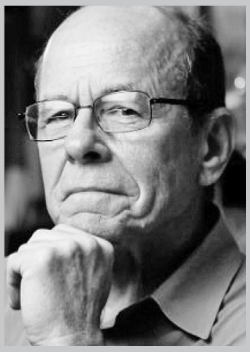


M. G. Finn received his scientific training at Caltech (BSc, 1980), MIT (PhD 1986 with K. B. Sharpless) and Stanford (postdoc 1988 with J. P. Collman), and has been a member of the faculties at the University of Virginia (1988–98), The Scripps Research Institute (1998–2013), and the Georgia Institute of Technology (since 2013). He is Editor-in-Chief of the journal ACS Combinatorial Science.



Nobel Laureate K. Barry Sharpless became W. M. Keck Professor of Chemistry at The Scripps Research Institute and The Skaggs Institute of Chemical Biology in 1990. Previously a professor at MIT and Stanford, he was educated at Dartmouth College (BA 1963), Stanford (PhD 1968 with E. E. van Tamelen; postdoc 1969 with J. P. Collman), and Harvard (postdoc 1970, K. E. Bloch).

a versatile click chemistry, encompassing both carbon- ($C\text{-}SO_2F$) and heteroatom-bound ($N\text{-}SO_2F$ and $O\text{-}SO_2F$) species.

As with most of click chemistry, the essential features of sulfur(VI) fluoride reactivity were first identified long ago. Indeed, a rich literature in RSO_2F and $ArSO_2F$ compounds appeared in the early 20th century in Germany, driven by the accessibility and dye properties of sulfur(VI) derivatives of benzenes, naphthalenes, and anthracenes available from coal tar.[6] While this reactivity is still important in dye manufacture, it faded from the view of most organic chemists rather abruptly in the mid-20th century, to judge from the publication record. We believe there are now other compelling reasons to pay attention to the SO_2F group, consistent with the fact that click reactions find their most facile applications in biological, medicinal, and materials chemistry. For example, the neutral diester sulfate unit linking two phenols, $ArO\text{-}SO_2\text{-}OAr'$, is a connector of low polarity and surprising stability. Although rare in the laboratory and largely unknown in biology, its properties suggest productive use as an unobtrusive linkage between modules. In addition, the SuFEx process has proven itself reliable for polymer synthesis such as the preparation of robust poly(diarylsulfonate) thermoplastic materials.[7]

3. Organic Sulfonyl Fluorides and their Derivatives

An understanding of the unique stability–reactivity pattern of sulfonyl fluorides rests on five contributing factors, illustrated by the results in Figure 1. More examples are available in the early and excellent review by Suter in 1944.[6c]

1) *Resistance to reduction*. Since fluorine is the most electronegative element in the periodic table, sulfonyl–fluorine bond cleavage is exclusively heterolytic with the formation of fluoride ion (although rarely, if ever, as uncomplexed F^-). In contrast, homolytic scission of S–Cl bonds is quite common.[8] Irreversible reduction to the sulfinic acid level ($ArS(O)OR$) occurs easily for $ArSO_2Cl$ with many nucleophiles, except alcohols and amines under limited conditions. Phosphines reduce sulfonyl chlorides rapidly to the corresponding thiol.[9] Sulfonyl bromides and iodides are even more prone to reduction and radical reactions than sulfonyl chlorides,[8,10] allowing sulfonyl chlorides, sulfonates, and sulfonic acids to be reduced cleanly if the iodide is generated in situ.[11] A remarkable example of the differences between chlorine and fluorine in sulfuryl chemistry is provided by the parent compounds: SO_2Cl_2 is a powerful oxidant, whereas sodium metal can be melted in hot liquid SO_2F_2 (under pressure) without chemical change in either species.[12]

2) *Thermodynamic stability*. Whereas substitution at all sulfur centers in oxidation states below VI is fast, including the sulfur(IV) oxyhalides SOF_2 and $SOCl_2$,[13] the very sluggishness of S^{VI} substitution chemistry makes it superior as a connector.[14] Furthermore, sulfonyl fluorides are much more stable than other sulfonyl halides toward nucleophilic substitution (including hydrolysis)[15] and thermolysis, making them the sulfonyl reagents of choice under demanding reaction conditions. These observations are consistent with

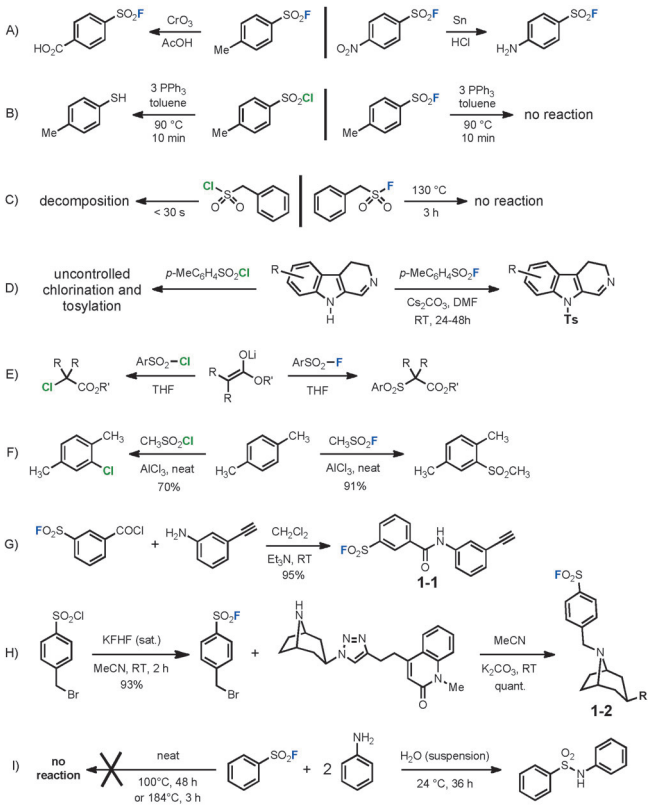
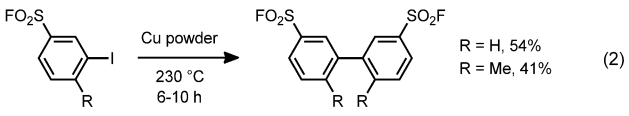


Figure 1. Reactions illustrating the properties of sulfonyl fluorides vs. other sulfonyl halides. A,B) Resistance of $ArSO_2F$ toward both oxidation[22a] and reduction;[6a] C) much greater stability of sulfonyl fluoride toward thermolysis; D–F) chlorination vs. desired sulfonylation in reactions with amines,[24] ester enolates[25] and under Friedel–Crafts conditions;[26] G,H) greater reactivity of acyl chloride and benzylic bromide compared to sulfonyl fluoride under non-activating conditions; I) the power of water in activating sulfonyl fluoride reactivity.

the measured bond strengths of $SO_2\text{–}F$ relative to $SO_2\text{–}Cl$: the homolytic bond dissociation energy of the S–F bond in SO_2F_2 (90.5 ± 4.3 kcal mol^{-1},[16] 81 ± 2 kcal mol^{-1}[17]) is far larger than the S–Cl bond in SO_2Cl_2 (46 ± 4 kcal mol^{-1}).[17] The difference is of similarly large magnitude (41 kcal mol^{-1}) in comparing the bond strengths of S–F vs. S–Cl bonds in SO_2FCl.[18]

These factors produce a surprising and highly useful passivity in the $\text{-}SO_2F$ group. A small gem of comparative observation was provided more than 40 years ago by gas chromatography analysis of sulfonyl halides, showing directly the thermal and hydrolytic fragility of RSO_2Cl compared to RSO_2F.[19] An even earlier and more striking case from Steinkopf and Jaeger described the Ullmann coupling of iodo-3-fluorosulfonylbenzenes over metallic copper powder at elevated temperatures, without decomposition of the SO_2F group [Eq. (2)].[6b] An aliphatic example is provided by



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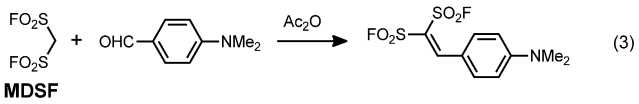
methanedisulfonyl fluoride [$(FSO_2)_2CH_2$, MDSF].[20] The SO_2F groups in this compound survive severe electrochemical oxidation conditions in the fluorination of the methylene



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group,[21] and base-mediated and -catalyzed alkylation and condensation reactions proceed easily [Eq. (3)]. The chloride analogue $(ClSO_2)_2CH_2$ decomposes under these circumstances. As a building block, MDSF should be especially useful for its dual potential to link with electrophiles at carbon via its conjugate base and with nucleophiles at each $O_2S{-}F$ bond. Most importantly, the notable stability of sulfonyl fluorides to aqueous conditions was first established by Steinkopf[6a] and by Davies and Dick[22] around 1930, and later elaborated by others.[23]

3) *Exclusive reaction at sulfur.* Along with the greater barriers to attack at sulfur(VI), the high polarizability of the chlorine center in $-SO_2Cl$ and related groups makes it vulnerable to reductive attack (by both one- and two-electron pathways, depending on nucleophile and conditions), so that reactions with carbon nucleophiles usually give mixtures resulting from both sulfonylation and chlorination. Examples from the literature include reactions with organolithium reagents,[27] sulfur ylides,[28] phosphorous ylides,[29] and electrophilic aromatic substitution.[26,30] In all these cases, sulfonyl fluorides provide only sulfonylation outcomes. The same reasoning applies to the use of sulfonimidoyl fluorides over parent chlorides.[31]

4) *Special nature of the fluoride–proton interaction.* Both addition–elimination and direct substitution pathways are reasonable for nucleophilic substitution reactions of sulfonyl fluorides.[15b,32] While the details of the SO_2 center's participation in this reaction are both relevant and incompletely understood, we focus on the key feature that makes SuFEx chemistry unique: it depends very much on stabilization of the developing fluoride ion in the substitution process.[15b,33] Other halides can be subject to similar effects,[34] but fluoride stands alone in the magnitude and spatiotemporal sensitivity of the phenomenon. Furthermore, the agents that accomplish such fluoride stabilization under practical conditions are H^+ (Figure 2) and R_3Si^+ (discussed in Sections 5, 8, and 9), making the SuFEx process controllable and useful in both biological and synthetic settings.

The special nature of the fluoride ion in water has long been recognized,[35] but is not often taken advantage of in a synthetic context.[36] Indeed, well-known "halex" (halogen exchange) processes that make aromatic fluorides from chlorides usually use basic F^- as the fluoride source. In Figure 2, the role of "HX" in stabilizing fluoride represents the potential virtues of specific protic centers in accelerating reactions of $-SO_2F$ electrophiles (as in reactions with proteins, discussed in Section 5), and the power of aqueous environments to transmit acidic stabilization to the fluoride center. To understand the unique properties of fluoride as base and

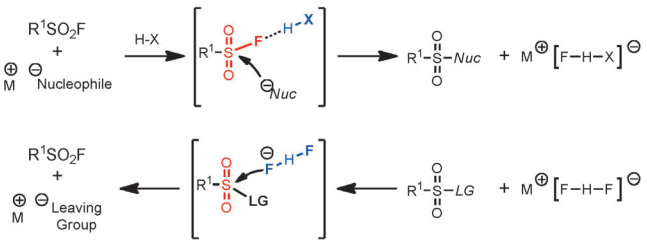

Figure 2. The essential role of fluoride stabilization and bifluoride attack in SuFEx chemistry.

leaving group, an appreciation of the bifluoride ion $(HF_2)^-$ is essential.[37] The $[F\text{-}H\text{-}F]^-$ hydrogen bond is worth a remarkable 40 kcal mol^{-1},[38] and so is formed when fluoride encounters any acid in water; higher adducts such as $[F\text{-}H\text{-}F\text{-}H\text{-}F]^-$ can also exist in equilibrium. In other words, F^- is a unique base: it gains strong stabilization in water by trapping a proton between two of itself, making a centrosymmetric 4-electron-3-center bond. The proton is therefore uniquely effective at stabilizing fluoride as a leaving group. In the exchange chemistry of sulfonyl fluorides in protic solvents, the reactivity of the bifluoride nucleophile, discussed in Section 4, is the complement to the helpful role of hydrogen bonding.

5) *Closely related functional groups. Aliphatic sulfonyl fluorides.* Aryl sulfonyl fluorides are significantly more resistant to hydrolysis than alkyl derivatives with α-hydrogens, and electron-withdrawing substituents on the aromatic ring increase the electrophilic nature of S^{VI} and make it more reactive.[23] Sulfonyl halides, including fluorides, bearing acidic protons in the α-position undergo reactions that often proceed via elimination to form sulfene-type intermediates ($RR'C{=}SO_2$).[39] A good example is phenylmethanesulfonyl fluoride (PMSF), a serine protease inhibitor widely used in the preparation of cell lysates.[40] However, this reaction pathway is fast only in the presence of base, allowing PMSF and other aliphatic sulfonyl fluorides to be stable and to selectively modify proteins in aqueous solution at moderate pH.[41] Also noteworthy is the far better $AlCl_3$-assisted Friedel–Crafts reactivity of alkyl-SO_2F compounds compared to alkyl-SO_2Cl.[26] Thus, while we focus more attention on arylsulfonyl connectors below, aliphatic derivatives also benefit from the unique chemistry of the SO_2F group.

Sulfonimidoyl fluorides. Although much less studied by us and others, sulfonimidoyl fluorides generally have the same advantageous properties as sulfonyl fluorides, and reactivity comparisons with sulfonimidoyl chlorides are similarly striking. However, the nitrogen substituent gives sulfonimidoyl fluorides an additional point for modification, and their reactivities toward nucleophiles can be dramatically altered by the nature of that substituent. Electron-withdrawing groups, such as acyl, carbonate and sulfonyl enhance the electrophilicity of S, making these classes of compounds very similar in reactivity to sulfonyl fluorides. In contrast, sulfonimidoyl fluorides with alkyl and aryl groups on N are remarkably stable, even under basic conditions (see Supporting Information). We have omitted further mention of sulfonimidoyl electrophiles here, but they certainly are potentially useful connectors.

4. Synthesis of Sulfonyl Fluorides from Chlorides

The most common processes of sulfonylation of aromatic and aliphatic molecules are summarized in Figure 3. The majority of these produce sulfonyl chlorides, making them the least expensive and most available substrates.[42] The exchange of fluoride for chloride in these systems would seem to be a simple matter, but the transformation's history is unusual in several instructive ways.

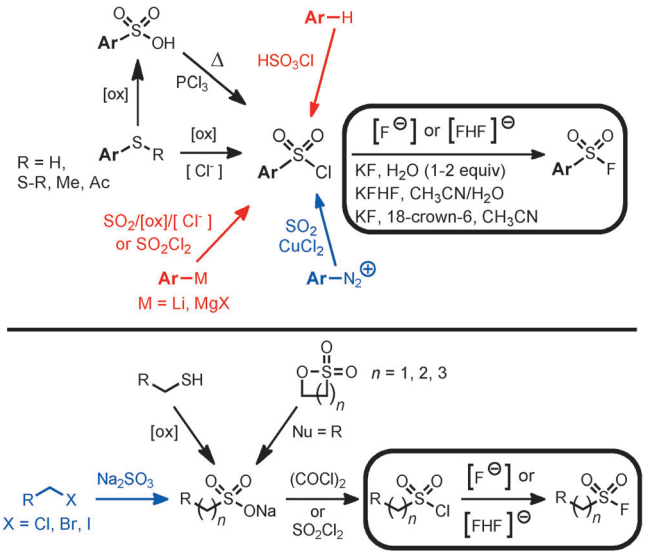

Figure 3. Common methods for the synthesis of aryl (top) and alkyl (bottom) sulfonyl chlorides and fluorides. The C–S bonds of these derivatives can be formed by nucleophilic attack of S^{IV} on organic electrophiles (blue) or attack of organic nucleophiles on electrophilic S^{VI} centers (red).

The parent fluoride salts of potassium, sodium, ammonium and zinc were the first reagents reported for sulfonyl chloride to fluoride conversion more than 80 years ago,[43] and continue to be used today.[44] The presence of water was found to be beneficial, and typical reaction conditions involved refluxing the water-organic biphasic mixtures.[45] However, yields rarely exceeded 80%. The use of "naked" fluoride (KF, dry acetonitrile, 18-crown-6) was considered to be advantageous and became the most accepted procedure for the preparation of sulfonyl fluorides, seeding a misplaced focus on fluoride ion basicity as the key to successful substitution at S^{VI}.[46] This perhaps led to the acceptance of side reactions derived from the strong basicity of "naked" fluoride as being unavoidable, diminishing the benefits of the method.[47] For example, exposure of alkyl sulfonyl fluorides to potassium fluoride was shown to assist hydrolysis in the presence of traces of water.[48] The answer to this problem has been available since 1949, when the reaction of sulfonyl chlorides with potassium bifluoride (a reagent first introduced into organic chemistry, as far as we can tell, by Borodin in 1863)[49] was described in a patent by Pound and Saunders.[50] However, the literature contains only a handful of reports employing this "acidic", but more nucleophilic, form of fluoride ion for the preparation of sulfonyl fluorides.

The bifluoride anion $(F\text{-}H\text{-}F)^-$ is almost impossible to avoid when fluoride is used,[51] since these H–F hydrogen bonds are extraordinarily strong,[38] We have found potassium bifluoride to be consistently and substantially superior to other reagents for sulfonyl chloride-to-fluoride conversion, allowing the use of mild reaction conditions, broad substrate scope, simple reaction setup, effortless product isolation, and easy scale up. Bifluoride seems to be especially effective when it can be used "on water"—that is, in reactions performed with a vigorously stirred or agitated water-organic interface.[52] Such reactions date back more than 80 years to the pioneering work of Steinkopf[6a,b] and Davis and Dick,[22b,43] who employed potassium fluoride in aqueous conditions, thereby accessing bifluoride. Since solvation and H-bonding is so critical to the state and reactivity of fluoride, we suspect that $[FHF]^-$ at aqueous-organic interfaces presents a destabilized and nucleophilic F^- atom to electrophiles in the organic phase, shown in schematic fashion in Figure 4. The same type of phenomenon has been proposed to account for the high reactivity of other species that are stabilized in the water lattice when presented at defects (interfaces) in that lattice.[53] Strong acid (HX) therefore has the counterintuitive effect of enhancing the utility of fluoride as a nucleophile, but not as a base, by generating a form of the anion (bifluoride) that can be presented more effectively at water interfaces.[54]

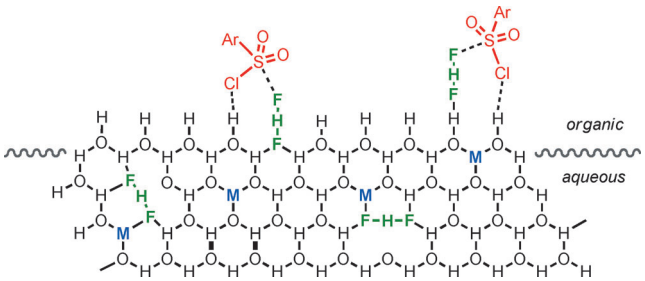

Figure 4. A speculative proposal for the special reactivity of bifluoride ion at the water–organic interface. $[FHF]^-$ molecules at the surface lose the key H-bonding interactions with water that stabilize this species in the bulk. As a result, bifluoride at the surface or interface is far more nucleophilic. Possible interactions with $ArSO_2Cl$ leading to substitution are shown. **M** = the counterion for bifluoride, usually K^+. Not shown is the bent $[H_2F_3]^-$ ion,[55] which is present in significant quantities along with bifluoride in the presence of excess HF. This figure is meant to be illustrative, and does not represent all of the structures, orientations, or H-bonding interactions that can occur with these species.

Examples of sulfonyl fluorides made from the corresponding chlorides in this way are shown in Figure 5. If technical grade starting material is used, the sulfonyl fluoride product occasionally requires purification by a wash with aqueous base and/or by chromatography on a short silica gel column. In our experience, however, the crude product is virtually free of impurities. Liquid sulfonyl chlorides are simply stirred vigorously with saturated aqueous KFHF solution.[52] Otherwise, acetonitrile is the co-solvent of

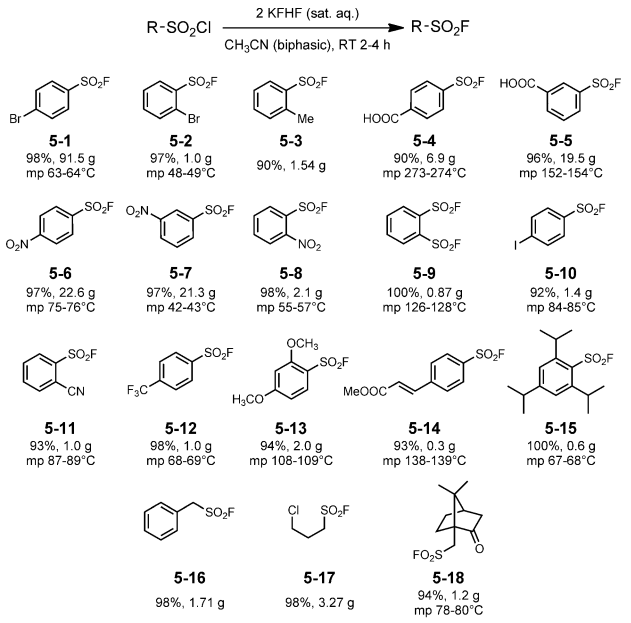

Figure 5. Sulfonyl fluorides made with potassium bifluoride.

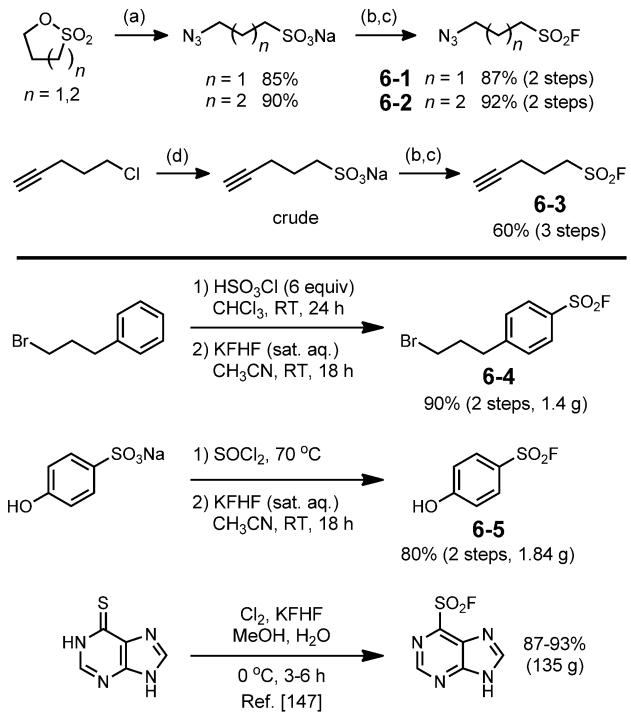

Figure 6. Alkyl (top) and aryl (bottom) sulfonyl fluorides made from sulfonic acids. a) NaN_3, acetone, H_2O, reflux, 8 h; b) $(COCl)_2$, CH_2Cl_2, DMF (cat.), RT, 18 h; c) KFHF (sat.), CH_3CN, RT, 6 h. d) Na_2SO_3 (1 equiv), H_2O, 95 °C, 16 h.

choice; THF or CH_2Cl_2 can be used as diluents to dissolve a hydrophobic substrate and present it to the aqueous interface where the reaction with bifluoride likely occurs. Full conversion is generally achieved within several hours.[56] When, as often happens, starting chloride and product fluoride overlap on TLC, reaction progress can be monitored by GC, LCMS, or ^{19}F NMR spectroscopy.

Examples from our laboratory of the easy installation of alkyl[57] and aryl sulfonyl groups using the general methods of Figure 3 are shown in Figure 6. In all cases, the intermediate sulfonyl chloride was subjected without purification to an aqueous phase of saturated KFHF. The desired fluoride product could be easily purified if necessary by simple washing, recrystallization, distillation, or column chromatography. Such in situ conversion to the fluoride is particularly advantageous for certain heterocyclic sulfonyl chlorides, often generated by oxidation of thiols such as the 6-mercaptopurine shown in Figure 6, that are unstable. KFHF acts as both nucleophile and buffer, in this case preventing nucleophilic replacement of entire sulfonyl group.[58]

Sulfonimidoyl chlorides and sulfamoyl chlorides[59] with electron withdrawing substituents on nitrogen[60] are very similar in their reactivity to sulfonyl chlorides (vide supra) and can be converted to the corresponding fluorides by treatment with saturated aqueous KFHF (Figure 7 A,B). When electron donating groups are present on nitrogen, bifluoride is not reactive enough, giving low yields under standard conditions. In these cases, Bolm's silver fluoride in acetonitrile conditions are used to produce the sulfonyl fluoride on a preparative scale (Figure 7 C,D).[31c]

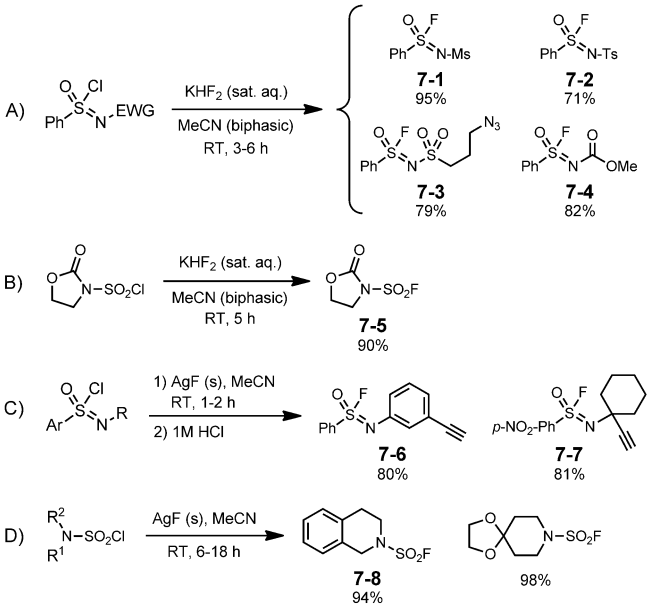

Figure 7. Sulfonimidoyl and sulfamoyl fluorides prepared from the corresponding chlorides. The acidic workup in reaction (C) is required to hydrolyze the silver acetylide formed under these conditions.

5. Sulfonyl Fluorides in Affinity Labeling and Drug Discovery

Small sulfonyl fluoride-containing molecules have been known as insecticides for approximately 100 years, with the

first reports of mechanism of action (inhibition of esterases) by Gold and Fahrney at Columbia University coming in the 1960s.[41] The combination of high kinetic barriers to, and strong thermodynamic driving force for, reaction with nucleophiles is unusual. Its full implications for drug discovery were first realized in the insightful work of Bernard R. Baker at the University of California, Santa Barbara: "*[the] SO_2F group reacts slowly, if at all, with proteins that are not reversibly complexed with the moiety bearing the SO_2F group. In contrast, when an SO_2F-bearing compound is complexed to a macromolecule such as an enzyme or cellulose, rapid covalent bond formation can occur.*"[61]

An overview of the extensive biomolecular data generated by the Baker group can be found elsewhere.[62] Some of the compounds developed by Baker and others, exploiting the affinity-driven activation of sulfonyl fluorides to form covalent linkages with the amino acid residues of protein binding sites, are shown in Figure 8. These include inhibitors of

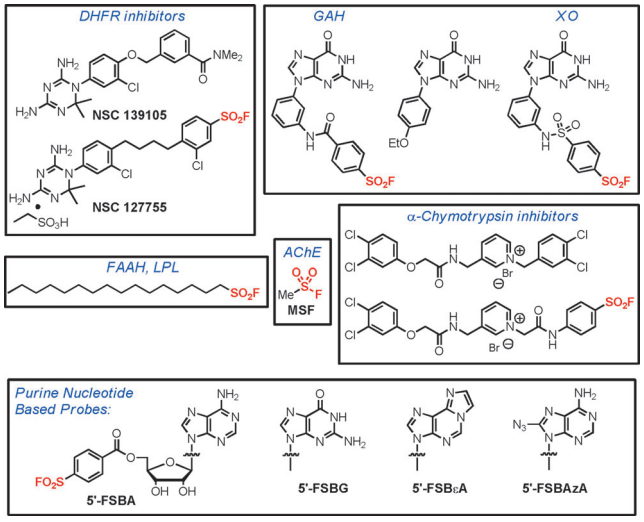

Figure 8. Examples of noncovalent inhibitors and SO_2F modified analogues, shown to be stable in serum or to have biological activity against the targets noted in blue.

dihydrofolate reductase (DHFR),[63] guanine deaminase (GAH),[64] xanthine oxidase (XO),[65] α-chymotrypsin,[66] estradiol dehydrogenase,[67] fatty acid amide hydrolase (FAAH),[68] and lipoprotein lipase (LPL).[69] The smallest member of this family, methyl sulfonyl fluoride (MSF), has been successfully tested for memory improvement in Alzheimer's disease patients as a selective and irreversible inhibitor of acetylcholinesterase (AChE).[70] The best known of the Baker sulfonyl fluoride inhibitors, NSC 127755, was later found to specifically modify tyrosine-31 of DHFR in chicken liver.[71] The relative non-reactivity of sulfonyl fluorides was recently exploited for the synthesis of ^{18}F-radiolabeled tracer compounds.[72]

Another major contributor to the field has been Roberta F. Colman of the University of Delaware. Her group developed fluorosulfonylbenzoyl nucleoside probes of the type illustrated at the bottom of Figure 8.[73] 5′-*p*-Fluorosulfonylbenzoyl adenosine (5′-FSBA) has been shown to specifically label NAD and ATP binding sites in more than 50 proteins,[74] and 5′-*p*-fluorosulfonylbenzoyl-1,N^6-ethenadenosine (5′-FSBεA) is a useful fluorescent affinity probe for measuring kinase activities.[75] Others have adapted this strategy for the inhibition of adenosine receptors[76] and Src-family tyrosine kinases[77] based on noncovalent inhibitor motifs. In our first biological application, we recently reported with colleagues at Scripps the use of aryl sulfonyl fluorides as kinetic traps of the protein transthyretin in non-aggregating forms.[78]

A survey of the above body of work yields the following general lessons that underpin our enthusiasm for the roles that sulfonyl fluorides can play in medicinal chemistry.

- As noted earlier, a small molecule sulfonyl fluoride group is unlikely to sulfonylate a protein unless its residence time on the protein[79] is extended by substantial noncovalent binding interactions. Noncovalent ligands can thereby be modified into irreversible inhibitors by introducing the SO_2F unit.[80] In an unfortunate locution, Baker designated these inhibition events as "endo-type" when the sulfonyl fluoride is captured by a residue in the active site of an enzyme, and "exo-type" when the nucleophilic site is found adjacent to the active site.[15c,63–66] But the concept is more powerful than the language: this strategy makes selective covalent modification of entities such as enzyme allosteric sites, receptors, ion channels, and structural proteins as accessible as mechanism-based bond formation in active sites.
- While the binding position and residence time are important in determining the positional selectivity of covalent modifications by sulfonyl fluoride agents, stabilization of the fluoride leaving group is also essential, as noted earlier (Figure 2). Given the ability of polypeptides to display hydrogen bond donors in well-oriented fashion—proteins being essentially rolled and crinkled-up organic-water interfaces—and the fact that hydrogen bonding controls the reactivity of fluoride more than that of any other leaving group, we believe that *protein surfaces provide molecular information that sulfonyl fluorides are particularly adept at reading*. Therefore, prospecting for covalent bond formation to enzymes with such reagents is likely to be far more selective than other types of electrophiles used in activity-based protein profiling (ABPP) and related endeavors.[81]
- Protein binding sites can also assist the hydrolysis of the sulfonyl fluoride group; the resulting sulfonic acid may then serve as a noncovalent binder.[82] This can be considered a prodrug approach, as the R-O-SO_3^- or R-SO_3^- group will have very different properties than the precursor R-O-SO_2-F or R-SO_2-F, including, in most cases, being cleared in vivo by renal excretion.
- When fluoride activation-stabilization is not provided, sulfonyl fluorides can bind to biomolecules without being modified, and should be regarded in these cases as a large trifluoromethyl group. Therefore, noncovalent (reversible) enzyme inhibition is also possible with sulfonyl fluorides. An early Baker example was reversible SO_2F inhibitors of guinea pig complement and phosphorylase in a rat tumor model.[83] It should be noted that the aryl SF_5 substituent

can serve a similar function, and a recent advance has made the synthesis of these molecules highly accessible.[84]

Sulfonyl fluorides have been regarded as poor probes for ABPP, although this seems to be changing for serine proteases at least.[85] Their use may have been limited by their relatively sluggish reactivity (which we regard as an advantage rather than a liability) and the perception that molecules containing both a sulfonyl fluoride warhead and a reporter moiety are not easy to access. Among the handful of reported examples include a sulfonyl fluoride inhibitor of α-thrombin conjugated to a nitroxide spin label,[86] biotinylated[87] and alkyne-bearing[77] FSBA analogs for kinase profiling, a biotinylated sulfonyl fluoride probe for triglycerol lipases,[88] and a ^{153}Eu isotope-labeled probe for serine protease quantification.[89] Several recent examples of focused libraries of sulfonyl fluoride analogues of biologically active compounds have appeared, including aryl sulfonyl fluorides[90] and amino acid based sulfonyl fluorides[91] as serine protease inhibitors, a small set of amine aryl sulfonyl compounds as NADPH oxidase inhibitors,[92] long-chain alkyl sulfonyl fluorides as an outer membrane phospholipase A inhibitors,[93] and unsymmetrical urea derivatives as antimicrobial and antifungal agents.[94] All of the above factors, bolstered by our recent work in this area,[78] convince us that many more exciting applications lie ahead for the felicitous match of proteins with aryl sulfonyl fluorides.

6. Pendant Functionalization with Sulfonyl Fluorides

Many applications of click chemistry in drug discovery and chemical biology have been enabled by the attachment of the desired reactive moiety to the scaffold of interest by a modular connector. The SO_2F group is well suited to this approach. Several dual-mode reagents are shown in Figure 9; the reactive electrophilic groups include benzyl bromide,[95] phenacyl bromide,[96] acyl halide,[96] isocyanate, and iodide. The weak reactivity of -SO_2F allows selective attachment to be made at the other electrophile, leaving the pendant sulfur(VI) fluoride available for subsequent controlled reactivity. Azide- and alkyne-modified sulfonyl fluorides will also be useful since the SO_2F group does not interfere with any form of the catalyzed or strain-promoted azide–alkyne ligation methods.[97]

The most powerful reagent for introduction of an SO_2F group is ethenesulfonyl fluoride (ESF), a strong Michael acceptor as well as Diels–Alder dienophile.[98] ESF is derived by elimination from 2-chloroethylsulfonyl fluoride, first described from the sulfonyl chloride in 1932[22b] and reported in large scale with elimination as a side reaction in 1979.[98] By optimizing sulfonyl fluoride generation with potassium bifluoride, we readily access ESF in large quantities (Figure 10). The related large-scale preparation of ESF from ethenylsulfonyl chloride (ESCl) was patented in

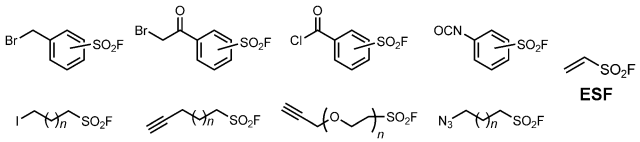

Figure 9. Small connector molecules allowing the installation of sulfonyl fluorides onto other functional structures.

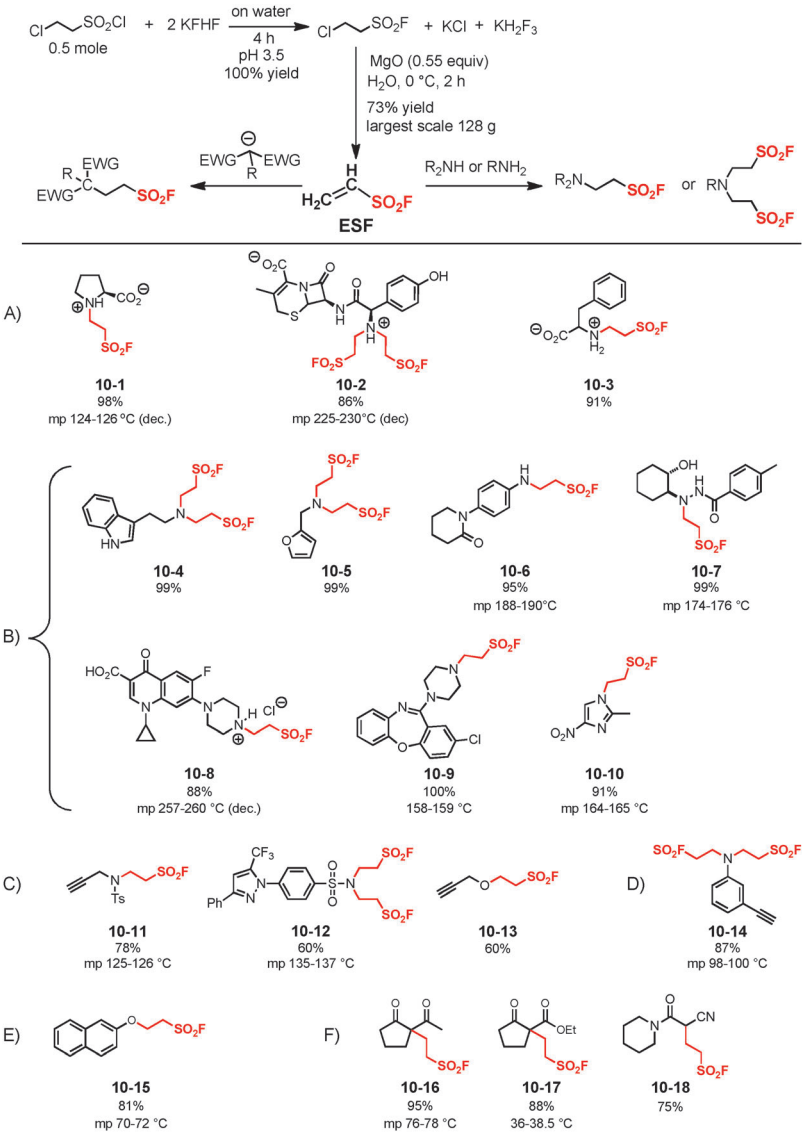

Figure 10. Synthesis (top) and use (bottom) of ESF in the decoration of nitrogen, oxygen, and carbon nucleophiles. Reaction conditions: A) ESF, 95:5 EtOH/H_2O, 5 min to hrs; B) ESF, solvent (usually CH_2Cl_2 or THF), 5 min to hours; C) ESF, PR_3 (10 mol%), CH_2Cl_2, 24 h; D) ESF, AcOH, reflux, 2 h; E) ESF, Bu_4NF (10 mol%), THF; F) ESF, quinine (10 mol%), CH_2Cl_2.

1950 by Hedrick (Dow Chemical), but with KF as the nucleophile rather than KFHF, resulting in a relatively low yield (75%).[99]

Krutak, Hyatt, and others described many cases in which ESF reacts cleanly with primary and secondary amines, anilines, certain nitrogen containing heterocyclic compounds, and thiols;[98,100] to this impressive list we add several additional examples shown in Figure 10. Reactions with active amines are usually complete within a few minutes at room temperature. The participation of amine-containing zwitterions such as amino acids achieves the full level of generality and convenience required of click reactions (Figure 10A). One simply stirs a slurry of starting zwitterion in aqueous ethanol, adds the requisite amount of ESF (one molar equivalent for secondary amines like proline, two equivalents for primary amines), and monitors the stirred suspension for conversion to the new zwitterion. Upon completion, the product is harvested by concentration and filtration. Indeed, for most ESF-amine conjugate additions, purification is rarely required. Details of the improved preparative procedure for ESF (Figure 10) can be found in Supporting Information; the literature also describes examples of fluorinated derivatives of ESF,[101] which should be similarly useful. *Caution!* ESF is a toxic molecule,[98] so strict attention to proper procedures for handling this volatile compound (boiling point 119°C) is recommended.

7. Sulfuryl Fluoride Gas (SO_2F_2) as a Sulfur(VI) Connector

While it is tempting to try to use sulfuryl chloride (SO_2Cl_2) as the brimstone analogue to phosgene, its substitution chemistry is fraught with complications as described above. Therefore, practical methods for making heteroatom connections to both sides of the sulfonyl group have rarely appeared in the literature. In contrast to the paucity of known diaryl sulfates, the literature is rich with triaryl phosphates, some of which are produced in thousands of tons annually as fire retardants. These phosphates are made in excellent yields by phenoxide substitutions of the three chlorides of $O{=}PCl_3$, highlighting the fact that reductive cleavage does not compete with substitutions of P^V–Cl bonds as it does with S^{VI}–Cl bonds. The ability of fluorine to moderate the chemistry of sulfur(VI) in this context is transformative, rendering S^{VI} easier to stitch into a structure than P^V. The power of this simple change is embodied most clearly in the chemistry of the parent reagent, SO_2F_2.

The smallest member of the S^{VI} oxyfluorides family, SO_2F_2 was first described in 1901 by Moissan[102] and subsequently developed by Dow Chemical in the 1950s as the pest control agent Vikane. At normal temperature and pressure, SO_2F_2 is a colorless, odorless gas, 3.5 times heavier than air (Table 1).[103] These properties, coupled with its high vapor pressure and ability to saturate air at concentrations lethal to pests, make SO_2F_2 an effective fumigant, presently used against insects and rodents. The global production of SO_2F_2 since 2000 averages approximately 3 million kilograms per year.[104] Due to the industrial scale of SO_2F_2 production and usage, a number of reports aimed at evaluation of its physiological toxicity and environmental impact have appeared.[105]

Table 1: Physical properties of SO_2F_2.

CAS number	2699-79-8
molecular weight	102.1 g mol^{-1}
density (25°C, 1 atm)	4.18 mg mL^{-1} (air: 1.18 mg mL^{-1})
boiling point	−55°C
vapor pressure	1611.47 kPa at 20°C
odor	odorless
appearance	colorless gas
flammability	non-flammable
solubility (25°C, g L^{-1})	water: 0.75, 1-octanol: 14, heptane: 22, 1,2-dichloroethane: 25, MeOH: 33, EtOAc: 59, acetone: 71

SO_2F_2 is relatively inert in gaseous form and is stable up to 400°C when dry.[105a] It is slowly hydrolyzed in water under neutral conditions and more rapidly under basic conditions to produce fluorosulfate and fluoride ions.[106] SO_2F_2 has relatively small magnetic and quadrupole moments,[107] does not undergo photolysis in the actinic region of solar radiation, and is inert toward ozone and the active radicals of the atmosphere (Cl·, OH·).[104] Again, comparison to sulfuryl chloride is instructive: SO_2Cl_2 is less thermally stable (decomposes at 100°C in an open system to chlorine and sulfur dioxide) and easily generates chlorine radicals.[108]

Uptake of SO_2F_2 by the oceans accounts for a very small percentage of annual emissions.[109] Therefore, alternative mechanisms of SO_2F_2 dissipation have been speculated to be of biological origin. Chemical stability coupled with biological activity is a recurring theme of S^{VI} oxyfluorides, and sulfuryl fluoride is no exception. Although colorless, odourless, and not immediately irritating to the eyes or skin, SO_2F_2 is a broad spectrum biocide upon exposure for a sufficient period of time and at a high enough concentration, and so should be handled only with adequate ventilation. Symptoms of extended SO_2F_2 exposure include nose, eye, throat, and respiratory irritation, nausea, abdominal pain, coughing, vomiting, muscle twitching, seizures, and pulmonary edema. Repeated exposures to high concentrations of sulfuryl fluoride may cause lung and kidney damage.[105b] Serious long-term mutagenic, carcinogenic and reproduction effects of SO_2F_2 have not been identified. Comprehensive data on the physiological toxicity of SO_2F_2 in various animal models can be found elsewhere.[105c] In insects[110] and rats,[111] fluoride ion derived from SO_2F_2 hydrolysis is believed to be the primary toxin, although we think it likely that protein sulfation plays an important role. Fluorosulfation of proteins with SO_2F_2 has been indicated in studies of food fumigation.[112] For example, a variety of household items exposed to radioisotopic $^{35}SO_2F_2$ showed very little radiolabel incorporation except for proteinaceous food products such as beef and milk.[112a] Early experiments of wheat flour exposed to the fumigant suggested fluorsulfation of N-terminal phenylalanine, histidine and lysine amino acid residues.[112b]

8. Synthesis and Reactivity of Fluorosulfates ($ROSO_2F$): Hydrogen Bonding as Mediator

Early published syntheses of fluorosulfates (also called sulfoxyl fluorides or sulfurofluoridates; fluorosulfonate is also used although this term should be reserved for compounds containing at least one carbon-sulfur bond) from phenols used $ClSO_2F + SOF_4$ or SO_2F_2 at high temperatures, giving poor results.[113] Chlorosulfates ($ROSO_2Cl$), unlike the organic sulfonyl chlorides described above, respond poorly to attempted substitution with KF.[114] Furthermore, aryloxy chlorosulfates are unattractive starting materials, as they are prone to self-chlorination and other radical decomposition processes at low temperatures.[113b] We, like pioneer William Firth in the context of polymer chemistry,[113b,115] therefore regarded the fluorosulfate unit as worthy of greater exploration. Better synthetic approaches were needed, and so we turned to sulfuryl fluoride as the obvious key reagent. The reaction of SO_2F_2 with preformed sodium[13,114b] and lithium phenolates[116] had previously been shown to provide better yields of fluorosulfates, but these procedures did not catch on. SO_2F_2 therefore represents a curious combination of ton-scale application in the field and poor appreciation in the laboratory.

Reaction of SO_2F_2 with oxygen nucleophiles in the presence of base gives fluorosulfates (Figure 11), which have long been known to be quite stable toward hydrolysis

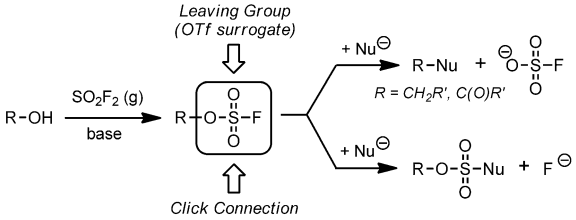

Figure 11. Dual modes of reactivity of fluorosulfates.

under neutral or acidic conditions.[117] Depending on the nature of the substituent R, the -OSO_2F unit can be a good leaving group or a robust connector. The former reactivity pattern includes the conversion of carboxylic acids and primary alcohols to acyl[118] and aliphatic fluorides, respectively, using SO_2F_2 in the presence of base.[119] Secondary fluorosulfates can be made and isolated when the carbinol center is embedded in the molecule between electron-withdrawing substituents that make both S_N1 and S_N2 substitution difficult, as is the case with a C6-fluorosulfated penicillin analogue tested as a covalent inhibitor of porcine pancretic elastase.[120] In addition, certain perfluorinated aliphatic fluorosulfates can be isolated and were shown to form stable sulfate and sulfamate connections.[121]

The simple reaction of SO_2F_2 with alcohols reaches its zenith for aromatic substrates, since the derived aryloxyfluorosulfates are very stable. Even more importantly for biological applications, *aromatic alcohols undergo selective modification by SO_2F_2 gas, leaving aliphatic alcohols, aliphatic and aromatic amines, and carboxylates untouched*. We find aromatic fluorosulfates to be stable for months in neutral buffers, and for up to two weeks in phosphate buffer at pH 10. They coexist with all natural amino acid sidechains and with functional groups present on the vast majority of natural products.

We have converted a wide variety of phenols to fluorosulfates in quantitative yields by exposure to gaseous SO_2F_2 and triethylamine (Figure 12). While preparing this report, we came upon recent patents from Ishii and co-workers (Central Glass Company, Japan) for the same process.[122] In our laboratory-scale reactions, SO_2F_2 was introduced from a balloon after the reaction flask was septum sealed, and the reactions were conducted with vigorous stirring of the liquid to facilitate gas dissolution in the condensed phases. The products were isolated by evaporative removal of solvent followed by acidic aqueous extraction to eliminate traces of base. Aqueous-organic biphasic conditions were found to suppress, almost completely, competitive fluorosulfonation of groups other than phenols in diversely functionalized molecules such as vancomycin. This selectivity for phenolic hydroxy groups is remarkable; see Figure 12B. Sterically hindered substrates performed best when phenolate anions were pre-formed. Cyclic sulfates were the exclusive products from 1,2-catechols under standard reaction conditions,[114b,123] obtained in much greater yields than is usually the case with sulfuryl chloride.[124]

Since no reliable methods were previously available for the synthesis of fluorosulfates, their chemistry has remained mostly unexplored. We regard the aryl-sulfate (Ar-O-SO_2-) connection as a vastly underappreciated linkage, now formed with sufficient reliability to be applied to a wide variety of targets in biology and materials science.[113b,125] For example, sulfates are phosphate isosteres, and several members of the alkaline phosphatase superfamily can cross-catalyze both phosphoryl and sulfuryl transfer.[126] The reactivity of aryl fluorosulfates towards nucleophiles, including hydroxide, is much diminished compared to the analogous sulfonyl fluorides.[6a] Thus, the unassisted reaction of fluorosulfates with secondary amines requires elevated temperatures in organic solvents.[127] The best way to activate these reagents for synthetic chemistry is with nucleophilic catalysts such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) as described below, but we have also found the process to be facilitated by vigorous stirring with an immiscible buffered aqueous phase. The blending of water with miscible cosolvents such as THF or acetonitrile will also aid the process, but with longer time for completion. A benefit of the two-phase process previously noted[52a] but not widely appreciated is that the interfacially-controlled biphasic reactions are usually cleaner than their homogeneous counterparts, even if rates are similar. Water-tolerant or water-assisted reactions such as the addition of nucleophiles to arylfluorosulfates should therefore always be tried first in a two-phase format with organic solvent.[52b] The productive interplay between O_2S-F and F^--H^+ interactions makes this especially true for SuFEx chemistry, as highlighted above (Figure 2).

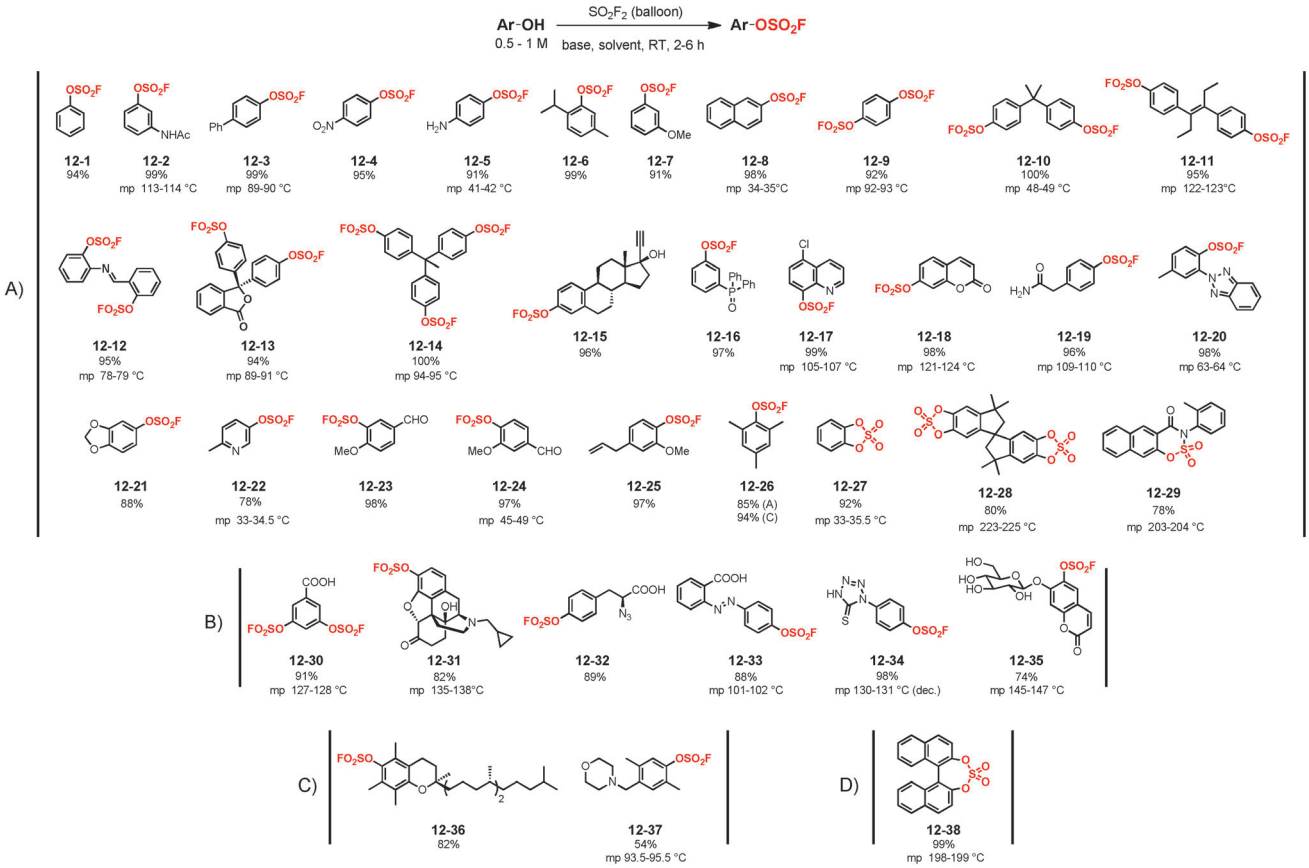

Figure 12. Aryl fluorosulfates prepared in our laboratory by a convenient procedure with gaseous SO_2F_2, in the presence of the following bases: A) Et_3N in CH_2Cl_2, B) Et_3N or iPr_2NEt in biphasic mixture (CH_2Cl_2/water), C) NaH in THF, D) DBU in MeCN.

9. Synthesis and Reactivity of Fluorosulfates ($ROSO_2F$): Silicon as Mediator

The synthesis and use of aryl fluorosulfates finds another powerful set of applications when silicon is brought into play. Early examples of this felicitous combination include the arylsulfonylation of a tertiary silyl ether with arylsulfonyl fluoride[128] and the perfluoroalkylsulfonylation of aryl silyl ethers,[129] both catalyzed by fluoride ion. We find that aryl silyl ethers are excellent substrates for conversion to fluorosulfates with sulfuryl fluoride gas in the presence of catalytic amounts of DBU (Figure 13, reaction A). This reactivity pattern relates to the previously-reported ability of organic bases to activate both sulfonyl fluorides and silyl groups in transformations such as the conversion of hydroxy groups to fluorides,[130] silyl ethers to tosylates,[131] and silyl ether hydrolysis.[131a] We observe trimethylsilyl ethers to give fluorosulfates instantly, whereas the bulkier *tert*-butyldimethylsilyl group requires several hours for the reaction to reach completion.

In a similar fashion, certain Lewis bases apparently mediate coupling between silyl ethers and fluorosulfates, representing the best synthesis of stable sulfate connections (Figure 13B). This reaction was first reported by Gembus and co-workers just a few years ago using tosyl fluoride,[131b] representing a vast improvement on the previous route to diarylsulfates (aryloxide attack on an intermediate chlorosulfate).[125a] Arylsulfates are generated in high yields with only inert (and sometimes volatile) silyl fluorides as byproducts. A wide variety of functional groups can be tolerated (Figure 13B), limited only by steric bulk at silicon and the presence of acidic protons that can quench the basic catalyst. The process therefore has many characteristics of a click reaction and so is suitable for the synthesis of polymeric materials, such as the sulfate analogue[7,115] of the well-known poly(bisphenol A carbonate) (Lexan, CAS# 25037-45-2) shown in Figure 13C. Additional iterations of this new polymerization process are described in a recent report by Dong et al.[7]

This conversion of aromatic silyl ethers into fluorosulfates and diarylsulfates is quite different from the popular use of silyl sulfonates (usually triflates) as catalysts in processes such as acetalization,[132] aldol, and allylation reactions.[133] In these and many other cases, silicon–oxygen bonds are swapped, or Si–C is exchanged for Si–O. In our case, sulfuryl–F bond is strong enough to avoid unwanted side reactions while allowing fluorine to be delivered to silicon as its thermodynamically favored destination via a well-controlled pathway.

Another important property of aromatic fluorosulfates is their ability to participate in transition metal catalyzed coupling reactions (Figure 14). The participation of fluorosulfates as electrophilic components in Negishi and Stille cross-couplings,[134] as well as palladium catalyzed alkoxycarbonylation reactions,[135] was originally investigated by the

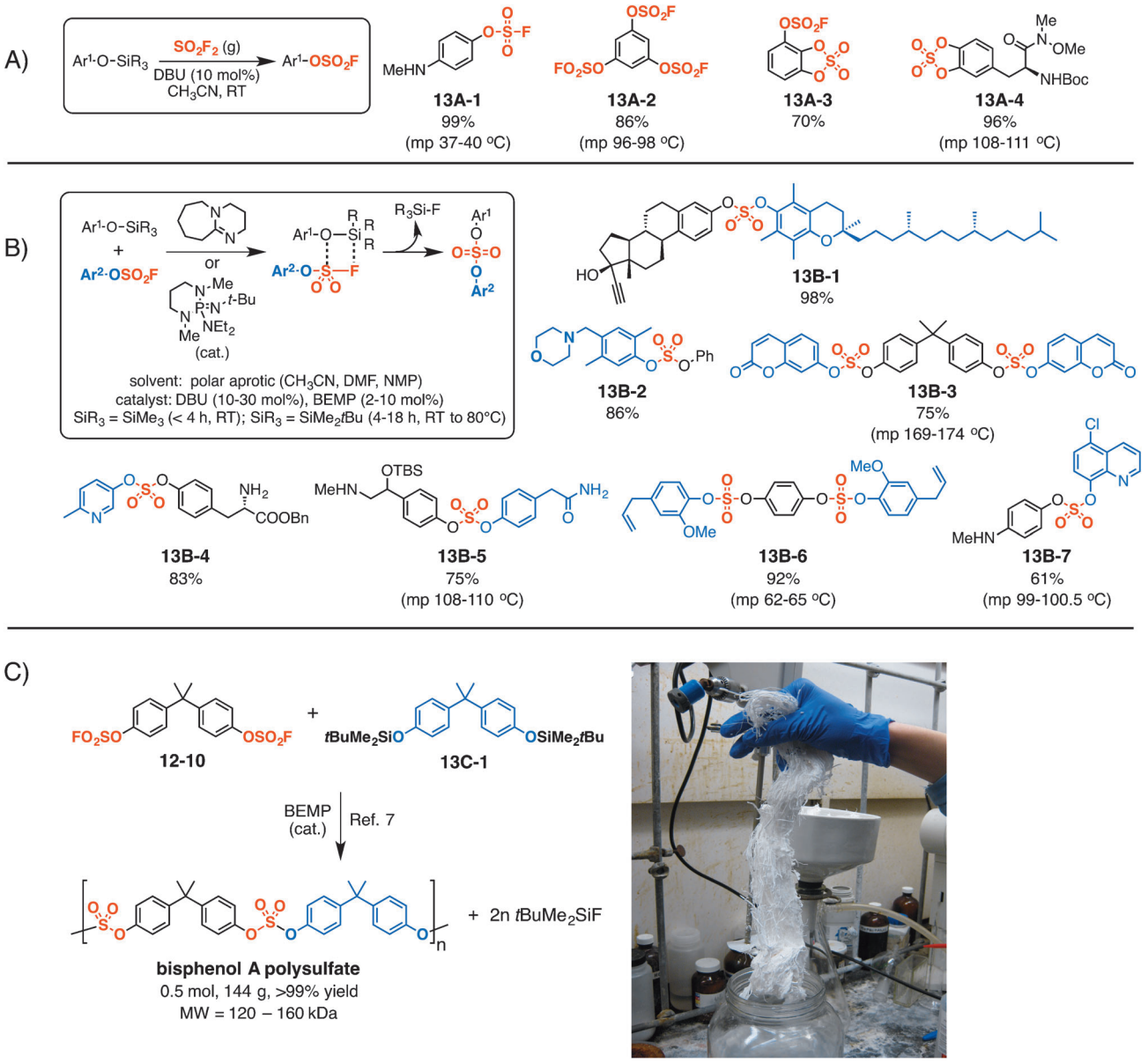

Figure 13. Conversions of aryl silyl ethers to fluorosulfates and diarylsulfates, with examples from this Review. The dotted lines in reaction (B) are meant to show connectivity, not mechanism. The photograph in part (C) shows the polymer obtained from the reaction at the left after precipitation from warm DMF (see Supporting Information).

process group at Bristol-Myers Squibb. Competition studies between phenyl fluorosulfate and phenyl triflate showed these groups to have similar coupling rates with an organotin reagent.[134] A dramatic illustration of the utility of fluorosulfate as an inexpensive triflate alternative was later provided by a process developed by SmithKline Beecham chemists.[136] Fluorosulfate prepared from the corresponding phenol and fluorosulfonic acid anhydride, the most common procedure at the time, engaged in efficient palladium catalyzed methoxycarbonylation on a 50-gallon scale.

The replacement of triflate (OTf) with fluorosulfate (OSO_2F) was also shown to be practical for enol ethers. Thus, fluorosulfonyl enolates participate in Stille[135b] and Suzuki cross-couplings,[137] and can also be used as precursors to allenes[138] and alkynes.[139] We have found SO_2F_2 to be an effective reagent for the synthesis of fluorosulfonyl enol ethers from the related lithium enolate or silyl ether (Figure 15).

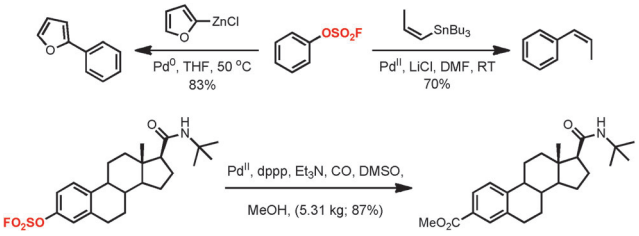

Figure 14. Aryl fluorosulfates in Pd-catalyzed coupling reactions reported by Bristol-Myers Squibb.

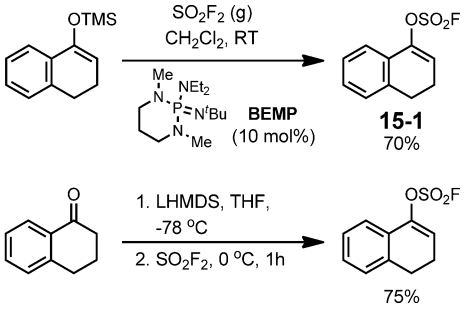

Figure 15. Preparations of enol fluorosulfates.

10. Synthesis and Reactivity of Sulfamoyl Fluorides (R_2NSO_2F)

Sulfamate esters ($R^1OSO_2NR^2R^3$) have long been appreciated as mildly electrophilic (and often covalent) inhibitors of sulfatase enzymes; sulfamates (usually $R^1OSO_2NH_2$) and sulfamides have been developed as popular noncovalent inhibitors of many other enzyme classes.[140] The synthesis of these molecules has only rarely been approached from sulfonyl fluoride intermediates.

Primary amines are rapidly fluorosulfated by SO_2F_2 gas, but the resulting adducts undergo facile elimination to azasulfene intermediates[141] by virtue of the acidic nature of the N-sulfamoyl proton. Capture by amine provides symmetrically substituted sulfamides (Figure 16A).[142] A few reports are available on the synthesis of monosubstituted sulfamoyl fluorides by other means. These include Hofmann rearrangement of aryl sulfonamides (Figure 16B),[143] halide exchange of parent alkyl sulfamoyl chlorides (Figure 16C),[144] and ring opening of an aziridine under fluorinating conditions (Figure 16D).[145] All of these processes were performed under acidic or neutral conditions to avoid the aforementioned elimination of HF from the products.

In contrast, secondary amines react smoothly with SO_2F_2 to give N-disubstituted sulfamoyl fluorides as remarkably stable compounds, dramatically more robust than analogous chlorides (Figure 17). Typically, an activating agent such DMAP or DABCO is required, ranging from 0.5 equiv for cyclic amines (exothermic reaction) to a full equivalent for acyclic amines. A variety of solvents can be used, with CH_2Cl_2 or THF providing the best reaction rates, and the reaction setup is identical to that described above for the synthesis of fluorosulfates (Figure 12). The resulting sulfamoyl fluorides are purified by a simple acidic wash. Poor nucleophiles such as disubstituted anilines

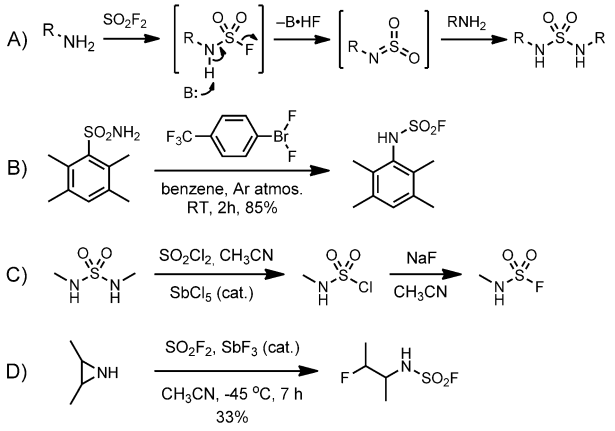

Figure 16. A) Attempted and B–D) known preparations of N-monosubstituted sulfamoyl fluorides.

do not participate in the reaction with SO_2F_2 under these conditions within a reasonable period of time.

We have found *N*-disubstituted sulfamoyl fluorides to be stable toward hydrolysis under basic conditions at room temperature for more than a week. Nucleophilic displacement of fluoride in this system requires heating and some assistance for the departure of fluoride by a hydrogen-bonding solvent: a separate water phase is usually best (Figure 18, top). Furthermore, this type of sulfamoyl fluoride is remarkably inert toward a wide range of nucleophiles at room temperature in organic solvents, including amines, phosphines, thiols, organolithium and Grignard reagents, hydride, phenoxide, and hydroxide. Figure 18 shows results from our tests of the compatibility of the R_2NSO_2F group with a variety of useful synthetic transformations, including those involving strong nucleophiles, reducing agents, oxidants, radicals, and strong acids and bases.

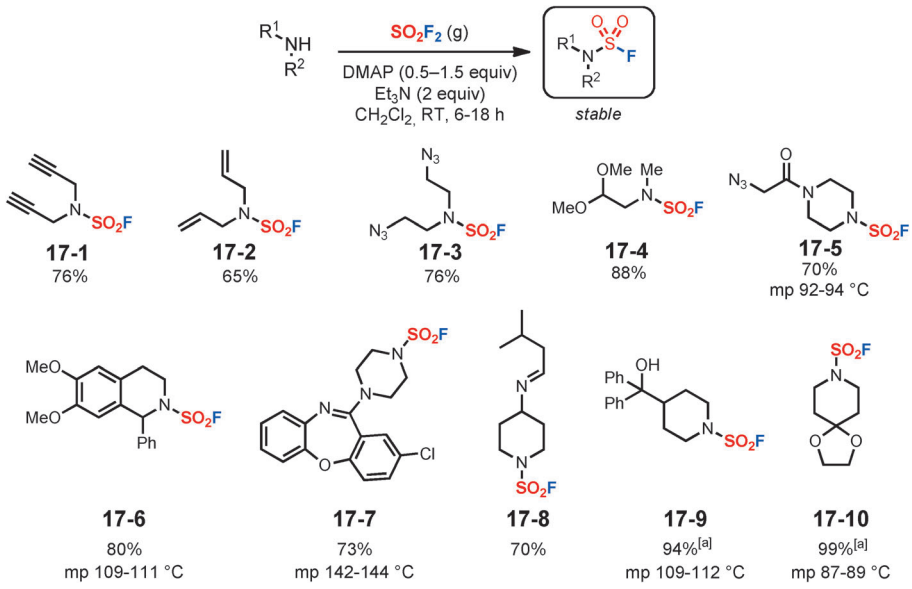

Figure 17. Formation of N-disubstituted sulfamoyl fluorides, with selected examples from our laboratory. Yields are of analytically pure material isolated after extraction. a) DMAP (30 mol%), MgO (5 equiv), 4:1 CH_2Cl_2/H_2O, RT, 18 h.

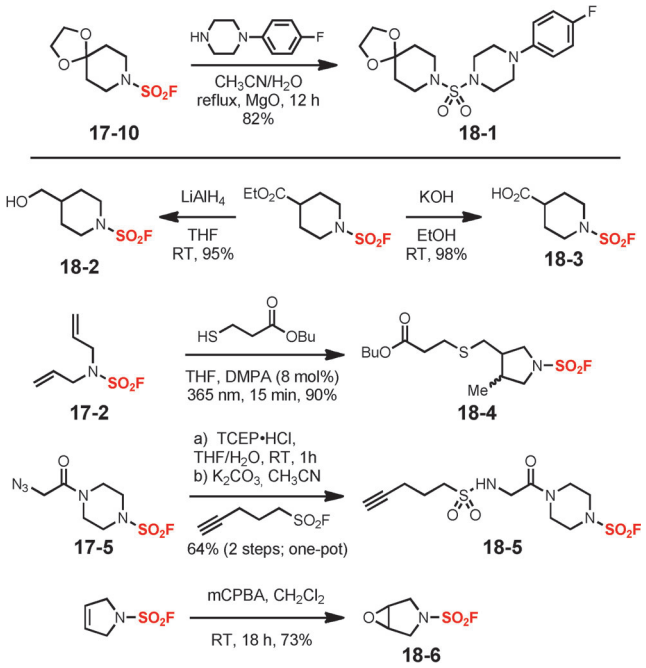

Figure 18. Top: Example of sulfamoyl fluoride substitution by secondary amine. Bottom: Examples of transformations performed in the presence of the sulfamoyl fluoride moiety.

11. Conclusions

We review here the basic principles of reactivity of sulfur(VI) fluorides, in order to introduce (or re-introduce) this class of compounds to those who may be unaware of their potential. As with most click reactions, the pioneering discoveries were made by others, usually a long time ago. In seizing on the best of these to create useful structures in our own laboratories, we have come to believe that two misconceptions may have hindered their widespread appreciation. The first is the expectation that fluorine chemistry is extreme, involving either wildly reactive reagents (F^+ equivalents for electrophilic fluorination) or supremely unreactive ones (halocarbons, solvated fluoride ion). A malleable middle ground, helpful to the development of useful transformations, seemed to be lacking. We show here that proton and silyl fragments provide both kinetic and thermodynamic tools to prod fluoride chemistry into the realm of substantial, yet controllable, activity. The second misconception is that the sulfuryl-oxygen bonds (such as in a sulfate diester, RO-SO_2-OR′) are hydrolytically unstable as compared, for example, to those in a phosphoryl triester ($O{=}P(OR)_3$). This is not generally true: in stable -OSO_2O- groups may be found very useful connectivity.

In our original description of click chemistry,[1] we identified the formation of sulfonamides from sulfonyl halides and amines as meeting the click standard. However, we failed to appreciate the special qualities of sulfonyl fluorides that allows them to be used in different contexts, and thereby missed the remarkable features inherent in these sulfur(VI) fluoride exchange (SuFEx) processes. Three key lessons have emerged from the literature and our own experiments. First, *the SO_2–F bond is unusually strong*, so that undesired substitution (such as hydrolysis) is minimized. This allows precise modifications of complex targets such as biopolymers. Second, *the fluoride radical is energetically inaccessible*, and so radical pathways that complicate the chemistry of the other sulfur(VI) halides do not exist for sulfonyl/sulfuryl fluorides. Third, *two partners offer versatile ways to make and activate SO_2–F bonds.* The proton forms unusually strong hydrogen bonds to fluoride. Even weakly acidic solvents, additives, and especially interfaces can thereby assist the heterolytic cleavage of the SO_2–F bond, and the bifluoride ion (FHF^-) is a unique source of tailorably nucleophilic fluoride for substitution reactions.[52b] Under non-protic conditions, silicon is useful, as Si and F form the strongest single bond in nature, allowing the rapid formation of SO_2–O bonds from very stable silyl ether precursors.

These factors provide robust methods for the synthesis of carbon-, oxygen-, and nitrogen-substituted sulfur(VI) fluorides spanning a wide range of stabilities and allowing them to be used in a predictable and powerful manner in a variety of settings. For synthetic chemists, the fluorosulfate group can function as an inexpensive triflate alternative. Medicinal chemists may consider the fluorosulfate and sulfamoyl fluoride groups as useful pharmacophores,[146] and as controllable covalent modifiers of biomolecules. Developers of polymers and materials can benefit from the robust method of stitching molecules together with stable sulfate connections. In all applications, simple, inexpensive, and easily scalable preparative methods are strongly enabling; we hope that those shown here using sulfuryl fluoride gas will spur the development of aromatic fluorosulfate building blocks for many useful purposes.

Overlaying all of these details, we encourage readers to consider the concept of "information content" in the context of click chemistry processes. Sulfonyl/sulfuryl fluorides possess a nearly ideal combination of synthetic accessibility, stability, and responsiveness to the presentation of proton or silyl activators—molecular cofactors that enhance reactivity in subtle and powerful ways. One can therefore use the SO_2F group to probe complex landscapes such as protein surfaces, or make small-molecule connections with absolute reliability. The capacity to ignore the irrelevant and respond forcefully to the desired target or condition is valuable molecular information indeed.

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