Sulfonyl fluorides as targets and substrates in the development of new synthetic methods

Terry Shing-Bong Lou and Michael C. Willis†

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, United Kingdom

†Email: michael.willis@chem.ox.ac.uk

Abstract | The advent of sulfur(VI)-fluoride exchange (SuFEx) processes as transformations with click-like reactivity has invigorated research into electrophilic species featuring a sulfur-fluorine bond. Amongst these, sulfonyl fluorides have emerged as the work-horse functional group, with diverse applications being reported. Sulfonyl fluorides are used as electrophilic warheads by both medicinal chemists and chemical biologists. The balance of reactivity and stability that is so attractive for these applications, particularly the resistance of sulfonyl fluorides to hydrolysis under physiological conditions, has provided opportunities for synthetic chemists. New synthetic approaches that start with sulfur-containing substrates include the activation of sulfonamides using pyrilium salts, the deoxygenation of sulfonic acids, and the electrochemical oxidation of thiols. Employing non-sulfur containing substrates has led to the development of transition-metal-catalysed processes based on palladium, copper and nickel, as well as the use of SO_2F_2 gas as an electrophilic hub. Selectively manipulating molecules that already contain a sulfonyl fluoride group has also proven to be a popular tactic, with metal-catalysed processes again at the fore. Finally, coaxing sulfonyl fluorides to engage with nucleophiles, when required, and under suitable reaction conditions, has led to new activation methods. This review provides an overview of the challenges in the efficient synthesis and manipulation of these intriguing functional groups.

Introduction

Sulfonyl fluorides have a century of history behind them, with the first sulfonyl fluoride being synthesised by treating toluene with fluorosulfonic acid in 1921, by workers at Oderberger Chemischen Werke, a German chemical company[1]. The 1921 date was disclosed by Steinkopf, in his 1927 account, in which he documents a personal communication from Oderberger Chemischen Werke. The Steinkopf account discusses the preparation and reactivity of arylsulfonyl fluorides, records their resistance to hydrolysis and oxidation, and draws comparisons with sulfonyl chlorides[1]. The report

also notes the discovery of bactericidal effects of sulfonyl fluoride-substituted benzoic acids towards *Bacillus subtilis* and lactic acid bacteria by Pribram and Zike. Despite these early encouraging reports regarding the use of sulfonyl fluorides in biochemistry, these molecules did not attract significant interest from organic chemists. However, Sharpless's 2014 publication[2], in which sulfur(VI)-fluoride exchange (SuFEx) was declared to be the next "click" reaction, has transformed the landscape for research into and around sulfonyl fluorides.

- *Properties of sulfonyl fluorides*

Sulfonyl fluorides are often compared with the analogous sulfonyl chlorides. While sulfonyl chlorides are excellent electrophiles, the fluoride variant only reacts with nucleophiles under specific conditions[1,3,4]. Such a difference in reactivity is also observed between sulfuryl fluoride (SO_2F_2) and sulfuryl chloride (SO_2Cl_2); the fluoride analogue is inert towards hydrolysis even when heated at 150 °C in a sealed tube, while the chloride reacts rapidly with water to give hydrogen chloride and sulfuric acid[5]. The stability and inertness of sulfonyl fluorides can be attributed to the exceptional strength of a S–F bond. As exemplified by sulfuryl chloride fluoride (SO_2ClF), the homolytic bond dissociation energy of S–F bond (84 ± 10 kcal mol^{-1}) is significantly higher than that of S–Cl bond (43 ± 10 kcal mol^{-1})[6], which suggests the ClO_2S–F bond is much stronger than the FO_2S–Cl bond. A similar trend is observed when comparing the S–F bonds (81 ± 2 kcal mol^{-1}) in SO_2F_2 with the S–Cl bonds (46 ± 4 kcal mol^{-1}) in SO_2Cl_2[6,7] (FIG. 1B).

The high oxidation state (VI) of sulfur in sulfonyl fluorides also contributes to their inertness, as sulfur centres with lower oxidation states, e.g. S(II) and S(IV), are more prone to substitution, hydrolysis or decomposition[5]. For example, sulfuryl fluoride (SO_2F_2) is soluble in water and only slowly undergoes hydrolysis, unless in basic solution[8-10]; thionyl fluoride (SOF_2), however, hydrolyses readily to give hydrogen fluoride and sulfur dioxide[5]. The shorter S–F bond length in SO_2F_2 (1.530 Å) compared to that in SOF_2 (1.583 Å) suggests the S–F bonds in the S(VI) compound are stronger. As a result of their high oxidation state and the presence of a strong S–F bond, sulfonyl fluorides are more stable than sulfinyl or sulfenyl fluorides, as well as sulfonyl chlorides.

- *Reactivities of sulfonyl fluorides*

When comparing the reactivities of sulfonyl fluorides and chlorides, one of the major differences is their hydrolytic stability and tolerance to aqueous acids[9,10]. While sulfonyl chlorides are useful synthetic intermediates for accessing varied sulfonyl-

containing functional groups, their hydrolysis and decomposition remain a key constraint. On the other hand, the stability of sulfonyl fluorides under aqueous conditions is often exploited in their application to synthetic chemistry[11-14] and chemical biology[15-21]. In fact, water plays an important role in controlling the "on-and-off" reactivity of sulfonyl fluorides, through stabilisation of fluoride when expelled as a leaving group. As the most electronegative element, fluorine forms some of the strongest hydrogen bonds[22]. For example, the hydrogen bond energy in bifluoride (FHF^-) is measured as 39 kcal mol^{-1}, which is comparable to a single covalent bond[23]. Therefore, through the formation of F–HX hydrogen bonding, fluoride can be stabilised in the presence of water. This stabilisation provides the enthalpic driving force for nucleophilic substitution – the exchange – of fluoride. In other words, the "on-water" reaction switches on the otherwise inert sulfonyl fluoride to substitution (FIG. 1C). Using a similar strategy, Lewis acids have also been demonstrated to facilitate the nucleophilic substitution of sulfonyl fluorides[24,25], and have played a significant role in the development of SuFEx click chemistry (see later section).

A further important difference between sulfonyl fluorides and chlorides in organic reactions, is the former's resistance to reduction. With sulfonyl chlorides, nucleophilic attack at the chlorine centre results in the formation of a sulfonyl radical, or SO_2 extrusion[2,26,27]. Such reductions often lead to undesirable sulfinate esters or chlorinated (instead of sulfonylated) side products. In contrast, nucleophilic attack at the fluorine centre of sulfonyl fluorides is uncommon. For instance, in the Friedel-Crafts reaction of *p*-xylene using $AlCl_3$ (eq 1, FIG. 1D), reaction with methanesulfonyl chloride delivers the chlorinated product 2,5-dimethylchlorobenzene in 70% yield; conversely, the sulfonylated product 1,4-dimethyl-2-(methylsulfonyl)benzene is obtained in 91% yield when methanesulfonyl fluoride is used. Reactions with a lithium enolate provide another example (eq 2); benzenesulfonyl chloride gives the α-chloroketone in 91% yield, while using benzenesulfonyl fluoride delivers the sulfonylated product[28]. These examples highlight the advantages of using sulfonyl fluorides over sulfonyl chlorides as sulfonylation reagents.

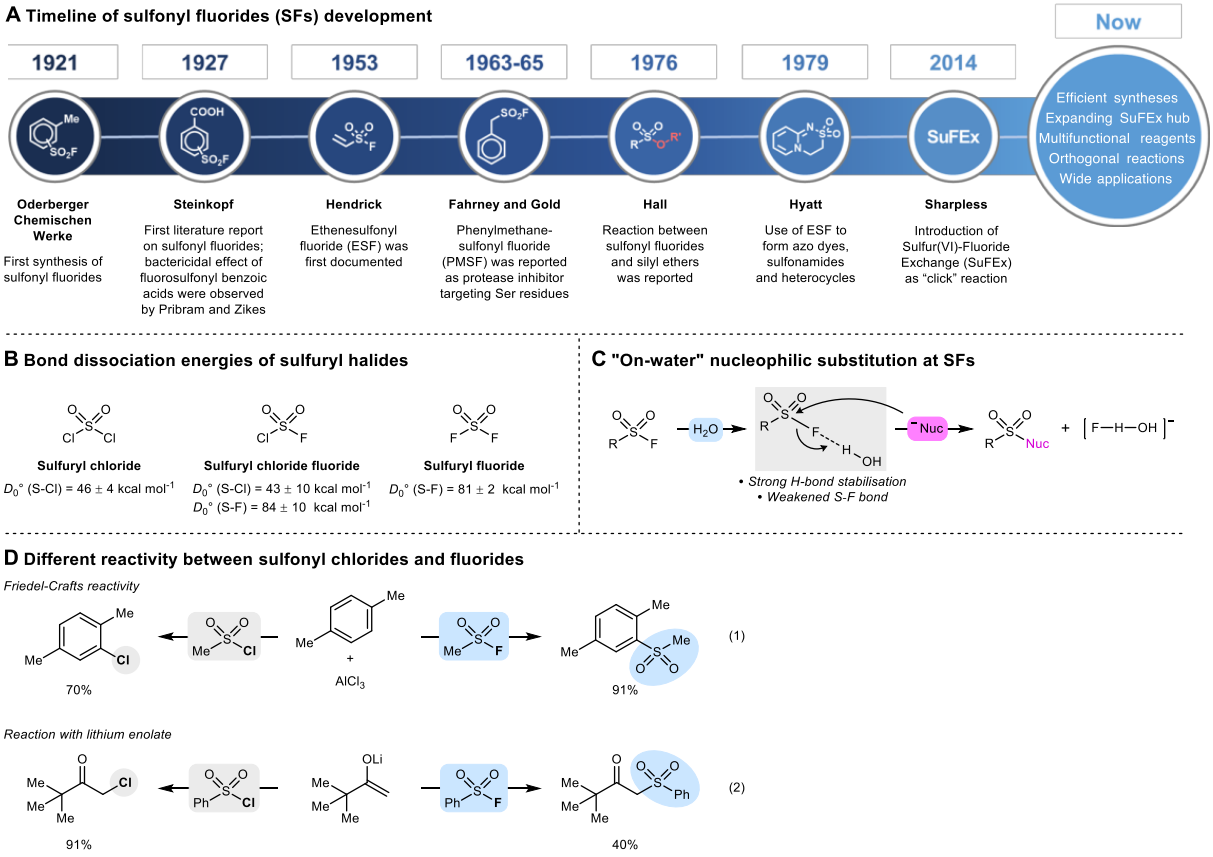

Fig. 1 | **Background of sulfonyl fluoride functional group. A** | A timeline showing the historical development of sulfonyl fluoride chemistry. **B** | Demonstration of the exceptional strength of S–F bonds as illustrated by the homolytic bond dissociation energies of S–Cl and S–F bonds of selected sulfuryl halides[6,7]. **C** | The presence of water activates sulfonyl fluorides towards nucleophilic substitution through hydrogen bonding[2]. **D** | Comparison of the reactivity between sulfonyl chlorides and fluorides[28].

Synthesis of sulfonyl fluorides

- *Fluorosulfonylation*

The first synthesis of sulfonyl fluorides reported by Steinkopf was achieved by treating aromatic hydrocarbons with fluorosulfonic acid[1]. Fluorosulfonic acid was also reacted with benzenesulfonyl chloride to yield the corresponding fluoride (eq 1, FIG. 2). With the risks associated with the preparation and handling of this acid, and the necessity of using metallic apparatus due to its glass-etching properties, chemists were indifferent to this process. Sulfonyl fluorides remained rather inaccessible until the discovery of the more convenient chloride-fluoride exchange method, developed by Davies and Dick[4].

Recently, in 2019, Kim and Kwon reported the fluorosulfonylation of arynes using gaseous sulfuryl fluoride (SO_2F_2)[29]. Later in the year, Ball and Sammis reported the

combination of SO_2F_2 and Grignard reagents[30] (eq 2). Both of these methods involve the *ex-situ* generation of SO_2F_2 gas. In 2020, Moses and coworkers described the preparation of alkynylsulfonyl fluorides using lithiated terminal alkynes and fluorosulfonic acid anhydride ($(FO_2S)_2O$)[31]. Despite the avoidance of using gaseous reagent, fluorosulfonic acid anhydride is highly toxic, and volatile, making it a less-than-ideal reagent for modern chemical synthesis[32]. Lately, Liao presented a single-electron version of fluorosulfonylation, in which fluorosulfonyl radicals were generated from sulfuryl chloride fluoride (FSO_2Cl) under mild photoredox conditions and trapped with olefins, forming various alkenylsulfonyl fluorides[33] (eq 3).

 Substitution and halogen exchange

The classic approach for sulfonyl fluoride synthesis is through the chloride-fluoride exchange on a sulfonyl chloride substrate. Initially reported by Davies and Dick in 1931, arylsulfonyl chlorides were refluxed in aqueous potassium fluoride solution to yield the corresponding sulfonyl fluorides[4]. It was found that the presence of water was crucial for the reaction, since *p*-toluenesulfonyl chloride remained unreacted after 5 days of heating in refluxing benzene with dry zinc fluoride, but the addition of water resulted in complete conversion within an hour. Given the insolubility of sulfonyl chlorides in water, hydrolysis to sulfonates was common, especially for high-melting sulfonyl chlorides[4]. Therefore, later syntheses adopted a biphasic approach which involved refluxing a water-organic mixture[34,35]. This method was further extended to aliphatic sulfonyl fluorides by the same laboratory in 1932[35], and an anhydrous procedure was also described for water-sensitive substrates, which involved heating the neat mixture of sulfonyl chlorides and zinc fluoride in a platinum flask. While the use of metallic apparatus was costly, and heating a neat mixture to reflux was potentially dangerous, phase-transfer catalysis approaches were introduced as an alternative. In 1977, Bianchi and Cate reported the use of 18-crown-6 and potassium fluoride, in acetonitrile, to convert sulfonyl chlorides into the corresponding fluorides, and demonstrated good yields for water-sensitive substrates[36] (eq 4). The “naked” fluoride was considered to be more basic and nucleophilic, hence promoting the chloride-fluoride exchange to take place at ambient temperature.

Due to the strong driving force for the formation of H–F hydrogen bonds, the presence of the bifluoride anion $(F–H–F)^-$ along with fluoride is almost inevitable, particularly in aqueous and acidic medium[23,37]. Following Dick’s discovery, the combination of potassium fluoride and hydrofluoric acid was used by Beaman and Robins for the preparation of purinesulfonyl fluorides in 1961[38]. Potassium bifluoride

(KHF_2), a safer alternative to HF/KF, was used by Brown in 1972[39] (eq 4). Sharpless in 2014 advocated for the use of aqueous KHF_2 for the chloride-fluoride exchange. The "on-water" biphasic synthesis using saturated aqueous KHF_2 solution delivered aryl and alkyl sulfonyl fluorides in excellent yields, representing a robust and reliable method of sulfonyl fluoride synthesis[2,40].

While sulfonyl chlorides are reactive substrates for nucleophilic substitution, the high reactivity also leads to challenges in their preparation and storage, hence limiting their availability. Pentafluorophenyl (PFP) sulfonate esters were introduced by Caddick as an alternative to sulfonyl chlorides[41,42]. With pentafluorophenolate being a good leaving group, these activated sulfonate esters are susceptible to nucleophilic substitution. In 2018, Vedovato and Willis showed that the PFP sulfonate ester of *p*-bromobenzene could be substituted by fluoride ion using KF in methanol, producing the corresponding sulfonyl fluoride in 78% yield[43] (eq 5).

 Oxidative chlorination-fluorination

While some simple sulfonyl chlorides are commercially available, more complex sulfonyl chlorides often require on-site preparation. Even so, isolation can still be challenging, as hydrolysis and decomposition during work-up and purification is common. Hence, the *in-situ* generation of reactive sulfonyl chlorides, followed by quenching with fluoride, has been developed as a solution. A common way to access sulfonyl chlorides is by the oxidative chlorination of thiols, which was first described in the early twentieth century[44-46]. Using this approach, Beaman and Robins reported the synthesis of heterocyclic compounds carrying sulfonyl fluorides in 1961, which was achieved by treating a methanolic solution of mercaptopurines with KF, aqueous hydrofluoric acid and chlorine gas at 0 °C[38]. The method was later improved by Brown and Hoskins for the preparation of pyrimidine sulfonyl fluorides, where KHF_2 was employed in place of hydrofluoric acid[39]. In 2006, Wright and Hallstrom developed a more general synthesis of sulfonyl fluorides from heteroaryl thiols using bleach (aqueous NaOCl) and KHF_2[47] (eq 6). Lately, Cornella has reported the preparation of arylsulfonyl fluorides from sulfenyl phthalimides, by treatment with an excess of trichloroisocyanuric acid and KF[48] (eq 7).

 Deoxychlorination-fluorination

Another approach for the *in-situ* generation of sulfonyl chlorides is through the deoxychlorination of sulfonic acids and their conjugate bases. Aryl sulfonic acids are

easily accessible through the direct sulfonylation of arenes, and have the benefit of being more stable than sulfonyl chlorides. Kim and Jang reported a one-pot procedure for sulfonyl fluoride synthesis using trichloroacetonitrile (Cl_3CCN) and PPh_3 for the deoxychlorination, and tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride [TBAF(*t*-BuOH)$_4$], a fluoride source with good solubility in organic solvent and low hygroscopicity, for subsequent fluorination[49] (eq 8). A similar strategy was adopted by Qin, who reported the combination of cyanuric chloride, catalytic TBAB and KHF_2 using various sulfonate salts and sulfonic acids as substrates[50] (eq 9).

- *Deaminochlorination-fluorination*

Cornella and Gómez-Palomino recently reported the formation of sulfonyl chlorides from primary sulfonamides, using a pyrylium salt and magnesium chloride[51]. This synthesis was extended to sulfonyl fluorides through the addition of potassium fluoride[52] (eq 10). As sulfonamides are common functional groups found in pharmaceuticals and agrochemicals, this transformation enables the late-stage derivatisation of primary sulfonamides into "clickable" sulfonyl fluorides, and will likely see applications in drug discovery.

- *Deoxyfluorination*

While the aforementioned methods either proceed through *in-situ* generated sulfonyl chloride intermediates, or sulfonyl chloride alternatives, a more straight-forward approach of deoxyfluorination was reported by Casida[53] and Liskamp[54] in 2003 and 2009, respectively. These syntheses made use of diethylaminosulfur trifluoride (DAST) as the deoxyfluorinating agent and directly converted sodium sulfonate salts into the corresponding sulfonyl fluorides (eq 11).

- *Oxidative fluorination*

Aside from deoxyfluorination, another approach which avoids sulfonyl chloride intermediates, oxidative fluorination, was adopted by Kirihara in 2011 and 2014, using Selectfluor with thiols or disulfides substrates[55,56] (eq 12). However, the use of super-stoichiometric amounts (6.5–7.5 equiv) of the costly reagent Selectfluor was not attractive, particularly for large-scale preparation. In an elegant solution to this challenge, in 2019 the Noël laboratory reported the first electrochemical synthesis of sulfonyl fluorides. Their approach converted thiols or disulfides into sulfonyl fluorides using anodic oxidation and cheap KF as the fluoride source[57]. In addition to the

oxidation of S(II) compounds (e.g. thiols and disulfides), oxidative fluorination of sulfinate salts has been achieved using Selectfluor (eq 13). This was first reported in 1996 by Banks[58], who also developed the Selectfluor reagent. This approach was later adopted by Willis, Ball, Moses and others to oxidatively fluorinate aryl or alkynyl sulfinates generated *in-situ*[31,59-62].

- *Transition-metal catalysis*

With the advances in using sulfur dioxide surrogates in transition-metal-catalysed sulfonylative cross-coupling pioneered by the Willis[63-66] and Toste[67] groups in recent years, Willis and Ball separately reported the preparation of (hetero)aryl sulfonyl fluorides in 2017 through the palladium-catalysed sulfination of aryl bromides or iodides, followed by electrophilic fluorination using Selectfluor or the cheaper *N*-fluorobenzenesulfonimide (NFSI)[61,62]. This strategy was further extended to (hetero)aryl boronic acid substrates through the employment of a copper(I)[68] or nickel(II)[69] catalysis. Alkenyl triflates could also be converted into sulfonyl fluorides using palladium catalysis[70] (eq 14). In 2020, Chen and Liu reported the Sandmeyer-type fluorosulfonylation using arenediazonium salts, a copper(II) catalyst, DABSO (a SO_2 surrogate) and KHF_2, which is an inexpensive nucleophilic fluoride source[71] (eq 15). Later, it was found similar reactivity could be achieved with copper-free methods[72-74], or by the use of an organic photoredox catalyst[75]. An attractive feature of these methods is that they commence with non sulfur-containing substrates, and instead introduce the sulfonyl (–SO_2–) unit from SO_2 surrogates. Several of the methods use (hetero)aryl halides as substrates, which enjoy wide commercial availability. The catalytic processes often only require mild conditions without the use of strong oxidising agents, acids or bases, hence allowing good functional group tolerance.

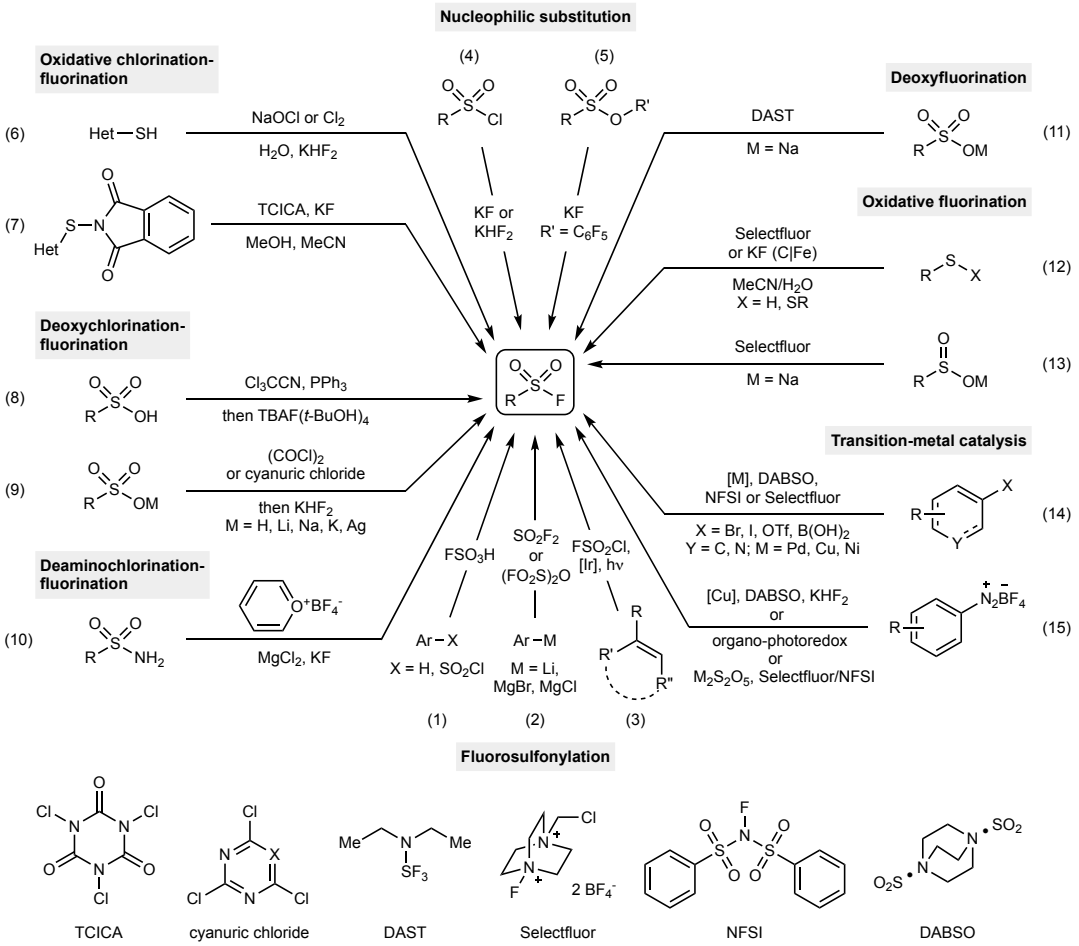

Fig. 2 | **Different established routes to the preparation of sulfonyl fluorides.**

Derivatization of sulfonyl fluorides

One of the key features that make sulfonyl fluorides so attractive is their controllable reactivity. Exploiting sulfonyl fluorides in chemoselective manipulations is a key area of research, including the development of new sulfur(VI)-fluoride exchange (SuFEx) reactions, and the development of bi- or multi-functional sulfonyl fluoride reagents which enable the straightforward installation of the sulfonyl fluoride functional group.

SuFEx reactions

In 1976, Hall reported the first reaction between alkoxytrimethylsilanes and benzenesulfonyl fluoride to form sulfonate esters[76]. The neat reaction was mediated by tetra-*n*-butylammonium fluoride (TBAF) and required excessive reaction times of up to three weeks. Gembus reported a similar, yet much more efficient reaction between tosyl fluoride and silyl ethers catalysed by DBU in 2008[77]. It was proposed that an activated sulfonyl ammonium fluoride salt intermediate was involved upon the substitution by the tertiary base, which would then activate the silyl ethers to form

sulfonate esters (FIG. 3A). The DBU-catalysed reaction represents a classical example of the SuFEx reaction, and the scope was later expanded by Sharpless and Qin using various β-aryl ethenesulfonyl fluorides and TBS ethers[78].

In 2014, Sharpless published a thorough review on "SuFEx", where he proposed such reactivity would be the next candidate for click chemistry[2]. The key feature of sulfur(VI)-fluoride compounds is their stability owing to the strong S–F bonds. On the other hand, the electronegativity of fluorine enables the formation of strong hydrogen bonds with acids or protic solvents, or bonding with silicon to form some of the strongest covalent single bonds. The formation of these strong interactions provides an enthalpic driving force for the substitution (or exchange) of fluoride[79,80], hence derivatizing the otherwise inert sulfur(VI)-fluorides, and has been referred to as "sleeping beauty" reactivity[81]. In an alternative approach to the preparation of sulfonate esters, Ball showed that using Cs_2CO_3 as base promoted the addition of alcohols to sulfonyl fluorides[62]. The substitution by amines to form sulfonamides represents another common SuFEx transformation (FIG. 3B). This was initially achieved using amines as solvent, as reported by Hyatt in 1979[82]. Moroz and Mykhailiuk compared the preparation of sulfonamides from sulfonyl fluorides and chlorides in 2014, with triethylamine added as base and acetonitrile used as solvent[11]. The role of complementary base in the SuFEx reactions was later studied by Tonner in 2020[83]. Recently, activation of various sulfur(VI) fluorides using a Lewis acid (calcium triflimide, $Ca(NTf_2)_2$), amines and DABCO has been reported by Ball, and represents a more efficient transformation to sulfonamides and related compounds[24,25]. Alternatively, sulfonamidation could also be achieved between sulfonyl fluorides and primary or secondary amines through organocatalysis, using 1 mol% of 1-hydroxybenzotriazole (HOBt) as catalyst and 1,1,3,3-tetramethyldisiloxane (TMDS) as an additive, as reported by Li and co-workers[84].

Other common examples of SuFEx reactions with sulfonyl fluorides include the DBU-catalysed synthesis of sulfonyl azides with trimethylsilyl azide ($TMSN_3$) (FIG. 3C)[85], and the bifluoride-mediated synthesis of trifluoromethylsulfones (triflones) using trifluoromethyltrimethylsilane ($TMSCF_3$) (FIG. 3D)[86]. Sulfonyl fluorides can also react with carbon nucleophiles for the formation of sulfones, through the electrophilic substitution of arenes[87], or by the nucleophilic substitution by organometallic reagents which would otherwise be challenging using sulfonyl chlorides due to competing chlorination (FIG. 3E)[28,88-90]. Furthermore, a halogen exchange (Halex) reaction enables the conversion of sulfonyl fluorides into reactive sulfonyl chlorides, albeit requiring harsh reaction conditions using $AlCl_3$ in refluxing DCE

(FIG. 3F)[91]. Sammis and Ball have recently reviewed catalytic methods for sulfonyl fluoride derivatisation[92].

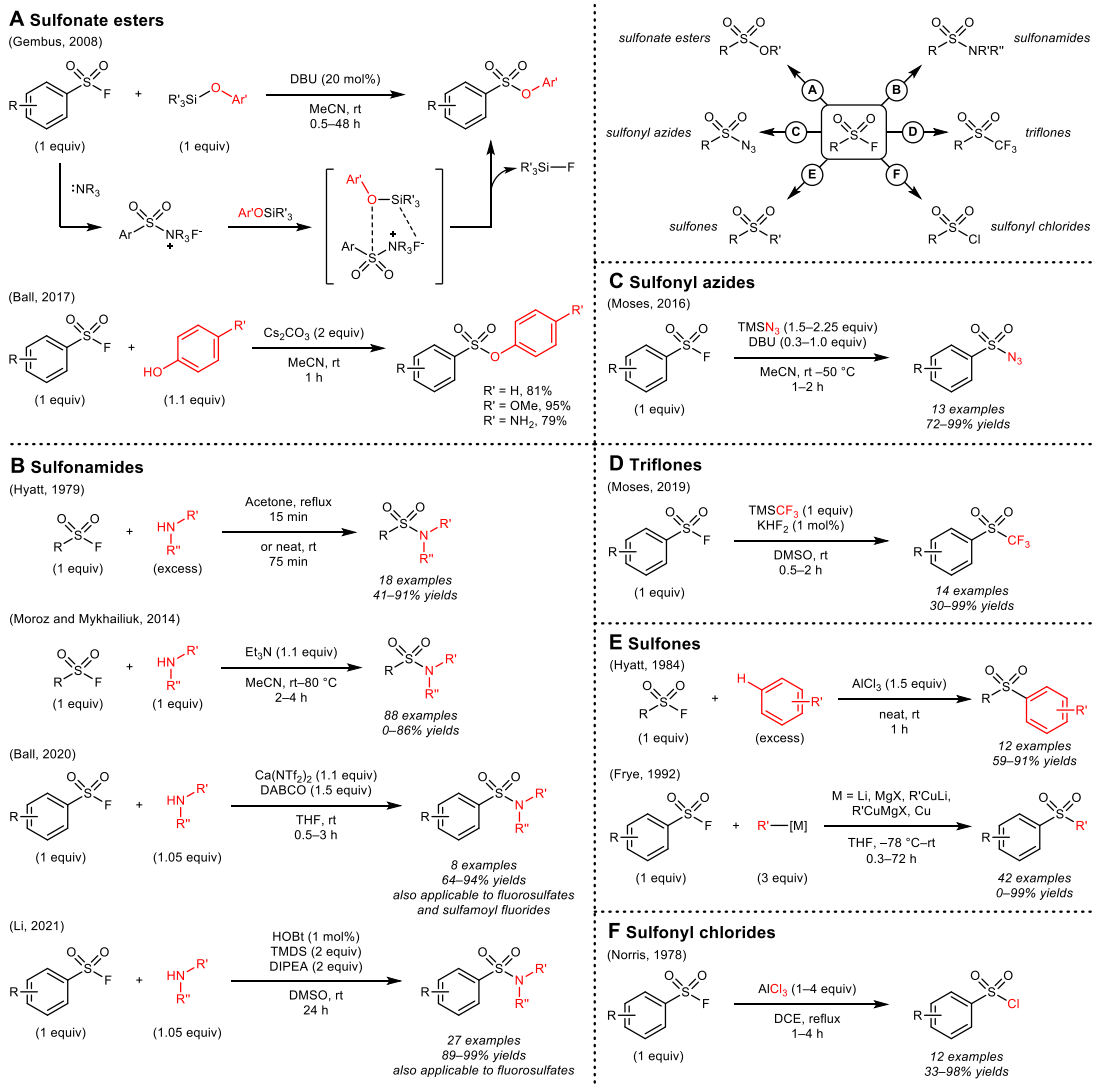

Fig. 3 | **Accessing various sulfonyl-containing functional groups from sulfonyl fluorides through SuFEx. A** | The DBU-catalysed reactions between sulfonyl fluorides and silyl ethers to form sulfonate esters mark the classical example of SuFEx reaction, driven by the formation of strong Si–F bonds[62,77]. **B** | Sulfonamides could be formed by the substitution on sulfonyl fluorides using excess amines[82], mediated by additional tertiary amine (Et_3N)[11,83], Lewis acid ($Ca(NTf_2)_2$)[24,25], or the organic catalyst 1-hydroxybenzotriazole (HOBt) with 1,1,3,3-tetramethyldisiloxane (TMDS) as additive[84]. **C&D** | Sulfonylazides[85] and trifluoromethylsulfones (triflones)[86] were formed through SuFEx using trimethylsilyl azide and trimethyl(trifluoromethyl)silane, respectively. **E** | Sulfones were derived from sulfonyl fluorides through electrophilic aromatic substitution or reactions with organometallic reagents[87,89]. **F** | The halogen-exchange (Halex) reaction of sulfonyl fluorides delivered sulfonyl chlorides using $AlCl_3$[91].

- *Multifunctional sulfonyl fluoride reagents*

To facilitate the introduction of sulfonyl fluoride functional groups, a number of bifunctional reagents bearing both a sulfonyl fluoride and a second reactive site have been developed. With the mature development of transition-metal-catalysed reactions, aryl halides have been widely exploited as cross-coupling substrates. Sulfonyl fluoride-substituted aryl halides have been used in most of the common palladium-catalysed coupling reactions (FIG. 4A), including the Suzuki-Miyaura reaction with boronic acids[93,94], Negishi cross-coupling with diethylzinc[94], Stille coupling with organotin reagents[95], and Sonogashira coupling reactions using terminal alkynes[96]. All of these approaches employ "electrophilic" sulfonyl fluoride fragments. In 2020, Lou and Willis reversed the polarity of these coupling reactions and reported the syntheses of sulfonyl fluoride-substituted boronic acids and their use in Suzuki-Miyaura reactions (FIG. 4B)[97]; a Rh(I)-catalysed conjugate addition with cyclohexanone was also presented[97].

Ethenesulfonyl fluoride (ESF), one of the simplest examples of a bifunctional alkenylsulfonyl fluoride, was first documented by Hedrick in 1953. In this report Hedrick anticipated it to be "a new polymerisable fluorine compound for making plastics with improved properties"[98]. Over a quarter of a century later, in 1979, Hyatt and co-workers reported the use of ESF in the fluorosulfonylethylation of anilines to form sulfonamides, which led to the preparation of a series of azo dyes[82]. Enamine cycloaddition, Diels-Alder reaction, and sultam formation with ESF were also described. Hyatt stated in 1979 that "Although ESF has been known for a number of years, the chemistry of this interesting difunctional compound has been little investigated." This statement held true for many years, until Sharpless' review on the SuFEx "click" reactions was published in 2014[2]. Since then[99], Sharpless and others have reported the use of ESF for the incorporation of sulfonyl fluorides through conjugate addition reactions[2,82,100], palladium-catalysed Heck-type couplings using aryl iodides[101], diazonium salts[78], or boronic acids[102], palladium-catalysed nondirected C–H alkenylation[103], rhodium(III)-catalysed directed C–H activation[104-106], and a copper(I)-catalysed three-component carbene transfer reaction for the construction of indolizine-related heterocycles[107] (FIG. 4C). Recently, the photo-catalysed fluorosulfonylethylations of aryl iodides[108] or *N*-hydroxyphthalimide esters[109] have also been reported, with Hantzsch ester being used as the reductant, and a manganese complex or eosin Y disodium salt as the photocatalyst, respectively. Enantioselective Michael additions to ESF was also been realised[110], with a 2021 example from Zhang

and Yan using a quinine derived squaramide as catalyst[111]. These reactions showcase the versatility of ESF for the introduction of the sulfonyl fluoride functional group onto target molecules. The bifunctional character of ESF has been exploited by Lupton[112], Qin[113,114] and Arvidsson[102,115], with β-arylethenesulfonyl fluorides being used to prepare a range of heterocycles, such as sultams and sultones.

A major drawback of ESF is the structural limitation that it imposes, in which only an ethyl or ethylene linker is added alongside the sulfonyl fluoride group. Health and safety concerns are also associated with the preparation and the usage of ESF, as it has been reported to be highly toxic (oral LD_{50} is 50 mg/kg for rats and 10 mg/kg for mice) and a severe lachrymator, and its preparation from 2-chloroethanesulfonyl chloride, which is also toxic, lachrymatory and corrosive, is undesirable.

Derivatives of ESF have also been studied[2,116-120]. Bromination of the alkene produced 1,2-dibromoethane-1-sulfonyl fluoride (DESF), and subsequent elimination yielded 1-bromoethene-1-sulfonyl fluoride (BESF)[117,118]. BESF can undergo 1,3-dipolar cycloaddition with nitrile oxides to form 5-fluorosulfonyl isoxazoles[119], or with azides to form 4-fluorosulfonyl triazoles[118] (FIG. 4D). The conjugate addition of amine nucleophiles to BESF was also reported[117], and when primary amines were employed, the resulting 2-amino-1-bromo-ethanesulfonyl fluoride could further cyclise to form 4-bromo-β-sultams. Recently, the Moses group presented a collection of alkynylsulfonyl fluorides (SASF) (FIG. 4E)[31]. 1,3- and 1,5-dipolar cycloadditions, as well as the Diels-Alder reactions using these compounds were described, delivering a variety of sulfonyl fluoride-substituted heterocycles and bridged bicyclic compounds. Qin has reported but-3-ene-1,3-disulfonyl difluoride (BDF) as a trifunctional reagent to rapidly access sultams and sulfonamides[121], as well as the synthesis of α-halo-1,3-dienylsulfonyl fluorides, which are potent substrates for palladium-catalysed coupling reactions[122]. Functionalised, saturated ESF-derivatives have also been reported. Qin showed that 2-azidoethane-1-sulfonyl fluoride (ASF) is a useful bifunctional reagent that features two distinct “clickable” functional groups (FIG. 4F)[123]. Reaction of ASF with terminal alkynes using Cu-catalysis provides triazoles, while the addition of amines proceeds via SuFEx reactivity to deliver sulfonamides. Isocyanide-substituted variants have also been reported and have been exploited in 4-component Ugi reactions to provide α-amino amide substituted sulfonyl fluorides (FIG. 4G)[124]. In 2019 and 2021, the Willis and Liao laboratories reported the synthesis of structurally diverse alkenylsulfonyl fluorides, respectively[33,70]. These compounds offer multiple reaction sites for orthogonal functionalization, and are rich in sp^3-hybridised carbon atoms, which is of topical interest in the drug discovery and medicinal chemistry communities.

 Orthogonal functionalisation

The aforementioned transition-metal-catalysed cross-coupling reactions using fluorosulfonylaryl halides or boronic acids, the Heck-type couplings, and the conjugate addition with ESF, represent useful and robust approaches to efficiently install the sulfonyl fluoride "click" handle. The sulfonyl fluoride unit is necessarily inert under these reaction conditions. The sulfonyl fluoride group is also tolerant to a variety of other transition-metal-catalysed reactions, such as copper-catalysed Ullmann coupling[3], iridium(I)-catalysed C–H borylation[96], palladium-catalysed asymmetric hydrophosphination[125], rhodium(I)-catalysed conjugate addition[97,126,127], rhodium(II)-catalysed carbene-mediated cycloaddition[128], and rhodium(III)-catalysed C–H activation[104,105]. Notably, arylsulfonyl fluorides can undergo directed *ortho*-lithiation using lithium diisopropyl amide (LDA), with the resulting aryl lithium trapped *in-situ* by chlorotrimethylsilane (TMSCl) or triisopropylborate ($B(O\textit{i}\text{-}Pr)_3$)[97,129]. In a 2018 review, Chinthakindi and Arvidsson documented the tolerance of sulfonyl fluorides towards a large collection of reaction conditions[12].

The emergence of more complex, multi-functionalized sulfonyl fluoride reagents has led to studies exploring orthogonal functionalization (FIG. 4H)[70]. For example, cyclic alkenylsulfonyl fluorides can participate selectively in the SuFEx-like formation of sulfonate esters and sulfonamides, the conjugate addition of thiols and thiophenols, and the palladium-catalysed hydrogenation of the alkenyl unit. Notably, a remote Boc-protected secondary amine could be deprotected, and the free amine combined with electrophiles, with the sulfonyl fluoride and activated olefin remaining intact. The amine could also couple with an amino acid, biotin or fluorescein. A benzyl-protected variant was transformed through a one-pot debenzylation-acylation sequence to install a terminal alkyne, which could then undergo an orthogonal copper(I)-catalysed alkyne-azide cycloaddition (CuAAC) "click" reaction.

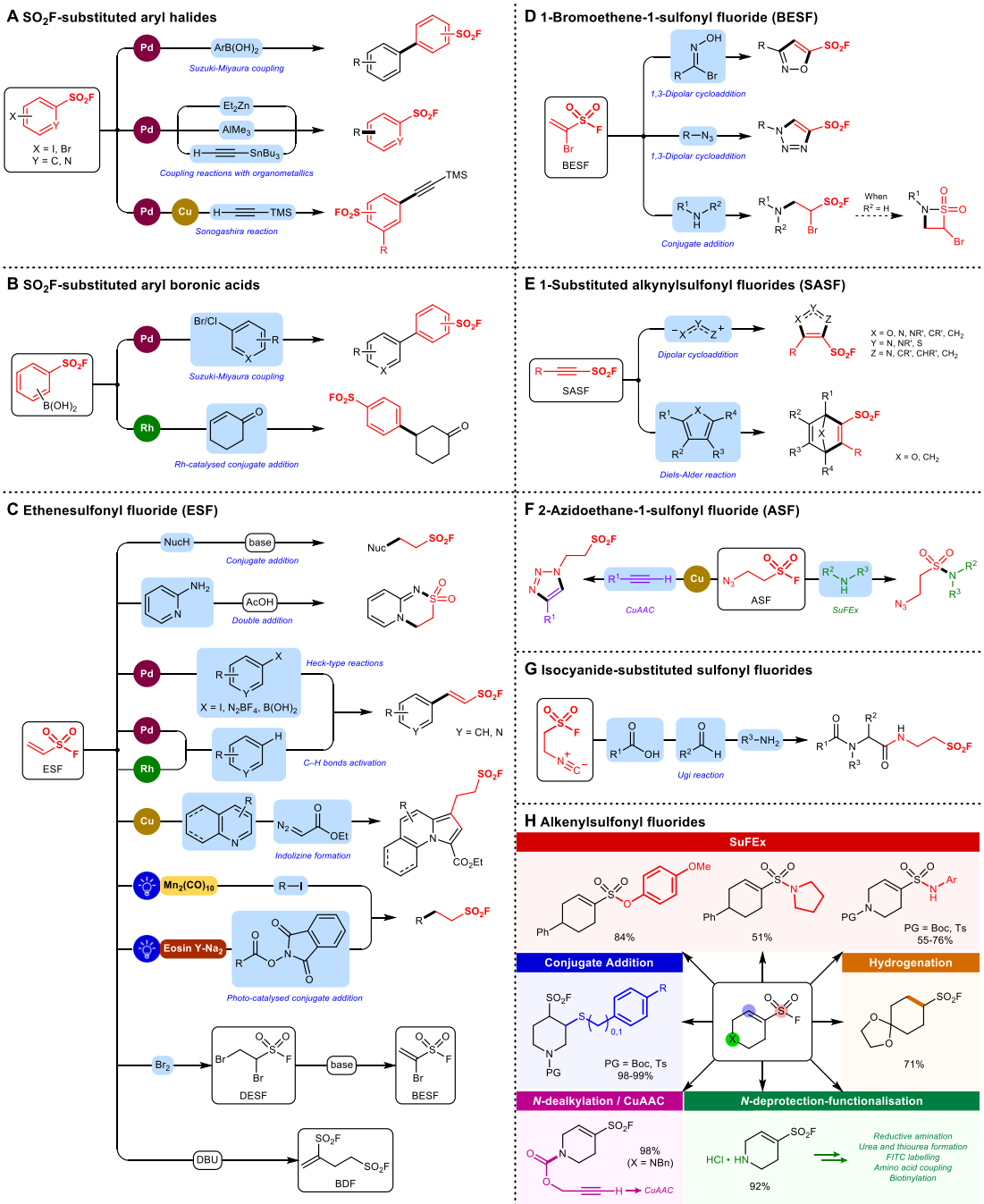

Fig. 4 | **Multifunctional sulfonyl fluoride reagents and their applications.** The thermodynamic stability and good tolerance to a range of reaction conditions enable sulfonyl fluorides with multiple reactive sites to be modular reagents to deliver the "clickable" sulfonyl fluoride group. **A** | (Hetero)aryl halides substituted with sulfonyl fluorides were capable electrophilic substrates in transition-metal catalysed coupling reactions[93-96]. **B** | Sulfonyl fluoride-substituted arylboronic acids were developed as nucleophilic reagents in Suzuki-Miyaura cross-coupling reactions and rhodium-catalysed conjugate addition[97]. **C** | Ethenesulfonyl fluoride (ESF) as a versatile reagent to deliver the sulfonyl fluoride motif with an ethyl or ethylene linkage, catalysed by acid[82], base[2,100], transition metals[78,101-107], or through photoredox processes[108,109]. ESF is also the progenitor to related sulfonyl fluoride reagents, such as

DESF[117], BESF[117-119] and BDF[121]. **D** | 1-Bromoethene-1-sulfonyl fluoride (BESF) could undergo 1,3-dipolar cycloadditions, or react with amine nucleophiles through conjugate addition. Further cyclisation took place when primary amine was employed to form 4-bromo-β-sultams[117]. **E** | 1-Substituted alkynylsulfonyl fluorides are competent in engaging dipolar cycloadditions or Diels-Alder reactions to generate a range of sulfonyl fluoride-substituted heterocycles[31]. **F** | 2-Azidoethane-1-sulfonyl fluoride (ASF) provides for cycloaddition chemistry at the azide group, and SuFEx reactivity at the sulfonyl fluoride to provide two separately clickable reaction sites[123]. **G** | Isocyanide-substituted sulfonyl fluorides have been prepared, and when combined with carboxylic acids, aldehydes, and amines, undergo Ugi 4-component reactions[124]. **H** | Alkenylsulfonyl fluorides containing multiple reaction warheads could undergo selective and orthogonal transformations, including SuFEx reaction at S, conjugate addition at β-C, Pd-catalysed hydrogenation, dealkylation-propargyloxycarbonylation of benzylamine for subsequent copper(I)-catalysed alkyne-azide cycloaddition (CuAAC), Boc deprotection, and various amine functionalisation in the presence of other electrophilic handles[70].

Applications of sulfonyl fluorides

The controllable reactivity of sulfonyl fluorides enables multiple different uses. In the following section, the applications of sulfonyl fluorides in dye chemistry, organic synthesis, material chemistry, chemical biology, radiochemistry and electrochemistry will be discussed.

Sulfonyl fluorides in azo dyes

In the first report on sulfonyl fluorides by Steinkopf in 1927, he described the preparations and the properties of azo dyes that contain sulfonyl fluoride groups.[1] Due to their tolerance to acid and resistance to reduction and substitution, nitro-substituted arylsulfonyl fluorides could survive the reduction to anilines, and subsequent diazotisation. Sulfonyl fluorides have continued to play a role in azo dye chemistry.[3,130] Of note, in 1979, Hyatt reported the use of ethenesulfonyl fluoride in the preparation of azo dyes, and their downstream transformation into different sulfonyl derivatives.[82]

Sulfonyl fluorides in organic synthesis

The SuFEx reactivity of sulfonyl fluorides enables them to act as electrophilic precursors to a variety of sulfonyl-containing functional groups, such as sulfones, sulfonamides, sulfonate esters, and sulfonyl azides[131,132]. The controlled inertness of sulfonyl fluorides allows the group to be pre-installed at an early stage of multi-step sequences, with the reactivity often exploited late in a synthesis. For example, electron-deficient sulfonyl fluorides can be combined with alcohols, phenols or silyl ethers to deliver activated sulfonate esters[133], which are good leaving groups for substitution or

elimination reactions, and are competent electrophilic substrates for a broader range of transition-metal-catalysed reactions[134-136]. For instance, nonafluorobutanesulfonyl fluoride (NfF or PBSF) reacts with phenols or enols readily to form aryl or alkenyl nonaflates (–ONf) (FIG. 5A). When aliphatic alcohols are employed, the lability of resulting nonaflates allows subsequent substitution by the F^- generated from the sulfonyl fluoride, producing alkyl fluorides as the final products (FIG. 5A)[137-139]. In the presence of base, the elimination of NfOH is also possible, forming olefin products[138]. Likewise, 2-pyridinesulfonyl fluoride (PyFluor) efficiently converts primary and secondary alcohols to the corresponding fluorides, and has been developed as a potent deoxyfluorinating agent[139,140]. Furthermore, (fluorosulfonyl)difluoroacetate derivatives are used for the *in-situ* generation of difluorocarbene through the elimination of CO_2, SO_2 and fluoride (FIG. 5B)[141-144]. Recently, the copper(I)-catalysed desulfonylation of arylethenesulfonyl fluorides and alkenyl sulfones was reported by Qin and co-workers (FIG. 5C)[145]. This chemistry gives access to terminal alkenes, and as such allows the addition of ESF-units, achievable in many ways, to be considered as the addition of terminal alkenes.

- *SuFEx in materials chemistry*

With the "click" chemistry features of SuFEx reactions justified by their robustness and reliability, the SuFEx reactions between sulfonyl fluorides and silyl ethers have seen applications in material chemistry, ranging from upstream polymerisation, to downstream surface modifications. Whilst polyester is one of the most used polymers in modern life, its sulfa-analogue, polysulfonate, is rarely reported in literature and has few industrial applications. Early reports on the preparation of polysulfonates date to the 1960s, and use disulfonyl chlorides and diphenol monomers[146,147]. Unfortunately, the unselective reactivity, such as the reduction and hydrolysis of sulfonyl chlorides, limits the preparation and use of these materials. The introduction of SuFEx reactions for polymerisations[148] has allowed the preparation of polysulfonates, and the related polysulfates, to become more practical. Initially catalysed by DBU, the polymerisation between silyl ethers and sulfonyl fluorides (for polysulfonates) or fluorosulfates (for polysulfates) was later improved using bifluoride salts as catalysts (FIG. 5D)[149,150]. The volatile fluorosilanes generated as the major by-products in these reactions can be easily removed, hence simplifying the purification processes. SuFEx chemistry has also led to the recent preparation of polysulfamide, a sulfa-analogue to polyamide, achieved using diamines, bis(sulfamoyl fluoride) monomers and DBU or pyridine as catalyst[151].

Beyond polymer synthesis, sulfonyl fluorides and SuFEx chemistry have also been used for the modification of polymers and surfaces. The general strategy exploits the inertness of sulfonyl fluorides towards free radicals, and requires the preinstallation of sulfonyl fluorides into appropriate monomers. Following radical polymerisation, the sulfonyl fluorides undergo reaction with silyl ethers, allowing access to derivatives of the original polymers (FIG. 5E)[152,153]. Similar strategies can also be applied to surface modification. For instance, Locklin used silicon wafers printed with poly(pentafluorophenyl acrylate), and modified the surface through the sequential replacement of the acrylate with a sulfonyl fluoride-bearing reagent, followed by SuFEx reactions with silyl ethers[154]. Zuilhof demonstrated the tethering of sulfonyl fluorides using ESF and a second click handle onto aluminum oxide surface. The subsequent SuFEx reaction with amines was shown to be orthogonal to the CuAAC and strain-promoted cyclooctyne quinone cycloaddition (SPOCQ) click reactions, hence opening up opportunities for potential diversification of different solid surfaces and materials[155]. Recently, SuFEx chemistry has been used for the surface modification of polyvinyl chloride (PVC) (FIG. 5F)[156], cellulose acetate[157], and metal-organic frameworks (MOF)[158]. It was also shown that the fabrication of multi-layered polymer films through SuFEx reactions of sulfonyl fluorides and silyl ethers was possible[159]. The reviews from Locklin[160] and Dong[161] cover this area in detail. Furthermore, 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF) hydrochloride was reported to improve the crystallisation quality and phase stability of formamidinium lead iodide ($FAPbI_3$) perovskite, which is used in solar cells, thus increasing the power conversion efficiency of the $FAPbI_3$-based photovoltaic[162]. In 2021, Hillesheim and Mirjafari reported a series of sulfonyl fluoride-containing task-specific ionic liquids (ILs), which demonstrated good thermodynamic stability against hydrolysis and thermolysis, and could be prepared in multigram scale with minimal purification[163]. Given the established biocompatibility of sulfonyl fluorides, the preparation of ILs of this type which also incorporate components of active pharmaceutical ingredients are expected to find biological applications.

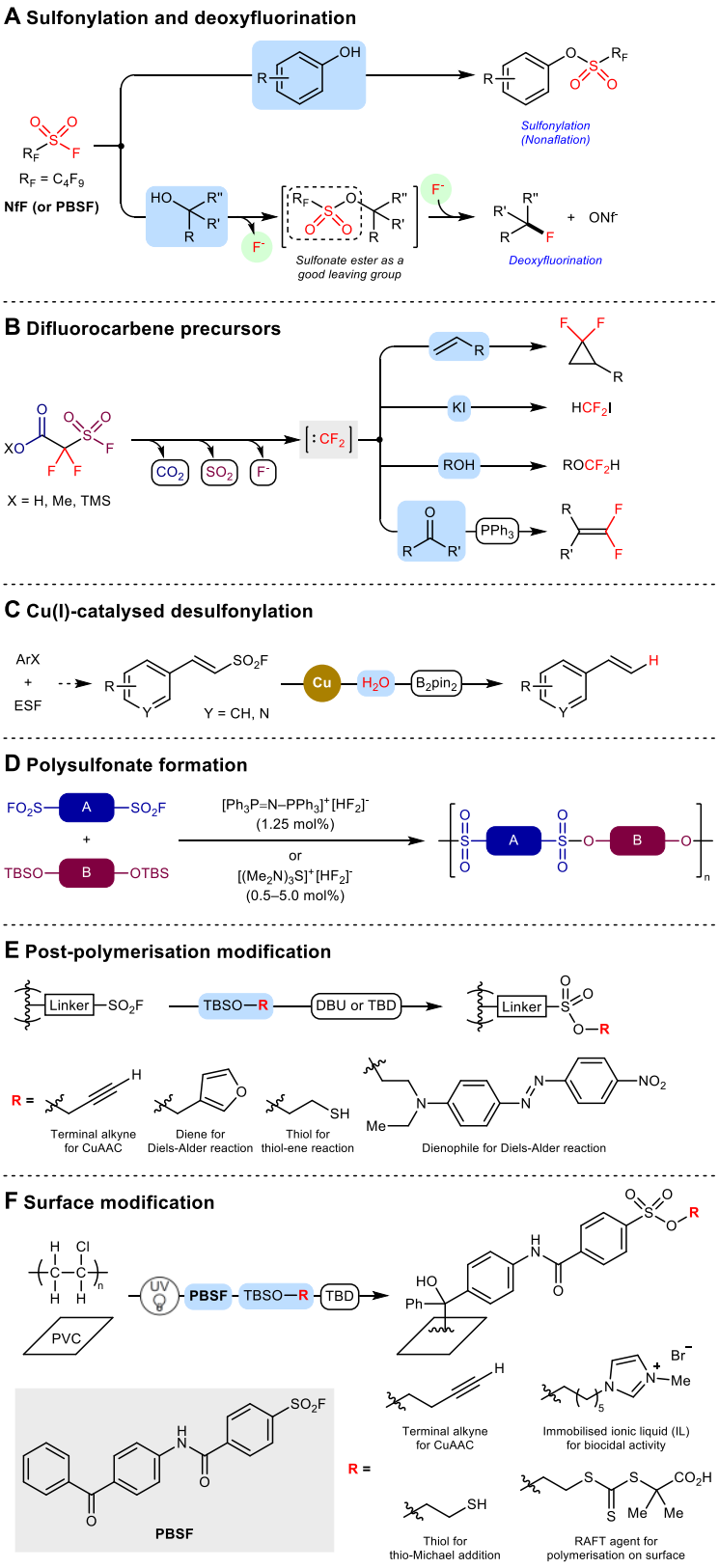

Fig. 5 | **Applications of sulfonyl fluorides in organic synthesis (A–C) and materials chemistry (D–F). A** | Electron-deficient sulfonyl fluorides react with alcohols to form sulfonate esters, as exemplified by nonafluorobutanesulfonyl fluoride (NfF)[133,139]. Nonaflates derived from aliphatic alcohols are prone

to further substitution by fluoride to produce alkyl fluorides as the end products. **B** | Difluorocarbene was generated from (fluorosulfonyl)difluoroacetate derivatives through the elimination of CO_2, SO_2 and fluoride, driven by the increased entropy. The resulting carbene provides di- or trifluoromethylated products[141]. **C** | Arylethenesulfonyl fluorides could undergo desulfonylation using copper catalysis to produce terminal olefins[145]. **D** | Co-polymerisation between bis-sulfonyl fluoride monomer (A) and bis-silyl ether monomer (B) through SuFEx catalysed by bifluoride salts[148-150]. **E** | Post-polymerisation modification of polymers with pendent sulfonyl fluoride handles for other chemical transformations[152,153]. **F** | Surface modification as exemplified by polyvinyl chloride (PVC), through the irradiation of UV light to a mixture of PBSF – a sulfonyl fluoride-containing benzophenone derivative, functionalised silyl ether and catalytic TBD on PVC surface[156]. The thus modified surface demonstrated different properties or was capable for further functionalisation.

- *SuFEx in chemical biology*

Hydrolytic stability represents the key feature of sulfonyl fluorides' uses in chemical biology, where aqueous or semi-aqueous media are often used to mimic physiological conditions. This stability also ensures that the sulfonyl fluoride group remains unreactive until appropriate activation is achieved, such as in the binding pocket of a protein[16]. These sites are often rich in hydrogen bond donors and acceptors, which can both activate the fluoride and position the electrophilic sulfonyl fluoride in close special proximity to nucleophilic residues, hence facilitating the sulfonylation of proteins[81]. Indeed, sulfonyl fluorides have long been considered biologically significant, as early reports documented potent bactericide and insecticide activities[1]. Myers and Kemp reported the inhibition of esterases by a series of sulfonyl fluorides in 1954[164], and Fahrney and Gold extended this work during the years 1963–1965[18,165,166]. In particular, phenylmethanesulfonyl fluoride (PMSF) was found to sulfonylate serine residue in the active site of chymotrypsin (FIG. 6A)[166]. In addition, in 1967, Baker and Lourens used sulfonyl fluorides for the irreversible inhibition of dihydrofolic reductases, with the site of covalent attachment being outside the enzyme active site[167]. Since then, substrate-derived protein inhibitors carrying sulfonyl fluoride warheads have been developed that target different nucleophilic residues[15,168]. For example, 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF)[19] was reported as an irreversible inhibitor for serine protease, and has been commonly used for the preparation of cell lysates, and 5'-*p*-fluorosulfonylbenzoyl adenosine (FSBA) targets the lysine residue of ATP-binding kinases[169,170].

The use of bifunctional molecular probes in selective protein marking, extraction, and functional investigation is well established[171]. By incorporating a second reactive

functional group, sulfonyl fluorides can serve as activity-based protein probes, with the "reporter site" being capable for further transformation (FIG. 6B)[17,21,172,173]. For instance, DAS1 resembles AEBSF in its affinity for serine proteases, and carries a pendant terminal alkyne as a "click" handle for the copper(I)-catalysed alkyne-azide cycloaddition[17,174]. A 2020 review by Jones and Kelly analysed the rational design of sulfonyl fluoride probes and their applications in identifying substrate binding sites[175]. Recent advancement in SuFEx click chemistry has enabled the use of sulfonyl fluorides beyond studying protein-small molecule bindings. For instance, sulfonyl fluorides, sugars, iminosugars, and calix[4]arene have been combined in the synthesis of (imino)sugar clusters (FIG. 6C)[176]; and the bifunctional sulfonyl fluoride NHSF was used to crosslink peptides (FIG. 6D)[177]. Applications in this area have been reviewed by Moses[13].

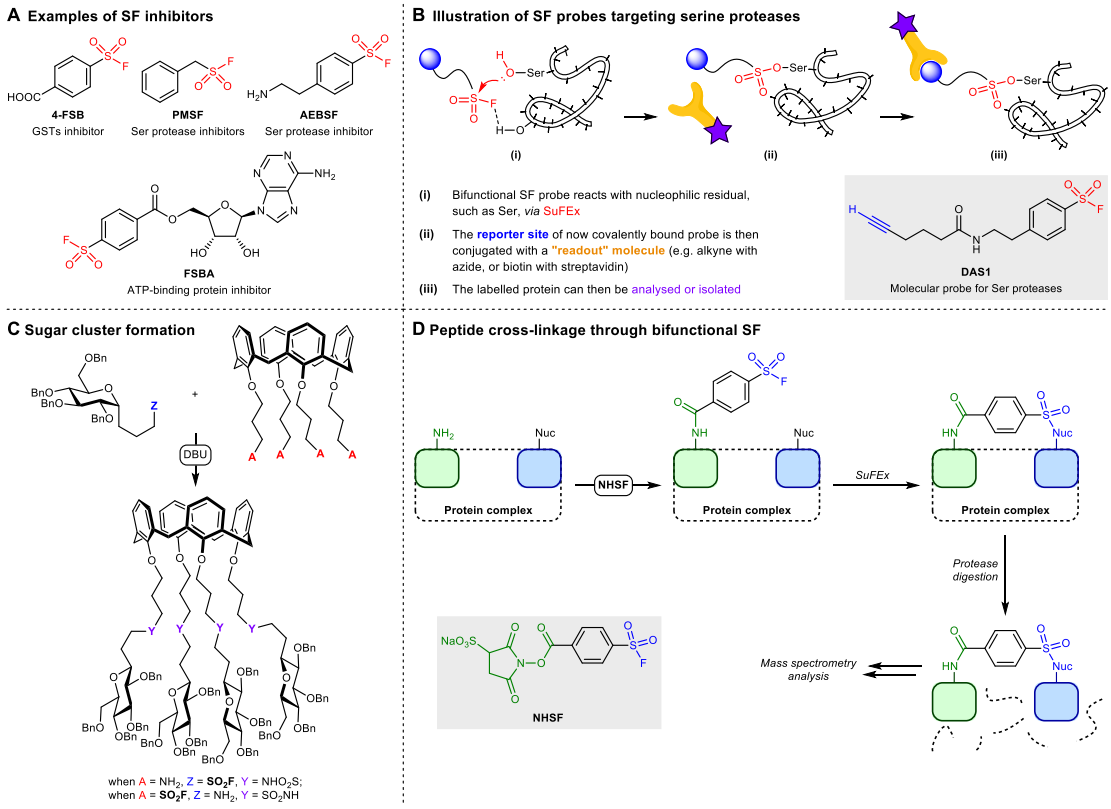

Fig. 6 | **Applications of sulfonyl fluorides in chemical biology. A** | Selected examples of sulfonyl fluoride-containing molecules that were used as protein inhibitors[19,166,169,170]. **B** | Bifunctional sulfonyl fluoride-based molecular probes covalently bound to target proteins through SuFEx with nucleophilic residues inside either the substrate binding site or other part of the proteins, and the reporter site could then interact with a second reagent to identify the labelled protein for further analysis or isolation[17,172]. **C** | Formation of sugar cluster between sulfonyl fluorides and amine warheads through SuFEx[176]. **D** | Bifunctional sulfonyl fluoride NHSF was capable to form a cross-linkage within a protein complex, which facilitated the structural analysis of target proteins[177].

- *Fluorine-18 radioactive labelling*

With advances in the use of positron emission tomography (PET) for medical imaging, fluorine-18 (^{18}F) has become the most popular radioisotope for labelling due to its favourable physical and chemical properties[178]. With a half-life of only 109.7 minutes, ^{18}F-radiolabelling processes have to be efficient and specific. In practise, this often means short reaction times, high radiochemical yields and easy purification. Two main approaches are adopted for ^{18}F-labelling – direct [^{18}F]fluorination of the target molecules, and reaction of the target molecules with a prosthetic compound carrying a radioactive fluorine-18[179].

Conventionally, [^{18}F]fluorination is achieved using anhydrous [^{18}F]fluoride and a phase transfer catalyst, where toxic crown ethers or cryptands such as Kryptofix 2.2.2 (K_{222}) are often employed. Given that [^{18}F]fluoride is produced in [^{18}O]water, the otherwise unreactive [^{18}F]fluoride has to be rigorously dried by repeated azeotropic distillations, which requires specialised apparatus and is time-consuming. Exploiting the water resistance and the robust "on-water" synthesis of sulfonyl fluorides, Inkster and co-workers designed a series of bifunctional [^{18}F]benzenesulfonyl fluoride derivatives as prosthetic compounds for potential radiolabelling (FIG. 7A)[180]. The syntheses of these [^{18}F]sulfonyl fluorides by-passed the laborious drying steps, avoided the use of toxic cryptands, and only required 15 min of reaction time. Optimisation of the radiosynthesis of [^{18}F]sulfonyl fluorides was later conducted by Fraser, with the reaction time being shortened to as little as 23 sec. They were also able to demonstrate the stability of the radiolabelled sulfonyl fluorides to the presence of water and other nucleophilic functional groups (FIG. 7B)[181]. The preparation of [^{18}F]sulfonyl fluorides using Magnetic Droplet Microfluidics (MDM) platform was discussed by Wang and van Dam[182].

The radiosynthesis of the fluorinating reagent [^{18}F]PyFluor has been reported (FIG. 7C)[140], and was applied to the deoxy-radiofluorination of a protected D-gluopyranose and gave promising results. In 2018, Zhou and Chu described the preparation of [^{18}F]tosyl fluoride and its use for [^{18}F]fluorination *via* nucleophilic aromatic substitution[183]. These two approaches potentially allow access to radiolabelled biomolecules that are challenging using conventional methods[184,185].

As ethenesulfonyl fluoride (ESF) has emerged as a key reagent in SuFEx chemistry, Fraser considered the radiolabelled [^{18}F]ESF as a potent prosthetic reagent for bioconjugation. He demonstrated the radiolabelling of various amino acids through

conjugate addition in 2018[186], and showed that [^{18}F]ESF could be stored on inert silica cartridges for convenient shipment between laboratories and medical facilities. Later, the same laboratory reported the [^{18}F]fluorination using [^{18}F]ESF in the presence of tetraethylammonium bicarbonate (Et_4NHCO_3), where [^{18}F]ESF was hydrolysed to generate an active [^{18}F]fluoride capable for substitution under "wet" conditions[187]. The use of sulfur(VI)-fluoride compounds in PET radiochemistry has been reviewed by Pascali[188].

- *Lithium-ion batteries*

It has been established that sulfonyl-containing compounds play important roles in lithium-ion batteries[189]. For example, sulfones are capable solvents with outstanding electrochemical stability under high voltage conditions, using lithium sulfonimide salts as electrolytes results in a protective-film forming on electrodes[190], and sulfuryl fluoride has been used as the cathode in Li-sulfuryl fluoride cells,[191] or as an additive to enhance the cycling life of Li-ion batteries[192].

In 2012, Angell and co-workers described the use of methanesulfonyl fluoride as a solvent in high voltage lithium cells. The methanesulfonyl fluoride-based electrolyte has the benefit of low viscosity, and thus enhanced conductivity.[193] It was also shown to form a solid electrolyte interface at a graphite electrode, hence improving cell performance[194]. A recent report by Xing and Li showed that using *p*-toluenesulfonyl fluoride as an additive enhanced the cyclic performance (the turnover number) of lithium ion batteries using a Ni-rich cathode[195]. As the sulfonyl fluoride was susceptible to both the deep oxidation and reduction in the cell, it formed a protective interphase film on both the graphite anode and the Ni-rich cathode. Such passivation reduces the impedance on the electrode/electrolyte interphase, the decomposition of electrolyte, and the dissolution of metal ions from the cathode, and therefore maintains the integrity of the cell when cycling at high voltage[195]. Shao-Horn, Johnson and Li, have used the closely related dimethylsulfamoyl fluoride and lithium bis(fluorosulfonyl)imide as the solvent and salt, respectively, to form a "full fluorosulfonyl" electrolyte for 4 V class lithium-metal batteries, and achieved excellent coulombic efficiency and good retention of cell capacity[196]. Sulfonyl fluorides have also been used as intermediates for the synthesis of lithium sulfonimides for use as electrolytes in Li-ion batteries[197], and Jin has reported the use of a perfluorinated sulfonyl fluoride as a precursor to lithium perfluorinated sulfonyl dicyanomethide (Li-PFSD), which is used for the preparation of perfluorinated ionomer membranes and electrolytes[198].

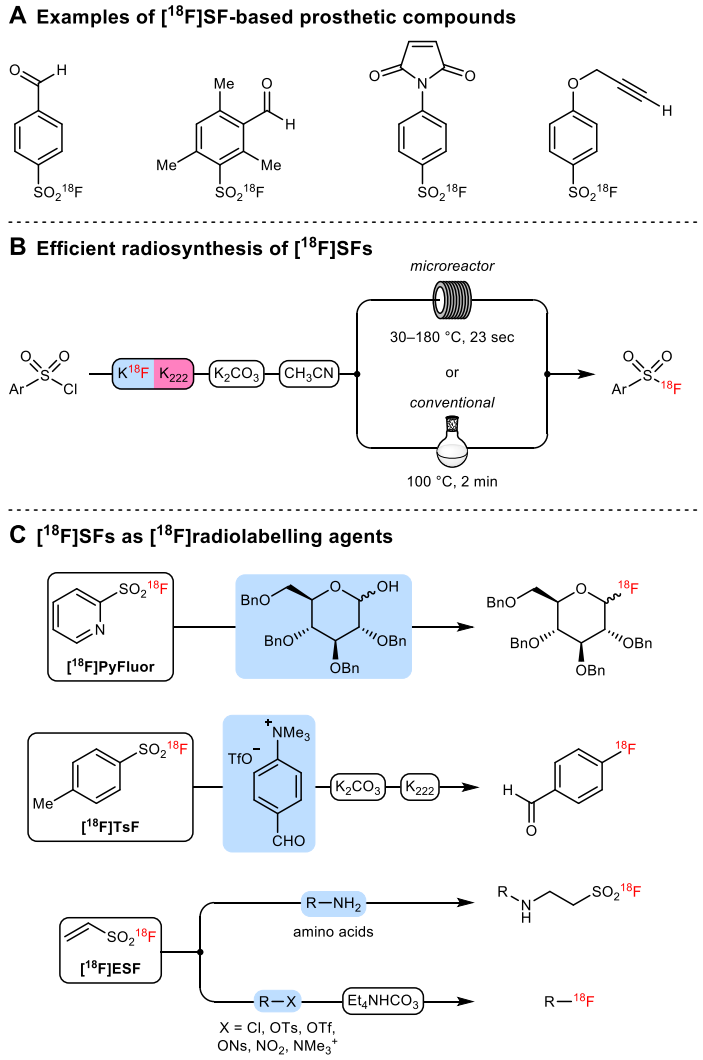

Fig. 7 | **Applications of sulfonyl fluorides in [^{18}F]radiolabeling. A** | Selected examples of fluorine-18-labelled prosthetic compounds for delivering the radioactive ^{18}F to target molecules[180]. **B** | The efficient radiosynthesis of [^{18}F]sulfonyl fluorides within minutes[181]. **C** | Reported examples of [^{18}F]sulfonyl fluorides acting as [^{18}F]radiolabeling agents to deliver ^{18}F through deoxyfluorination[140], nucleophilic aromatic substitution (S_NAr)[183], fluorosulfonylethylation[186], or nucleophilic substitution[187].

Outlook for sulfonyl fluoride chemistry

- *Synthesis of sulfonyl fluorides*

There are many challenges and opportunities remaining in the context of sulfonyl fluoride synthesis. SO_2F_2 and fluorosulfonic acid anhydride represent synthetic equivalents for the "SO_2F^+" synthon, but the highly reactive nature of pre-formed organometallic reagents, such as Grignard reagents and organolithium reagents, has limited their use with these building blocks. However, SO_2F_2 has been used extensively in reactions with alcohols and amines for the preparation of fluorosulfates (R–O–SO_2F)

and sulfamoyl fluorides (R–NR'–SO_2F), respectively. Although SO_2F_2 performs well in these chemistries, that the reagent is a gas limits the uptake of these methods, as the required laboratory equipment may not be available, or there may be local regulations in place restricting the use of gaseous reagents. This has led to the development of solid "SO_2F^+" surrogates, such as [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF)[199] and fluorosulfuryl imidazolium salts[151,200]. These bench-stable reagents, however, have yet to see successful use with carbon nucleophiles to form sulfonyl fluorides. It can be anticipated that new reagents equivalent to the "SO_2F^+" synthon will emerge, and that new chemistries exploiting the existing reagents, but that realise sulfonyl fluorides will be developed. Only a single example of the FSO_2 radical being used for sulfonyl fluoride synthesis has been reported[33]. In this case the radical was generated from $ClSO_2F$, which is again a gaseous reagent and is subject to the same limitations as SO_2F_2. Advances in the development of new reagents for, or methods to generate, the FSO_2 radical can be expected.

The Late Stage Functionalisation (LSF) of complex molecules, often pharmaceuticals, has emerged as a popular tactic to access new bioactive molecules[201]. Given the plethora of functional groups that are often encountered in such approaches, the key reactions need to operate under mild reaction conditions and be tolerant of multiple Lewis basic sites. Catalytic reactions are often popular choices in these circumstances, and as such the development of new catalytic methods for the introduction of sulfonyl fluoride groups, perhaps exploiting C–H functionalisation, would allow applications to LSF. The direct installation of sulfonyl fluoride groups from C–H functionalisation has yet to be achieved.

- *Sulfonyl fluorides and emerging synthesis technologies*

The use of flow chemistry techniques is one strategy to allow the safe handling of toxic or highly reactive reagents. Gases are often included in these categories[202]. For example, Ley and co-workers have shown that sulfur dioxide can be used effectively using flow apparatus[203]. Application of these methods to gases such as SO_2F_2 and $ClSO_2F$ would add to the methods available for sulfonyl fluoride synthesis. Electrochemistry is an emerging technology in organic synthesis, and has recently been exploited by Noël for the preparation of sulfonyl fluorides by the oxidative fluorination of thiols. However, the use of electrochemistry to generate "linking" reactive intermediates appropriate for sulfonyl fluoride synthesis, has not been reported.

Although sulfonyl fluorides have been employed as the key reagents in a machine

learning approach to the fluorination of alcohols, these machine learning techniques have not been applied to sulfonyl fluoride preparation[139].

 Related S(VI)-functional groups

Sulfonyl fluorides are undoubtedly the core functional group in most applications of SuFEx chemistry. However, a number of related functional groups are emerging that possess complementary reactivity, or offer alternative methods for introduction. Included here are groups such as fluorosulfates ($RO–SO_2–F$), sulfamoyl fluorides ($R_2N–SO_2–F$), and sulfonimidoyl fluorides (R–S(O)(NR')–F)[16,204-210]. The latter group features a stereogenic sulfur atom, and as such offers opportunities for the development of diastereo- and enantioselective syntheses, as well as the exploitation of these chiral centres in selective reactions with nucleophiles. The employment of thionyl tetrafluoride (SOF_4) for synthesis has also enabled access to a range of novel sulfur(VI) fluoride functional groups, such as iminosulfur oxydifluorides ($S(O)(NR)F_2$) and sulfuramidimidoyl fluorides ($R_2N–S(O)(NR')–F$)[211-213]. As discussed above, the reliance on a gaseous precursor might be expected to slow the use of these groups.

Conclusion

It is the characteristic reactivity of sulfonyl fluorides, and in particular, how this can be exploited in approaching biological challenges, that has led to this functional group becoming such a popular synthetic target. This in turn has led to a host of new synthetic strategies, which range from "updates" of classical syntheses, to procedures that exploit the most up-to-date synthetic technologies. Efforts to enhance, or retard, this characteristic reactivity have similarly led to inventive new synthetic methods. The embrace of SuFEx concepts by synthetic chemists and chemical biologists can be expected to provide an increasing number of tools to advance these fields.

Reference

1 Steinkopf, W. Über Aromatische Sulfofluoride. *J. Prakt. Chem.* **117**, 1-82, doi:10.1002/prac.19271170101 (1927).

2 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.* **53**, 9430-9448, doi:10.1002/anie.201309399 (2014).

3 Steinkopf, W. & Jaeger, P. Über Aromatische Sulfofluoride. II. Mitteilung. *J. Prakt. Chem.* **128**, 63-88, doi:10.1002/prac.19301280104 (1930).

4 Davies, W. & Dick, J. H. CCLXXXVI.—Aromatic sulphonyl fluorides. A convenient method of preparation. *J. Chem. Soc.*, 2104-2109, doi:10.1039/JR9310002104 (1931).
5 Wiberg, E. & Holleman, A. F. *Inorganic Chemistry*. (Academic Press, 2001).
6 Takacs, G. A. Heats of formation and bond dissociation energies of some simple sulfur- and halogen-containing molecules. *J. Chem. Eng. Data* **23**, 174-175, doi:10.1021/je60077a020 (1978).
7 Wray, K. L. & Feldman, E. V. Shock Tube Study of the Decomposition Kinetics of SO2F2. *J. Chem. Phys.* **54**, 3445-3449, doi:10.1063/1.1675363 (1971).
8 Cady, G. H. & Misra, S. Hydrolysis of sulfuryl fluoride. *Inorg. Chem.* **13**, 837-841, doi:10.1021/ic50134a016 (1974).
9 Aberlin, M. E. & Bunton, C. A. Spontaneous hydrolysis of sulfonyl fluorides. *J. Org. Chem.* **35**, 1825-1828, doi:10.1021/jo00831a024 (1970).
10 Swain, C. G. & Scott, C. B. Rates of Solvolysis of Some Alkyl Fluorides and Chlorides1. *J. Am. Chem. Soc.* **75**, 246-248, doi:10.1021/ja01097a520 (1953).
11 Bogolubsky, A. V. *et al.* Sulfonyl fluorides as alternative to sulfonyl chlorides in parallel synthesis of aliphatic sulfonamides. *ACS Comb Sci* **16**, 192-197, doi:10.1021/co400164z (2014).
12 Chinthakindi, P. K. & Arvidsson, P. I. Sulfonyl Fluorides (SFs): More Than Click Reagents? *Eur. J. Org. Chem.* **2018**, 3648-3666, doi:10.1002/ejoc.201800464 (2018).
13 Barrow, A. S. *et al.* The growing applications of SuFEx click chemistry. *Chem. Soc. Rev.* **48**, 4731-4758, doi:10.1039/C8CS00960K (2019).
14 Ball, N. D. in *Emerging Fluorinated Motifs* (eds Cahard, J. & Ma, J.-A.) 621-674 (Wiley-VCH, 2020).
15 Narayanan, A. & Jones, L. H. Sulfonyl fluorides as privileged warheads in chemical biology. *Chem. Sci.* **6**, 2650-2659, doi:10.1039/c5sc00408j (2015).
16 Mukherjee, H. *et al.* A study of the reactivity of S(VI)–F containing warheads with nucleophilic amino-acid side chains under physiological conditions. *Org. Biomol. Chem.* **15**, 9685-9695, doi:10.1039/C7OB02028G (2017).
17 Shannon, D. A. *et al.* Sulfonyl fluoride analogues as activity-based probes for serine proteases. *ChemBioChem* **13**, 2327-2330, doi:10.1002/cbic.201200531 (2012).
18 Fahrney, D. E. & Gold, A. M. Sulfonyl Fluorides as Inhibitors of Esterases. I. Rates of Reaction with Acetylcholinesterase, α-Chymotrypsin, and Trypsin. *J. Am. Chem. Soc.* **85**, 997-1000, doi:10.1021/ja00890a037 (1963).
19 Markwardt, F., Drawert, J. & Walsmann, P. Synthetic low molecular weight

inhibitors of serum kallikrein. *Biochem. Pharmacol.* **23**, 2247-2256, doi:10.1016/0006-2952(74)90554-1 (1974).

20 Kamps, M. P., Taylor, S. S. & Sefton, B. M. Direct evidence that oncogenic tyrosine kinases and cyclic AMP-dependent protein kinase have homologous ATP-binding sites. *Nature* **310**, 589-592, doi:10.1038/310589a0 (1984).

21 Hett, E. C. *et al.* Rational Targeting of Active-Site Tyrosine Residues Using Sulfonyl Fluoride Probes. *ACS Chem. Biol.* **10**, 1094-1098, doi:10.1021/cb5009475 (2015).

22 Emsley, J. & Overill, R. E. Defining the bond energy of a strong hydrogen bond. *Chem. Phys. Lett.* **65**, 616-617, doi:10.1016/0009-2614(79)80304-8 (1979).

23 Larson, J. W. & McMahon, T. B. Gas-phase bifluoride ion. An ion cyclotron resonance determination of the hydrogen bond energy in fluoride ion (FHF-) from gas-phase fluoride transfer equilibrium measurements. *J. Am. Chem. Soc.* **104**, 5848-5849, doi:10.1021/ja00385a077 (1982).

24 Mukherjee, P. *et al.* Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides. *Org. Lett.* **20**, 3943-3947, doi:10.1021/acs.orglett.8b01520 (2018).

25 Mahapatra, S. *et al.* SuFEx Activation with Ca(NTf2)2: A Unified Strategy to Access Sulfamides, Sulfamates, and Sulfonamides from S(VI) Fluorides. *Org. Lett.* **22**, 4389-4394, doi:10.1021/acs.orglett.0c01397 (2020).

26 Chatgilialoglu, C., Griller, D. & Guerra, M. Experimental and theoretical approaches to the optical absorption spectra of sulfonyl radicals. *J. Phys. Chem.* **91**, 3747-3750, doi:10.1021/j100298a007 (1987).

27 Chatgilialoglu, C., Griller, D., Kanabus-Kaminska, J. M. & Lossing, F. P. Sulfur–chlorine bond dissociation enthalpies in methane- and benzene-sulfonyl chlorides. *J. Chem. Soc., Perkin Trans. 2*, 357-360, doi:10.1039/P29940000357 (1994).

28 Hirsch, E., Hünig, S. & Reißig, H.-U. Darstellung von (2,2-Dimethyl-1-methylenpropyl)-methansulfonat und -trifluoracetat. *Chem. Ber.* **115**, 399-401, doi:10.1002/cber.19821150138 (1982).

29 Kwon, J. & Kim, B. M. Synthesis of Arenesulfonyl Fluorides via Sulfuryl Fluoride Incorporation from Arynes. *Org. Lett.* **21**, 428-433, doi:10.1021/acs.orglett.8b03610 (2019).

30 Lee, C., Ball, N. D. & Sammis, G. M. One-pot fluorosulfurylation of Grignard reagents using sulfuryl fluoride. *Chem. Commun.* **55**, 14753-14756, doi:10.1039/C9CC08487H (2019).

31 Smedley, C. J. *et al.* Diversity Oriented Clicking (DOC): Divergent Synthesis

of SuFExable Pharmacophores from 2-Substituted-Alkynyl-1-Sulfonyl Fluoride (SASF) Hubs. *Angew. Chem. Int. Ed.* **59**, 12460-12469, doi:10.1002/anie.202003219 (2020).

32 So, C. M. & Kwong, F. Y. Palladium-catalyzed cross-coupling reactions of aryl mesylates. *Chem. Soc. Rev.* **40**, 4963-4972, doi:10.1039/C1CS15114B (2011).

33 Nie, X. *et al.* Radical Fluorosulfonylation: Accessing Alkenyl Sulfonyl Fluorides from Alkenes. *Angew. Chem. Int. Ed.* **60**, 3956-3960, doi:10.1002/anie.202012229 (2021).

34 Boiko, V. N. *et al.* A convenient synthetic route to 2,4,6-tris(chlorosulfonyl)- and 2,4,6-tris(fluorosulfonyl)phenol, aniline and chlorobenzene. *J. Fluor. Chem.* **132**, 1219-1226, doi:10.1016/j.jfluchem.2011.06.045 (2011).

35 Davies, W. & Dick, J. H. 57. Aliphatic sulphonyl fluorides. *J. Chem. Soc.*, 483-486, doi:10.1039/JR9320000483 (1932).

36 Bianchi, T. A. & Cate, L. A. Phase transfer catalysis. Preparation of aliphatic and aromatic sulfonyl fluorides. *J. Org. Chem.* **42**, 2031-2032, doi:10.1021/jo00431a054 (1977).

37 Kang, S. O., Powell, D., Day, V. W. & Bowman-James, K. Trapped Bifluoride. *Angew. Chem. Int. Ed.* **45**, 1921-1925, doi:10.1002/anie.200504066 (2006).

38 Beaman, A. G. & Robins, R. K. Potential Purine Antagonists. XXVII. Synthesis and Reactions of Some Purinesulfonyl Fluorides1. *J. Am. Chem. Soc.* **83**, 4038-4044, doi:10.1021/ja01480a021 (1961).

39 Brown, D. J. & Hoskins, J. A. Simple pyrimidines. Part XIV. The formation and reactions of some derivatives of simple pyrimidinesulphonic acids. *J. Chem. Soc., Perkin Trans. 1*, 522-527, doi:10.1039/P19720000522 (1972).

40 Narayan, S. *et al.* "On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension. *Angew. Chem. Int. Ed.* **44**, 3275-3279, doi:10.1002/anie.200462883 (2005).

41 Caddick, S., Wilden, J. D., Bush, H. D., Wadman, S. N. & Judd, D. B. A New Route to Sulfonamides via Intermolecular Radical Addition to Pentafluorophenyl Vinylsulfonate and Subsequent Aminolysis. *Org. Lett.* **4**, 2549-2551, doi:10.1021/ol026181m (2002).

42 Caddick, S., Wilden, J. D. & Judd, D. B. Observations on the reactivity of pentafluorophenyl sulfonate esters. *Chem. Commun.*, 2727-2728, doi:10.1039/B501212K (2005).

43 Vedovato, V., Talbot, E. P. A. & Willis, M. C. Copper-Catalyzed Synthesis of Activated Sulfonate Esters from Boronic Acids, DABSO, and Pentafluorophenol. *Org. Lett.* **20**, 5493-5496, doi:10.1021/acs.orglett.8b02445

(2018).

44 Zincke, T. & Frohneberg, W. Über Dithiohydrochinon. *Ber. Dtsch. Chem. Ges.* **42**, 2721-2736, doi:10.1002/cber.190904202193 (1909).

45 Douglass, I. B. & Johnson, T. B. The Interaction of Chlorine with Different Types of Organic Sulfur Compounds. *J. Am. Chem. Soc.* **60**, 1486-1489, doi:10.1021/ja01273a062 (1938).

46 Caldwell, W. T. & Kornfeld, E. C. Substituted 2-Sulfonamido-5-aminopyridines. *J. Am. Chem. Soc.* **64**, 1695-1698, doi:10.1021/ja01259a063 (1942).

47 Wright, S. W. & Hallstrom, K. N. A Convenient Preparation of Heteroaryl Sulfonamides and Sulfonyl Fluorides from Heteroaryl Thiols. *J. Org. Chem.* **71**, 1080-1084, doi:10.1021/jo052164+ (2006).

48 Wang, L. & Cornella, J. A Unified Strategy for Arylsulfur(VI) Fluorides from Aryl Halides: Access to Ar-SOF3 Compounds. *Angew. Chem. Int. Ed.* **59**, 23510-23515, doi:10.1002/anie.202009699 (2020).

49 Kim, J.-G. & Jang, D. O. A Convenient, One-Pot Procedure for the Preparation of Acyl and Sulfonyl Fluorides Using Cl3CCN, Ph3P, and TBAF(t-BuOH)4. *Synlett* **2010**, 3049-3052, doi:10.1055/s-0030-1259051 (2010).

50 Jiang, Y., Alharbi, N. S., Sun, B. & Qin, H.-L. Facile one-pot synthesis of sulfonyl fluorides from sulfonates or sulfonic acids. *RSC Advances* **9**, 13863-13867, doi:10.1039/C9RA02531F (2019).

51 Gómez-Palomino, A. & Cornella, J. Selective Late-Stage Sulfonyl Chloride Formation from Sulfonamides Enabled by Pyry-BF4. *Angew. Chem. Int. Ed.* **58**, 18235-18239, doi:10.1002/anie.201910895 (2019).

52 Pérez-Palau, M. & Cornella, J. Synthesis of Sulfonyl Fluorides from Sulfonamides. *Eur. J. Org. Chem.* **2020**, 2497-2500, doi:10.1002/ejoc.202000022 (2020).

53 Segall, Y., Quistad, G. B. & Casida, J. E. Cannabinoid CB1 Receptor Chemical Affinity Probes: Methods Suitable for Preparation of Isopropyl [11,12-3H]Dodecylfluorophosphonate and [11,12-3H]Dodecanesulfonyl Fluoride. *Synth. Commun.* **33**, 2151-2159, doi:10.1081/SCC-120021043 (2003).

54 Brouwer, A. J., Ceylan, T., Linden, T. v. d. & Liskamp, R. M. J. Synthesis of β-aminoethanesulfonyl fluorides or 2-substituted taurine sulfonyl fluorides as potential protease inhibitors. *Tetrahedron Lett.* **50**, 3391-3393, doi:10.1016/j.tetlet.2009.02.130 (2009).

55 Kirihara, M., Naito, S., Ishizuka, Y., Hanai, H. & Noguchi, T. Oxidation of

disulfides with Selectfluor™: concise syntheses of thiosulfonates and sulfonyl fluorides. *Tetrahedron Lett.* **52**, 3086-3089, doi:10.1016/j.tetlet.2011.03.132 (2011).

56 Kirihara, M. *et al.* Oxidation of disulfides with electrophilic halogenating reagents: concise methods for preparation of thiosulfonates and sulfonyl halides. *Tetrahedron* **70**, 2464-2471, doi:10.1016/j.tet.2014.02.013 (2014).

57 Laudadio, G. *et al.* Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride. *J. Am. Chem. Soc.* **141**, 11832-11836, doi:10.1021/jacs.9b06126 (2019).

58 Banks, R. E., Besheesh, M. K., Mohialdin-Khaffaf, S. N. & Sharif, I. N-Halogeno compounds. Part 18. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts: user-friendly site-selective electrophilic fluorinating agents of the N-fluoroammonium class. *J. Chem. Soc., Perkin Trans. 1*, 2069-2076, doi:10.1039/P19960002069 (1996).

59 Toulgoat, F., Langlois, B. R., Médebielle, M. & Sanchez, J.-Y. An Efficient Preparation of New Sulfonyl Fluorides and Lithium Sulfonates. *J. Org. Chem.* **72**, 9046-9052, doi:10.1021/jo701318n (2007).

60 Emmett, E. *Development of Catalytic Methods to Exploit Sulfur Dioxide in Organic Synthesis* DPhil thesis, University of Oxford (2014).

61 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.* **8**, 1233-1237, doi:10.1039/c6sc03924c (2017).

62 Tribby, A. L., Rodriguez, I., Shariffudin, S. & Ball, N. D. Pd-Catalyzed Conversion of Aryl Iodides to Sulfonyl Fluorides Using SO2 Surrogate DABSO and Selectfluor. *J. Org. Chem.* **82**, 2294-2299, doi:10.1021/acs.joc.7b00051 (2017).

63 Nguyen, B., Emmett, E. J. & Willis, M. C. Palladium-Catalyzed Aminosulfonylation of Aryl Halides. *J. Am. Chem. Soc.* **132**, 16372-16373, doi:10.1021/ja1081124 (2010).

64 Richards-Taylor, C. S., Blakemore, D. C. & Willis, M. C. One-pot three-component sulfone synthesis exploiting palladium-catalysed aryl halide aminosulfonylation. *Chem. Sci.* **5**, 222-228, doi:10.1039/C3SC52332B (2014).

65 Emmett, E. J., Hayter, B. R. & Willis, M. C. Palladium-catalyzed synthesis of ammonium sulfinates from aryl halides and a sulfur dioxide surrogate: a gas- and reductant-free process. *Angew. Chem. Int. Ed.* **53**, 10204-10208, doi:10.1002/anie.201404527 (2014).

66 Deeming, A. S., Russell, C. J. & Willis, M. C. Palladium(II)-Catalyzed Synthesis of Sulfinates from Boronic Acids and DABSO: A Redox-Neutral,

Phosphine-Free Transformation. *Angew. Chem. Int. Ed.* **55**, 747-750, doi:10.1002/anie.201508370 (2016).

67 Johnson, M. W. *et al.* Application of Fundamental Organometallic Chemistry to the Development of a Gold-Catalyzed Synthesis of Sulfinate Derivatives. *Angew. Chem. Int. Ed.* **53**, 4404-4407, doi:10.1002/anie.201400037 (2014).

68 Chen, Y. & Willis, M. C. Copper(i)-catalyzed sulfonylative Suzuki-Miyaura cross-coupling. *Chem. Sci.* **8**, 3249-3253, doi:10.1039/c6sc05483h (2017).

69 Lo, P. K. T., Chen, Y. & Willis, M. C. Nickel(II)-Catalyzed Synthesis of Sulfinates from Aryl and Heteroaryl Boronic Acids and the Sulfur Dioxide Surrogate DABSO. *ACS Catalysis* **9**, 10668-10673, doi:10.1021/acscatal.9b04363 (2019).

70 Lou, T. S.-B., Bagley, S. W. & Willis, M. C. Cyclic Alkenylsulfonyl Fluorides: Palladium-Catalyzed Synthesis and Functionalization of Compact Multifunctional Reagents. *Angew. Chem. Int. Ed.* **58**, 18859-18863, doi:10.1002/anie.201910871 (2019).

71 Liu, Y. *et al.* Arenesulfonyl Fluoride Synthesis via Copper-Catalyzed Fluorosulfonylation of Arenediazonium Salts. *Org. Lett.* **22**, 2281-2286, doi:10.1021/acs.orglett.0c00484 (2020).

72 Liu, S., Huang, Y., Xu, X.-H. & Qing, F.-L. Fluorosulfonylation of arenediazonium tetrafluoroborates with Na2S2O5 and N-fluorobenzenesulfonimide. *J. Fluor. Chem.* **240**, 109653, doi:10.1016/j.jfluchem.2020.109653 (2020).

73 Lin, Q. *et al.* Arenesulfonyl Fluoride Synthesis via Copper-free Sandmeyer-type Fluorosulfonylation of Arenediazonium Salts. *Chinese Journal of Chemistry* **38**, 1107-1110, doi:10.1002/cjoc.202000175 (2020).

74 Zhong, T. *et al.* Copper-free Sandmeyer-type Reaction for the Synthesis of Sulfonyl Fluorides. *Org Lett* **22**, 3072-3078, doi:10.1021/acs.orglett.0c00823 (2020).

75 Louvel, D. *et al.* Metal-Free Visible-Light Synthesis of Arylsulfonyl Fluorides: Scope and Mechanism. *Chemistry* **27**, 8704-8708, doi:10.1002/chem.202101056 (2021).

76 Ykman, P. & Hall, H. K. One-step conversion of alkoxytrimethylsilanes to alkyl benzenesulfonates. *J. Organomet. Chem.* **116**, 153-159, doi:10.1016/S0022-328X(00)91790-X (1976).

77 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, doi:10.1055/s-2008-1078407 (2008).

78 Qin, H.-L., Zheng, Q., Bare, G. A. L., Wu, P. & Sharpless, K. B. A Heck–

Matsuda Process for the Synthesis of β-Arylethenesulfonyl Fluorides: Selectively Addressable Bis-electrophiles for SuFEx Click Chemistry. *Angew. Chem. Int. Ed.* **55**, 14155-14158, doi:10.1002/anie.201608807 (2016).

79 Ciuffarin, E., Senatore, L. & Isola, M. Nucleophilic substitution at four-co-ordinate sulphur. Mobility of the leaving group. *J. Chem. Soc., Perkin Trans. 2*, 468-471, doi:10.1039/P29720000468 (1972).

80 Pienta, N. J. & Kessler, R. J. Pentaenyl cations from the photolysis of retinyl acetate. Solvent effects on the leaving group ability and relative nucleophilicities: an unequivocal and quantitative demonstration of the importance of hydrogen bonding. *J. Am. Chem. Soc.* **114**, 2419-2428, doi:10.1021/ja00033a017 (1992).

81 Zheng, Q. *et al.* SuFEx-enabled, agnostic discovery of covalent inhibitors of human neutrophil elastase. *Proc. Natl. Acad. Sci.* **116**, 18808-18814, doi:10.1073/pnas.1909972116 (2019).

82 Krutak, J. J., Burpitt, R. D., Moore, W. H. & Hyatt, J. A. Chemistry of ethenesulfonyl fluoride. Fluorosulfonylethylation of organic compounds. *J. Org. Chem.* **44**, 3847-3858, doi:10.1021/jo01336a022 (1979).

83 Luy, J.-N. & Tonner, R. Complementary Base Lowers the Barrier in SuFEx Click Chemistry for Primary Amine Nucleophiles. *ACS Omega* **5**, 31432-31439, doi:10.1021/acsomega.0c05049 (2020).

84 Wei, M. *et al.* A Broad-Spectrum, Catalytic Amidation of Sulfonyl Fluorides and Fluorosulfates. *Angew. Chem. Int. Ed.* **60**, 7397-7404, doi:10.1002/anie.202013976 (2021).

85 Barrow, A. S. & Moses, J. E. Synthesis of Sulfonyl Azides via Lewis Base Activation of Sulfonyl Fluorides and Trimethylsilyl Azide. *Synlett* **27**, 1840-1843, doi:10.1055/s-0035-1561626 (2016).

86 Smedley, C. J. *et al.* Bifluoride Ion Mediated SuFEx Trifluoromethylation of Sulfonyl Fluorides and Iminosulfur Oxydifluorides. *Angew. Chem. Int. Ed.* **58**, 4552-4556, doi:10.1002/anie.201813761 (2019).

87 Hyatt, J. A. & White, A. W. Synthesis of Aryl Alkyl and Aryl Vinyl Sulfones via Friedel-Crafts Reactions of Sulfonyl Fluorides. *Synthesis* **1984**, 214-217, doi:10.1055/s-1984-30774 (1984).

88 Shirota, Y., Nagai, T. & Tokura, N. The Reaction Between Benzylsulfonyl Halide and Phenyllithium. *Bull. Chem. Soc. Jpn.* **39**, 405-405, doi:10.1246/bcsj.39.405 (1966).

89 Frye, L. L., Sullivan, E. L., Cusack, K. P. & Funaro, J. M. Sulfonylation of organometallic reagents with arenesulfonyl fluorides: a simple one-step synthesis of sulfones. *J. Org. Chem.* **57**, 697-701, doi:10.1021/jo00028a053

(1992).

90 Jang, W. B., Jeon, H. J. & Oh, D. Y. Direct Sulfonylation of Lithiated Alkyl Phosphonates with Benzenesulfonyl Fluoride; Facile Method for Preparation of α-Sulfonyl Alkyl Phosphonates and Vinyl Sulfones. *Synth. Commun.* **28**, 1253-1256, doi:10.1080/00397919808005967 (1998).

91 Norris, T. The reaction of arenesulphonyl fluorides with anhydrous aluminium chloride. *J. Chem. Soc., Perkin Trans. 1*, 1378-1380, doi:10.1039/P19780001378 (1978).

92 Lee, C. *et al.* The Emerging Applications of Sulfur(VI) Fluorides in Catalysis. *ACS Catal* **11**, 6578-6589, doi:10.1021/acscatal.1c01201 (2021).

93 Chinthakindi, P. K., Kruger, H. G., Govender, T., Naicker, T. & Arvidsson, P. I. On-Water Synthesis of Biaryl Sulfonyl Fluorides. *J Org Chem* **81**, 2618-2623, doi:10.1021/acs.joc.5b02770 (2016).

94 Cherepakha, A. Y. *et al.* Hetaryl Bromides Bearing the SO2F Group – Versatile Substrates for Palladium-Catalyzed C–C Coupling Reactions. *Eur. J. Org. Chem.* **2018**, 6682-6692, doi:10.1002/ejoc.201801270 (2018).

95 Hett, E. C. *et al.* Rational targeting of active-site tyrosine residues using sulfonyl fluoride probes. *ACS Chem Biol* **10**, 1094-1098, doi:10.1021/cb5009475 (2015).

96 Fadeyi, O. *et al.* Chemoselective Preparation of Clickable Aryl Sulfonyl Fluoride Monomers: A Toolbox of Highly Functionalized Intermediates for Chemical Biology Probe Synthesis. *ChemBioChem* **17**, 1925-1930, doi:10.1002/cbic.201600427 (2016).

97 Lou, T. S.-B. & Willis, M. C. Arylsulfonyl fluoride boronic acids: Preparation and coupling reactivity. *Tetrahedron* **76**, 130782, doi:10.1016/j.tet.2019.130782 (2020).

98 Hedrick, R. M. Ethylene Sulfonyl Fluoride and Its Method of Preparation. US patent US2653973 (1953).

99 Meng, Y.-P. *et al.* Ethenesulfonyl Fluoride (ESF) and Its Derivatives in SuFEx Click Chemistry and More. *Synthesis* **52**, 673-687, doi:10.1055/s-0039-1690038 (2019).

100 Chen, J., Huang, B.-q., Wang, Z.-q., Zhang, X.-j. & Yan, M. Asymmetric Conjugate Addition of Ethylene Sulfonyl Fluorides to 3-Amido-2-oxindoles: Synthesis of Chiral Spirocyclic Oxindole Sultams. *Org. Lett.* **21**, 9742-9746, doi:10.1021/acs.orglett.9b03911 (2019).

101 Zha, G. F. *et al.* Palladium-Catalyzed Fluorosulfonylvinylation of Organic Iodides. *Angew. Chem. Int. Ed.* **56**, 4849-4852, doi:10.1002/anie.201701162 (2017).

102 Chinthakindi, P. K. *et al.* A Synthesis of "Dual Warhead" β-Aryl Ethenesulfonyl Fluorides and One-Pot Reaction to β-Sultams. *Org. Lett.* **19**, 480-483, doi:10.1021/acs.orglett.6b03634 (2017).

103 Chen, X.-Y., Wu, Y., Zhou, J., Wang, P. & Yu, J.-Q. Synthesis of β-Arylethenesulfonyl Fluoride via Pd-Catalyzed Nondirected C–H Alkenylation. *Org. Lett.* **21**, 1426-1429, doi:10.1021/acs.orglett.9b00165 (2019).

104 Wang, S.-M., Li, C., Leng, J., Bukhari, S. N. A. & Qin, H.-L. Rhodium(iii)-catalyzed Oxidative Coupling of N-Methoxybenzamides and Ethenesulfonyl fluoride: a C–H Bond Activation Strategy for the Preparation of 2-Aryl ethenesulfonyl fluorides and Sulfonyl fluoride Substituted γ-Lactams. *Org. Chem. Front.* **5**, 1411-1415, doi:10.1039/c7qo01128h (2018).

105 Wang, S.-M., Moku, B., Leng, J. & Qin, H.-L. Rh-Catalyzed Carboxylates Directed C-H Activation for the Synthesis of ortho-Carboxylic 2-Arylethenesulfonyl Fluorides: Access to Unique Electrophiles for SuFEx Click Chemistry. *Eur. J. Org. Chem.* **2018**, 4407-4410, doi:10.1002/ejoc.201800762 (2018).

106 Ncube, G. & Huestis, M. P. Directed Cp*RhIII-Catalyzed Fluorosulfonylvinylation of Arenes. *Organometallics* **38**, 76-80, doi:10.1021/acs.organomet.8b00327 (2019).

107 Chen, H.-R., Hu, Z.-Y., Qin, H.-L. & Tang, H. A novel three-component reaction for constructing indolizine-containing aliphatic sulfonyl fluorides. *Org. Chem. Front.* **8**, 1185-1189, doi:10.1039/D0QO01430C (2021).

108 Zhang, X., Fang, W.-Y., Lekkala, R., Tang, W. & Qin, H.-L. An Easy, General and Practical Method for the Construction of Alkyl Sulfonyl Fluorides. *Adv. Synth. Catal.* **362**, 3358-3363, doi:10.1002/adsc.202000515 (2020).

109 Xu, R., Xu, T., Yang, M., Cao, T. & Liao, S. A rapid access to aliphatic sulfonyl fluorides. *Nature Communications* **10**, 3752, doi:10.1038/s41467-019-11805-6 (2019).

110 Zhu, D. Y., Zhang, X. J. & Yan, M. Enantioselective Addition of Azlactones to Ethylene Sulfonyl Fluoride via Dual Catalysis. *Org Lett* **23**, 4228-4232, doi:10.1021/acs.orglett.1c01193 (2021).

111 Chen, J., Zhu, D.-y., Zhang, X.-j. & Yan, M. Highly Enantioselective Addition of N-2,2,2-Trifluoroethylisatin Ketimines to Ethylene Sulfonyl Fluoride. *J. Org. Chem.* **86**, 3041-3048, doi:10.1021/acs.joc.0c02511 (2021).

112 Ungureanu, A., Levens, A., Candish, L. & Lupton, D. W. N-Heterocyclic Carbene Catalyzed Synthesis of delta-Sultones via alpha,beta-Unsaturated Sulfonyl Azolium Intermediates. *Angew. Chem. Int. Ed.* **54**, 11780-11784, doi:10.1002/anie.201504633 (2015).

113 Chen, X. *et al.* Synthesis of a Class of Fused δ-Sultone Heterocycles via DBU-Catalyzed Direct Annulative SuFEx Click of Ethenesulfonyl Fluorides and Pyrazolones or 1,3-Dicarbonyl Compounds. *Adv. Synth. Catal.* **359**, 3254-3260, doi:10.1002/adsc.201700887 (2017).

114 Chen, X., Zha, G. F., Fang, W. Y., Rakesh, K. P. & Qin, H. L. A portal to a class of novel sultone-functionalized pyridines via an annulative SuFEx process employing earth abundant nickel catalysts. *Chem Commun (Camb)* **54**, 9011-9014, doi:10.1039/c8cc04032j (2018).

115 Khumalo, M. F. *et al.* Synthesis of novel 1,2,4-thiadiazinane 1,1-dioxides via three component SuFEx type reaction. *RSC Advances* **8**, 37503-37507, doi:10.1039/C8RA07627H (2018).

116 Zheng, Q., Dong, J. & Sharpless, K. B. Ethenesulfonyl Fluoride (ESF): An On-Water Procedure for the Kilogram-Scale Preparation. *J. Org. Chem.* **81**, 11360-11362, doi:10.1021/acs.joc.6b01423 (2016).

117 Smedley, C. J. *et al.* 1-Bromoethene-1-sulfonyl fluoride (BESF) is another good connective hub for SuFEx click chemistry. *Chem. Commun.* **54**, 6020-6023, doi:10.1039/c8cc03400a (2018).

118 Thomas, J. & Fokin, V. V. Regioselective Synthesis of Fluorosulfonyl 1,2,3-Triazoles from Bromovinylsulfonyl Fluoride. *Org. Lett.* **20**, 3749-3752, doi:10.1021/acs.orglett.8b01309 (2018).

119 Leng, J. & Qin, H.-L. 1-Bromoethene-1-sulfonyl fluoride (1-Br-ESF), a new SuFEx clickable reagent, and its application for regioselective construction of 5-sulfonylfluoro isoxazoles. *Chem. Commun.* **54**, 4477-4480, doi:10.1039/C8CC00986D (2018).

120 Leng, J., Tang, W., Fang, W. Y., Zhao, C. & Qin, H. L. A Simple Protocol for the Stereoselective Construction of Enaminyl Sulfonyl Fluorides. *Org Lett* **22**, 4316-4321, doi:10.1021/acs.orglett.0c01360 (2020).

121 Li, C., Zheng, Y., Rakesh, K. P. & Qin, H.-L. But-3-ene-1,3-disulfonyl difluoride (BDF): a highly selective SuFEx clickable hub for the quick assembly of sultam-containing aliphatic sulfonyl fluorides. *Chem. Commun.* **56**, 8075-8078, doi:10.1039/D0CC03248D (2020).

122 Zhang, Z.-W., Wang, S.-M., Fang, W.-Y., Lekkala, R. & Qin, H.-L. Protocol for Stereoselective Construction of Highly Functionalized Dienyl Sulfonyl Fluoride Warheads. *J. Org. Chem.* **85**, 13721-13734, doi:10.1021/acs.joc.0c01877 (2020).

123 Zhang, X., Moku, B., Leng, J., Rakesh, K. P. & Qin, H.-L. 2-Azidoethane-1-sulfonylfluoride (ASF): A VersatileBis-clickable Reagent for SuFEx and CuAAC Click Reactions. *European Journal of Organic Chemistry* **2019**,

1763-1769, doi:10.1002/ejoc.201801825 (2019).

124 Xu, S. & Cui, S. SuFExable Isocyanides for Ugi Reaction: Synthesis of Sulfonyl Fluoro Peptides. *Org Lett* **23**, 5197-5202, doi:10.1021/acs.orglett.1c01734 (2021).

125 Li, X.-R. *et al.* Palladacycle promoted asymmetric hydrophosphination of α,β-unsaturated sulfonyl fluorides. *J. Organomet. Chem.* **899**, 120912, doi:10.1016/j.jorganchem.2019.120912 (2019).

126 Moku, B., Fang, W.-Y., Leng, J., Kantchev, E. A. B. & Qin, H.-L. Rh(I)–Diene-Catalyzed Addition of (Hetero)aryl Functionality to 1,3-Dienylsulfonyl Fluorides Achieving Exclusive Regioselectivity and High Enantioselectivity: Generality and Mechanism. *ACS Catalysis* **9**, 10477-10488, doi:10.1021/acscatal.9b03640 (2019).

127 Moku, B. *et al.* Rh-Catalyzed Highly Enantioselective Synthesis of Aliphatic Sulfonyl Fluorides. *iScience* **21**, 695-705, doi:10.1016/j.isci.2019.10.051 (2019).

128 Fang, W.-Y., Wang, S.-M., Zhang, Z.-W. & Qin, H.-L. Clickable Transformation of Nitriles (RCN) to Oxazolyl Sulfonyl Fluoride Warheads. *Org. Lett.* **22**, 8904-8909, doi:10.1021/acs.orglett.0c03298 (2020).

129 Talko, A., Antoniak, D. & Barbasiewicz, M. Directed ortho-Metalation of Arenesulfonyl Fluorides and Aryl Fluorosulfates. *Synthesis* **51**, 2278-2286, doi:10.1055/s-0037-1610877 (2019).

130 Parker, R. P. & Hofmann, C. M. Sulfonyl fluorides of amino azo dyestuffs. US patent US2576037 (1947).

131 Abdul Fattah, T., Saeed, A. & Albericio, F. Recent advances towards sulfur (VI) fluoride exchange (SuFEx) click chemistry. *J. Fluor. Chem.* **213**, 87-112, doi:10.1016/j.jfluchem.2018.07.008 (2018).

132 Zhong, T., Chen, Z., Yi, J., Lu, G. & Weng, J. Recent progress in the synthesis of sulfonyl fluorides for SuFEx click chemistry. *Chinese Chemical Letters*, in press, doi:10.1016/j.cclet.2021.03.035 (2021).

133 Niederprüm, H., Voss, P. & Beyl, V. Über Perfluoralkansulfonsäurearylester. *Justus Liebigs Ann. Chem.* **1973**, 20-32, doi:10.1002/jlac.197319730105 (1973).

134 Anderson, K. W., Mendez-Perez, M., Priego, J. & Buchwald, S. L. Palladium-Catalyzed Amination of Aryl Nonaflates. *J. Org. Chem.* **68**, 9563-9573, doi:10.1021/jo034962a (2003).

135 Barluenga, J., Florentino, L., Aznar, F. & Valdés, C. Synthesis of Polysubstituted Olefins by Pd-Catalyzed Cross-Coupling Reaction of Tosylhydrazones and Aryl Nonaflates. *Org. Lett.* **13**, 510-513,

doi:10.1021/ol102884g (2011).

136 Shekhar, S., Dunn, T. B., Kotecki, B. J., Montavon, D. K. & Cullen, S. C. A General Method for Palladium-Catalyzed Reactions of Primary Sulfonamides with Aryl Nonaflates. *J. Org. Chem.* **76**, 4552-4563, doi:10.1021/jo200443u (2011).

137 Bennua-Skalmowski, B. & Vorbrüggen, H. A facile conversion of primary or secondary alcohols with n-perfluorobutane-sulfonyl fluoride/1,8-diazabicyclo[5.4.0]undec-7-ene into their corresponding fluorides. *Tetrahedron Lett.* **36**, 2611-2614, doi:10.1016/0040-4039(95)00355-G (1995).

138 Yin, J., Zarkowsky, D. S., Thomas, D. W., Zhao, M. M. & Huffman, M. A. Direct and Convenient Conversion of Alcohols to Fluorides. *Org. Lett.* **6**, 1465-1468, doi:10.1021/ol049672a (2004).

139 Nielsen, M. K., Ahneman, D. T., Riera, O. & Doyle, A. G. Deoxyfluorination with Sulfonyl Fluorides: Navigating Reaction Space with Machine Learning. *J. Am. Chem. Soc.* **140**, 5004-5008, doi:10.1021/jacs.8b01523 (2018).

140 Nielsen, M. K., Ugaz, C. R., Li, W. & Doyle, A. G. PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent. *J. Am. Chem. Soc.* **137**, 9571-9574, doi:10.1021/jacs.5b06307 (2015).

141 Zhang, C.-P., Chen, Q.-Y., Guo, Y., Xiao, J.-C. & Gu, Y.-C. Difluoromethylation and trifluoromethylation reagents derived from tetrafluoroethane β-sultone: Synthesis, reactivity and applications. *Coord. Chem. Rev.* **261**, 28-72, doi:10.1016/j.ccr.2013.11.010 (2014).

142 Chen, Q. & Zhu, S. 全氟和多氟烷基磺酸的研究——XV.由α-氟砜基二氟甲基乙酸甲酯形成二氟卡宾和氟砜基二氟甲基阴离子. *Sci. Sin., Ser. B*, 561-568, doi:10.1360/zb1986-16-6-561 (1986).

143 Chen, Q. & Wu, S. Perfluoro- and polyfluorosulfonic acids. 21. Synthesis of difluoromethyl esters using fluorosulfonyldifluoroacetic acid as a difluorocarbene precursor. *J. Org. Chem.* **54**, 3023-3027, doi:10.1021/jo00274a012 (1989).

144 Tian, F. *et al.* A Novel and Highly Efficient Synthesis of gem-Difluorocyclopropanes. *Org. Lett.* **2**, 563-564, doi:10.1021/ol0055622 (2000).

145 Jiang, Y., Fang, W.-Y., Rakesh, K. P. & Qin, H.-L. Copper-catalyzed mild desulfonylation of vinyl sulfonyl molecules. *Org. Chem. Front.* **7**, 1696-1702, doi:10.1039/D0QO00468E (2020).

146 Thomson, D. W. & Ehlers, G. F. L. Aromatic polysulfonates: Preparation and properties. *Journal of Polymer Science Part A: General Papers* **2**, 1051-1056, doi:10.1002/pol.1964.100020303 (1964).

147 Work, J. L. & Herweh, J. E. Thermal and mechanical properties of some

polysulfonates. *Journal of Polymer Science Part A-1: Polymer Chemistry* **6**, 2022-2030, doi:10.1002/pol.1968.150060723 (1968).

148 Dong, J., Sharpless, K. B., Kwisnek, L., Oakdale, J. S. & Fokin, V. V. SuFEx-Based Synthesis of Polysulfates. *Angew. Chem. Int. Ed.* **53**, 9466-9470, doi:10.1002/anie.201403758 (2014).

149 Wang, H. *et al.* SuFEx-Based Polysulfonate Formation from Ethenesulfonyl Fluoride-Amine Adducts. *Angew. Chem. Int. Ed.* **56**, 11203-11208, doi:10.1002/anie.201701160 (2017).

150 Gao, B. *et al.* Bifluoride-catalysed sulfur(VI) fluoride exchange reaction for the synthesis of polysulfates and polysulfonates. *Nat. Chem.* **9**, 1083-1088, doi:10.1038/nchem.2796 (2017).

151 Kulow, R. W., Wu, J. W., Kim, C. & Michaudel, Q. Synthesis of unsymmetrical sulfamides and polysulfamides via SuFEx click chemistry. *Chem. Sci.* **11**, 7807-7812, doi:10.1039/D0SC03606D (2020).

152 Brooks, K. *et al.* SuFEx Postpolymerization Modification Kinetics and Reactivity in Polymer Brushes. *Macromolecules* **51**, 297-305, doi:10.1021/acs.macromol.7b02372 (2018).

153 Yatvin, J., Brooks, K. & Locklin, J. SuFEx on the Surface: A Flexible Platform for Postpolymerization Modification of Polymer Brushes. *Angew. Chem. Int. Ed.* **54**, 13370-13373, doi:10.1002/anie.201506253 (2015).

154 Brooks, K. *et al.* Multifunctional Surface Manipulation Using Orthogonal Click Chemistry. *Langmuir* **32**, 6600-6605, doi:10.1021/acs.langmuir.6b01591 (2016).

155 Gahtory, D. *et al.* Quantitative and Orthogonal Formation and Reactivity of SuFEx Platforms. *Chem. Eur. J.* **24**, 10550-10556, doi:10.1002/chem.201802356 (2018).

156 Liu, W., Dong, Y., Zhang, S., Wu, Z. & Chen, H. A rapid one-step surface functionalization of polyvinyl chloride by combining click sulfur(vi)-fluoride exchange with benzophenone photochemistry. *Chem. Commun.* **55**, 858-861, doi:10.1039/C8CC08109C (2019).

157 Dong, Y. *et al.* “Click-chemical” modification of cellulose acetate nanofibers: a versatile platform for biofunctionalization. *Journal of Materials Chemistry B* **6**, 4579-4582, doi:10.1039/C8TB01401A (2018).

158 Park, S. *et al.* SuFEx in Metal–Organic Frameworks: Versatile Postsynthetic Modification Tool. *ACS Applied Materials & Interfaces* **10**, 33785-33789, doi:10.1021/acsami.8b14065 (2018).

159 Liu, S., Cao, Y., Wu, Z. & Chen, H. Reactive films fabricated using click sulfur(vi)–fluoride exchange reactions via layer-by-layer assembly. *Journal of*

Materials Chemistry B **8**, 5529-5534, doi:10.1039/D0TB00908C (2020).

160 Yatvin, J., Brooks, K. & Locklin, J. SuFEx Click: New Materials from SOxF and Silyl Ethers. *Chem. Eur. J.* **22**, 16348-16354, doi:10.1002/chem.201602926 (2016).

161 Xu, L., Wu, P. & Dong, J. in *Synthetic Polymer Chemistry: Innovations and Outlook* Ch. 1, 1-31 (The Royal Society of Chemistry, 2019).

162 Shen, C. *et al.* Stabilizing Formamidinium Lead Iodide Perovskite by Sulfonyl-Functionalized Phenethylammonium Salt via Crystallization Control and Surface Passivation. *Solar RRL* **4**, 2000069, doi:10.1002/solr.202000069 (2020).

163 Siegel, D. J. *et al.* Molecular design principles of ionic liquids with a sulfonyl fluoride moiety. *New J. Chem.* **45**, 2443-2452, doi:10.1039/D0NJ05603K (2021).

164 Myers, D. K. & Kemp, A. Inhibition of Esterases by the Fluorides of Organic Acids. *Nature* **173**, 33-34, doi:10.1038/173033a0 (1954).

165 Gold, A. M. & Fahrney, D. Sulfonyl Fluorides as Inhibitors of Esterases. II. Formation and Reactions of Phenylmethanesulfonyl α-Chymotrypsin. *Biochemistry* **3**, 783-791, doi:10.1021/bi00894a009 (1964).

166 Gold, A. M. Sulfonyl Fluorides as Inhibitors of Esterases. III. Identification of Serine as the Site of Sulfonylation in Phenylmethanesulfonyl α-Chymotrypsin*. *Biochemistry* **4**, 897-901, doi:10.1021/bi00881a016 (1965).

167 Baker, B. R. & Lourens, G. J. Irreversible Enzyme Inhibitors. CV.1,2 Differential Irreversible Inhibition of Vertebrate Dihydrofolic Reductases by Derivatives of 4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-s-triazines Substituted with a Terminal Sulfonyl Fluoride3. *J. Med. Chem.* **10**, 1113-1122, doi:10.1021/jm00318a029 (1967).

168 Jones, L. H. in *Annu. Rep. Med. Chem.* (Academic Press, 2020).

169 Pal, P. K., Wechter, W. J. & Colman, R. F. Affinity labeling of the inhibitory DPNH site of bovine liver glutamate dehydrogenase by 5'-fluorosulfonylbenzoyl adenosine. *J. Biol. Chem.* **250**, 8140-8147, doi:10.1016/S0021-9258(19)40827-2 (1975).

170 Colman, R. F. Affinity labeling of purine nucleotide sites in proteins. *Annu. Rev. Biochem* **52**, 67-91, doi:10.1146/annurev.bi.52.070183.000435 (1983).

171 Parker, C. G. & Pratt, M. R. Click Chemistry in Proteomic Investigations. *Cell* **180**, 605-632, doi:10.1016/j.cell.2020.01.025 (2020).

172 Gu, C. *et al.* Chemical Proteomics with Sulfonyl Fluoride Probes Reveals Selective Labeling of Functional Tyrosines in Glutathione Transferases. *Chemistry & Biology* **20**, 541-548, doi:10.1016/j.chembiol.2013.01.016

(2013).

173 Zhao, Q. *et al.* Broad-Spectrum Kinase Profiling in Live Cells with Lysine-Targeted Sulfonyl Fluoride Probes. *J. Am. Chem. Soc.* **139**, 680-685, doi:10.1021/jacs.6b08536 (2017).

174 Yan, X. *et al.* Europium-Labeled Activity-Based Probe through Click Chemistry: Absolute Serine Protease Quantification Using 153Eu Isotope Dilution ICP/MS. *Angew. Chem. Int. Ed.* **51**, 3358-3363, doi:10.1002/anie.201108277 (2012).

175 Jones, L. H. & Kelly, J. W. Structure-based design and analysis of SuFEx chemical probes. *RSC Medicinal Chemistry* **11**, 10-17, doi:10.1039/C9MD00542K (2020).

176 Zelli, R., Tommasone, S., Dumy, P., Marra, A. & Dondoni, A. A Click Ligation Based on SuFEx for the Metal-Free Synthesis of Sugar and Iminosugar Clusters. *Eur. J. Org. Chem.* **2016**, 5102-5116, doi:10.1002/ejoc.201600732 (2016).

177 Yang, B. *et al.* Proximity-enhanced SuFEx chemical cross-linker for specific and multitargeting cross-linking mass spectrometry. *Proc. Natl. Acad. Sci.* **115**, 11162-11167, doi:10.1073/pnas.1813574115 (2018).

178 Miller, P. W., Long, N. J., Vilar, R. & Gee, A. D. Synthesis of 11C, 18F, 15O, and 13N Radiolabels for Positron Emission Tomography. *Angew. Chem. Int. Ed.* **47**, 8998-9033, doi:10.1002/anie.200800222 (2008).

179 Schirrmacher, R. *et al.* Small Prosthetic Groups in 18F-Radiochemistry: Useful Auxiliaries for the Design of 18F-PET Tracers. *Seminars in Nuclear Medicine* **47**, 474-492, doi:10.1053/j.semnuclmed.2017.07.001 (2017).

180 Inkster, J. A. H. *et al.* Sulfonyl Fluoride-Based Prosthetic Compounds as Potential 18F Labelling Agents. *Chem. Eur. J.* **18**, 11079-11087, doi:10.1002/chem.201103450 (2012).

181 Matesic, L. *et al.* Ascertaining the Suitability of Aryl Sulfonyl Fluorides for [18F]Radiochemistry Applications: A Systematic Investigation using Microfluidics. *J. Org. Chem.* **78**, 11262-11270, doi:10.1021/jo401759z (2013).

182 Wang, J. & van Dam, R. M. High-Efficiency Production of Radiopharmaceuticals via Droplet Radiochemistry: A Review of Recent Progress. *Molecular Imaging* **19**, 1536012120973099, doi:10.1177/1536012120973099 (2020).

183 Zhou, D. *et al.* Preliminary evaluation of a novel 18F-labeled PARP-1 ligand for PET imaging of PARP-1 expression in prostate cancer. *Nuclear Medicine and Biology* **66**, 26-31, doi:10.1016/j.nucmedbio.2018.08.003 (2018).

184 Eby, R. & Schuerch, C. The use of 1-O-tosyl-d-glucopyranose derivatives in

α-d-glucoside synthesis. *Carbohydr. Res.* **34**, 79-90, doi:10.1016/S0008-6215(00)80372-9 (1974).

185 Ametamey, S. M., Honer, M. & Schubiger, P. A. Molecular Imaging with PET. *Chem. Rev.* **108**, 1501-1516, doi:10.1021/cr0782426 (2008).

186 Zhang, B. *et al.* Synthesis, bioconjugation and stability studies of [18F]ethenesulfonyl fluoride. *J. Label. Compd. Radiopharm.* **61**, 847-856, doi:10.1002/jlcr.3667 (2018).

187 Zhang, B. *et al.* [18F]Ethenesulfonyl Fluoride as a Practical Radiofluoride Relay Reagent. *Chem. Eur. J.* **25**, 7613-7617, doi:10.1002/chem.201900930 (2019).

188 Pascali, G. *et al.* Sulfur - fluorine bond in PET radiochemistry. *EJNMMI Radiopharmacy and Chemistry* **2**, 9, doi:10.1186/s41181-017-0028-6 (2017).

189 Montanino, M., Passerini, S. & Appetecchi, G. B. in *Rechargeable Lithium Batteries* (ed Alejandro A. Franco) 73-116 (Woodhead Publishing, 2015).

190 Li, Q., Chen, J., Fan, L., Kong, X. & Lu, Y. Progress in electrolytes for rechargeable Li-based batteries and beyond. *Green Energy & Environment* **1**, 18-42, doi:10.1016/j.gee.2016.04.006 (2016).

191 Razzini, G., Rovellini, S., Alessandrini, F., Di Pietro, B. & Scrosati, B. The lithium-sulfuryl chloride battery: Discharge behaviour. *J. Power Sources* **5**, 263-271, doi:10.1016/0378-7753(80)80005-X (1980).

192 Fu, X. *et al.* Sulfuryl chloride as a functional additive towards dendrite-free and long-life Li metal anodes. *Journal of Materials Chemistry A* **7**, 25003-25009, doi:10.1039/C9TA09068A (2019).

193 Lee, S.-Y., Ueno, K. & Angell, C. A. Lithium Salt Solutions in Mixed Sulfone and Sulfone-Carbonate Solvents: A Walden Plot Analysis of the Maximally Conductive Compositions. *J. Phys. Chem. C* **116**, 23915-23920, doi:10.1021/jp3067519 (2012).

194 Xue, L., Ueno, K., Lee, S.-Y. & Angell, C. A. Enhanced performance of sulfone-based electrolytes at lithium ion battery electrodes, including the LiNi0.5Mn1.5O4 high voltage cathode. *J. Power Sources* **262**, 123-128, doi:10.1016/j.jpowsour.2014.03.099 (2014).

195 Che, Y. *et al.* Protective electrode/electrolyte interphases for high energy lithium-ion batteries with p-toluenesulfonyl fluoride electrolyte additive. *J. Energy Chem.* **52**, 361-371, doi:10.1016/j.jechem.2020.04.023 (2021).

196 Xue, W. *et al.* FSI-inspired solvent and "full fluorosulfonyl" electrolyte for 4 V class lithium-metal batteries. *Energy & Environmental Science* **13**, 212-220, doi:10.1039/C9EE02538C (2020).

197 Conte, L., Gambaretto, G., Caporiccio, G., Alessandrini, F. & Passerini, S.

Perfluoroalkanesulfonylimides and their lithium salts: synthesis and characterisation of intermediates and target compounds. *J. Fluor. Chem.* **125**, 243-252, doi:10.1016/j.jfluchem.2003.07.003 (2004).

198 Jin, Z., Xie, K. & Hong, X. Electrochemical performance of lithium/sulfur batteries using perfluorinated ionomer electrolyte with lithium sulfonyl dicyanomethide functional groups as functional separator. *RSC Advances* **3**, 8889-8898, doi:10.1039/C3RA41517A (2013).

199 Zhou, H. *et al.* Introduction of a Crystalline, Shelf-Stable Reagent for the Synthesis of Sulfur(VI) Fluorides. *Org. Lett.* **20**, 812-815, doi:10.1021/acs.orglett.7b03950 (2018).

200 Guo, T. *et al.* A New Portal to SuFEx Click Chemistry: A Stable Fluorosulfuryl Imidazolium Salt Emerging as an “F−SO2+” Donor of Unprecedented Reactivity, Selectivity, and Scope. *Angew. Chem. Int. Ed.* **57**, 2605-2610, doi:10.1002/anie.201712429 (2018).

201 Börgel, J. & Ritter, T. Late-Stage Functionalization. *Chem* **6**, 1877-1887, doi:10.1016/j.chempr.2020.07.007 (2020).

202 Brzozowski, M., O’Brien, M., Ley, S. V. & Polyzos, A. Flow Chemistry: Intelligent Processing of Gas–Liquid Transformations Using a Tube-in-Tube Reactor. *Acc. Chem. Res.* **48**, 349-362, doi:10.1021/ar500359m (2015).

203 Malet-Sanz, L., Madrzak, J., Ley, S. V. & Baxendale, I. R. Preparation of arylsulfonyl chlorides by chlorosulfonylation of in situ generated diazonium salts using a continuous flow reactor. *Org. Biomol. Chem.* **8**, 5324-5332, doi:10.1039/C0OB00450B (2010).

204 Liu, Z. *et al.* SuFEx Click Chemistry Enabled Late-Stage Drug Functionalization. *J. Am. Chem. Soc.* **140**, 2919-2925, doi:10.1021/jacs.7b12788 (2018).

205 Mortenson, D. E. *et al.* “Inverse Drug Discovery” Strategy To Identify Proteins That Are Targeted by Latent Electrophiles As Exemplified by Aryl Fluorosulfates. *J. Am. Chem. Soc.* **140**, 200-210, doi:10.1021/jacs.7b08366 (2018).

206 Wang, N. *et al.* Genetically Encoding Fluorosulfate-l-tyrosine To React with Lysine, Histidine, and Tyrosine via SuFEx in Proteins in Vivo. *J. Am. Chem. Soc.* **140**, 4995-4999, doi:10.1021/jacs.8b01087 (2018).

207 Martín-Gago, P. & Olsen, C. A. Arylfluorosulfate-Based Electrophiles for Covalent Protein Labeling: A New Addition to the Arsenal. *Angew. Chem. Int. Ed.* **58**, 957-966, doi:10.1002/anie.201806037 (2019).

208 Kassick, A. J. *et al.* SuFEx-based strategies for the preparation of functional particles and cation exchange resins. *Chem. Commun.* **55**, 3891-3894,

doi:10.1039/C9CC00036D (2019).

209 Xu, H. *et al.* DNA-Encoded Libraries: Aryl Fluorosulfonates as Versatile Electrophiles Enabling Facile On-DNA Suzuki, Sonogashira, and Buchwald Reactions. *Advanced Science* **6**, 1901551, doi:10.1002/advs.201901551 (2019).

210 Zheng, Q. *et al.* Sulfur [18F]Fluoride Exchange Click Chemistry Enabled Ultrafast Late-Stage Radiosynthesis. *J. Am. Chem. Soc.* **143**, 3753-3763, doi:10.1021/jacs.0c09306 (2021).

211 Li, S., Wu, P., Moses, J. E. & Sharpless, K. B. Multidimensional SuFEx Click Chemistry: Sequential Sulfur(VI) Fluoride Exchange Connections of Diverse Modules Launched From An SOF4 Hub. *Angew. Chem. Int. Ed.* **56**, 2903-2908, doi:10.1002/anie.201611048 (2017).

212 Liu, F. *et al.* Biocompatible SuFEx Click Chemistry: Thionyl Tetrafluoride (SOF4)-Derived Connective Hubs for Bioconjugation to DNA and Proteins. *Angew. Chem. Int. Ed.* **58**, 8029-8033, doi:10.1002/anie.201902489 (2019).

213 Kitamura, S. *et al.* Sulfur(VI) Fluoride Exchange (SuFEx)-Enabled High-Throughput Medicinal Chemistry. *J. Am. Chem. Soc.* **142**, 10899-10904, doi:10.1021/jacs.9b13652 (2020).