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Review

Unconventional reactivity of sulfonyl fluorides

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Sulfonyl fluorides are now established click reagents that find broad applications in synthesis, chemical biology, and drug discovery. Sulfonyl fluorides owe their popularity to their increased stability compared with their sulfonyl chloride cousins and to their high selectivity for the reaction pathway of fluoride exchange (SuFEx reaction). Other reaction pathways were unavailable to sulfonyl fluorides. However, recent reports have challenged this paradigm, showing unconventional leaving group capabilities of the whole SO_2F group as part of Suzuki–Miyaura or defluorosulfonylative (deFS) couplings. This review highlights such early developments, discusses the key mechanistic aspects responsible for the alternative reactivity, and recognises potential avenues for future research in this exciting new area.

Highlights

Sulfonyl fluoride compounds are popular click reagents that reliably react in a sulfur–fluoride exchange fashion (SuFEx). However, recent studies have shown that sulfonyl fluorides can also follow alternative reaction pathways to yield products with potential in synthetic chemistry and beyond.

Under the right conditions, aryl sulfonyl fluorides underwent oxidative addition with a palladium complex and yielded biaryl structures after transmetallation and reductive elimination in a Suzuki–Miyaura-type cross-coupling.

Isolated reports showed that sulfonyl fluorides also serve as leaving groups in cycloaddition, nucleophilic aromatic substitution reactions (S_NAr), and cyclopropanation reactions.

Oxetane sulfonyl fluorides defluorosulfonylate under mild thermal activation (60°C) to generate oxetane carbocations that can be trapped with various nucleophiles in an S_N1 reaction to yield 3,3-disubstituted oxetanes as potential isosteres.

Sulfonyl fluorides: from oddity to powerful click reagents

Although long known to the dye industry [1–4], sulfonyl fluoride motifs have only recently gained popularity amongst the broad chemistry community and were coined by Sharpless as **click reagents** (see Glossary) in 2014 [5]. The general concept of click reactions was introduced by Sharpless in the early 2000s as a class of highly reliable and simple reactions that meet stringent criteria [6]: (i) modular, (ii) high-yielding, (iii) wide in scope, (iv) regio- and stereospecific, (v) insensitive to water and oxygen, (vi) generate only inoffensive by-products, and (vii) possess a large thermodynamic driving force (>20 kcal mol^{-1}). These criteria have served to design, recognise, and establish reactions that will likely be biocompatible (i.e., reactions that will be successful in complex biological environments). The development of click reactions has been a significant advance for the chemical sciences, finding broad applications beyond chemistry, most notably as linkages between biomolecules and reporter molecules, or as bioorthogonal reactions inside living cells, and for which the Nobel Prize in Chemistry 2022 was awarded to Bertozzi, Meldal, and Sharpless [7]. The most notable examples of click reactions are the **1,3-dipolar cycloaddition** between azides and alkynes (copper-catalysed or strain-promoted), the thiol-ene reaction, and most recently, the sulfur–fluoride exchange reaction between sulfonyl fluorides and nucleophiles (**SuFEx**; Figure 1A, Key figure).

Sulfonyl fluorides are best known for their combination of high stability yet reliable reactivity with nucleophiles under precise activating conditions to yield S(VI) derivatives as part of the SuFEx click reaction. Sulfonyl fluorides are considerably more stable than related sulfonyl chlorides (and other halides) thanks to the highly polarised S–F bond, which confers sulfonyl fluorides with increased thermodynamic stability (S–F bond-dissociation energy (BDE): 81 ± 2 kcal mol^{-1}; S–Cl BDE: 46 ± 4 kcal mol^{-1}) [8] and, in contrast to sulfonyl chlorides, inertness towards reductive processes. Key to the 'click' behaviour of sulfonyl fluorides is the activation of fluoride as a **leaving group**. Fluoride normally being a sluggish leaving group, sulfonyl fluorides are stable towards nucleophilic and hydrolytic conditions. However, specific fluoride activators (first identified as protons and silylium reagents, R_3Si^+) transform the complexed fluoride into a good leaving group, potentially under defined kinetic and spatial constraints, and allow for clean redox-neutral substitution reactions at sulfur(VI).

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Key figure

Typical versus alternative reactivity of sulfonyl fluorides and comparison with sulfonyl chlorides

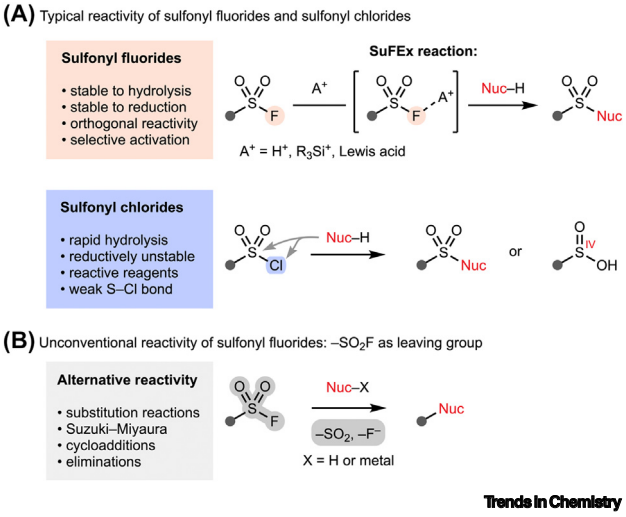

Figure 1. (A) Properties and reactivity of sulfonyl fluorides and sulfonyl chlorides. (B) Alternative reactivity of sulfonyl fluorides: $–SO_2F$ as a non-classical leaving group.

The unique properties of sulfonyl fluorides have allowed their notable application as warheads in chemical biology and **covalent inhibitors** in drug discovery [9] (for reviews see [10–14]). Once attached to a selective ligand, the sulfonyl fluoride head can be spatially activated inside the target protein pocket through close-contact H-bonding interactions with protein residues and undergo irreversible SuFEx reaction with nucleophilic side chains such as lysine, serine, or tyrosine. Further applications have been seen in materials and polymer science [15–17]. Several excellent reviews have been published on the general chemistry of sulfonyl fluorides [5,18–21], applications to synthesis [22–26], medicinal chemistry and chemical biology [10–14], and catalysis [27].

Recent years have seen many advances in the field of sulfonyl fluoride chemistry, including new synthetic approaches [28–33] functional sulfonyl fluoride reagents [34–37], and applications to chemical biology [38–40], radiolabelling [41–43], drug discovery campaigns [44–46], and as covalent inhibitors [47–51]. Most relevant to reactivity, however, have been the advances to accelerate SuFEx reactions [52–58].

SuFEx reactions, although in theory 'clickable', often suffer from sluggish reactivity, indeed due to the inertness and stability of the sulfonyl fluoride substrates. Alkyl sulfonyl fluorides are particularly challenging due to their decreased electrophilicity at sulfur and the acidity of the α protons (for primary and secondary substrates), which impedes the use of strong bases, because they often lead to dimerisation and oligomerisation reactions via α deprotonation, followed by SuFEx (or the reverse order) [59–61]. It is hence of value to develop chemical systems that accelerate SuFEx reactions, to reduce reaction times and avoid elevated temperatures, which could degrade sensitive chemical matter.

Glossary

Click reagents: reagents that partake in click reactions. Chemical functional groups that will react specifically with other specific functionality in high yields under mild conditions. Typically involving cycloaddition reactions and, specifically, the copper catalysed azide alkyne cycloaddition (CuAAC or Huisgen cycloaddition).
Covalent inhibitors: type of therapeutic that binds irreversibly to its protein target by formation of a covalent chemical bond.
1,3-Dipolar cycloaddition: the reaction between a 1,3-dipole (molecules that can be represented by a zwitterionic resonance structure, e.g., diazo compounds or azides) and a dipolarophile (molecules with a π-system that can react with 1,3-dipoles, e.g., alkenes or alkynes) to form a five-membered ring.
E_i mechanism: internal or intramolecular elimination. Also termed *syn* elimination and involves the concerted elimination of two vicinal groups through a cyclic transition state to yield an alkene. Unlike other mechanisms of elimination, E_i only requires thermal activation and no exogenous acids or bases.
Isosteres: chemical groups that mimic the physicochemical- and/or biological properties of another compound. Also termed bioisosteres when referring to the biological properties of the compounds.
Leaving group: an atom or group of atoms that depart from the main molecule during a chemical reaction.
Oxidative addition: a process that increases the oxidation state and coordination number of a metal centre.
σ Meisenheimer complexes: the anionic intermediates formed during nucleophilic aromatic substitution reactions (S_NAr) after the attack of a nucleophile at an electron-poor arene.
S_N1 mechanism: the mechanism of unimolecular substitution reactions. These are substitution reactions whose rate depend only on the concentration of one species (i.e., unimolecular). Typically, the rate-determining (slowest) step is the formation of a carbocation by loss of a leaving group. The carbocation reacts rapidly with the nucleophile in the second step.
SuFEx: sulfur–fluoride exchange. The reaction between sulfonyl fluorides and nucleophiles to yield S(VI) derivatives.

To this purpose, catalytic and stoichiometric additives were developed to accelerate SuFEx couplings, broadening the scope of both less reactive sulfonyl fluoride substrates and nucleophiles. Lewis acidic [52–54] and Lewis basic (i.e., nucleophilic) [55–58] additives were discovered that significantly expedite SuFEx reactions. Recently, further alternative ways to activate sulfonyl fluoride substrates have also been reported, including intramolecular chalcogen bonds [60] and single-electron activation to generate sulfonyl radicals, followed by reaction with alkenes [62–64] or aryl boronic acids [65]. The S(VI), 'SuFEx-type' products were obtained in all cases. It is remarkable that, despite the potential ability as leaving group of the $-SO_2F$ fragment, exclusive SuFEx reactivity was observed under all the activating conditions with Lewis acids and bases.

Alternative reactivity of sulfonyl fluorides

The value of the sulfonyl fluoride motif as a clickable SuFEx handle is beyond question. However, recent reports from various research groups have demonstrated intriguing alternative, non-SuFEx reactivity of sulfonyl fluoride substrates (Figure 1B). This review will describe such unconventional reactivity of sulfonyl fluorides, focusing on key discoveries, mechanistic aspects, and potential future avenues. One such example was reported by Sharpless and Dong, who developed fluorosulfuryl azide as a diazotransfer reagent for the azidation of primary amines and as an alternative to the common-use diazotizing reagent triflyl azide ($CF_3SO_2N_3$) (Figure 2) [66–68]. The reaction is fast, insensitive to moisture or air, and selective for primary amine functionality. The diazotransfer was thought to proceed by an unusual pathway whereby the amine nucleophile attacked the terminal nitrogen on the azide and released sulfamoyl fluoride as by-product [69,70]. Here, we concentrate on examples that involve the elimination of the sulfonyl fluoride in productive reaction processes.

Suzuki–Miyaura couplings

Sulfones and sulfinates have long been recognised as attractive reagents for cross-coupling reactions [71–73] Recently, aryl fluorosulfates ($ArOSO_2F$) have also emerged as useful coupling partners for transition metal-catalysed transformations [74–76]. However, the same cannot be said of related sulfonyl fluoride reagents, which have only received significant attention as part of SuFEx processes. A notable exception is the deFS **Suzuki–Miyaura coupling (SMC)** of aryl sulfonyl fluorides with boronic acids, developed independently by Moran [77] (Figure 3A)

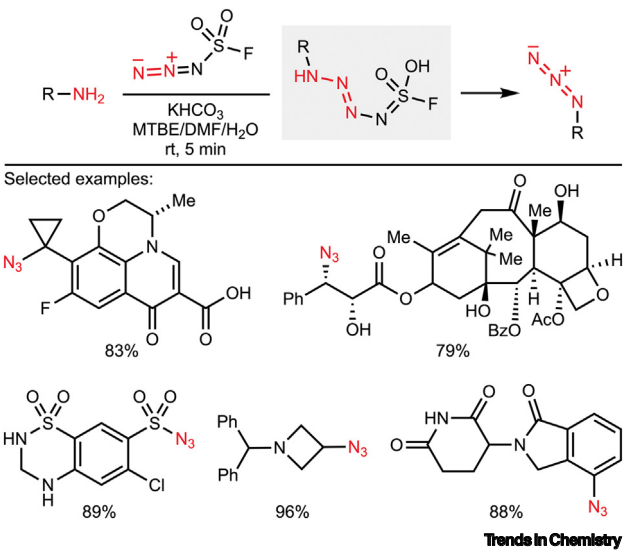

Figure 2. Diazotization of primary amines using fluorosulfuryl azide as a diazotransfer reagent [66].

Suzuki–Miyaura coupling (SMC): the metal-catalysed (usually palladium) cross-coupling of an organohalide and a boronic acid, typically to yield biaryl products. Named after Akira Suzuki and Norio Miyaura.

Transmetallation: the transfer of a ligand from one metal to another.

Turnover limiting step: refers to the step in a catalytic cycle that controls the efficiency of the process and limits the 'turnover', or regeneration, of the catalyst. In a catalytic cycle this corresponds to the step with the greatest energetic span, which may correspond to the highest energy transition state or the smallest rate constant *k*.

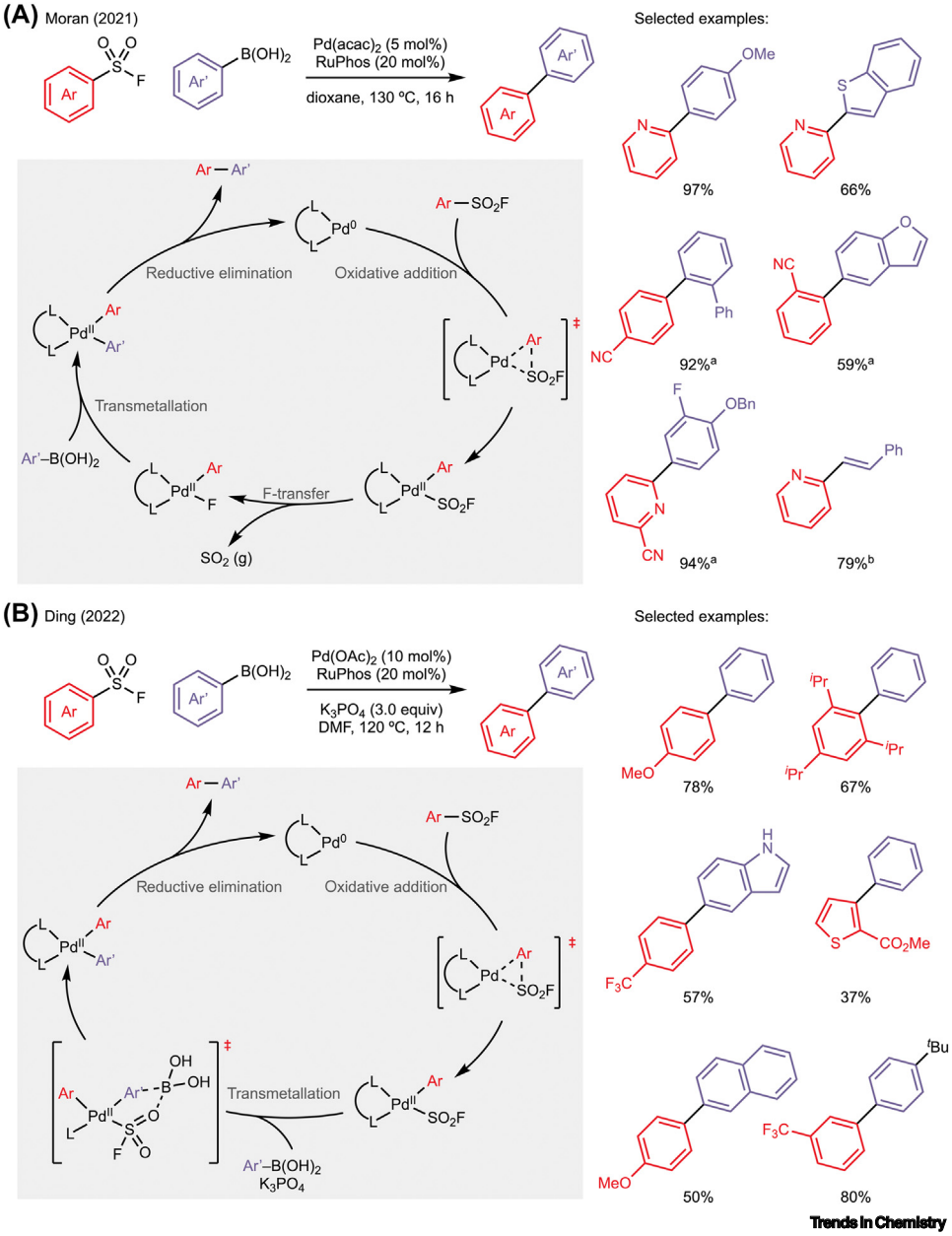

Figure 3. Suzuki–Miyaura couplings (SMC) of aryl sulfonyl fluorides. (A) Base-free SMC conditions reported by Moran involving an F-transfer step [77]. SMC of aryl sulfonyl fluorides reported by Ding involving a base-mediated transmetallation step [78]. [a]Additives: Cu(IPr)Cl (2.5 mol%), KHF_2 (50 mol%). [b]6 h.

and Ding [78] (Figure 3B) in 2021 and 2022, respectively. In both cases, experimental and computational evidence suggested **oxidative addition** of the sulfonyl fluoride to be the **turnover limiting step** (in accordance with the SMC of aryl sulfones [79]) and to proceed through the C–S instead of S–F bond. One difference between both reports is noticeable: whilst the base additive was indispensable in Ding's SMC, no base was required in Moran's conditions. This basic disparity is reflected on the **transmetallation** pathways proposed. Whilst experimental (inhibition by $LiBF_4$, gas evolution) and computational observations suggested F-transfer from sulfur to palladium to occur prior to

transmetallation in Moran's work, Ding proposed a base-assisted transmetallation directly on the FO_2S–Pd species.

Moran's conditions were limited to 2-pyridyl and cyanophenyl sulfonyl fluorides. The addition of base in Ding's work expanded the scope of aryl sulfonyl fluorides to include electron-rich and -poor phenyl rings with varied substitution patterns. The SMC reactivity of 2-pyridyl sulfonyl fluorides was also investigated by Grygorenko [80], and later by Ball and Love [81]. The latter report thoroughly assessed the effect of reaction variables on the reaction outcome with a wide array of (hetero)aromatic boronic acids and esters. These developments are particularly relevant in the context of the orthogonality of sulfonyl fluorides to cross-coupling conditions [5,18–20].

Defluorosulfonylation reactions

Instead of F^-, the whole SO_2F group has also served as leaving group in various processes. For example, ethenesulfonyl fluoride (ESF) derivatives such as styrene **1** have been employed as dipolarophiles in 1,3-dipolar cycloaddition reactions with diazonium betaines, whereby the sulfonyl fluoride group was eliminated to yield aromatic products (Figure 4A) [82–85]. The initial triazoline and pyrazoline intermediates were not observed but rather underwent *in situ* elimination of SO_2F to yield triazoles and pyrazoles, proposedly via an **E_i mechanism**. Through this strategy Moses and coworkers developed a platform to generate a varied library of 1-substituted triazoles from organic azides (aliphatic and aromatic substituents tolerated) and ESF [82]. Later, Swamy expanded the scope of this cycloaddition to substituted ESF substrates (aromatic) and also $TMSN_3$ to generate 5-substituted triazoles [85]. The same report developed the cycloaddition between ESFs and diazoacetate to yield 3,4-disubstituted pyrazoles (Figure 4A). Further elimination examples have been reported that proceeded through an intramolecular SuFEx reaction, followed by *syn* elimination [86,87].

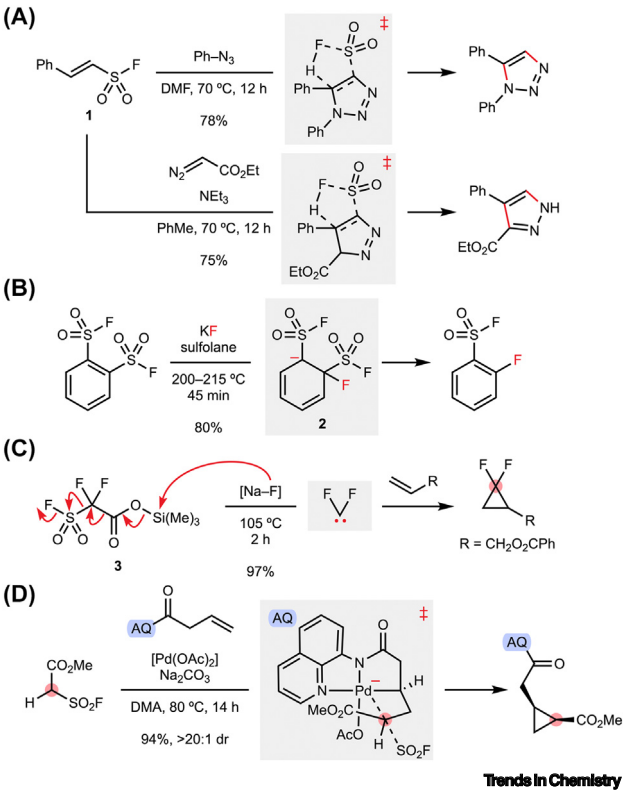

Figure 4. Sulfonyl fluorides as leaving group. (A) 1,3-Dipolar cycloadditions of sulfonyl fluoride styrene **1** with diazo compounds and azides to yield heterocycles [82–85]. (B) $–SO_2F$ as a leaving group in S_NAr reactions (nucleophilic aromatic substitution reactions) [88,89]. (C) Use of sulfonyl fluoride-difluoro acetate **3** as a precursor to difluorocarbenes [90,91]. (D) Pd-catalysed cyclopropanation of 8-aminoquinoline (AQ) alkenes with alkyl sulfonyl fluorides via oxidative addition of an alkyl sulfonyl fluoride into palladium(II) [93].

Sulfonyl fluoride substituents have served as stabilising groups for **σ Meisenheimer complexes** (**2**) of S_NAr reactions using external fluoride nucleophiles (Figure 4B) [88,89]. Whilst the two examples reported so far are important proof-of-principle studies, the methods suffer from harsh conditions (typically temperatures >200°C required) and are limited to fluoride nucleophiles. The development of milder conditions and compatibility with other nucleophiles (e.g., amines), perhaps by way of catalysis, could render this transformation synthetically useful.

Difluoroacetate sulfonyl fluoride **3** has also shown intriguing applications as difluorocarbene precursor (Figure 4C) [90–92]. Thermal activation triggered decarboxylation, which was followed by defluorosulfonylation to generate the carbene, used in difluorocyclopropanation reactions [91]. The reported scope of difluorocyclopropanes was brief and included only mono-substituted alkenes with alkyl or ester groups. An alternative cyclopropanation reaction using alkyl sulfonyl fluorides and palladium catalysis was also recently reported by Liu, Sharpless, and Engle (Figure 4D) [93]. Kinetic, stereochemical, and computational data were suggestive of a rate- and stereodetermining intramolecular oxidative addition of Pd(II) into the alkyl sulfonyl fluoride to generate a pallada(IV)-cyclobutane intermediate that yields the cyclopropane product after reductive elimination (see Figure 4D for the proposed transition state). Despite the requirement of an 8-aminoquinoline (AQ) directing group on the alkene and acidic α-protons on the alkyl sulfonyl fluoride fragment (e.g., stabilised by an ester, nitrile, or arene), the AQ can be removed subsequently and the scope of the transformation is broad, tolerating, for example, heteroaromatics and polysubstitution on both alkene and sulfonyl fluoride components. This report represents the first example of an oxidative addition into an alkyl sulfonyl fluoride and could pave the way for the development of further methods that involve such substrates. Despite the robustness of sulfonyl fluorides towards reduction, scattered reductive processes have also been disclosed with silyl iodides [94] or boron halides [95] to generate disulfides.

Bull and coworkers reported the synthesis and reactivity of oxetane sulfonyl fluoride reagents (OSFs; **4**) [96,97] These species did not show the typical SuFEx reactivity of sulfonyl fluorides but, instead, underwent a deFS coupling reaction with nucleophiles to yield 3,3-disubstituted oxetane products **5**–**10** (Figure 5A). The deFS reaction of oxetane sulfonyl fluorides was shown to proceed with various nucleophiles including alcohols (**5**), N-heterocycles (**6**,**7**), and most notably amines (**8**–**10**), which yielded amino-oxetanes as potential **isosteres** of amides. Robustness and applicability to drug discovery settings was demonstrated with the late-stage functionalisation of complex amines, the synthesis of oxetane drug analogues of benzamide drugs, and the generation of a small amino-oxetane library through a 30-compound array. Recently, a broader range of nucleophiles was demonstrated compatible, along with a similar process with azetidine sulfonyl fluoride reagents [98].

Kinetic and computational data suggested the deFS reaction pathway to proceed by an **S_N1 mechanism** through elongation of the C–S bond and the rate-determining formation of a planar benzylic oxetane carbocation stabilised by the electron-rich arene (Figure 5B) [96]. SO_2F^- is released (which rapidly dissociates to SO_2 and F^-) and the carbocation is trapped by the nucleophile in a chemo-determining step. Of relevance to the general reactivity of sulfonyl fluoride substrates, it was shown that preference of the deFS over the SuFEx pathway was primarily related to the relative stability of the resulting carbocation. For example, non-electron-rich Ph OSF **4a** was entirely unreactive towards amine nucleophiles, both in SuFEx and deFS pathways (Figure 5C). Similarly, primary benzylic sulfonyl fluoride **11** showed exclusive SuFEx reactivity, the pathway further benefitting from lower steric hindrance around the reactive sulfur centre (Figure 5D). On the other side of the spectrum, cyclobutane sulfonyl fluoride **12**, which would generate a more stable carbocation than the oxetane analogue due to the absence of the electron-withdrawing oxygen

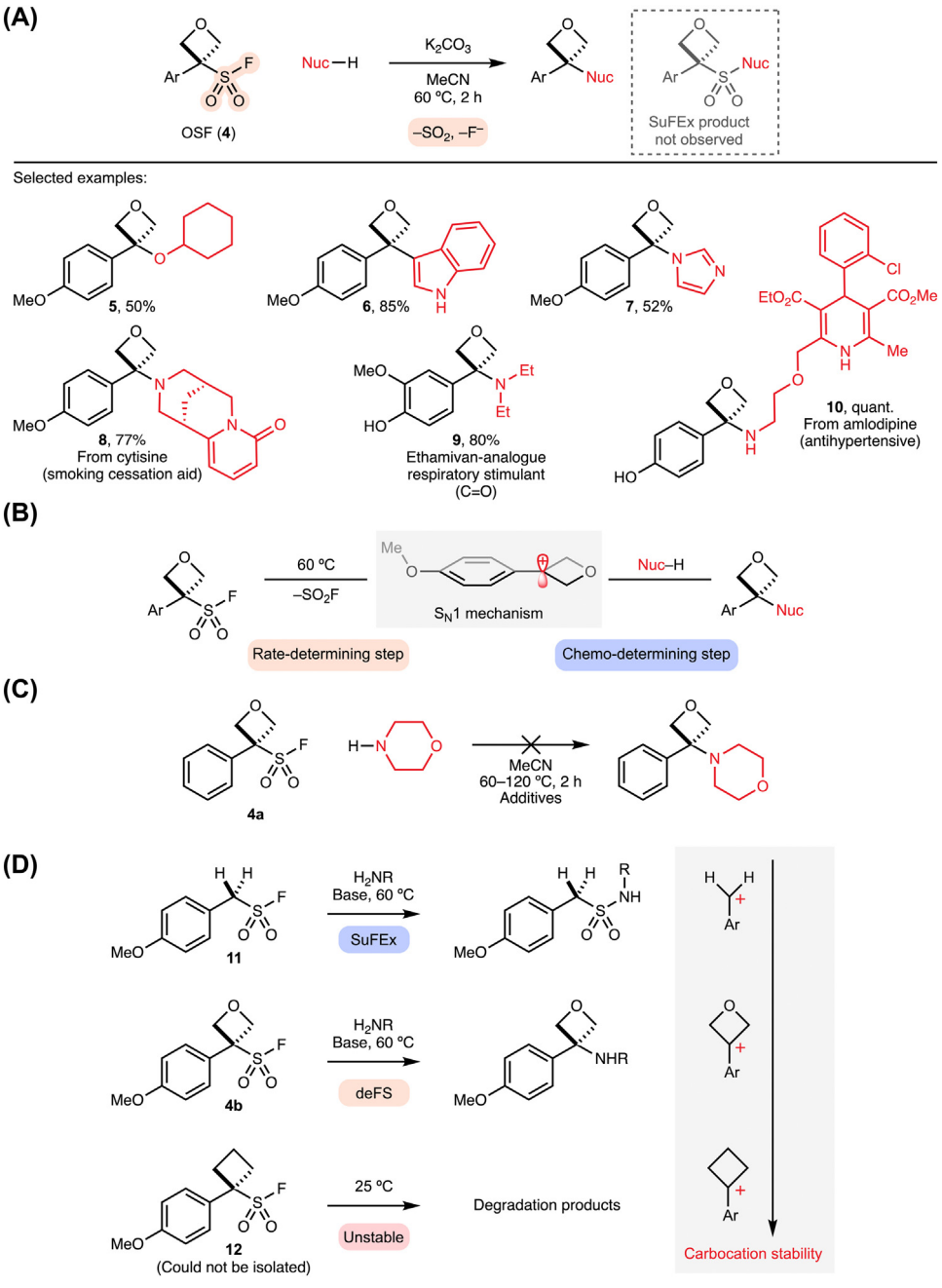

Figure 5. Defluorosulfonylative (deFS) coupling of oxetane sulfonyl fluorides with nucleophiles [96–98]. (A) Selected scope of the deFS coupling of oxetane sulfonyl fluorides **4** with amines, alcohols, and heterocycles. (B) S_N1 (unimolecular nucleophilic substitution) mechanism of the defluorosulfonylation of oxetane sulfonyl fluorides. (C) Inertness of non-electron-rich phenyl-oxetane sulfonyl fluoride **4a** in the reaction with amine nucleophiles under various conditions. (D) Schematic correlation between the reactivity of different sulfonyl fluoride compounds (methylene **11**, oxetane **4b**, and cyclobutane **12**) and the stability of the corresponding carbocations. Abbreviations: OSF, oxetane sulfonyl fluoride reagent; SuFEx, sulfur–fluoride exchange.

atom, was unstable and degraded during preparation. Oxetane sulfonyl fluorides seemed to occupy a privileged reactivity window: sufficiently stable under ambient conditions to allow on-the-bench handling, but selectively reactive on mild thermal activation (60°C).

Concluding remarks

Sulfonyl fluoride-containing scaffolds have gained universal value in the chemical and biological sciences as convenient and predictable click reagents [5]. However, increasingly sulfonyl fluoride substrates have been shown to react as non-typical leaving groups and embark in alternative reaction pathways which generate defluorosulfonylated products. Aryl sulfonyl fluorides were shown to be successful substrates for Pd-catalysed Suzuki–Miyaura cross-coupling reactions under the right activating conditions to generate biaryl products [77,78]. The $–SO_2F$ motif was also shown to act as a leaving group as part of cycloaddition [82–85] and S_NAr reactions [88,89] and for the generation of difluorocarbenes [90,91]. Recently, a class of oxetane sulfonyl fluorides was demonstrated to be precursors to oxetane carbocations, which were coupled to diverse nucleophiles [96–98].

The recent non-SuFEx developments of sulfonyl fluoride substrates described herein challenge the perception of this functional group and establish the $–SO_2F$ motif as potential leaving group. This realization will impact the synthetic chemistry community and related areas such as the pharmaceutical industry and materials science. The development of alternative, non-classical leaving groups is important because it can enable retrosynthetic disconnections that had previously failed due to the unavailability or instability of the precursors (e.g., alkyl halides). Such alternative transformations could facilitate a more cost-effective way to access valuable chemical matter, for example, active pharmaceutical ingredients. Awareness of all potential reaction pathways of sulfonyl fluorides will also aid researchers to recognise challenges and pitfalls when dealing with this class of compounds.

Looking ahead (see Outstanding questions), with the demonstration that aryl sulfonyl fluorides can undergo oxidative addition to transition metals, further cross-coupling reactions could be envisaged, for example, Buchwald–Hartwig or Negishi couplings. In particular, it would be valuable for diversity-oriented synthesis if a sulfonyl fluoride fragment could be reacted selectively with an amine nucleophile either in a SuFEx manner, or as part of a Buchwald–Hartwig cross-coupling process, by simply changing the reaction conditions. Similarly, the development of cross-coupling reactions with alkyl sulfonyl fluoride substrates would be of immense value, since it would expand the libraries of potential coupling partners and would be particularly useful for cases where the corresponding halides or pseudo-halides are not available (or stable). Further, the use of alkyl sulfonyl fluorides as precursors to carbocations could be further developed beyond oxetanyl substrates, as a useful general bond-forming strategy. The deFS pathway of sulfonyl fluorides could be envisioned to have applications beyond synthetic chemistry, most notably in chemical biology and drug discovery. Sulfonyl fluorides are established covalent warheads that can selectively react with protein residues in a SuFEx manner upon spatial-chemical activation inside protein cavities. Competitive formation of non-SuFEx linkages would have implications in these fields and could be leveraged towards alternative molecular tools and potential therapeutics or imaging probes.

Outstanding questions

Can aryl sulfonyl fluoride compounds take part in further cross-coupling reactions apart from SMCs? Currently, aryl sulfonyl fluorides have only been engaged in Suzuki–Miyaura-type cross-coupling reactions but their successful oxidative addition to palladium is promising for further development.

Could alkyl sulfonyl fluorides also undergo oxidative addition into transition metals?

There is a recent report of such reactivity in a biased intramolecular system. The successful oxidative addition of aryl sulfonyl fluorides to palladium, as well as the known oxidative addition of alkyl halides, also provide promising precedent for the development of such reactivity.

Is the generation of carbocations from sulfonyl fluorides limited to oxetanyl and azetidinyl substrates? Aryloxetane and azetidine sulfonyl fluorides are currently the only types of substrates that have been demonstrated to generate carbocations on defluorosulfonylation. However, the defluorosulfonylative pathway might be a general explanation for the anecdotal instability of alkyl sulfonyl fluoride systems.

Could the defluorosulfonylation pathway have applications in chemical biology and drug discovery? This pathway could serve as an alternative to the established SuFEx reactivity developed for sulfonyl fluoride probes.

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Declaration of interests

No interests are declared.

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