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Complete List of Authors:	Barrow, Andrew; La Trobe University College of Science Health and Engineering, Smedley, Christopher; La Trobe University College of Science Health and Engineering, Zheng, Qinheng; Scripps Research Institute, Chemistry Li, Suhua; Sun Yat-sen University, Chemistry Dong, JiaJia; Shanghai institute of organic chemistry, Key Laboratory of Organofluorine Chemistry Moses, John; La Trobe University , La Trobe Institute For Molecular Science

ARTICLE

The Growing Applications of SuFEx Click Chemistry

A. S. Barrow,[a] C. J. Smedley,[a] Q. Zheng,[b] S. Li,[c] J. Dong[d] and J. E. Moses*[a]

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Dedicated to K. B. Sharpless on the occasion of his 78th birthday.

SuFEx (Sulfur Fluoride Exchange) is a modular next generation family of click reactions, geared towards the rapid and reliable assembly of functional molecules. This review discusses the growing number of applications of SuFEx, which can be found in nearly all areas of modern chemistry; from drug discovery to materials science.

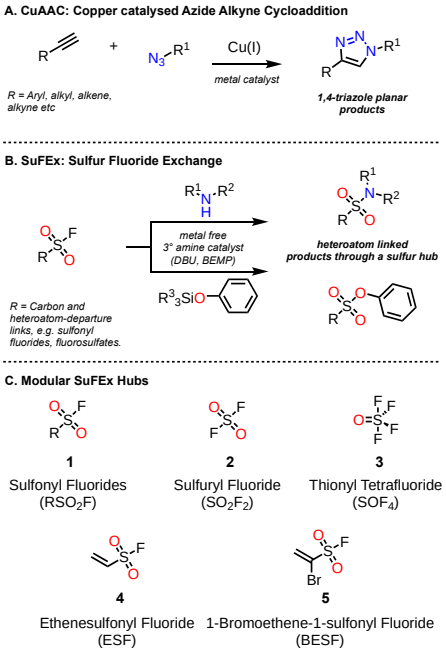
Introduction

Click chemistry (CC) is a synthesis philosophy that was conceived, primarily, to help catalyse the discovery and development of reliable and robust reactions. The need for such '*near-perfect*' reactivity drives the engine of CC discovery—an engine fuelled by one core goal: *the discovery of functional molecules*.[1,2] Since first described by Kolb, Finn and Sharpless in 2001, CC has had a profound impact on modern chemistry, and is one of the most significant developments in enabling synthesis technologies.[3–5]

> ***"Reactivity isn't everything; it's the only thing"***[6]
>
> K. B. Sharpless

From inception, CC was geared to primarily help streamline and accelerate the discovery of new medicines, advocating the use of only reliable and scalable reactions in all discovery endeavours. The click philosophy has indeed had a significant impact in drug-discovery, but has also became far more than perhaps intended, rapidly evolving as a 'go-to' technology in almost every corner of the molecular sciences.[2]

Historically, the inspiration behind CC can be traced back to a reassessment of the way traditional medicinal chemistry approached discovery challenges, and the notion that: *"the way organic synthesis is done has pervasive effects on the entire process of drug discovery, development, and manufacture"*.[1] While this sentiment may have provoked some controversy from members of the synthesis community,[7] it was offered as a practical response to help identify new drugs from an estimated pool of 10^{62} and 10^{63} 'reasonable' drug candidates .[8]



Scheme 1: A) Copper catalysed Azide-Alkyne Cycloaddition (CuAAC); B) Sulfur-Fluoride Exchange (SuFEx); C) Modular SuFExable hubs for click chemistry.

This astonishing structural space is daunting and in practical terms, it makes little sense to search in hard-to-reach places for a desired function. Instead, CC is governed by a fundamental rule: ***"all searches must be restricted to molecules that are easy to make"***. CC has since evolved to be one of the most important strategies for making molecular connections—a process realised through the creation of intermolecular linkages through carbon-heteroatom and heteroatom-heteroatom bond formation, somewhat mirroring the approach by which Nature creates its most important life molecules: the primary metabolites. However, while conceptually straightforward, the

[a] *La Trobe Institute for Molecular Science, La Trobe University, Melbourne, VIC 3086, Australia. E-mail: j.moses@latrobe.edu.au.*
[b] *Department of Chemistry, The Scripps Research Institute 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*
[c] *School of Chemistry, Sun Yat-Sen University 135 Xingang Xi Road, Guangzhou 510275, P. R. China*
[d] *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences. 345 Ling-Ling Road, Shanghai 200032, P.R. China.*

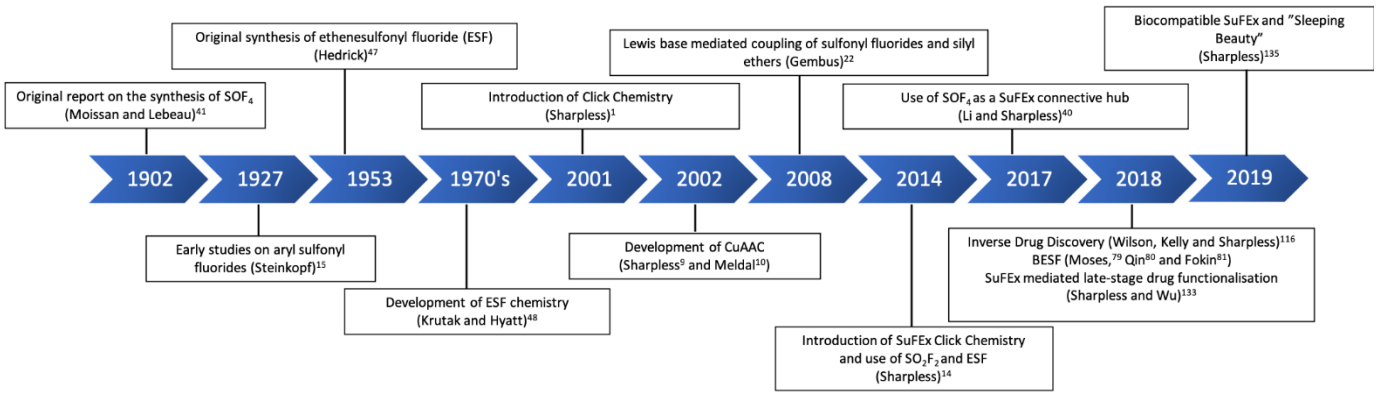


Figure 1: Timeline illustrating the historic development of sulfur-fluoride chemistry and SuFEx click chemistry.

synthetic challenges to achieve such perfect and connectivity remain significant.

Aspiring to match the efficiency of Nature's near perfect synthesis machinery, a set of stringent criteria for a reaction to earn CC status was defined, highlighting the need for 'near-perfect' reactions to aid in the rapid synthesis of functional molecules.[1]

The subsequent discovery of the Cu(I) catalysed azide–alkyne cycloaddition (CuAAC; Click-I) in 2002 (Scheme 1A),[9,10] transformed CC from a working concept to an accepted reality. CuAAC is undoubtedly one of the most powerful fusion reactions discovered; having incredible breadth of versatility and application in fields as diverse as materials science,[11] bioconjugation[12] and drug discovery.[13] While CuAAC is just one of several click-reactions identified, the provenance and reputation of this transformative reaction as the 'cream of the crop' has led to CuAAC being considered: *THE click reaction*—and while formally this description somewhat deviates from the founding concept of CC, it is perhaps justified given the extensive and ubiquitous up-take of the powerful methodology.

In 2014, Sharpless and co-workers launched the next embodiment on the development of CC: Sulfur (VI)-Fluoride Exchange (SuFEx; Click-II). Like the foundation of many click reactions, SuFEx is a reinvigoration of old-school chemistry—born-again as a powerful technology for creating molecular connections with absolute reliability under metal free conditions.[14] The chemistry of higher organosulfur fluoride chemistry has a long-history, with origins traced back as far as the mid 1800s. However, it wasn't until Steinkopf's seminal work in the 1920s that the incredible properties of organosulfur fluorides' were truly recognised—a realisation that ultimately led to the development of SuFEx click chemistry almost a century later.[15] Foremost, and unlike their more common S-Cl counterparts, S-F bonds are incredibly stable and can tolerate unusually harsh reaction conditions; yet with the right activation, a latent reactivity is unleashed with nucleophilic S-F exchange occurring with exquisite control (Scheme 1B). This incredible reactivity gap and 'alien-like properties' of higher valent sulfur-fluorides reflect the world where click-reactivity is so often found. These click-like properties can be attributed to a special blend of kinetic stability and near-perfect reactivity—rendering SuFEx a near-perfect reaction. However, apart from a few sporadic reports appearing in the literature since Steinkopf's early studies on the chemistry of aryl sulfonyl fluorides, the exploration of higher valent sulfur-fluorides remained effectively over-looked.

The essential features and fundamentals of SuFEx click chemistry were comprehensively described in the seminal 2014 manifesto, hence the purpose of the current article is to provide an overview of recent developments in SuFEx click chemistry. We pay particular attention to the *'molecular plugin'* concept for creating intermolecular connections, and cover the emerging area of Bio-SuFEx, highlighting selected topics including: bio-conjugation, Inverse Drug Discovery (IDD), and a new SuFEx-enabled approach towards drug discovery employing *'Sleeping Beauty' style probes*.

The review is designed to emphasise key fields where SuFEx click chemistry has had the most substantial impact. Following a brief introduction to the concept of SuFEx hubs, the article is sub-divided into 3 further sections covering the applications of SuFEx in: i) synthetic methodology; ii) Bio-SuFEx and drug discovery, and iii) polymers and materials science. Due to space limitations and the structure of the review, it was not possible to comprehensively cover every topic or example where SuFEx click chemistry has had impact, and we apologise to those whose work has been omitted. We also direct the reader to more subject specific reviews where SuFEx has played a significant role.[16–19] In this article we attempt to cover a broad and diverse selection of SuFEx topics, ranging from the historical origins of sulfur fluoride chemistry in the early 1900's up-to modern SuFEx developments in early 2019.

Before delving straight into the applications of SuFEx click chemistry, it is appropriate to first briefly recap the key features of SuFEx and highlight what makes it distinct from other CC. As

already mentioned, for a reaction to obtain click-status, it must meet strict criteria: primarily, a click reaction must be wide in scope, modular and create function by linking together simple building blocks.[1] CuAAC, the quintessential click reaction, embodies this approach by fusing together a terminal alkyne with an organic azide under copper(I) catalysis to create 1,4-triazole linkages (Scheme 1A). SuFEx reactions are different: first and foremost, they proceed under metal-free conditions; this has particular significance in the biological and drug discovery applications discussed below. Secondly, in contrast to the defined 1,4-triazole fused connections formed by CuAAC, the departure links created through SuFEx connections are more diverse—allowing new bonds to be formed through S-F exchange with aryl silyl ethers (also free aromatic alcohols, and in certain cases, silyl protected saturated alcohols), with amines and with carbon nucleophiles: a feature that offers much scope for achieving the overarching goal of CC to create diverse functional molecules.

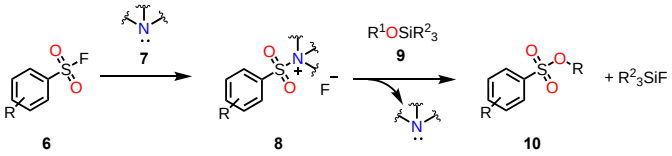
Another key difference between SuFEx and CuAAC involves the reacting functional substrates. In CuAAC centred CC, it is often necessary to first install the complementary terminal alkyne and azide functional groups into the framework of the reacting coupling partners. While evidently not prohibitory, this does require additional synthetic steps. SuFEx is generally more flexible in this regard, although the exception being perhaps sulfonyl fluorides and silyl enol ether functionality, which must sometimes be installed in a substrate. The linkages created by SuFEx CC are formed by uniting common native functional groups (e.g. 1° & 2° amines and phenols) through discrete connective SuFExable-hubs, such as SO_2F_2, SOF_4 and ethenesulfonyl fluoride (ESF), colloquially referred to as '*molecular plugins*', and discussed in more detail below (Scheme 1C).

SuFEx Activation and Catalysis

While SuFEx reactions are uncomplicated transformations, the exact activation mechanism behind SuFEx catalysis are yet to be fully determined. Key to the prodigious reactivity is a special ability of fluoride ion to transit from a strong covalent bond to a leaving group—assisted by interactions with 'H^+' and/or 'R_3Si^+' in close proximity under strict kinetic and spatial constraints. SuFEx is especially accelerated by basic-nitrogen (Et_3N, DBU etc) catalysts—and thought to involve bifluoride counterion species. The build-up to SuFEx as a platform click-technology was preceded by a few reports in the literature that may themselves now be considered as early manifestations of SuFEx, albeit unrecognised or conceptualised.

In 1995, Vorbrüggen and co-workers reported the conversion of primary or secondary alcohols into fluorides through a combination of nonafluorobutanesulfonyl fluoride (NfF) and DBU.[20,21] The reaction proceeds with inversion of stereochemistry, which suggests the involvement of a nonafluorobutanesulfonate intermediate. In addition to DBU, the phosphazene base P_4-*t*-Bu was also shown to be an effective reagent for this transformation, while subsequent reports showed the utility of a wide range of bases.[21] Vorbrüggen concluded that while DBU acts as a strong base in this particular reaction, the direct combination of DBU and NfF can result in the formation of sulfonamide *via* an intermediate σ-complex.

In 2008, Gembus and co-workers described the organocatalysed reaction of silyl ethers and *p*-toluenesulfonyl fluoride to form sulfonate esters.[22] They proposed a mechanism involving DBU as a nucleophilic catalyst: reacting first with a sulfonyl fluoride **6**, DBU is suggested to form an activated arylsulfonyl ammonium fluoride salt **8**, which may in turn activate the silyl ether **9** through release of a fluoride anion promoting the arylsulfonyl transfer to form the sulfonate product **10** (Scheme 2).[22] The postulated intermediate aligns closely with the findings of Vorbrüggen; however due to the high basicity of the fluoride ion and the hydrogen-bonding requirements necessary for its activation, the mechanism is likely more complex and a deeper understanding of the finer details of SuFEx catalysis will hopefully emerge over time.



Scheme 2: Gembus and co-workers' mechanistic proposal for the activation of sulfonyl fluorides with tertiary amine bases.

As introduced throughout this review, catalysts other than DBU are known to accelerate SuFEx transformations. The choice of base catalyst is often dependent upon the reactivity of the coupling substrates, and in particularly challenging cases, phosphazine catalysts such as BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) are sometimes required. As a general rule-of-thumb, the order of reactivity is proportional to the pKb of the base catalyst: Et_3N < DBU < BEMP.

SuFEx Connectors and *SuFExable* Molecular Plugins

We briefly introduced the concept of SuFExable '*molecular plugins*' – the notion that molecules containing the valuable S-F bond can act as connective hubs, allowing multiple linkages to be formed around a central sulfur core. The robust reactivity of SuFEx allows for the rapid construction of complex molecules through the formation of these heteroatom connections, and it is therefore appropriate to discuss the '*molecular plugin*' in more detail before exploring their use in a range of applications.

A number of SuFEx connectors have already been developed and exploited, and no-doubt several more will emerge over the coming years. By intention, each SuFExable hub offers a unique reactivity profile and contributes to the ever-growing SuFEx toolbox. To date, we identify five discrete classes of SuFEx connective hubs, namely: sulfonyl fluorides (R-SO_2F, **1**); sulfuryl fluoride (SO_2F_2, **2**); thionyl tetrafluoride (SOF_4, **3**); ethene sulfonyl fluoride (ESF, **4**) and 1-bromoethene-1-sulfonyl fluoride (BESF, **5**) (Scheme 1C).

The SuFEx products of a selection of these hubs, derived from reactions with aryl silyl ethers and amines show a general trend, and will be discussed in more detail. First it is interesting to highlight the muted physical properties of compounds of the SuFEx world, which tend to be relatively apolar as characterised by their retention factors after elution on a silica TLC plate (10% EtOAc in hexanes). For example, phenyl fluorosulfate (**11**) is particular apolar, with an R_f value of 0.76, with the derivatives of the SuFEx reaction of **11** with silyl protected ethers (**12**) and amines (**13**) showing a slight increase in polarity (Figure 2). This trend is replicated with the iminosulfur oxyimine **14**, and its derivatives **15-18**, with polarity increasing as the number of nitrogen and oxygen atoms increase.

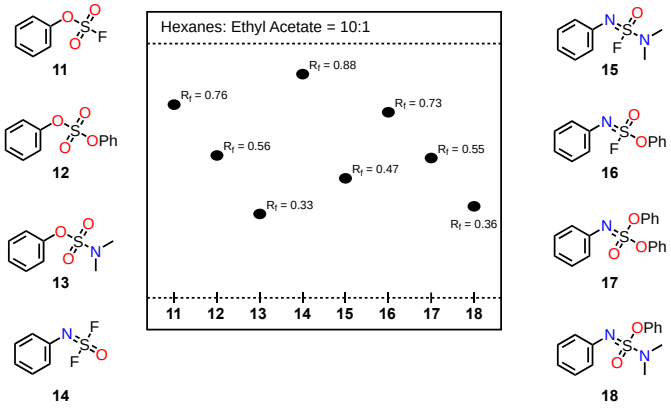


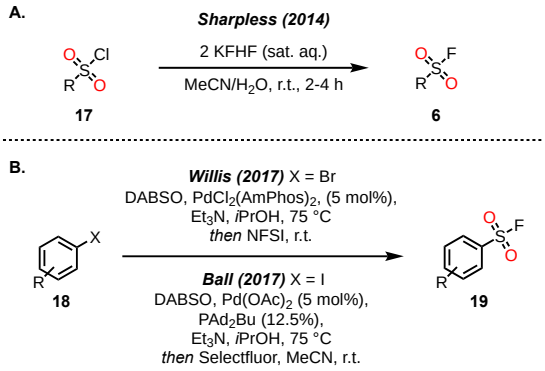
Figure 2: Polarity of a range of SuFEx products, as shown by their R_f values, after elution on a silica gel TLC plate.

Aryl Sulfonyl Fluorides (Ar-SO_2F)

Aryl sulfonyl fluorides were first identified by Sharpless and co-workers as SuFExable connectors and as intimated above, they somewhat stand apart from other SuFEx hubs by comprising a sulfur-carbon (S-C) bond that must first be installed into the native reaction modules.

In contrast to the corresponding aryl sulfonyl chlorides which are ubiquitous in organic chemistry, examples of aryl sulfonyl fluorides are relatively rare. The most practical synthesis of aryl sulfonyl fluorides is through the direct HalEx reaction of a sulfonyl chloride with suitable fluoride source. A range of methods have been developed, which often require both a crown ether to aid solubility of the inorganic fluoride source, and also the exclusion of moisture, although it should be noted that earlier syntheses of sulfonyl fluorides often required the addition of water.[23,24] A more convenient and straightforward method to transform a sulfonyl chlorides (e.g. **17**) to the fluoride (e.g. **1**), employs a biphasic mixture of aqueous acetonitrile and saturated potassium hydrogen bifluoride, as demonstrated by Sharpless and co-workers (KFHF, Scheme 3A).[14] A further improved procedure was reported by Barbasiewicz using catalytic amount of phase-transfer catalyst to boost the relatively slow reaction of alkyl sulfonyl chlorides based on the Sharpless procedure.[25]

More recent approaches to aryl sulfonyl fluorides were independently described by the groups of Willis and Ball (Scheme 3B). Using aryl halide **18** precursors, both protocols are mediated through palladium catalysis with DABSO (1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) as the sulfur source. Mechanistically, the reaction occurs through an intermediate sulfonate salt followed by subsequent reaction with an electrophilic fluorine source to give the corresponding sulfonyl fluoride **19** in good yield.[26,27]

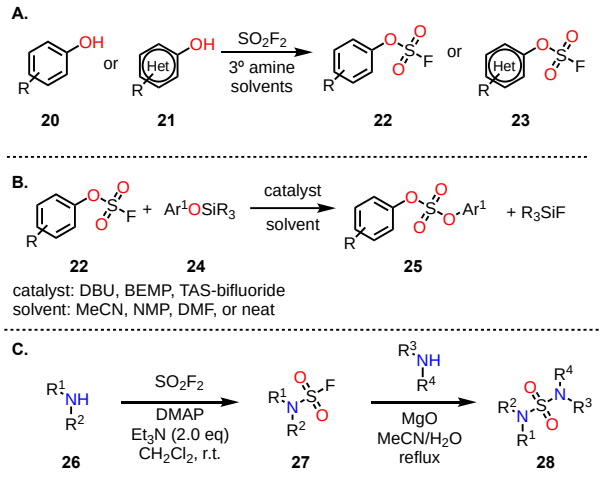


Scheme 3: A) Potassium bifluoride mediated synthesis of sulfonyl fluorides; B) Palladium catalysed formation of sulfonyl fluorides from aryl bromides (Willis) and aryl iodides (Ball).

Sulfuryl Fluoride (SO_2F_2)

Sulfuryl fluoride (SO_2F_2) is a colourless, odourless gas at normal temperature and pressure, and is stable up to 400 °C under anhydrous conditions.[28] The gas is widely used as a pest control agent, with the global production between 2000 and 2009 averaging approximately 3 million kilograms per year.[29]

Sharpless and co-workers first recognised the potential of SO_2F_2 (**7**) as a versatile SuFEx connector in 2014, reporting a series of procedures for the synthesis of functional (hetero)aromatic fluorosulfates (**22** and **23**) from the corresponding phenols (**20** and **21**) (Scheme 4A).[14] Earlier syntheses of fluorosulfates often involved the pyrolysis of diazonium salts,[30] the reaction of perfluoroalkyl or alkyl sulfites with chlorine fluoride,[31] or through the reaction of phenols with either $ClSO_2F$, SO_2F_2 or fluorosulfonic anhydride ($(FSO_2)_2O$) under relatively harsh conditions, obtaining less than satisfactory results.[32–37] Under SuFEx conditions, using triethylamine in a solution of dichloromethane, the functional aromatic fluorosulfates are formed in excellent yield.[14]



Scheme 4: A) Synthesis of (hetero)aryl fluorosulfates; B) SuFEx reactivity of aryl fluorosulfates and aryl silyl ethers; C) Reactivity of secondary amines to SO_2F_2.

To demonstrate their 'plugin' potential the SO_2F_2 derived fluorosulfates (**22**) were shown to react efficiently with aryl silyl ethers (**24**) in the presence of catalytic amounts of DBU, BEMP and/or TAS-bifluoride from room temperature to 120 °C, forming the stable sulfate linked products (**25**) (Scheme 4B). The union of two phenols through a sulfur-hub by heteroatom-connections nicely demonstrates the simple concept of a SuFExable-plugin and modularity. In true click fashion, the power of the system is in the simplicity and reliability of the reaction—a fundamental principle of CC philosophy.

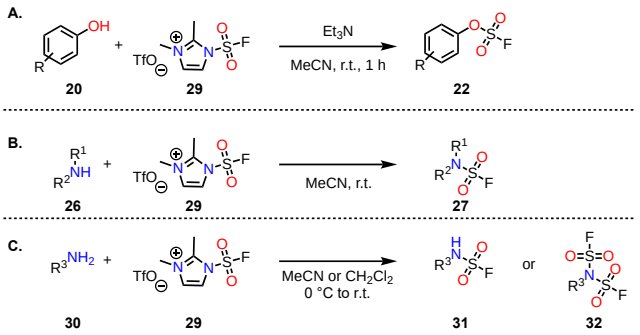
SO_2F_2 also reacts with secondary amines (**26**) to give the corresponding sulfamoyl fluorides (**27**). As with sulfonyl fluorides, the *N*-disubstituted sulfamoyl fluorides show remarkable stability under a range of conditions—requiring high temperatures and a hydrogen-bonding solvent to assist in further reaction with another secondary amine (Scheme 4C).

Sulfuryl Fluoride Surrogates

Fluorosulfuryl imidazolium salts have recently emerged as bench stable donors of 'F-O_2S^+'and a convenient alternative to the parent gas. First reported by Dong and co-workers, the now commercially available salt is prepared by reaction of 2-methylimidazole with SO_2F_2, followed by methylation of the imidazole with methyl triflate.[38] The stable imidazolium salt **29** displays enhanced reactivity over SO_2F_2, enabling shorter reaction times for the fluorosulfonylation of phenols due to the ability of alkylated imidazoliums to function as good leaving groups.

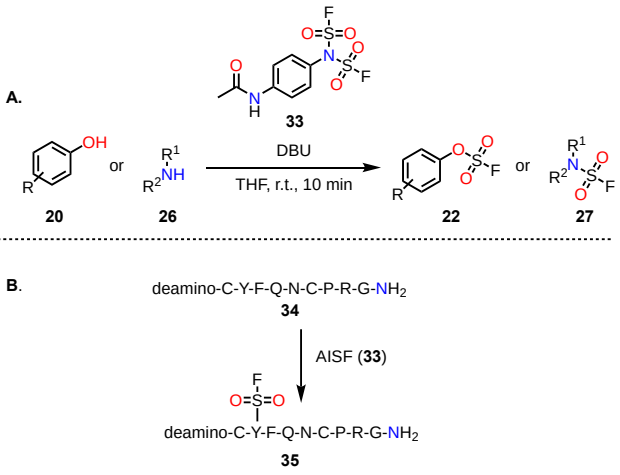
More importantly, the reaction of **29** with primary amines yields *NH*-sulfamoyl fluorides (**31**); a class of compound that were previously inaccessible *via* reaction with the parent SO_2F_2 gas (due to their instability under basic conditions).

The reaction of SO_2F_2 to give sulfamoyl fluorides is therefore limited to secondary amines, whereas **29** reacts readily with both primary and secondary amines under base-free conditions, which in the case of primary amines can be controlled to give either the mono- (*NH*-sulfamoyl fluoride) (**31**) or bis(fluorosulfonyl) imide (**32**) in excellent yield (Scheme 5).



Scheme 5: Reactivity of imidazolium salt **29**.

Ende and co-workers have since reported AISF ([(acetylamino)phenyl]imidodisulfuryl difluoride) (**33**) as a reagent for the synthesis of fluorosulfates and sulfamoyl fluorides.[39] AISF is reportedly a shelf stable 'F-O_2S^+' donor, that once mixed with a phenol or secondary amine and DBU, affords the corresponding fluorosulfate (**22**) or sulfamoyl fluoride (**27**) in good to excellent yield. For example, the reagent was demonstrated in the selective functionalisation of a tyrosine residue on a peptidic macrocycle (**34**) under aqueous conditions (Scheme 6).



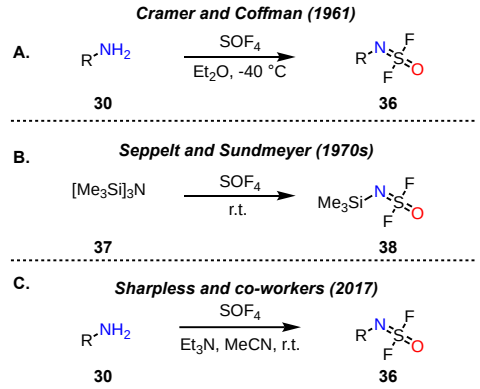
Scheme 6: Reactivity of SO_2F_2 surrogate AISF (**33**).

Thionyl tetrafluoride ($O{=}SF_4$)

The toolkit of available SuFEx connectors was transformed in 2017 with the introduction of thionyl tetrafluoride (SOF_4, **8**) as the first multidimensional click-linker.[40] The preparation of SOF_4 was reported in 1902 by Moissan and Lebeau,[41] with the synthesis of this colourless gas later improved by Smith and Engelhardt in 1960 at CRD DuPont.[42]

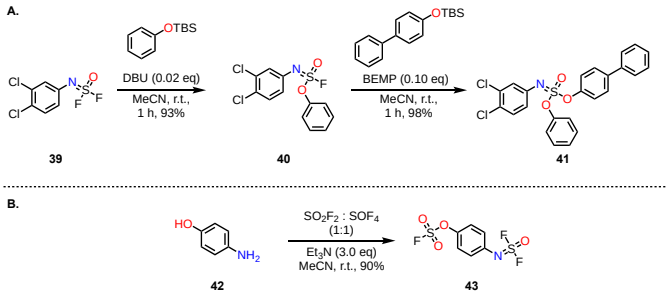
In 1961, Cramer and Coffman studied the reactivity of the trigonal bipyramidal SOF_4 (**8**) with a selection of amine nucleophiles, forming the corresponding tetrahedral iminosulfur oxydifluorides **36** in moderate yields (Scheme 7A).[43] Seppelt and Sundermeyer (1970's) identified an early manifestation of silyl-mediated SuFEx chemistry using the TMS-protected amines (**37**) to give the protected iminosulfur oxydifluorides **38** (Scheme 7B).[44,45] Following these early pioneering studies, the chemistry of SOF_4 remained unexplored for decades.

Using SOF_4 in combination with a tertiary base such as triethylamine and a primary amine, Li and co-workers from the Sharpless group demonstrated that iminosulfur oxydifluorides **36** could be readily accessed in excellent yields with increased reaction rates (Scheme 7C).[40]



Scheme 7: A) Cramer and Coffman's synthesis of iminosulfur oxydifluorides; B) Seppelt and Sundermeyer's early manifestation of SuFEx chemistry; C) synthesis of iminosulfur oxydifluorides by Sharpless and co-workers.

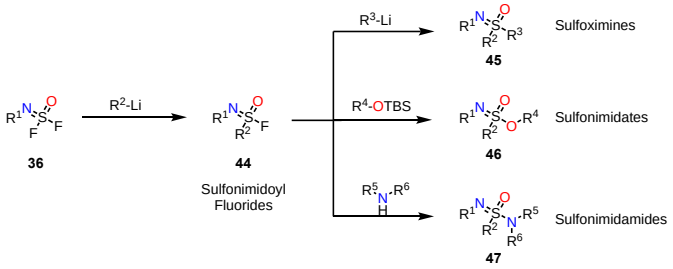
Of particular significance, and in contrast to all other click-linkers reported to-date, the SOF_4 (**8**) derived tetrahedral iminosulfur oxydifluorides (**36**) are '3-dimensional'; allowing CC to finally escape 'flatland'. These iminosulfur oxydifluorides (**36**) possess two further SuFExable handles, and under judicious choice of catalyst each can be sequentially exchanged with two different phenols, or one phenol and one secondary amine to create 3-dimensional covalent departure vectors from the tetrahedral sulfur hub (Scheme 8A).[40]



Scheme 8: A) Sequential reactivity of iminosulfur oxydifluoride **39** with two different silyl-protected phenols; B) Orthogonal reactivity of 4-aminophenol (**42**) with sister gases SO_2F_2 and SOF_4.

It is noteworthy that SOF_4 and sister gas SO_2F_2 show different trends in the presence of amines and phenols. The former favours reactions with primary amines, whereas the latter smoothly converts phenols to the corresponding fluorosulfate. This was nicely demonstrated through the reaction of 4-aminophenol with a 1:1 mixture of gaseous SO_2F_2 and SOF_4 to generate a functional product that contained both fluorosulfate and iminosulfur oxydifluoride handles (Scheme 8B). A series of competition experiments were performed in order to gauge the relative reactivity of the SuFExable group; suggesting that the reactivity of S-F bonds towards aryl silyl ethers follows the general order: $-N{=}SOF_2 > -SO_2F > -OSO_2F > -N{=}S(O)(OAr)F$.

In 2018, Sharpless and co-workers expanded the scope of iminosulfur oxydifluorides **36**, demonstrating their reaction with lithiated carbon based nucleophiles to obtain the corresponding sulfonimidoyl fluorides **44**.[46] Exposing the iminosulfur oxyfluorides **36** to a small excess of the lithiated reagent (1.35 equivalents) resulted in the selective formation of the mono-addition product (**44**). These products could then be further modified by either a second addition of a lithiated species or through a SuFEx reaction with either an aryl silyl ether or an amine (Scheme 9).



Scheme 9: Organolithium reagent addition into iminosulfur oxydifluoride **36**, and further elaboration into sulfoximines (**45**), sulfonimidates (**46**) and sulfonimidamides (**47**).

The controlled installation of the S-C linkages enables efficient access to diverse sulfonimidoyl fluorides (**44**), sulfoximines (**45**), sulfonimidates (**46**) and sulfonimidamides (**47**) from the parent SOF_4 hub, adding much scope to the growing arsenal of SuFEx click chemistry.

Ethene Sulfonyl Fluoride (ESF)

Together with the gaseous SuFEx hubs described above, another class of functional SuFEx connectors have been identified, namely ethene sulfonyl fluoride (ESF, $CH_2{=}CH\text{-}SO_2F$, **9**) and derivatives. The advantage of ESF as a connector stems from the additional modes of reactivity for creating stable linkages through the activated double bond. ESF (**4**) was first described by Hedrick of Monsanto Company in 1953.[47] Almost a quarter of a century later in 1979, Hyatt and colleagues at the Eastman Kodak company published a masterful piece of work on the chemistry of ESF.[48] Since then, the extraordinary Michael reactivity of ESF (**4**) has been used in industry for the production of dyestuffs,[49] ion-exchange resins,[50] photoresist materials,[51] lubricating oil additives[52] and in medicinal chemistry (Figure 3).[53–55] However, until the development of SuFEx chemistry by

Sharpless and co-workers in 2014, this small, highly connective module had otherwise been largely overlooked by the chemistry research community for close to half a century.

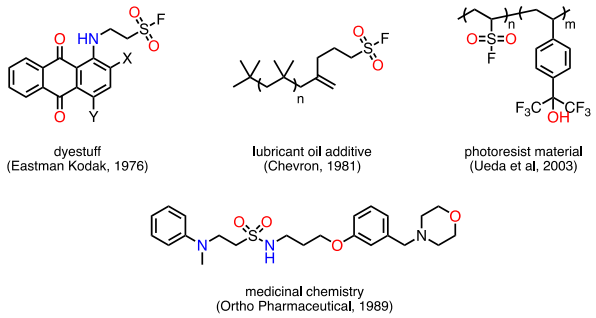
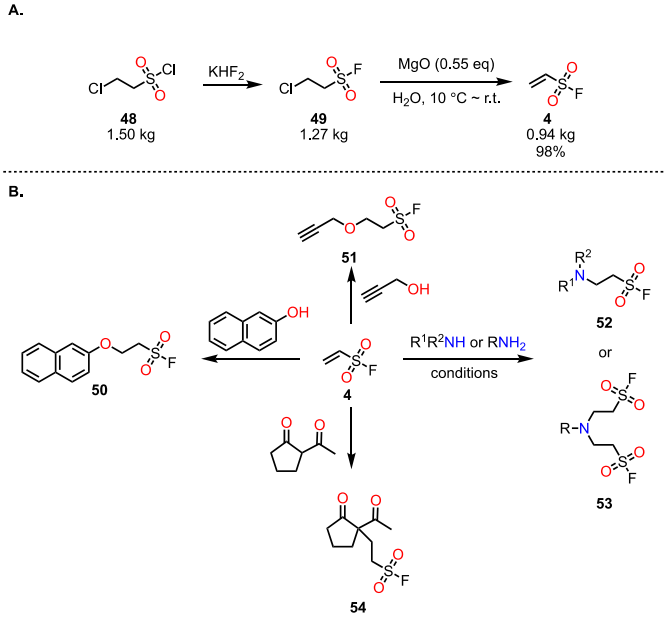


Figure 3: Industrially relevant compounds synthesised with ESF (**4**).

As with SO_2F_2 and SOF_4, ESF (**4**) is a modular clickable-hub, but unlike its counterparts it offers two distinct trajectories of reactivity. In addition to the SuFEx ready sulfonyl fluoride group,[56] ESF (**4**) offers further connective pathways as a diene/dipolarophile and Michael acceptor—according to Sharpless, *"the most perfect Michael acceptor ever found"*.[14,57]



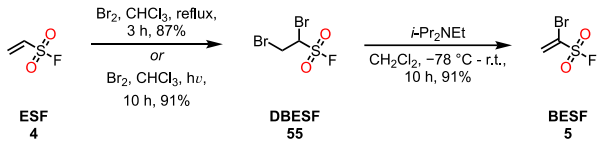
Scheme 10: A) Kilogram scale synthesis of ethene sulfonyl fluoride (ESF, **4**); B) Representative reactivity of ESF (**4**).

Readily prepared on kilogram-scale through a two-step sequence developed by Zheng and Sharpless [chloride-fluoride exchange of 2-chloroethenesulfonyl chloride (**48**), and dehydrochlorination of 2-chloroethanesulfonyl fluoride (**49**)][58] ESF (**4**) displays remarkable orthogonal reactivity at its two reactive sites, i.e., Michael addition trajectory at vinyl group and SuFEx trajectory at sulfonyl fluoride group.

For example, highly efficient Michael addition reactions with amines, propargyl alcohols, phenols and even stabilised carbon nucleophiles have been reported, while leaving the sulfonyl fluoride moiety untouched (Scheme 10).[14,59] The selective reactivity of ESF allows a host of molecules to be decorated in a predictable and modular fashion, enabling a wide range of applications described below.

1-Bromoethene-1-sulfonyl Fluoride (BESF)

The synthesis of 1-bromoethene-1-sulfonyl fluoride (BESF, **5**)[60] was first described by Vessiere and co-workers through the dehydrobromination of 1,2-dibromoethane-1-sulfonyl fluoride (DBESF, **55**, Scheme 11).[61] While BESF can readily undergo transformations analogous to ESF, further opportunities are opened by the additional reactive bromo-group, thereby increasing the utility of BESF as a potent SuFEx hub as discussed below.



Scheme 11: Synthesis of DBESF (**55**) and BESF (**5**).

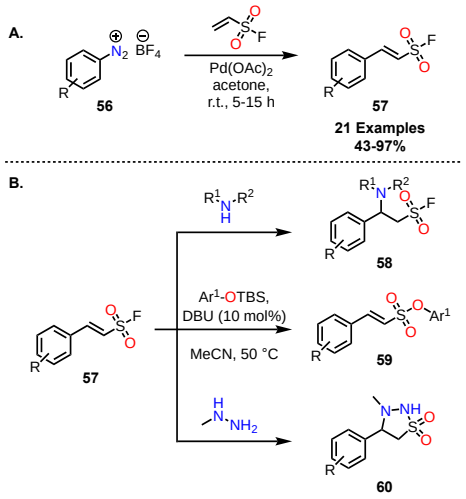
Applications of SuFEx Click Chemistry in Synthetic Methodology

Installation of SuFEx Building Blocks

Besides the development of the SuFExable hubs, a number of reports focused on new techniques to install SuFEx functionality into a range of molecular scaffolds have appeared.

Sharpless and co-workers were first to report a Heck-Matsuda cross-coupling approach between ESF (**4**) and arenediazonium tetrafluoroborate salts (**56**), yielding β-arylethenesulfonyl fluorides (**57**) (Scheme 12A).[62] Since the β-aryl ESF products retain an activated C=C bond, they remain effective bifunctional connectors, which themselves can be further functionalised through conjugate addition pathways or/and SuFEx transformations.

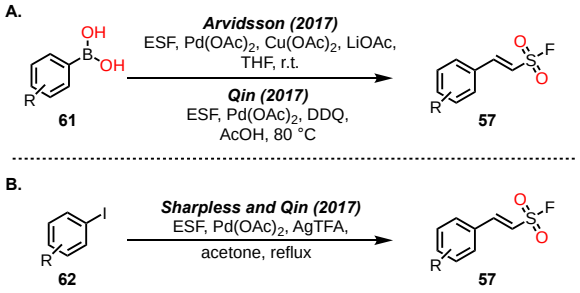
The dual-functional nature of the substituted β-aryl ESF substrates was demonstrated through reaction with: silyl ethers and DBU to carry out SuFEx transformations on vinyl sulfonyl fluorides; the addition of an amine nucleophile to the highly electrophilic double bond; or the addition of methyl hydrazine to both (Scheme 12B).[62]



Scheme 12: A) Matsuda-Heck coupling of tetrafluoroborate diazonium salts and ESF (**4**); B) Addition of amine nucleophiles to the electrophilic double bond, SuFEx reaction on the sulfonyl fluoride and addition of methyl hydrazine to both the electrophilic double bond and sulfonyl fluoride.

The development of the novel cross-coupling approach was a significant advance, offering a shortcut from the multi-step synthetic routes that were earlier required. [59,63,64]

Arvidsson and co-workers have since reported an additive free oxidative Heck coupling between aryl boronic acids and ESF to give β-arylethenesulfonyl fluorides in reasonable yields (Scheme 13A), while also describing a one-pot synthesis of β-sultams through the subsequent addition of excess amine.[65] Qin and co-workers developed a similar transformation using DDQ or silver nitrate as a terminal oxidant.[66] A wide range of aryl and heteroaryl substrates were tolerated, with reactions being performed open to the atmosphere and on a 10 mmol scale.

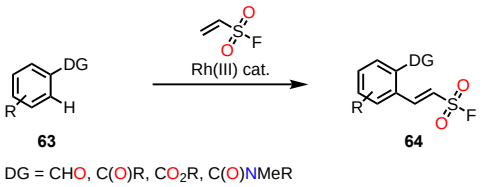


Scheme 13: A) Oxidative Heck reaction for the synthesis of β-arylethenesulfonyl fluorides; B) Synthesis of β-arylethenesulfonyl fluorides from aryl iodides.

Sharpless, Qin, and co-workers have developed a synthesis of β-(hetero)arylethenesulfonyl fluorides (**57**) from (hetero)aryl/alkenyl iodides (**62**) and ESF (**4**). The reaction relied upon catalytic amounts of $Pd(OAc)_2$ in the presence of silver trifluoroacetate, resulting in excellent yields for over 80 substrates (Scheme 13B).[67] The method can also be applied to vinyl iodides to isolate unprecedented dienylsulfonyl fluorides for a wide substrate scope in good to excellent yields.

Aside from the conversion of (hetero)aryl halides and boronic acids to the corresponding β-(hetero)arylethenesulfonyl fluorides, a number of developments involving C-H activation have been described.

Qin and co-workers used a rhodium catalyst to install the vinyl sulfonyl fluoride moiety *ortho*- to a variety of directing groups, including *N*-methoxybenzamides,[68] esters,[69] as well as aldehydes and ketones (Scheme 14).[70]



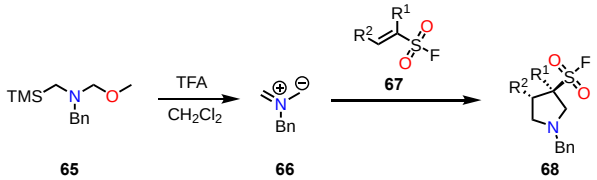
Scheme 14: Rhodium-catalysed directed fluorosulfonylvinylation.

A set of unified conditions for directed fluorosulfonylvinylation have been reported by Huestis and Ncube.[71] A rhodium half-sandwich complex was used to catalyse the reaction of a wide range of aromatic compounds with ESF to form the targeted vinyl sulfonyl fluoride products (**64**). Although some of the yields were modest, the range of applicable directing groups was vastly expanded, providing a solid foundation for further development in this area.

A recent report by Wang, Yu, and co-workers explored the possibility of non-directed C-H functionalisation with ESF to prepare β-aryl vinyl sulfonyl fluorides.[72]

Vinyl sulfonyl fluorides (**57**) have been shown to undergo a diverse range of cycloaddition reactions at the double bond.[73–75] The cycloaddition chemistry of vinyl sulfonyl fluorides date back to 1958 and the work of Gladshtein and co-workers.[76,77]

In 2016, Grygorenko and co-workers reported the synthesis of pyrrolidine-3-sulfonyl fluorides through the [3+2] cycloaddition of azomethine ylides and vinyl sulfonyl fluorides (Scheme 15).[78] Reaction of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (**65**) with TFA led to the *in-situ* formation of the azomethine ylide **66**, which itself could be trapped with a variety of vinyl sulfonyl fluoride analogues, including ESF (**9**). The pyrrolidine products were isolated as single diastereomers, suggesting that the reaction proceeds through a synchronous pathway.

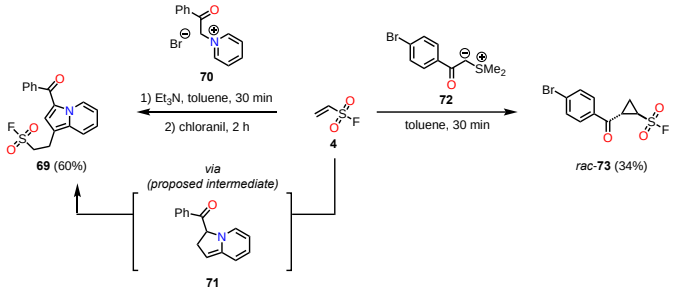


Scheme 15: Grygorenko and co-workers' synthesis of pyrrolidine-3-sulfonyl fluorides **68** through the cycloaddition of *in-situ* generated azomethine ylides **66**.

As part of a wider study, Mayr and co-workers reported the reaction of ESF with sulfonium and pyridinium ylides *via* cyclopropanation and 1,3-dipolar cycloaddition reactions, respectively (Scheme 16).[57] A racemic mixture of cyclopropane **73** is formed through the reaction of ESF (**4**) with sulfonium ylide

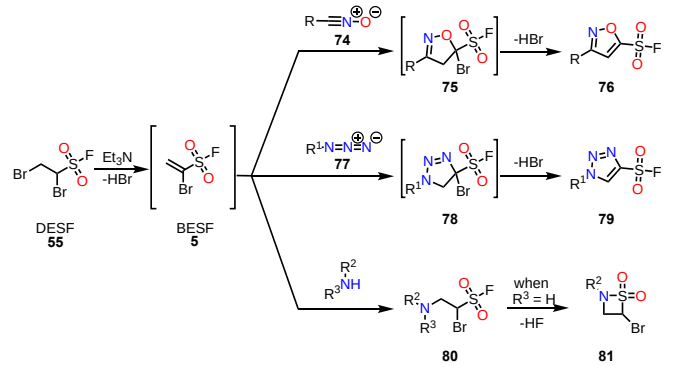
72 after stirring at room temperature, but it is perhaps that the reaction with pyridinium ylide **70** that is more interesting.

The reaction proceeds through a 1,3-dipolar cycloaddition followed by base-induced elimination of HSO_2F to give the enamine **71**, which itself subsequently reacts with an additional equivalent of ESF (**4**). Subsequent oxidative workup delivers the pyrroloquinoline **69**, complete with the SuFExable pendant sulfonyl fluoride.



Scheme 16: Mayr's synthesis of pyrroloquinoline **69** and cyclopropane **73** through the 1,3-dipolar cycloaddition of ESF (**4**).

The availability of a diverse selection of SuFExable building blocks is key for future development of SuFEx click chemistry, and new methods and hubs will always be a welcome addition. Recently, the groups of Qin, Moses and Fokin independently reported the development of the SuFEx hub and reagent, 1-bromo-ESF (**5**, BESF). While each group developed a slightly different application and take on the reagent, their complimentary approaches ultimately enabled the synthesis of a range of heteroaromatic rings decorated with pendant sulfonyl fluorides—these SuFEx-ready hubs will no doubt play a key role in the future of SuFEx click chemistry.



Scheme 17: Moses and co-workers' *in-situ* generation of BESF (**5**) and formation of heterocycles **76** and **77**, sultam **81** and tertiary amines **80**. Adapted from Ref. 79 with permission from The Royal Society of Chemistry.

Concurrent reports by the groups of Qin and Moses described the synthesis of novel 3-substituted-5-sulfonyl fluoride isoxazoles.[79,80] Moses and co-workers demonstrated that the reactive intermediate BESF could be readily generated *in-situ* through the dehydrobromination of 1,2-dibromoethane-1-sulfonyl fluoride (DBESF, **55**).[79] Addition of base into a cold solution of DBESF (**55**) resulted in the formation of BESF (**5**), which was subsequently trapped by reaction with a series of nitrile oxides **74** (themselves formed through base-mediated dehydrochlorination of chlorooximes). A further dehydrobromination of the intermediate species **75** yielded the 3-substituted isoxazoles-5-sulfonyl fluorides (**76**) in good to excellent yield (Scheme 17). Qin and co-workers reported a similar route to the isoxazole products (**76**), but instead using a large excess of pre-formed BESF (**5**).[60,80]

In concert with the novel SuFExable isoxazole products, Moses and co-workers described the synthesis of 4-sulfonyl fluoride substituted triazoles (**79**) through the cycloaddition of BESF (**5**) with a selection of organic azides. BESF (**5**) was further shown to be a powerful Michael acceptor, generating 1,4-addition products (**80**) through reaction with secondary amines and 4-bromo-β-sultams (**81**) with primary amines.[79] The reaction of a series of these products under SuFEx conditions confirmed that the S-F bonds were still amenable to exchange reactions.

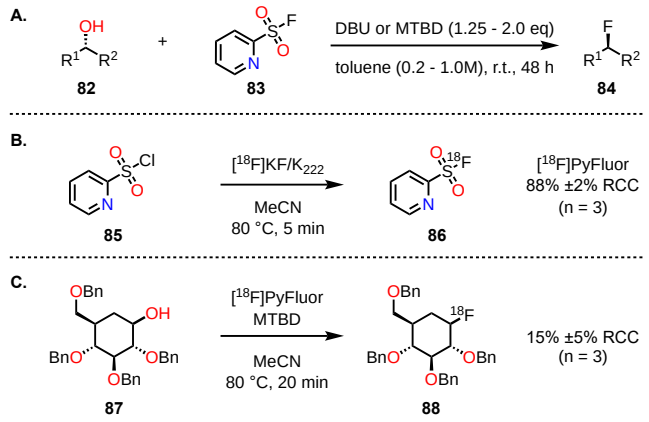
The application of BESF as 1,3-dipolarophile in cycloaddition chemistry was further explored by Fokin and co-workers, with a particular focus on the synthesis of triazoles. The reaction of pre-formed BESF with organic azides in DMF at 50 °C yielded the targeted triazole products in excellent yield.[81] Collectively, these studies demonstrate BESF as valuable addition to the toolbox of SuFExable hubs.

SuFEx building blocks as functional reagents

Alongside the rapid development of SuFEx chemistry as a technology for creating connections, there has been a significant expansion in the range of methodologies designed not only to synthesise S-F bond containing substrates, but also as reagents in their own right. While this deviates from the core '*molecular plugin*' concept of SuFEx, the development of these valuable methodologies and transformations have only been possible due to the emergence of the family of SuFEx reactions.

Central Glass developed a dehydroxyfluorination procedure for the conversion of alkyl alcohols, employing SO_2F_2 as the fluorine source.[82,83]

This area of research was expanded with Doyle and co-workers' development of 2-pyridinesulfonyl fluoride – 'PyFluor' (**83**) as a reagent for deoxyfluorination of alcohols (**82**).[84]

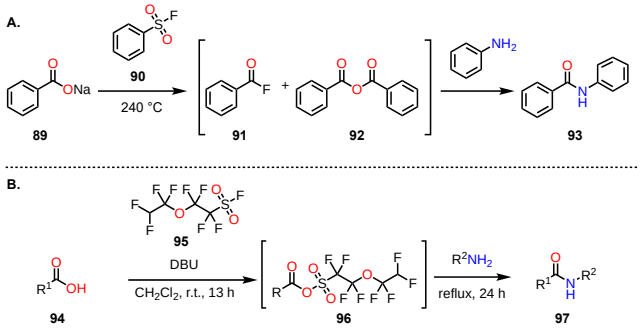


Scheme 18: A) PyFluor deoxyfluorination of alcohols; B) Synthesis of [^{18}F]PyFluor (**86**); C) Radiolabelling with [^{18}F]PyFluor (**86**).

As with conventional SuFEx reactions, strong amidine or guanidine bases such as DBU or MTBD were used, albeit in super-stoichiometric quantities. This results in the rapid formation of an intermediate sulfonate species that slowly reacts with free fluoride ions to generate alkyl fluorides (**83**) in good to excellent yield (Scheme 18A). A modified ^{18}F PyFluor **(86)** was shown to be an effective reagent for incorporating the radioactive label into molecules with short reaction times (Scheme 18B-C).[84]

As well as deoxyfluorination chemistry, sulfonyl fluorides have shown significant potential as amide coupling reagents. This mode of reactivity was first explored by Steinkopf and Jaeger in 1930, who converted sodium benzoate (**89**) into a mixture of benzoyl fluoride (**91**) and benzoic anhydride (**92**) upon treatment with benzenesulfonyl fluoride (**90**) (Scheme 19A). The reaction required extremely forcing conditions and gave an inseparable mixture of products, which were "detected only by the smell and by the conversion into benzanilide (**93**)".[85]

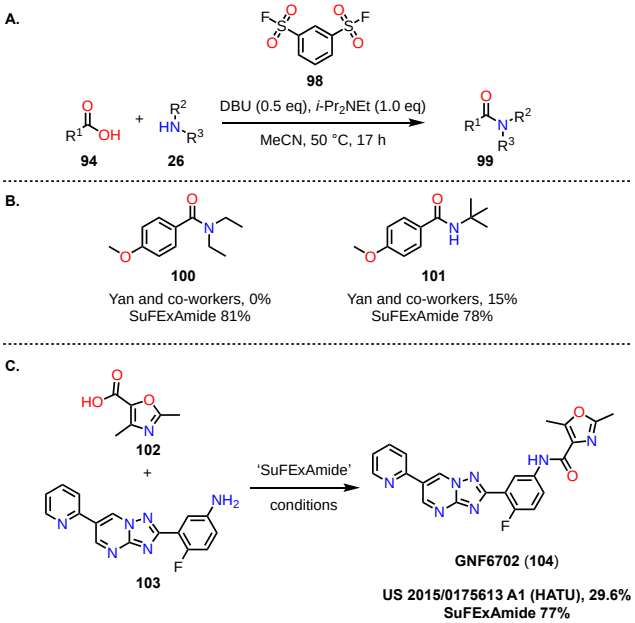
Yan and co-workers developed 5*H*-3-oxa-octafluoropentanesulfonyl fluoride (**95**) as a useful reagent (Scheme 19B).[86] The sulfonyl fluoride **95** was employed a coupling agent for a selection of transformation, including: esterification, amidation and anhydridisation, albeit with limited substrate scope. The authors suggest the reaction proceeds through an unstable mixed anhydride species (**96**), which is susceptible to attack by nucleophiles at the carbon centre.



Scheme 19: A) Synthesis of benzanilide by Steinkopf and Jaeger using benzene sulfonyl fluoride[85]; B) Synthesis of amides by Yan and co-workers using 5*H*-3-oxa-octafluoropentanesulfonyl fluoride.

In 2017, Smedley, Moses and co-workers described the application of sulfonyl fluorides as coupling reagents for the synthesis of sterically hindered and electron deficient amides.[87]

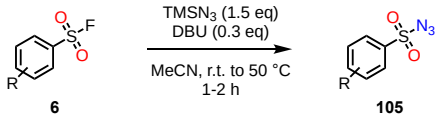
Acyl fluorides are frequently used for the couplings of sterically hindered amino-acids, with the small size of the departing fluoride ion minimising steric hindrance with the sterically encumbered nucleophile.[88,89] 'SuFExAmide' is an inexpensive bench stable benzene-1,3-disulfonyl fluoride reagent (**98**) to generate acyl fluorides *in-situ* from a range of carboxylic acid precursors (**94**) (Scheme 20A). In combination with bulky and/or electron deficient amines, the *in-situ* formed acyl fluorides generated an impressive array of challenging secondary and tertiary amides in excellent yields without the need for column chromatography, thereby significantly broadening the substrate scope reported by alternative procedures (Scheme 20B).



Scheme 20: A) SuFExAmide (**98**) synthesis of sterically hindered and electron deficient amides; B) Comparison of SuFExAmide to Yan and co-worker's methodology; C) Synthesis of GNF6702 (**104**) using SuFExAmide.

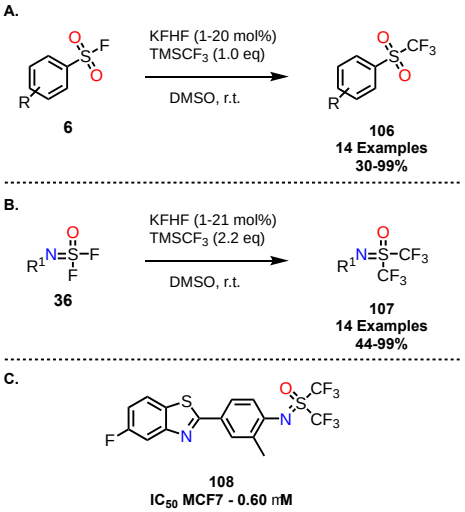
The practicality of the SuFExAmide methodology was exemplified with through the synthesis of the kinetoplastid proteasome inhibitor GNF6702 (**104**). An improved yield of 77% yield was obtained, compared to that previously reported of 29.6% achieved through the use of the popular coupling agent HATU (Scheme 20C).[90,91]

Barrow and Moses developed a SuFEx synthesis of sulfonyl azides (**105**) *via* base-activated sulfur fluoride–azide exchange, using DBU as a Lewis base and $TMSN_3$ as the azide source (Scheme 21).[92] One-pot diazotransfer was performed *in-situ* without the need to isolate the intermediate sulfonyl azide, and offering an alternative to other diazotransfer agents.[93,94]



Scheme 21: Synthesis of sulfonyl azides through SuFEx based chemistry.

Smedley, Moses and co-workers have also developed a SuFEx mediated trifluoromethylation protocol for the synthesis of triflones (**106**) and bis(trifluoromethyl)sulfur oxyimines (**107**) from sulfonyl fluorides (**6**) and iminosulfur oxydifluorides (**36**), respectively (Scheme 22).[95] This method employs substoichiometric amounts of KFHF in combination with Ruppert's reagent ($TMSCF_3$) in anhydrous DMSO, enabling the first reported conversion of iminosulfur oxydifluorides (**36**) to bis(trifluoromethyl)sulfur oxyimines (**108**). The team recognised the potential of these fluorine rich compounds, previously only accessible through the alkylation of bis(trifluoromethyl)sulfur oxyimine ($(CF_3)_2S(O)$=NH or $(CF_3)_2S(O)$=NAg, as potential pharmacophores.[96] This was demonstrated through the synthesis of the benzothiazole derived bis(trifluoromethyl)sulfur oxyimine (**109**),which was shown to display high selectivity and greater potency for MCF7 breast cancer cell over MCF10a human mammary epithelial cells.

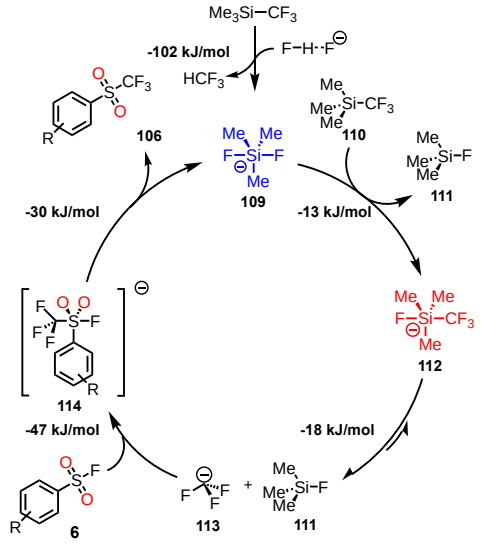


Scheme 22: Moses and co-workers synthesis of A) aryl triflones (**106**); B) bis(trifluoromethyl)sulfur oxyimines (**107**) and C) biologically relevant bis(trifluoromethyl)sulfur oxyimines (**108**).

A bifluoride-initiated mechanism supported by molecular modelling was suggested for the formation of the triflone products (Scheme 23).

Bifluoride ion and $TMSCF_3$ yield fluoroform and the siliconate complex **109**. The intermediate **109** engages with an additional equivalent of $TMSCF_3$ (**110**) to form the siliconate complex **112**, which can reversibly dissociate into the free $^-CF_3$ anion (**113**) and TMSF (**111**).[97]

Nucleophilic attack by the free $^-CF_3$ ion at the sulfur centre of the sulfonyl fluoride (**6**) generates the penta-coordinate sulfur intermediate (**114**) that upon dissociation of fluoride reforms the siliconate complex **109**, and releasing the triflone product (**106**).



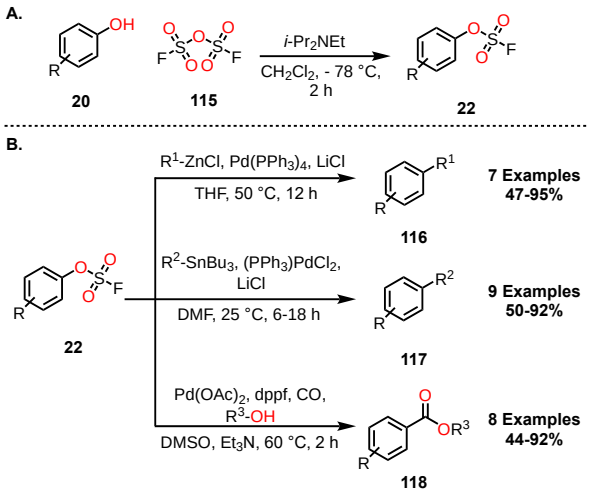
Scheme 23: Proposed mechanism for the conversion of aryl sulfonyl fluorides (**105**) to the corresponding aryl triflone (**106**). Adapted from Ref. 95 with permission of *Angewandte Chemie.*

Transition-metal-catalysed cross-coupling reactions have revolutionised the construction of C-C bonds and are used ubiquitously in modern-day synthetic chemistry. The common electrophilic partners for cross-coupling reactions are aryl, vinyl and heteroaromatic halides, but due to their high costs and environmental toxicity, they present obstacles to their industrial application.[98]

The development of aryl electrophiles derived from phenols have become a key focus—and in particular, sulfate linkages. Although recent advances have allowed the coupling of aryl tosylates (OTs) and mesylates (OMs), these reactions generally require the use of complex ligands.[99] Conversely, aryl triflates (OTf) show a higher level of reactivity, but their practical application is disadvantaged by the instability and high cost of the reagents required to install the triflate functionality.

The process group at Bristol-Myers Squibb (BMS) were the first to investigate the use of (hetero)aryl fluorosulfates as electrophilic components in cross-coupling reactions as triflate surrogates for a range of reactions, including Negishi, Stille and

alkoxy carbonylation reactions (Scheme 24B).[100–102] While the cross coupling of aryl fluorosulfates is not a SuFEx reaction per se (given that no S-F exchange occurs), these reaction are now made possible by the application of SuFEx in the synthesis of the reactants.

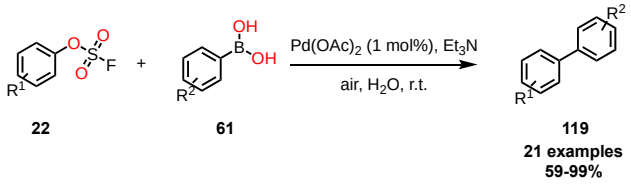


Scheme 24: A) BMS group's synthesis of (hetero)aryl fluorosulfates from fluorosulfonate anhydride **115**; B) Negishi, Stille and palladium-catalysed alkoxy carbonylation reactions of aryl fluorosulfates **22**.

The BMS group employed fluorosulfonic anhydride (**115**) to prepare the aryl fluorosulfate substrates, which was considered an improvement to previously reported procedures involving the pyrolysis of arenediazonium salts and the use of $ClSO_2F$ (Scheme 24A). However, fluorosulfonic anhydride is highly volatile and toxic, and the methods employing this compound often suffer from dangerous conditions and low yields.[99,103]

The challenges of fluorosulfate synthesis has now largely been addressed through the use of commercially available SO_2F_2, as introduced by Sharpless and co-workers, along with the SO_2F_2 surrogates AISF (**33**) and the imidazolium salt **29**.[14,38,39]

Sharpless, Jiang and co-workers subsequently described the application of the aryl fluorosulfate moiety as a highly activated coupling partner in an additive free Suzuki-Miyaura reaction with aryl boronic acids, obtaining a range of biaryl products in good to excellent yields (Scheme 25).[98] Additionally, the reactivity of the fluorosulfate moiety towards other coupling partners in palladium-catalysed reactions was examined, with satisfactory yields of the target products obtained.

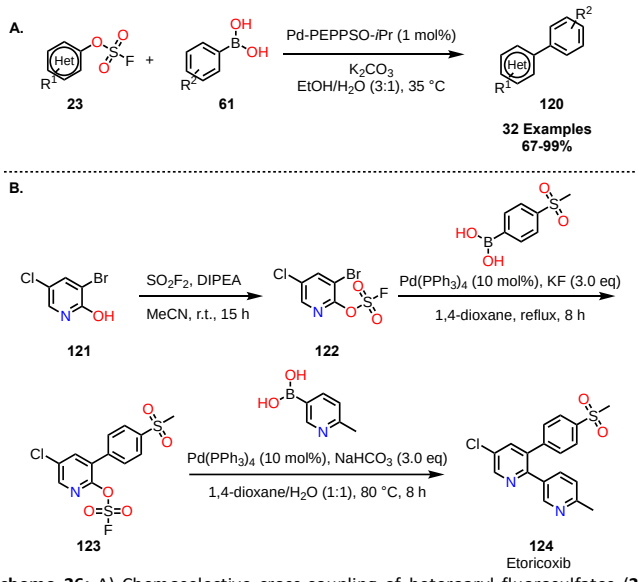


Scheme 25: Additive-free Suzuki-Miyaura cross-coupling of boronic acids and aryl fluorosulfates.

Kruper and co-workers reported a systematic study of aryl fluorosulfates in cross-coupling reactions, describing a number of important competition experiments.[104] Their studies revealed that the relative reactivity of the aryl fluorosulfate moiety is comparable to aryl triflates and aryl bromides, and significantly more reactive than the corresponding chloro-, tosyl- and mesyl- analogues.

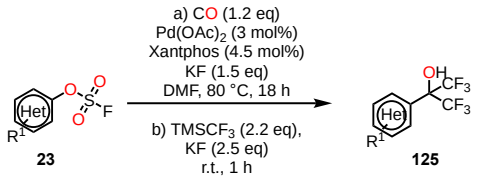
The researchers also reported two sets of optimised Suzuki cross-coupling conditions using palladium and nickel phosphine catalyst combinations. Complementary reactivity was observed, with nickel catalysts giving higher yields with electron-rich aryl fluorosulfates, and palladium catalysts giving increased yields on electron-poor substrates.

In 2016, a report by Zhang and co-workers further broadened the scope of fluorosulfate cross-coupling chemistry.[103] An array of heteroaromatic fluorosulfates (**21**) were synthesised and coupled with boronic acids under palladium catalysis (Scheme 26A). Competition studies unveiled the relative reactivity of leaving groups on substituted pyridines to be -Br ≥ -OTf > -OSO_2F > -Cl, which was agreement with the finding of Kruper and co-workers. [104] This trend was exploited in the impressive sequential and selective synthesis of tri-substituted pyridines. The methodology was then further illustrated in the concise synthesis of the COX-2 inhibitor Etoricoxib (**124**) in an overall yield of 40.3% (Scheme 26B).



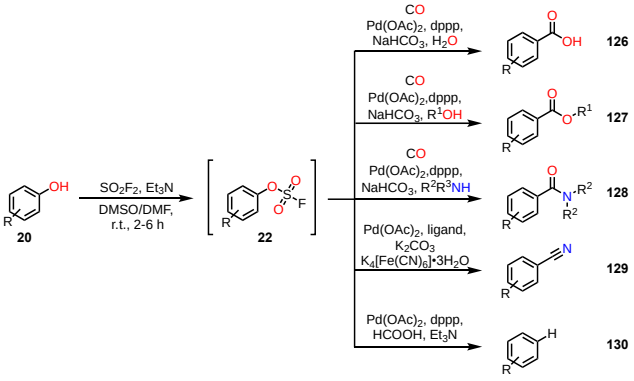
Scheme 26: A) Chemoselective cross-coupling of heteroaryl fluorosulfates (**23**) with boronic acids (**61**); B) Application of the chemoselective methodology in the a 3-step synthesis of the COX-2 inhibitor Etoricoxib (**124**).

The relative reactivity of leaving groups observed by Zhang and co-workers contrasts with that described by Skrydstrup. For the conversion of aryl bromides or fluorosulfates into the corresponding aryl bis(trifluoromethyl)carbinols (**125**) *via* a palladium catalysed carbonylation reaction, it was noted that in a competition reaction, the aryl fluorosulfate reacted significantly faster (Scheme 27).[105]



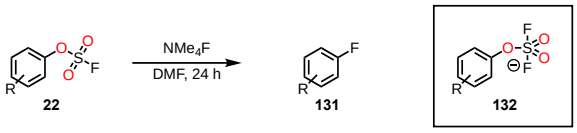
Scheme 27: Formation of (hetero)aryl bis(fluoromethyl)carbinols **125** from (hetero)aryl fluorosulfates **23**.

Qin and co-workers have extended the application of aryl fluorosulfates through the palladium catalysed one-pot synthesis of carboxylic acids, esters, amides and nitriles from phenols (Scheme 28).[106–108] Phenols (**20**) were converted to the corresponding aryl fluorosulfates (**22**), and then subjected to palladium-catalysed carbonylation in the presence of water, alcohols or amines to yield the corresponding carboxylic acids (**126**), esters (**127**) and amides (**128**) respectively. For the synthesis of the benzonitrile products (**129**), the intermediate fluorosulfate **22** was reacted under palladium catalysis with the non-toxic cyanide source potassium ferrocyanide. Interestingly, when cyclic amines are used as reactants, the sulfonamide products are formed through the direct reaction of fluorosulfate and amine. Further, the researchers also developed reactions conditions that allowed access to the deoxygenation products (**130**).[109]



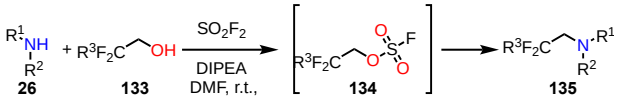
Scheme 28: Palladium catalysed reactions of *in-situ* generated aryl fluorosulfates to form benzoic acids (**126**), esters (**127**), amides (**128**), nitriles (**129**) and deoxyhydrogenated products (**130**).

In 2017, the Sanford group reported a deoxyfluorination process for the conversion of phenols to fluoroarenes **131** *via* the aryl fluorosulfonate (**22**) (Scheme 29).[110] The phenols were first fluorosulfonylated by SO_2F_2, then tetramethylammonium fluoride effected the *ipso*-substitution of aryl fluorosulfonate (**22**) under mild (anhydrous) conditions. The reaction was proposed to proceed through a penta-coordinate difluorosulfonate intermediate (**132**).[111]



Scheme 29: Tetramethylammonium fluoride mediated *ipso*-fluorination of aryl fluorosulfates (**22**).

Sammis and co-workers expanded the use of sulfuryl fluoride as a new reagent for the trifluoroethylation and 1,1-dihydrofluoroalkylation of primary and secondary amines (**135**) (Scheme 30).[112] Alkyl fluorosulfates (**134**) were generated *in situ* from the corresponding alcohol, and subsequently reacted with amines. Interestingly, when the same conditions were used instead in the presence of trifluoroethyl iodide, tosylates and mesylate, no reaction was observed and performing the one-pot procedure with triflic anhydride resulted in no product formation.



Scheme 30: Trifluoroethylation and 1,1-dihydrofluoroalkylation of amines using *in-situ* generated alkyl fluorosulfates.

To summarise this subsection, it is clear than since the inception of SuFEx click chemistry in 2014, the growth of new methods developed to furnish SuFExable functionality into modular building blocks has been rapid and widespread. The installation of vinylsulfonyl fluoride moieties onto (hetero)aromatic scaffolds, either from the corresponding (hetero)aryl halide or boronic acid, or *via* myriad of directing groups has been reported. Furthermore, the 1,3-dipolar cycloaddition chemistry of the latest SuFEx hub BESF (**10**) has been successfully employed to generate novel functionalised heterocycles. The breadth of accessible S-F containing molecules bodes extremely well for the application of future SuFEx research across a variety of fields.

The advent of SuFEx has also had other consequences: the reinvigoration of sulfonyl fluorides and fluorosulfates containing molecules as chemical reagents. In recent years, these moieties have been shown to act as amide-coupling agents, as precursors to synthetically useful sulfonyl azides and as efficient deoxyfluorination reagents. However, it is perhaps their superiority as triflate surrogates that aryl fluorosulfates may ultimately find most utility—being straightforward to install, reliable and yet highly active in transition metal catalysed cross-coupling reactions.

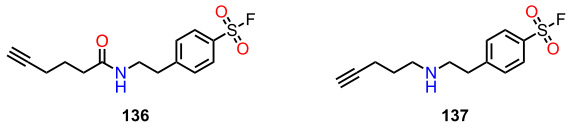
Bio-SuFEx: Applications of SuFEx Click Chemistry in Chemical Biology and Drug Discovery

Chemical Biology

The exchange of sulfur-fluoride bonds to form covalent linkages has long been appreciated in chemical biology— with reports of aryl sulfonyl fluorides being employed as electrophilic probes from as early as the 1950's. Myer and Kemp's pioneering work on sulfonyl fluoride inhibition of proteases, followed by Fahrney and Gold's work on serine protease inhibitors are seminal contributions.[113–115] In contrast to other common electrophilic functionality such as acrylamides, vinyl sulfones and fluorophosphonates, the S-F based probes are comparably unreactive. [116] For activation of the S-F centres, assistance from the surrounding amino acid sidechains is often required. Despite this, S-F based probes have been known to target active serine, tyrosine, lysine, threonine, histidine and cysteine residues.

The surprising properties and unexpected selectivity of sulfonyl fluorides electrophiles was first remarked upon by Baker in 1969, during his studies on irreversible inhibitors dihydrofolate reductase.[117] Baker observed that while the sulfonyl fluoride moiety is inert to hot water, alcohol and pyridine, the species become highly reactive when complexed to a macromolecule such as cellulose or an enzyme.

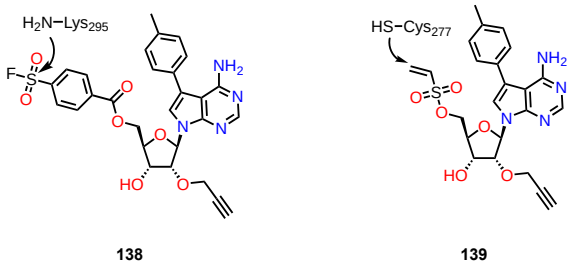
Sulfonyl fluorides have been used as probes in the activity-based protein profiling of serine proteases by van der Hoorn, Weerapana and co-workers.[118] Alkynylated analogues (**136** and **137**) of a pan-serine protease inhibitor, (4-(2-aminoethyl)benzenesulfonyl fluoride) were synthesised, and their ability to act as activity based probes examined. Alkyne **136** enabled the enrichment of protease from complex proteomes and subsequently, their analysis and identification by mass spectrometry (Figure 4).



136 **137**

Figure 4: Alkynated sulfonyl fluorides (**136** and **137**) used by van der Hoorn, Weerapana and co-workers.

Taunton and co-workers demonstrated the high selectivity of arylsulfonyl fluoride group against nucleophiles at the active site of protein kinase Src-family.[119] Sulfonyl fluoride tagged molecules (**135** and **136**) reacted exclusively with the conserved catalytic lysine (Lys295), while a vinyl sulfonate tagged molecule reacted with a proximal cysteine (Cys277) (Figure 5). The researchers also showed the ability of these two probes for competitive profiling versus different kinase subsets in living cells.



138 **139**

Figure 5: Reactivity of sulfonyl fluoride probes (**138** and **139**) at the active site of the protein kinase Src-family.

Recognising the growing importance of S-F based probes in chemical biology, Robinson, Jones and co-workers introduced a toolbox of functionalised arylsulfonyl fluoride probes (Figure 6).[120] These 'minimalist' tools incorporated three distinct reactive centres: i) a sulfonyl fluoride for covalent protein modification, ii) an alkyne substituent as a reporter tag for subsequent pull-down experiments and, iii) a functional handle used to attach the drug/drug fragment of interest.

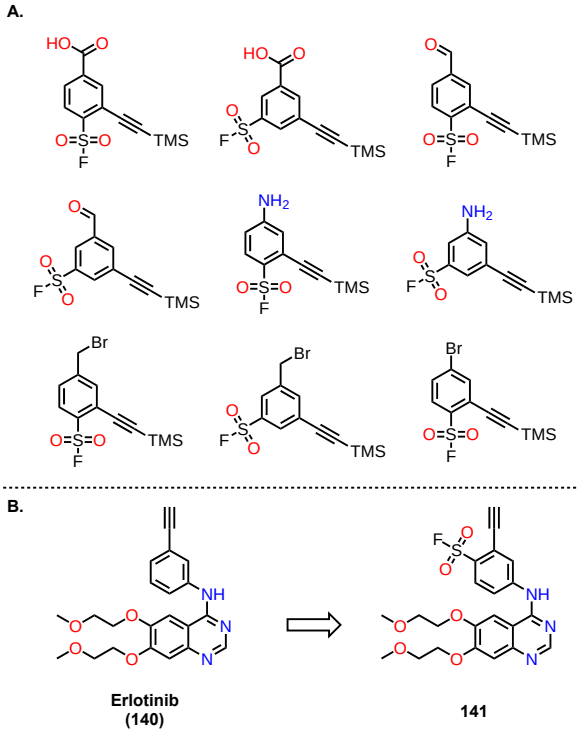


Figure 6: Robinson and Jones' minimalist toolbox of sulfonyl fluoride containing probes.

Exploiting the stability of sulfonyl fluorides, Robinson, Jones, and co-workers at Pfizer prepared a set of chemical probes, to allow conjugation with the target drug molecules. An array of drug analogues of different drug classes were synthesised, incorporating functionality for subsequent click reactions.

The authors of this study prepared an analogue (**141**) of the epidermal growth factor receptor (EGFR) inhibitor erlotinib **140**, and was shown to label to the EGFR protein through a close proximity lysine residue. The low electrophilicity of the sulfonyl fluoride moiety, except when binding, resulted in a high level of

specificity, as confirmed by concentration-dependant labelling competition with the parent drug molecule.

Whereas the application of sulfonyl fluorides in chemical biology endeavours have been extensively documented,[115] the analogous aryl fluorosulfate functionality has been comparatively underexplored;[113] perhaps a consequence of their historical limited availability.

Fluorosulfates are generally less reactive than sulfonyl fluorides, and tend only to react with biological targets when positioned in a particular activating environment, giving them potential as covalent drugs, where avoiding off-target reactivity is highly desirable.

A study by the Kelly and Sharpless groups highlighted the selective nature of fluorosulfates in comparison to their corresponding sulfonyl fluoride analogues.[116] The fluorosulfates **143** and **144** were incubated with HeLa cell lysates, followed by CuAAc labelling with fluorescent rhodamine-azide. To determine which proteins(s) had reacted with the probes, SDS-PAGE in-gel fluorescence analysis was used (Figure 7).

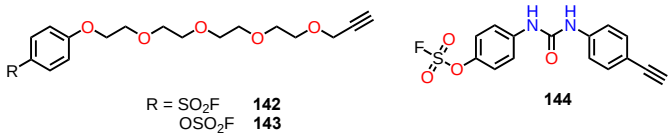


Figure 7: Kelly and Sharpless application of sulfonyl fluoride (**142**) and aryl fluorosulfate (**143**-**144**) probes in the study of HeLa cell lysates.

Although the probes (**143** & **144**) were not designed to specifically explore the reactivity of the HeLa proteome, some target selectivity was observed. Of the two aryl fluorosulfate compounds, **143** was particularly selective for proteins in the 15 kDa band—subsequently identified as the fatty acid bind proteins FABP3 and FABP5 from the intracellular lipid binding (iLBP) family. In contrast, the analogous sulfonyl fluoride **142** demonstrated relatively more promiscuous labelling, forming conjugates with a host of proteome members, highlighting the '*muted reactivity*' of the fluorosulfate functional group.

Analysis of recombinant protein modified by **143** by tandem mass spectrometry confirmed that modification occurred at a tyrosine residue of a conserved Arg ~ Arg ~ Tyr binding motif. The researchers proposed that the proximal arginine residues result in a lowering of the pKa of the tyrosine, while simultaneously catalysing the SuFEx reaction by facilitating the departure of the fluoride ion.

In another study, Kelly, Sharpless and co-workers demonstrated the application of both the sulfonyl fluoride and fluorosulfate motifs as chemical probes in specifically designed molecules (Figure 8).[121] The chemoselective reaction of sulfonyl fluoride **145** at the inner thyroxine binding subsite of transthyretin (TTR) prevents the subsequent formation of amyloid fibrils.[122]

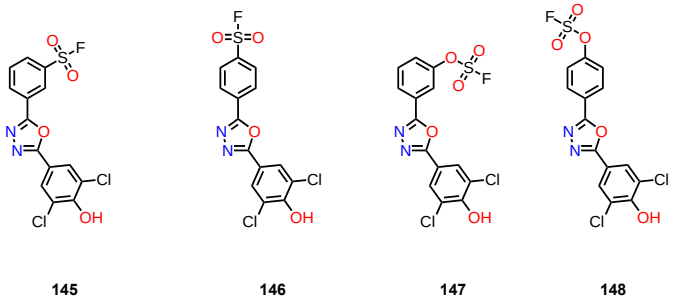


Figure 8: Sulfonyl fluoride (**145**-**146**) and fluorosulfate (**147**-**148**) probes for chemical biology studies by the groups of Kelly and Sharpless.

The interactions of isomer **146** and corresponding fluorosulfate derivatives **147** and **148** with TTR were also investigated.[121] The researchers observed that in contrast to the **145**-**148** probes, the 1,3,4-oxadiazole-based aryl fluorosulfate **148** did not react covalently with the binding site of TTR significantly during the course of imaging experiments. Instead, **148** acted as a non-covalent fluorogenic probe resulting in a shifted emission when in close proximity to the TTR binding pocket.

The 2,4-diaminoquinazolines (such as DAQ1, **149**) are a family of compounds that inhibit the de-capping scavenger enzyme DcpS, and are currently under investigation as potential treatments of spinal muscular atrophy. Jones and co-workers designed the sulfonyl-fluoride analogue (**150**), which acted as an irreversible inhibitor of the enzyme through formation of a covalent linkage between **150** and tyrosine residues present in the active site.[123]

Seeking to advance this study further, the researchers next designed and synthesised the corresponding fluorosulfate containing compound **151**. However the anticipated reaction with the nearby tyrosine residue was not the predominant product (Figure 9).[124] Jones and co-workers suggest that the additional oxygen atom restricts the ability of the tyrosine residue to react with the weakly electrophilic fluorosulfate **151**. Instead, a nearby serine residue reacts with the fluorosulfate **151**, which after a subsequent β-elimination leads to the formation of a dehydrated protein containing a new dehydroalanine residue.

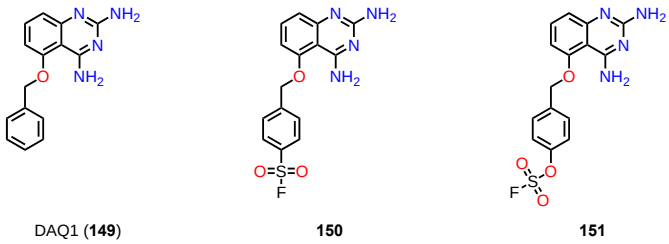
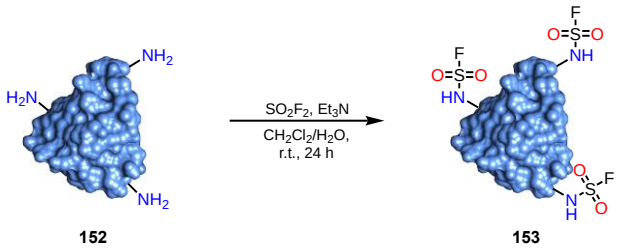


Figure 9: Sulfonyl fluoride (**150**) and fluorosulfate (**151**) containing inhibitors of DcpS.

Averick and co-workers reported an alternative approach to the use of SuFEx in chemical biology, by using SO_2F_2 to incorporate the RSO_2F moiety directly into proteins (Scheme 31).[125] Incubation of bovine serum albumin (BSA, **152**) with SO_2F_2 in

basic conditions led to the formation of, on average, 4 new N-S bonds as confirmed by mass spectrometric analysis. Interestingly, it was noted that upon heating under basic conditions, the SO_2F_2-modified BSA (**153**) self-reacted to generate a hydrogel which could then be used in co-culture with HEK 293 cells.

Aside from the SuFEx reactivity with SO_2F_2, the reactivity with PEG-lyated aryl fluorosulfates was also described, demonstrating that the lysine residues on BSA selectivity reacted in a SuFEx reaction under a variety of basic pH levels (7.4, 9 and 11.3).



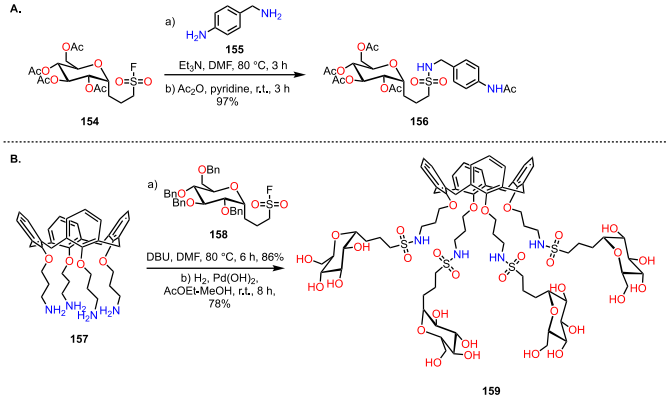
152 153

Scheme 31: Protein functionalisation with SO_2F_2 gas.

Marra and Dondoni have applied SuFEx methodology in bioorganic chemistry; specifically in the modification of glycosylated substrates.[126,127] En route to the synthesis of sulfonamide **156**, it was noted that the reactivity of a sulfonyl chloride precursor was hampered due to undesired dehydrohalogenation. In contrast, switching to the sulfonyl fluoride analogue **154** resulted in near-quantitative sulfonamide formation with **155**, with complete chemoselective between the benzyl and aryl amine functionality (Scheme 32A).

The group extended application of their methodology in the multiple functionalisation of the complex poly-aminated calix[4]arene **157**. Here, treatment of the polyamine **157** and a protected sugar-containing sulfonyl fluoride (**158**) with DBU resulted in the formation of the functionalised calix[4]arene **159** after hydrogenation (Scheme 32B).

The reaction proved equally efficient regardless of the position of the sulfonyl fluoride, either on the protected sugar or as part of the calixarene core, again highlighting the incredible reliability of the SuFEx protocol.



Scheme 32: A) Selective SuFEx modification of an acetate protected sugar (**154**); B) Functionalisation of a polyamino calixerene **157** with a sulfonyl fluoride substituted sugar derivative **158**.

Taunton and co-workers recently demonstrated the application of aryl sulfonyl fluorides in the profiling of a large number of kinases.[128] The researchers designed three lysine-targeted sulfonyl fluoride compounds based on the core structure of pyrimidine 2-aminopyrazole kinase-recognition scaffold, which all contain an alkyne tag for further biochemical ligation (Figure 10). One of the compounds (**161**) was found to cover all major branches of the kinome tree. The development of such chemoproteomic probes may aid in future evaluation of kinase-inhibitor occupancy in live cells to avoid and to address its off-target issue.[128]

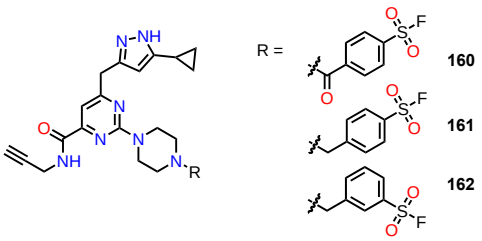
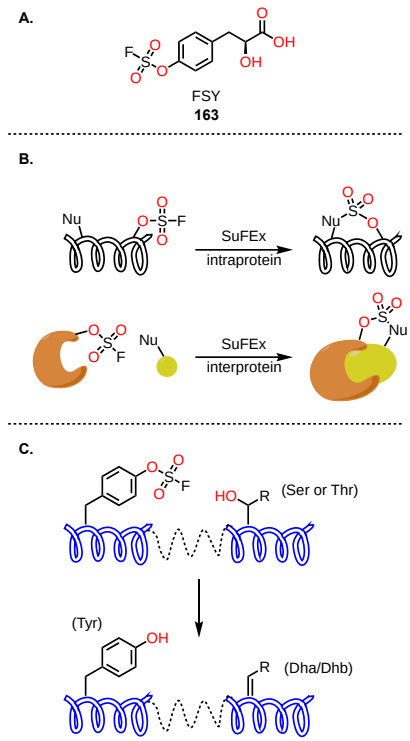


Figure 10: Sulfonyl fluoride decorated 2-aminopyrazoles (**160**–**162**) used for the profiling of kinases.

The Wang group recently reported the synthesis of the unnatural amino acid fluorosulfate-L-tyrosine (FSY, **163**). The amino acid was shown to be nontoxic to *E. coli* and mammalian cells.

It was shown that the incorporation of FSY (**163**) into proteins allowed the reactive fluorosulfate group to react with proximal lysine, histidine, and tyrosine residues *via* SuFEx reactions. These reactions were shown to occur where the FSY (**163**) and nucleophilic amino acid were located on the same protein or on two interacting proteins in living cells (Scheme 33).[129] In a follow-up report, DeGrado, Wang and co-workers further explored SuFEx reactivity using genetically encoded FSY (**163**) to study protein assemblies and complex protein interaction networks through chemical cross-linking mass spectrometry.[130]

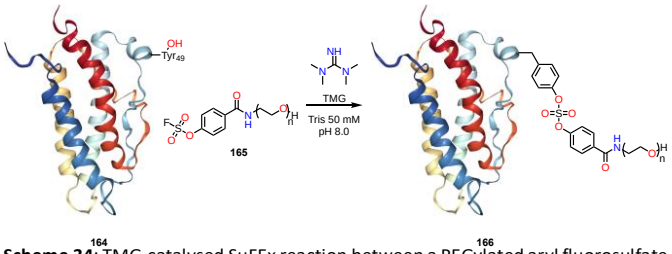


Scheme 33: Wang's exploration of the chemical of the unnatural aryl fluorosulfate containing amino acid fluorosulfate-L-tyrosine (FSY, **163**).

In 2019, Degrado, Wang and co-workers extended their pioneering work with FSY (**163**) further, employing the unnatural amino acid to selectively generate reactive dehydroalanine (Dha) and dehydrobutyrine (Dhb) moieties into live proteins (Scheme 32C).[131] Using the Genetically Encoded Chemical COnversion (GECCO) strategy to harness proximity enabled reactivity, FSY (**163**) was shown to convert nearby serine and threonine residues into Dha and Dhb respectively, with the concomital generation of a tyrosine residue from the unnatural FSY (**163**).

The GECCO strategy proved to be successful both intra- and inter-protein, and presents a powerful approach to the installation of reactive, electrophilic amino acid acids into live proteins.

A recent report by Kim and co-workers disclosed tetramethyl guanidine (TMG) as a superior SuFEx catalyst in aqueous solution. The authors first showed that the TMG-catalysed SuFEx reaction of aryl fluorosulfate has excellent selectivity for nucleophiles on amino acid sidechains, with phenol-bearing tyrosine the preferred reactive site. The authors demonstrated the method was biocompatible by conjugating a PEGylated aryl fluorosulfate (**165**) to recombinant human erythropoietin (**164**) in aqueous buffer containing TMG (Scheme **34**). This work represents the first catalytic, non-recognition-based SuFEx reaction of biomacromolecules in aqueous solution.[132]

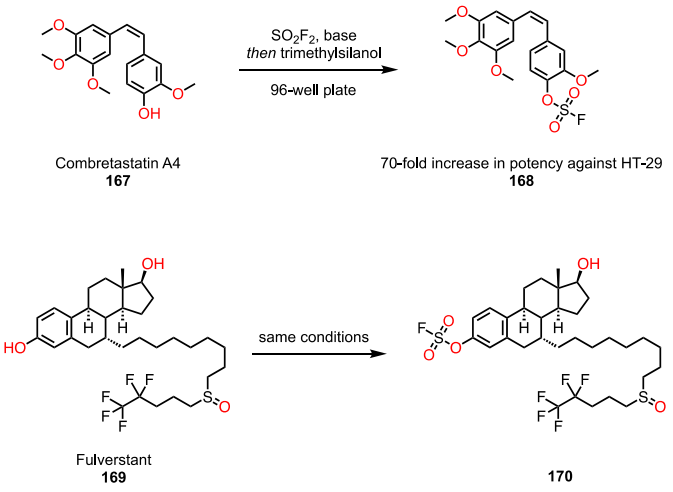


Scheme 34: TMG-catalysed SuFEx reaction between a PEGylated aryl fluorosulfate and human erythopoietin.

Drug Discovery

A pioneering study by Wu and co-workers showcased SuFEx click chemistry as a useful tool for late-stage functionalisation (LSF) of bioactive molecules.[133] LSF has become an increasingly important technique over the past decade, enabling the rapid diversification of drug-like molecules late in the synthetic sequence—an effort to improve both the physical and pharmacokinetic properties.

Using SO_2F_2, Wu's team converted a panel of NIH approved anticancer drugs into their fluorosulfate derivatives directly in a 96-well plate. This allowed the biological activity to be assessed in direct comparison with the parent compounds (Scheme 35). Screening a library of 39 compounds, three of the aryl fluorosulfates displayed enhanced anti-cancer activity. Of particular interest was the fluorosulfate derivative (**168**) of combretastatin A4 (**167**), which displayed a dramatic 70-fold increase in potency against the colon cancer cell line HT-29. In addition, the fluorosulfonylated analogue (**170**) of fulvestrant (**169**), a selective estrogen receptor down regulator (SERD), had a stronger binding affinity towards ERα than the parent compound.



Scheme 35: Wu and co-workers latestage fluorosulfonylation of combretastatin A4 (**167**) and fulvestrant (**169**) results in significant improved anticancer potency.

The groups of Sharpless, Wilson and Kelly have explored the selectivity of fluorosulfates towards the family of intracellular lipid binding proteins (iLBPs) using a series of compounds (**171**-**176**) as latent electrophiles in a strategy coined 'Inverse Drug Discovery'.[134] In contrast to conventional drug screening, which

often involves screening against a specific protein target or cell-based phenotypic assay, 'Inverse Drug Discovery' matches compounds with weak electrophiles directly to proteins either directly in the cell, or cell-lysate. With their relatively muted activity, fluorosulfates are well-suited for this approach, since as already stated above, reactions with proteins generally only occur under precise activation conditions in the active site. The iLBPs therefore present an ideal proof-of-concept model, as the binding site of these proteins contain not only a tyrosine residue, but also the side-chain functionality required to catalyse the SuFEx reaction.

Three distinct aryl fluorosulfate probes (**171**, **173** and **175**) of intermediate complexity were synthesised and shown to bind to specific proteins. The probes were designed to incorporate an alkyne moiety to allow for the subsequent identification and CuAAC enabled pull-down of labelled proteins (Figure 11).

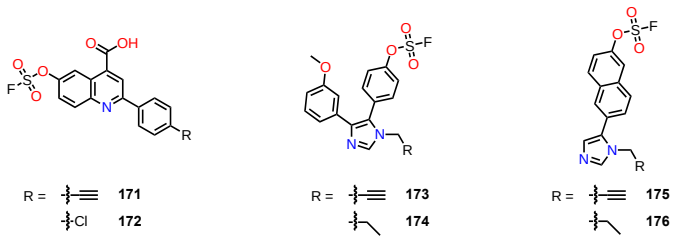


Figure 11: Chemical probes (**171**-**176**) used to demonstrate the 'inverse drug discovery' strategy.

Several competitor probes **172**, **174** and **176** were also synthesised as analogues to **171**, **173** and **175**, respectively, but without the alkyne required for conjugation experiments. The competitor probes were required to gain insight into whether the proteins identified were of low abundance, and reacted quantitatively with the aryl fluorosulfate, or of high abundance and only reacting fractionally with the fluorosulfate probe.

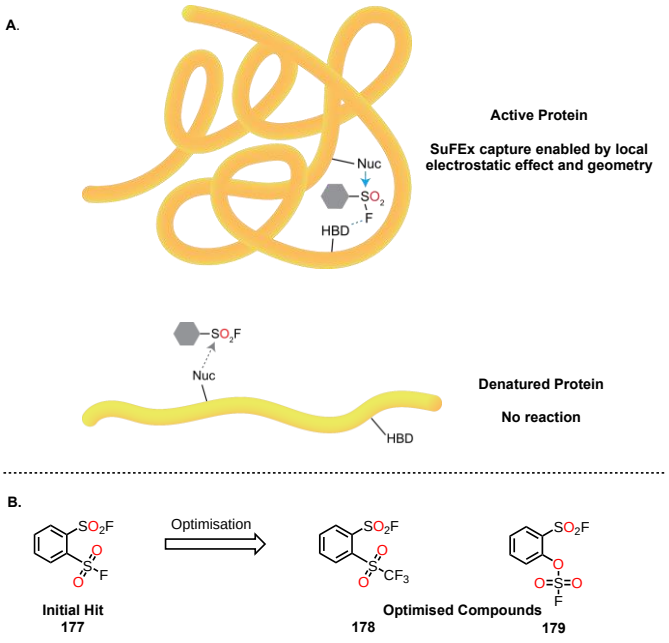
The addition of a large excess of the competitor probes (**172**, **174** or **176**), alongside the corresponding fluorosulfate (**171**, **173** or **175**) results in the blocking of conjugation of the alkyne-containing molecule, which can be observed by diminishing fluorescence after CuAAC reaction with a fluorescent probe. Conversely, if the level of fluorescence remains unchanged, it can be concluded that a highly abundant protein is only partially reacting with the aryl fluorosulfate.

In total 11 protein targets were validated, with further reactions between the aryl fluorosulfates and the recombinant purified protein confirming that labelling occurs in a well-defined binding pocket. These pockets tend to contain multiple residues with cationic side chains, and it was suggested that the presence of these residues near to the fluorosulfate reactive residue (typically tyrosine or lysine) either modulate the pKa of nucleophile, or catalyse the SuFEx reaction by stabilising the departing fluoride.

The researchers suggested that there is significant scope for the use of the 'Inverse Drug Discovery' technique with other latent electrophiles. This approach has the potential to identify new covalent probes that, with further elaboration, could be developed into either covalent or non-covalent drug candidates.

More recently, the groups of Sharpless and Wolan disclosed an agnostic approach for the discovery of SuFExable small molecule covalent medicines employing *'sleeping beauty'* probes.[135] Their work summarised the special features of sulfur fluorides as covalent warheads, especially the great enhancement of rate of covalently capturing only their correctly folded protein partner but not the denatured form of the latter (Scheme 36A)

The team screened a focussed library consisting of 105 randomly picked compounds from a principle collection of >1000 in-house made sulfur fluoride compounds against human neutrophil elastase (hNE). The compounds were assigned to a subset as defined by their different sulfur fluoride functional groups. The benzenoid compound—benzene-1,2-disulfonyl fluoride (**177**) was identified as a covalent modifier of hNE with an IC_{50} of 3.3 µM. Structure determination of the covalent protein-drug complex by X-ray crystallography, revealed that the mechanism of the inhibition of hNE was the sulfonylation of Ser195 by the sulfonyl fluoride (Scheme 36B). Further optimisation of the hit compound using SuFEx revealed two new compounds that displayed superior activity and selectivity to the parent compound (**177**). These include the 2-fluorosulfonylphenyl triflone (**178**) (IC_{50} 1.1 µM), itself made using Moses's late-stage SuFEx trifluoromethylation protocol, and the 2-fluorosulfonylphenyl fluorosulfate (**179**) (IC_{50} 0.24 µM), which itself demonstrated greater than 833-fold selectivity over the homologous neutrophil serine protease, cathepsin G .[95]



Scheme 36: A) SuFEx protein capture is enabled by local electrostatic effects and geometry. Nuc = nucleophilic sidechain. HBD = H-bonding donor; B) Optimisation of benzene-1,2-disulfonyl fluoride (**177**) as a covalent modifier of HNE.

Along with the development of covalent inhibitors through the installation of the fluorosulfate group, SuFEx click chemistry has also been employed in the synthesis of a number of potential drug candidates.

Kim and co-workers demonstrated that biaryl sulfate analogues of daclatasvir (**180**), a hepatitis C virus NS5A inhibitor, showed both high antiviral activities as well as promising additive effects when used in combination with a NSFB inhibitor.[136] The strategy used to construct the biaryl sulfates involved the reaction of phenols with sulfonyl diimidazole. While this method was effective, the synthesis of non-symmetrical analogues in synthetically useful yields proved problematic.

To overcome this issue the team opted to use SuFEx click chemistry to generate the required biaryl sulfate core (Figure 12).[137] The benefits of switching strategy were two-fold: 1) both symmetric and nonsymmetric compounds could be now be synthesised, and 2) a wider range of substituted phenols were now tolerated. A library of compounds was constructed and tested, with two-digit pM EC_{50} values achieved for a range of inhibitors, with both the symmetric compound **182** and nonsymmetric **181** showing impressive potency.

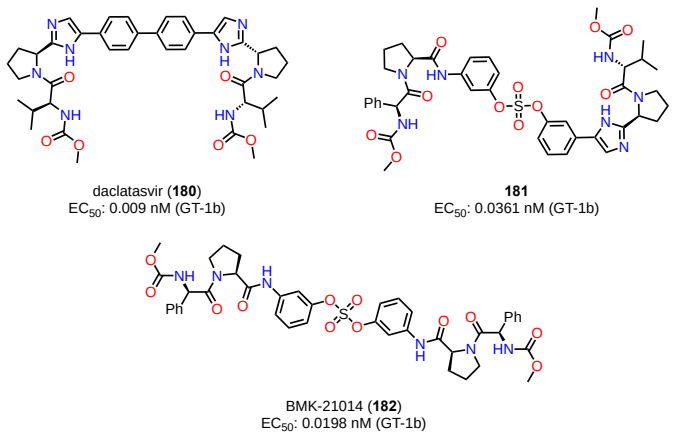
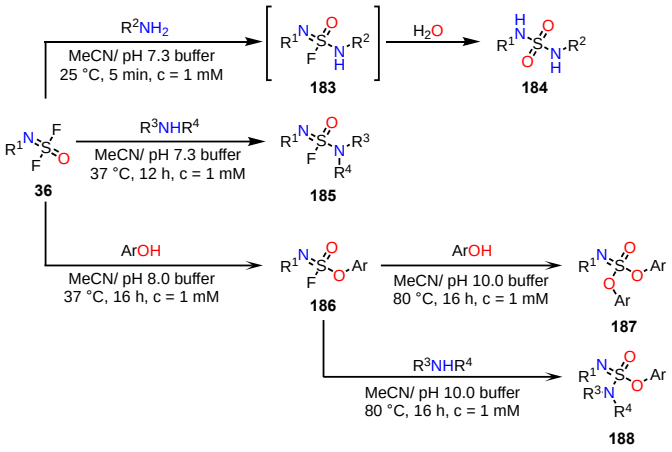


Figure 12: SuFEx enabled synthesis of homo- and cross-coupled biaryl sulfate analogues of daclatasvir (**180**), a hepatitis C virus NS5A inhibitor.

In a very recent report, Liu, Sharpless and co-workers developed a series of biocompatible SuFEx transformations for bioconjugation to proteins and DNA.[138] This seminal work demonstrates the ability of iminosulfur oxydifluorides to undergo SuFEx reactions in buffered solution (Scheme 37). The reaction of primary amines with iminosulfur oxydifluorides **36** proceeds rapidly at room temperature, providing the sulfamide **184** products in good to excellent yields upon hydrolysis of the sulfuramidimidoyl fluoride intermediate **183**.

A slightly higher temperature of 37 °C was required for reactions with secondary amines, however in this instance, no hydrolysis product was detected and only the sulfuramidimidoyl fluoride product **185** isolated. Although these products contain one S-F bond and the potential to undergo further SuFEx reactions, no such reactivity was observed even under forcing conditions.

The combination of iminosulfur oxydifluorides **36** with phenols in the buffered aqueous solution resulted in the formation of sulfurofluoridoimidates **186**, which in contrast to the sulfuramidimidoyl fluorides **185**, could undergo further reactions with amines and phenols to generate sulfonimidates **188** and sulfurimidates **187** respectively.



Scheme 37: SuFEx reactions of iminosulfur oxydifluorides **36** in aqueous buffer.

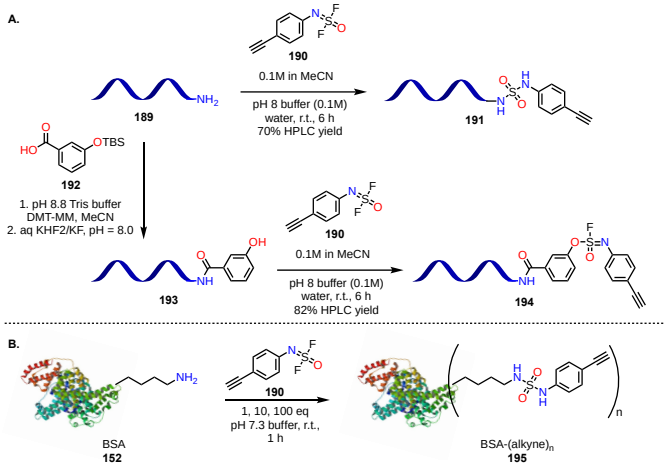
Taking the concept of biocompatible SuFEx chemistry of SOF_4 derivatives further, the same team next demonstrated application of the methodology in bioconjugation (Scheme 38). This is of vital importance, as while there has been enormous developments in the development of bio-orthogonal click chemistry in the last decade, there remains a pressing need for chemical transformations that can be performed in complex biological media in physiological conditions.

Single strands of DNA which terminated with a primary amine (**189**) were selected as an ideal model substrate for the SuFEx conjugation reaction. The DNA strand **189** and the iminosulfur oxydifluoride **190** were agitated for 6 hours in an aqueous buffer, resulting in the successful formation of the conjugated product **191**.

Reaction of the DNA strand **189** with the carboxylic acid **192** yielded the phenol terminated DNA strand **193**. Under the optimised conjugation conditions, **193** was reacted with an iminosulfur oxydifluoride (**190**) to generate the sulfurofluoridoimidate **194** in a HPLC yield of 82%.

Bovine serum albumin (BSA, **152**) was subsequently used as a model protein, with mass spectrometry used to confirm the successful conjugation of up to 8 iminosulfur oxydifluorides onto the lysine residues of the protein (**190**).

The development of a series of biocompatible SuFEx click reactions is a valuable addition to the ever-growing click chemistry toolbox and will likely find wide application in a host of fields in the coming years.



Scheme 38: Biocompatible SuFEx reactions between iminosulfur oxydifluorides (**36**) and single-strand DNA (**189**) and BSA (**152**).

Application of SuFEx Click Chemistry in Materials Science

The industrial processes that dominate polymer chemistry align tightly with the overarching philosophy of CC: extremely high reaction efficiencies, coupled with minimal purification procedures. In true CC fashion, simple modular units are stitched together to generate new materials with useful properties.

The development of CuAAC resulted in a rapid and widespread uptake in materials science, overcoming a variety of synthetic challenges. In the few years since SuFEx was introduced, it is evident that this latest iteration in CC technology may have equal, if not greater impact.

The modular nature of SuFEx has resulted in two distinct applications in polymer chemistry. Firstly, the SuFEx reaction has been used to construct the core backbone of polymers through sulfur-centred linkages. Secondly, owing to the orthogonal reactivity of SuFExable groups, these handles can be easily incorporated as side chains onto monomers pre-assembly; subsequently providing handles for post-polymerisation modification of polymers.

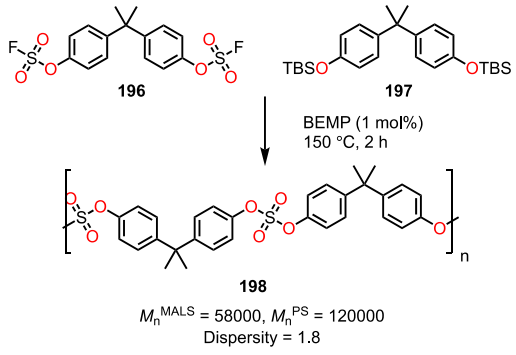
Polysulfate or polysulfonate-based polymers

The majority of synthetic polymers can be categorised into two distinct classes: 1) those forming new carbon-carbon bonds, and 2) those that generate carbon-heteroatom linkages. Carbon-heteroatom centred polymers are ubiquitous, and include the well-known polyesters, polyimides and polyamides. On the other hand, polymers with -SO_2- cores are notably scarce and underdeveloped.

Poly(aryl sulfate) polymers were initially described in the 1970's by Firth, through the direct reaction of biphenol di-sodium salts with sulfuryl fluoride (SO_2F_2) or the bisfluorosulfate.[32,33] Although novel materials were produced, laborious purifications were needed to remove a prominent by-product, thereby reducing their applicability in an industrial setting.

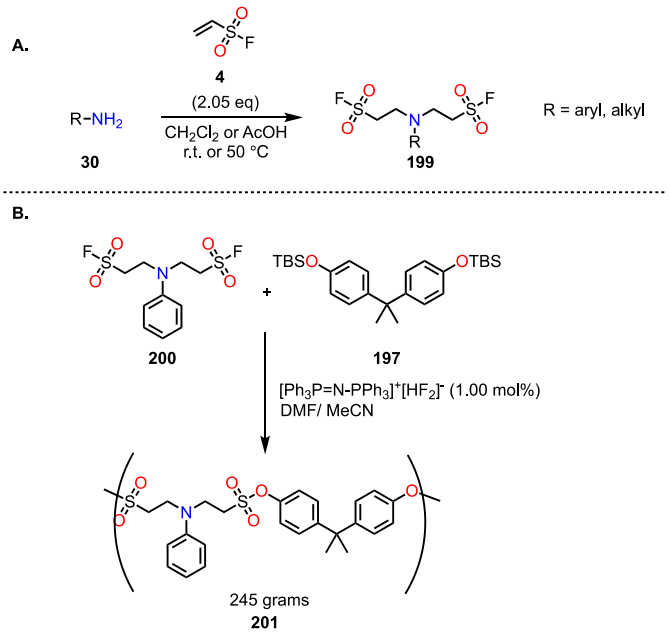
The first practical application of SuFEx click chemistry for use in materials science was described in the seminal SuFEx paper.[14,139] Following their established SuFEx conditions, the bis(aryl fluorosulfates) **196** were combined with bis(aryl silyl ethers) **197** in the presence of either organic bases (DBU, BEMP) or fluoride salts (e.g. CsF). Following purification by precipitation with methanol or distillation of the benign by-products, high molecular weight polysulfates (**198**) with low polydispersity were isolated with near-quantitative yields (Scheme 39). Crucially, as for any potential industrial polymer, the procedure proved to be tolerant of a wide range of functionality, and scalable, due to a low exothermic reaction profile.

While a selection of aryl silyl ethers proved amenable to the polymerisation conditions, bis(aryl silyl ethers) containing the *tert*-butyldimethylsilyl (TBS) moiety emerged as the optimal monomers, with low loadings of catalysts producing polymers of large molecule weights. A range of physical tests were employed to compare the polysulfate **198** to the commonly encountered BPA-polycarbonate, with BPA-PS emerging as significantly more resistance to hydrolysis and exhibiting a low oxygen permeability, while retaining a similar mechanical behaviour.



Scheme 39: SuFEx mediated synthesis of polysulfates. M_n^{MALS} refers to values calculated by multi-angle light scattering. M_n^{PS} values are in reference to polystyrene standards.

In 2017, Wu and co-workers reported a related approach for the formation of polysulfonates, resulting from the co-polymerisation of bisphenol silyl ethers and bisalkylsulfonyl fluorides.[140] The required bisalkylsulfonyl fluorides are readily accessed from the direct reaction between ESF (**4**) and the required amine, with aniline derivatives requiring slightly more forcing conditions (Scheme 40A).



Scheme 40: A) Synthesis of bisalkylsulfonyl fluorides from ESF; B) Large scale bifluoride promoted formation of polysulfonate.

In contrast to the previously reported SuFEx promoted polysulfate synthesis, in this case DBU proved to be an ineffective catalyst, with only oligomeric products detected (M^{nps} = 7.5 kDa). The researchers postulated that this was due to deprotonation of the alkyl sulfonyl fluoride, resulting in dehydrofluorination and termination of the polymerisation process.

A solution to the problem was found through screening of an array of neutral and slightly acidic bifluoride catalysts, with $[Ph_3P=N\text{-}PPh_3]^+[HF_2]^-$ showing the superior activity. Near-quantitative conversion of a range of monomers into polymer was noted after just 10 minutes in the presence of a 1.25 mol% catalytic loading, producing polysulfonates with a PDI ranging between 1.2 to 1.7.

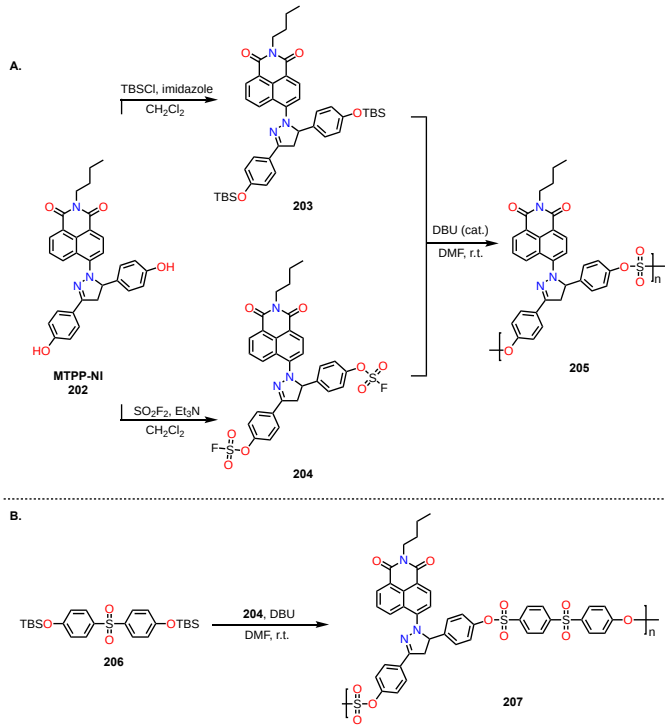
The improved conditions were amenable to a selection of both monomeric species, with both aryl and alkyl amine precursors tolerated. As with the production of polyarylsulfonates, the exothermic polycondensation reaction of bisalkylsulfonyl fluoride **200** and bisphenol silyl ether **197** was also scalable, with a 0.5 mol reaction producing 245 grams of polysulfate **201** (M_n^{PS} = 15 kDa, PDI = 1.2) , which demonstrated impressive stability at a range of pH values (Scheme 40B). The orthogonal nature of the SuFEx polymerisation protocol was also described, with the retention of functionality including alkynes, alkenes and aryl iodides, potentially allowing for subsequent modification.

Considering the promising results generated by the bifluoride catalysts, a further report by Dong, Wu and Sharpless re-examined the co-polymerisation of bis-silyl ethers with both bis-sulfonyl fluorides and bis-fluorosulfates.[141] In contrast to the organosuperbases previously employed, the acidic nature of the bifluoride ion resulted in aliphatic sulfonyl fluorides becoming viable substrates, vastly increasing the substrate scope. Significantly lower loading of the bifluoride salt catalysts were required (down to 0.05 mol%), with protocols developed for facile catalyst preparation thereby providing the groundwork for potential industrial applications.

In 2018, Xu and Lu prepared novel polysulfates based upon a pyrazoline-naphthylamide core, and explored their potential as candidates for electronic storage.[142] There is a considerable quantity of research focussed on exploring polymers containing side chains with pyrazolinyl or naphthalidimide functionality, but until now, the aforementioned functionality had not been incorporated into the polymer backbone.

Starting from the small molecule MTPP-NI (**202**), the researchers prepared the corresponding bis-fluorosulfate (**204**) and bis-silyl ether (**203**), as well as the bis-silyl ether derivative (**206**) of bisphenol S. Two polymers were subsequently prepared: the homopolymer from **203** and **204**, and the co-polymer resulting from the reaction of **204** and **206** (Scheme 41).

A reaction screen with varying solvents and temperatures revealed that DMF at room temperature (20 °C) provided the optimum balance of high molecular weight polymers, whilst retaining a low polydispersity index (PDI). TGA analysis confirmed the thermal stability of the polymers, which also exhibited substantially higher decomposition temperatures than similar polymers which contain pyrazoline groups in the side-chains.[143] Furthermore, the team highlighted the potential



Scheme 41: Synthesis of polysulfate polymer comprising of a pyrazoline-naphthylamide backbone.

applications of the aforementioned polymers by incorporating them into a number of memory devices, which showed non-volatile flash type memory performance.

Niu, Yang and Flynn demonstrated an iterative strategy towards the synthesis of polydisperse sequence-controlled polymers and monodisperse sequence-defined oligomers, through the combination of orthogonal CuAAC and SuFEx click reactions (Figure 13).[144]

Polydisperse sequence-controlled polymers can be defined as polymers with either block sequence $[(A)_x(B)_y(C)_z....]$, or periodic sequence motifs $[(ABCD)_x]$. Conversely, monodispersed sequene-defined polymers are characterised as having the monomers located in a predefined sequence. Both classes of polymer have their unique advantages, and the researchers explored the use of click chemistry in their synthesis.

The researchers confirmed, in a quantitative manner, that SuFEx and CuAAC click reactions are orthogonal to one other, regardless of which order they are performed, making them ideal complimentary reactions to synthesise sequence-controlled polymers. Next, the one-pot copolymerisation of monomers **208** and **209** was performed, generating polymer **210**. The researchers observed that varying the concentrations of monomers had a dramatic impact on both the polydispersity and molecular weight of the resulting polymer. Performing the reaction at 1M resulted in polymer **210** with a molecular weight of 29.7 kDa and a broad polydispersity of 3.00, which was postulated to be due to the formation of small quantities of ultra-high weight polymer.

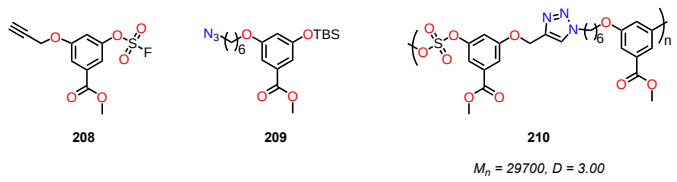


Figure 13: Monomers employed in the orthogonal and compatible SuFEx and CuAAC click polymerisation reactions by Niu and co-workers.

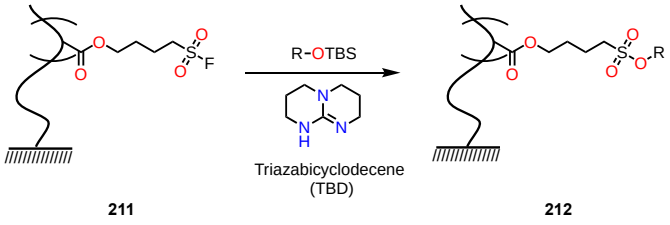
Niu and co-workers then further explored the use of orthogonal CuAAC and SuFEx click reactions, to generate more elaborate monomers for the synthesis of polydisperse sequence-controlled polymers. Monodisperse sequence-defined oligomers were also synthesised, using an iterative click reaction sequence starting from a resin-bound monomer.

Post-Polymerisation Modification

While SuFEx is well suited for the generation of polymers containing a sulfate or sulfonate backbone, there is also significant scope for other applications in polymer chemistry, including the functionalisation of pre-formed polymers. This approach has been nicely demonstrated by Locklin and co-workers in the post-polymerisation modification of polymer brushes.[145,146]

Polymer brushes refer to an array of polymeric molecules, either biological or synthetic, that are densely tethered at one end to a surface and exhibit unusual properties. The 'grafting from' approach is often used to synthesise polymer brushes, using monomers in bulk solution adding to an initiator previously deposited onto the substrate surface.[147] The polymer brush produced through this method display dramatically different properties from the parent-structure, which can subsequently be further modified through post-polymerisation modification.

There are several examples where CC has been employed to modify polymer brushes with high efficiency, however the development of this approach has been hindered due to the difficulty in installing unprotected reactive moieties into the original monomer pre-polymerisation. The robust sulfonyl fluoride moiety overcomes these inherent issues, allowing the formation of polymer brushes with pendant sulfonyl fluorides. Polymer brushes were grown from monomeric 3-(fluorosulfonyl)propyl methacrylate *via* radical polymerisation, resulting in a brush with sulfonyl fluoride moieties (**211**). Locklin and co-workers demonstrated the facile decoration of the synthesised polymer brushes through SuFEx modification with a variety of TBS-protected alcohols— subsequently allowing further post-polymerisation modification through additional click reactions (Scheme 42).



Scheme 42: Post-polymerisation SuFEx modification of polymer brushes mediated by TBD.

Interestingly, although DBU proved to be an effective catalyst for the polymer brush modification, the use of the guanidine base triazabicyclodecene (TBD) as an alternative resulted in a significant rate enhancement.[145]

Locklin and co-workers later described the reactivity and rates of polymer brush modification with SuFEx chemistry using three different polymer brush systems containing alkyl sulfonyl fluorides (**215**), aryl sulfonyl fluorides (**213**) and aryl fluorosulfates (**214**) reacted with three silyl ether derivatives (aryl, alkyl, benzyl) using different catalysts (Figure 14).[148] Aryl sulfonyl fluorides emerged as the most reactivity moiety, followed by alkyl sulfonyl fluorides and then aryl fluorosulfates, while it was also observed that aryl silyl ethers had a lower reaction rate than the corresponding alkyl species.

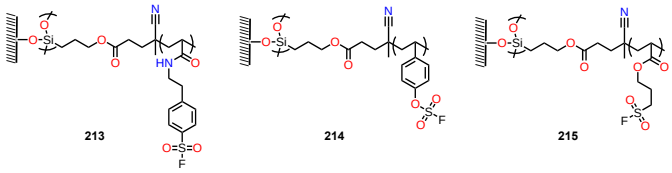
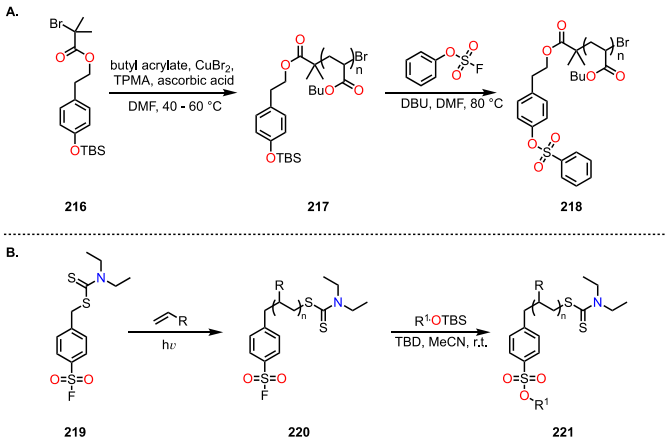


Figure 14: Functionalised polymer brushes used to explore reactivity of different sulfur fluoride moieties.

Reversing the reaction system to have TBDMS ethers on the surface of the polymer brushes to react with sulfonyl fluorides or fluorosulfates surprisingly did not occur.[148] Intriguingly, in direct contrast to results observed by Sharpless and co-workers for polysulfate synthesis,[141] the use of a bifluoride catalyst (TBABF) resulted in significantly slower reaction kinetics, when compared to the use of TBD and DBU. These and other interesting observations will no doubt contribute to the unravelling of the fine details of the underlying mechanisms behind SuFEx catalysis.

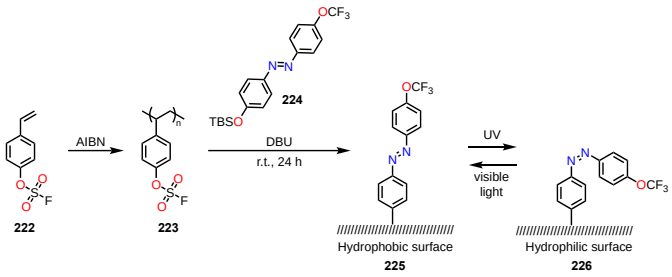
A related approach was pursued by Averick and co-workers, who employed SuFEx reactivity to functionalise the chain-ends of polymers prepared by electron transfer atom transfer radical polymerisation (Scheme 43A).[149] The activators of this technique were designed to include aryl silyl ethers, which were subsequently modified post-polymerisation. A small selection of chain-end functionalised polymers was synthesised using this methodology, once again highlighting that SuFEx is an extremely useful technique this field.

Chen and co-workers developed 4-(fluorosulfonyl)benzyl diethylcarbamodithioate (FSB-DECT, **219**) as a new photoinitiator that was also primed to undergo SuFEx reactions (Scheme 43B).[150] FSB-DECT was used to prepare a series of sulfonyl fluoride end-functionalised polymers (**220**), which were further functionalised by SuFEx reactions with aryl silyl ethers.



Scheme 43: A) SuFEx functionalisation of silyl ether protected polymer chain-ends by Averick and co-workers; B) Polymerisation and functionalisation of FSB-DECT (**215**) by Chen and co-workers.

SuFEx click chemistry has been used in a novel strategy for the separation of oil and water. Wu, Lu and co-workers employed the exchange reaction to install a photoreactive azobenzene (**224**) onto poly(4-vinylphenol sulfofluoridate) (**223**).[151] The SuFEx reaction produced a hydrophobic surface, with the azobenzene orientated in a *trans*-configuration (**225**). Subjecting the surface to ultraviolet light resulted in the isomerisation of the azo-linkage to the *cis*-configuration, generating a hydrophilic surface (**226**). This isomerisation proved reversible in the presence of visible light, therefore the material could be used for the selective separation of oils and water (Scheme 44).

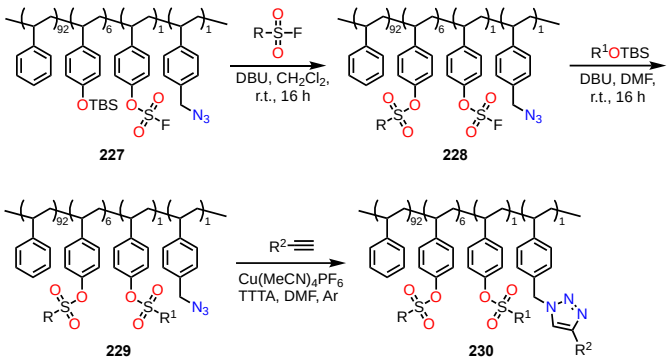


Scheme 44: The combination of SuFEx click chemistry and photoirradiation of azobenzenes to create hydrophobic and hydrophilic surfaces

In 2016, Fokin, Oakdale and Kwisnek applied SuFEx click chemistry in tandem with CuAAC to create a powerful and orthogonal post-polymerisation technique.[152] Co-polymers incorporating silyl ethers and fluorosulfates, for SuFEx reactivity, along with azides, for CuAAC, were synthesised with a radical initiator.

To demonstrate the orthogonal properties of the combined click-precursors, the copolymer was sequentially derivatised with functionalised dye molecules (Scheme 45). Under modified SuFEx conditions, the aryl silyl ether moiety on the copolymer was selectively reacted with a sulfonyl fluoride substrate, with minimal, if any, gelation noted due to potential cross-reactivity between the fluorosulfate and silyl ether groups. The impressive selectively is underpinned by the significantly higher reactivity of sulfonyl fluorides to the analogous fluorosulfate, particularly in less polar solvents.

Following the initial functionalisation, further highly efficient modifications through SuFEx and CuAAC reactions led to a triply functionalised polymer (**230**). Due to the distinct λ_{max} values of the different dyes (360, 425 and 550 nm respectively), the formation of the functionalised polymer could be elegantly demonstrated through GPC UV-vis detection.



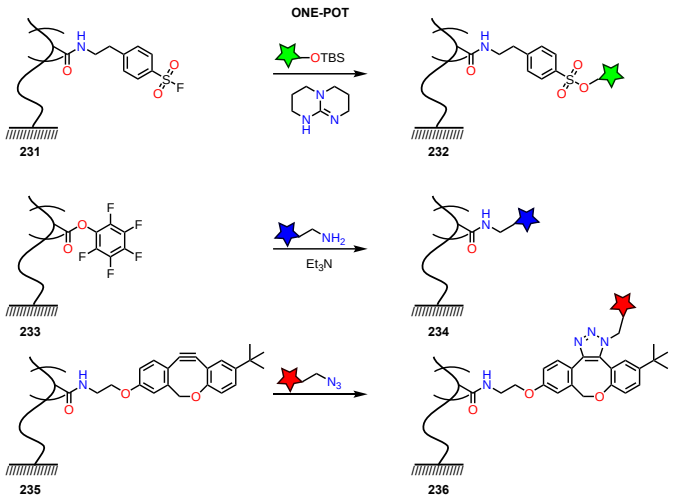
Scheme 45: Sequential and orthogonal SuFEx and CuAAC reactions in the synthesis of a triply functionalised polymer.

Further studies revealed that the SuFEx and CuAAC reactions were completely orthogonal, regardless of the order in which they were performed. It is also notable that the choice of CuAAC ligand (tris((1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl)-amine (TTTA) was completely benign under SuFEx conditions.

The SuFEx modification of co-polymers by Fokin and co-workers was complemented by related work of the Locklin group, where three distinct click reactions were performed in a simultaneous and orthogonal one-pot procedure to produce a tri-functionalised surface.[153]

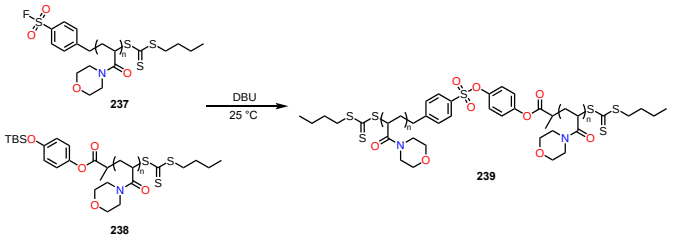
As a continuation of the post-polymerisation modification discussion (Scheme 42), poly(pentafluorophenylacrylate) brushes were synthesised, and areas selectively decorated with CC precursors, through reactive microcapillary printing (R-μCaP). The resultant surface contained aryl sulfonyl fluoride, oxa-dibenzocyclooctyne and pentafluorophenylacrylate moieties, which were primed to undergo SuFEx, SPAAC (strain-promoted alkyne-azide cycloaddition) and aminolysis reactions respectively (Scheme 46). Fluorescent dyes containing the complementary click functionality were added to the surface, and shown to react selectively, resulting in the formation of a checkboard patterned surface.

In 2017, Brendel and Perrier described a use of SuFEx click chemistry that contains elements of both of the above two subsections; polymers were synthesised to incorporate terminal SuFEx moieties, which were then employed to stitch together two different polymers in an equimolar manner (Scheme 47).[154] Two chain transfer agents (CTAs) were synthesised; one containing an aryl sulfonyl fluoride, and the other a complementary TBS-protected phenol. Materials were generated using RAFT polymerisation, with both the sulfonyl fluoride and silicon protecting group displaying excellent stability under radical conditions.



Scheme 46: Orthogonal, one-pot reaction of three distinct click reactions to a modified polymer brush.

Addition of a catalyst into a crude mixture of both CTAs (**237** and **238**) resulted in a polymer-polymer coupling reaction to form a sulfate linked polymer (**239**). Catalytic quantities of DBU resulted in excellent conversion, whereas the use of TBD gave substantially lower conversions, potentially due to the formation of a side product caused by nucleophilic attack of the guanidine moiety. Interestingly, the researchers highlighted the activity of TBAF trihydrate as a SuFEx catalyst. Near quantitative yields were generated rapidly, with a rate of reaction faster than that observed when using BEMP, the exemplar catalyst for SuFEx.



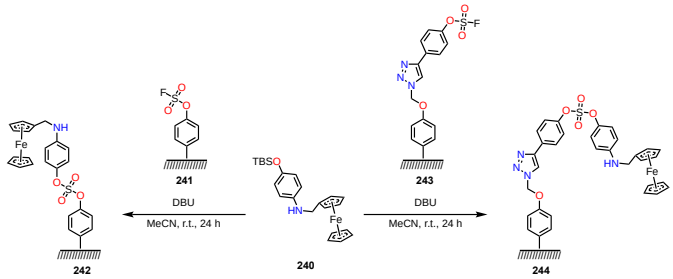
Scheme 47: Polymer-polymer coupling *via* SuFEx.

To expand the scope for further applications of SuFEx mediated polymer-polymer coupling, further classes of polymers were investigated. Styrenic (pS), acrylamido (pNAM) and acrylate (p(*t*-BA)) polymers classes were all explored, with both polystyrene and acrylamido polymers demonstrating excellent conversions in both homocoupling and cross-coupling experiments.

The work of Brendel and Perrier truly epitomises the underlying principles of SuFEx. The two key components (the sulfonyl fluoride and silyl ether in this instance) can be carried through a synthetic route silently, survive intact under forceful conditions (in this case, the use of radicals) and yet, when required, can be called upon to react rapidly with very high efficiency, even in crude polymerisation mixtures.

Surface functionalisation

In 2018, Moses and Henderson described the SuFEx modification of carbon fibre surfaces.[155] Two complementary approaches were employed; a 'pseudo-Graft to' approach, where a functionalised surface was fluorosulfonylated with SO_2F_2, and a 'pseudo-Graft from' approach, where an aryl fluorosulfate was directly installed onto the surface by electrochemical deposition (Scheme 48).



Scheme 48: Modification of carbon fibers by SuFEx click chemistry.

Surfaces **241** and **243** were treated with ferrocenyl silyl ether **240** to yield surface **242**, which contained a key sulfate linker, and surface **244**, which contained both a 1,2,3-triazole and sulfate functionality. Electrochemical examination of the surfaces, through the application of a potential sweep from – 1 V to +1 V showed remarkably distinct voltammograms. While surface **244** displayed a characteristic oxidation peak on the first sweep, the magnitude of this oxidation decreased markedly upon subsequent sweeps. Conversely, the cyclic voltammogram of surface **242** showed a stable signal over multiple sweeps. From these results, the researchers could infer that the 1,2,3-triazole is electrochemically unstable, whereas the sulfate linker installed by SuFEx shows superior stability.

Since the advent of SuFEx click chemistry, the majority of applications have centred around the exchange of the S-F bond with a phenol, forming new S-O linkages. The groups of Sharpless, Moses and Zuilhof noted that while extremely effective, this technique required the prior installation of silyl ethers, and instead postulated that the lesser explored S-N bond formation may be preferential for surface modification.[156]

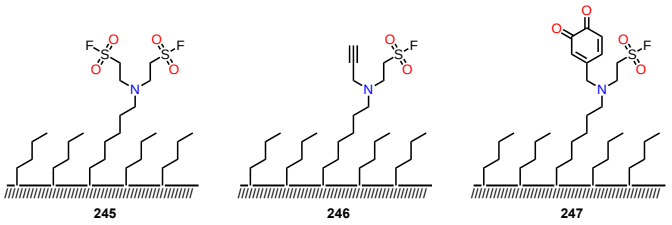


Figure 15: Surfaces decorated with SuFEx, CuAAC and SPOCQ functionality.

Amine terminated surfaces were prepared and reacted with ESF to quantitatively form the SuFExable surface **245** (Figure 15). Similarly, bromo-terminated surfaces were sequentially derivatised to provide the dual-functionalised surfaces **246** and **247**. The surfaces were then further functionalised by orthogonal SuFEx, CuAAC or SPOCQ reactions sequentially. Direct analysis in real time-high resolution mass spectrometry (DART-HRMS) and XPS measurements confirmed that the SuFEx reactions performed on these surfaces provided quantitative conversion, even in sterically congested environments.

Conclusions

In summary, we have presented and discussed a number of diverse and important examples of the growing applications of SuFEx click chemistry. No doubt the number of applications will continue to grow as SuFEx increasingly becomes a 'go-to' technology for the creation of functional molecules.

A significant challenge for the immediate future of SuFEx research is in the detailed understanding of the reaction mechanism. Numerous catalysts have been shown to be effective, and several general mechanistic observations realised, yet a unified mechanistic hypothesis accounting for all these observations has proven elusive. It is our view that a complete mechanistic understanding of the Sulfur-Fluoride exchange reaction will lay the foundations for the true potential of SuFEx to be exploited in the coming years and decades.

As for the future of click chemistry, well that is a question on history can truly answer—but guided by history and the plethora of discoveries that have been enabled by click principles and the 'blue collar' CuAAC and SuFEx click reactions, we can be confident that the future is certainly bright.

"On my thoughts about the future of click chemistry; probably the best are for SuFEx not for CuAAC. After all, CuAAC is a pretty brutally, single-minded business, but SuFEx is another beast entirely, which I sense holds the most 'magic' in the future I see for click chemistry.

Anyway it's the part that humans will come to love forever—the part, that, like life itself remains emergent and inscrutable, and teases us mercilessly into thinking we understand stuff.
But now we've got a reason smile and give her a taste of her own medicine — i.e. the 'sleeping beauty' phenomena —

Moreover, I would like to say that life and 'sleeping beauty's' do all their chemistry work at oil-water interfaces = the only place where life could possibly have 'been born' in this universe."[157]

K. B. Sharpless

Conflicts of interest

There are no conflicts to declare.

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