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ARTICLE

Synthetic Strategies for Fluorosulfonylated Compounds. Applications to Click Chemistry Reactions

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The syntheses and applications of fluorosulfonylated organic compounds have flourished in the last ten years due to their versatility to participate in click chemistry (SuFEx) reactions. Also, organic architectures that combine the SO_2F group and other ancillary functional moieties such as olefin, alkyne, etc. (i.e.: bis-electrophiles) have augmented the applications and diversity of the end compounds. To that effect, the association of an alkyne functionality and the *Suffexable* group within one structure, was shown to encompass two-in-one click chemistry sequential protocols with the aim of building on the diversity of scaffolds by two consecutive click processes. We next examine the syntheses of (hetero)aromatic-, alkyl-, alkenyl-, and alkynyl sulfonyl fluorides, β-keto-sulfonyl fluorides, and the syntheses of compounds bearing N-SO_2F and O-SO_2F bonding (Tables 1-4) through diverse catalytic methods, illustrating examples of their SuFEx click chemistry and other ancillary functional group reactivity

A.- INTRODUCTION

The association of sulfur and fluorine atoms has granted organic, biological and medicinal chemistry and material sciences, with most valuable groups, such as -SF_5,[1–3] -SF_4Cl,[1,2] -OSO_2F,[4–6] -SO_2CF_3,[7–10] -S(O)CF_3,[11,12] -SO_2R_F, -S(=O)(=N)(R)F,[13] and -SO_2F,[14] among others.

Sulfonyl fluorides (R(Ar)-SO_2F) are chemically stable towards reduction,[15] and hydrolysis,[16] and bear special proton-mediated reactivity.[14] The -SO_2F group, which is known to be stable under physiological conditions, has relevance in biological chemistry; as such, it encompasses a class of pharmacophores that provides permanent inhibition of target proteins. Furthermore, sulfonyl fluoride biological probes are being used worldwide.[17] Aromatic sulfonyl fluorides react chemoselectively with tyrosine in the presence of other nucleophilic amino residues. For instance, phenyl methyl sulfonyl fluoride (PMSF) and 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride (AEBSF, *Pefabloc®*) are protease inhibitors, and in the case of PMSF is widely applied in biochemistry.[18,19] In addition, there are above 150 approved drugs in the market that contain S(VI) functionalities.[20,21]

Sulfonyl fluorides have also widespread applications in the field of organic chemistry, as fluorinating reagents,[22,23] and synthetic precursors for the preparation of sulfonamides,[24] sulfones,[25] sulfonate esters,[4] and also ^{18}F radiolabeling.[26,27] Nonetheless, the most relevant application of sulfonyl fluorides is the sulfur(VI) fluoride exchange (SuFEx), considered a valuable click reaction as firstly proposed by Sharpless and coworkers in their seminal paper of 2014.[14] As definition of click reactions go, "*simple synthetic operational processes that work under oxygen, are water tolerant, afford products in high yields and with minimal purification requirements effecting carbon-heteroatom linkages*",[14] the sulfonyl fluoride group plays a central role as precursor of SO_2 connectors. Hence, sulfonyl fluorides have a particular interest in drug discovery as click functionality, which facilitate rapid derivatization of sulfonylated analogs in structure-activity relationships.

A typical approach to introduce the SO_2F is by fluorination of sulfonyl chlorides, employing KF/18-crown-6 in water,[28] or KHF_2.[14] Many reagents have been developed in the SuFEx field. Sulfuryl fluoride (SO_2F_2)[29], a gas reagent, can react with oxygen or nitrogen nucleophiles to afford fluorosulfates (or fluorosulfonates) or fluorosulfonamides, respectively, which in turn can function as click connectors for ulterior nucleophilic substitutions.

Ethene sulfonyl fluoride (ESF) (*vide infra*, Section C.2.2)[20] is considered a *bis*-electrophile for click chemistry.[30a,b] Thionyl tetrafluoride (SOF_4)[30c] provides two click sites by reaction with primary amino groups. 1-Bromoethene-1-sulfonyl fluoride (1-Br-ESF), with a bromide moiety connected to the vinyl group adjacent to the fluoride, has also been proposed as SuFEx reagent.[31]

Radical sulfur dioxide insertion/fluorination employing employing DABSO (1,4-diazabicyclo[2.2.2]octane bis(sulfur

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dioxide) adduct) as a SO_2 surrogate followed by electrophilic fluorination (or by inorganic fluoride sources) is another approach for obtaining sulfonyl fluorides.[32] Thus, there is a significant need for alternative methods (one-pot procedures) to synthesize aromatic and aliphatic sulfonyl fluorides, that allow the simultaneous incorporation of both SO_2 and F groups, without the requirement of previously installed SO_2 or F functionalities.

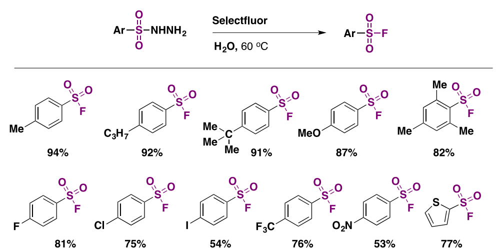
Recent review articles on the applications and reagents,[33] properties and reactions,[34a] of sulfonyl fluorides have been advanced, as well as an account on classification[34b] based on families of organic fluorosulfonylated compounds.[33,35] Radical synthetic procedures to obtain fluorosulfonylated *aliphatic compounds* have very recently been reviewed.[36,37] The extraordinary progress in the past years on the chemistry of sulfonyl fluorides is driven by the SuFEx chemistry which represents one of the most significant click reactions, with relevance in numerous fields and research areas.[38]

We next examine, from the organic chemistry perspective, the catalytic syntheses of (hetero)aromatic-, alkyl-, alkenyl-, and alkynyl sulfonyl fluorides, β-keto-sulfonyl fluorides, and the syntheses of compounds with N-SO_2F and O-SO_2F bonding, illustrating examples of their SuFEx chemistry and other ancillary functional group reactivity. A summary of all reactions is presented in Tables 1-4.

B.-Fluorosulfonylation of (Hetero)aromatic Compounds

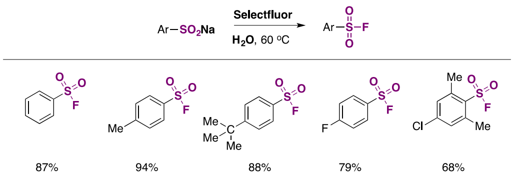
Apart from the classical Cl / F exchange in aryl sulfonyl chlorides, the synthesis of aromatic sulfonyl fluorides has been studied for some time. The reaction of disulfides with 6.5 equivalents of Selectfluor in refluxing acetonitrile/water (10:1) provided the sulfonyl fluoride in high yields.[39–41] Aryl sulfonamides can also be used as starting substrates for the synthesis of aryl sulfonyl fluorides.[42]

In 2016, an indirect metal-free method (a method employing substrates that already contain S) to obtain aromatic sulfonyl fluorides was reported by Tang, Wang, and collaborators.[43a] The method required pre-synthesized aryl sulfonyl hydrazides as starting materials but ran without catalyst or additives and was carried out in water under air atmosphere; the fluorinating agent was Selectfluor. The authors[43a] also attempted the fluorination in water from sodium arylsulfinates, resulting in good yields of arylfluorosulfonylated products. The scope of the reaction regarding sufonylhydrazides is depicted in Scheme 1.



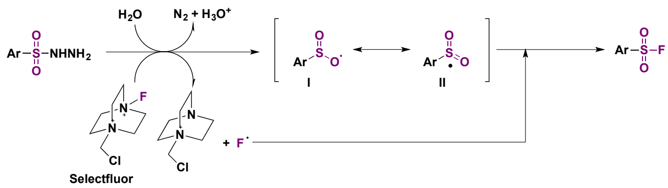
Scheme 1. Selected examples of fluorination of arylhydrazides in water

Substrates bearing both electron withdrawing and releasing groups afforded good yields of fluorosulfonylated products (Scheme 1). The scope regarding sodium arylsulfinates is presented in Scheme 2.



Scheme 2. Selected examples for the fluorination of sodium arylsulfinates in water

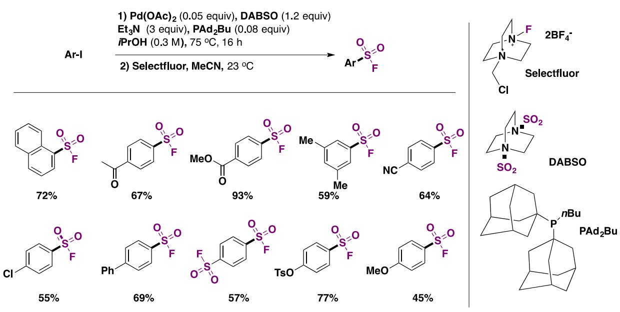
The authors studied the reaction mechanism. When radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperridinyloxy) was introduced in the reacting mixture, the formation of fluorosulfonylated product was suppressed, suggesting a free radical pathway. However, TEMPO had no effect on the reaction of sodium arylsulfinate salts. Consequently, the authors[43a] proposed a mechanism where the aryl sulfonylhydrazide reacts with Selectfluor to afford fluorine radical and radical intermediate **I**, releasing gaseous nitrogen in the presence of water and the acidic solution is formed (Scheme 3). Resonance forms **I** and **II** (Scheme 3) undergo fluorine atom transfer from Selectfluor to yield the sulfonyl fluoride.



Scheme 3. Proposed reaction mechanism

One advantage of the work of Wang[43a] is the innocuous reaction medium. However, the use of expensive Selectfluor limits the large-scale application of the protocol.

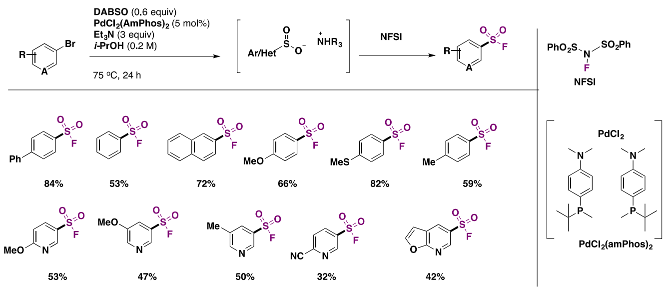
In 2017 Tribby, Ball and collaborators[4] have come up with a relatively simple method to convert aryl iodides to aryl sulfonyl fluorides, employing a Pd catalyst, DABSO as a SO_2 surrogate, Selectfluor as source of fluorine, in *iso*propyl alcohol as solvent, at 75 °C for 16 h. This protocol is a one-pot procedure and requires only column chromatography for product purification. The scope of the transformation is illustrated in Scheme 4.



Scheme 4. Selected examples for the fluorosulfonylation of aryl iodides

Aryl iodides with electron releasing and withdrawing groups could be converted to the respective sulfonyl fluorides (Scheme 4). Even 1,4-di-iodobenzene afforded the disubstitution product in good yield.The authors[4] utilized the above-described synthesized sulfonyl fluorides in click reactions with nucleophiles, obtaining coupling products with imidazole, phenol, 4-methoxyphenol, 4-aminophenol, among others.

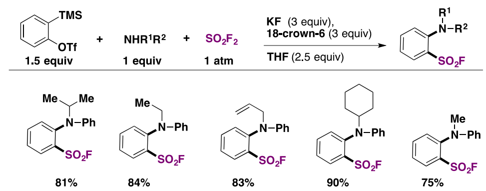
Later in 2017, Davies, Bagley, Willis and colleagues[32] employed (hetero)aryl bromides in a Pd-catalyzed fluorosulfonylation in the presence of DABSO as SO_2 surrogate, triethylamine, in *iso*propanol as solvent, at 75 ºC for 24 h. The scope of the transformation is illustrated in Scheme 5.



Scheme 5. Selected examples for the fluorosulfonylation of (hetero)arylbromides

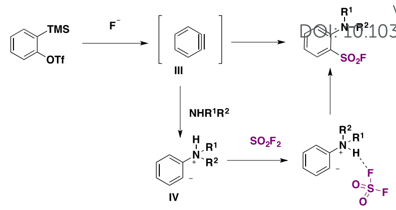
Aryl bromides with electron donating and neutral groups rendered good yields of fluorosulfonylated products. Bromopyridines with either electron donating or withdrawing groups rendered good yields of products as well. A comparison with the work of Ball and colleagues[4] shows that, in general, bromides render lower overall product yields than iodides, and somewhat harsher reaction conditions with regards to temperature should be applied in the case of bromides as compared to iodides.

A transition metal-free synthesis of arenesulfonyl fluorides from arynes was developed in 2019 by Kwon and Kim.[44] SO_2F_2 was used as fluorosulfonylating reagent. The aryne precursor was 2-(trimethylsilyl)phenyl trifluoromethanesulfonate in the presence of aniline derivative, KF/18-crown-6 in THF as solvent, according to Scheme 6.



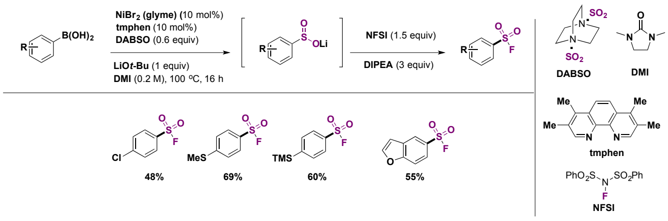
Scheme 6. Selected examples for the fluorosulfonylation of arynes

The authors[44] suggested a reaction mechanism such as that illustrated in Scheme 7. The aryne **III** is formed *in situ* by KF attack on 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, giving rise to zwitterion **IV**, which reacts with SO_2F_2 to render the product.



Scheme 7. Proposed reaction mechanism

In 2019 Lo, Wills and colleagues[45] carried out the syntheses of various (hetero)arylsulfones by Ni-catalysis from aryl boronic acids, among which the synthesis of (hetero)aryl fluorosulfones resulted quite convenient by this methodology. Selected examples are illustrated in Scheme 8.

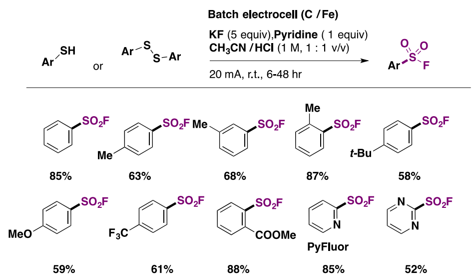


Scheme 8. Selected examples for the fluorosulfonylation of (hetero)aryl boronic acids

From Scheme 8, it is observed that aryl boronic acids with either electron withdrawing or releasing groups afforded good yields of fluorosulfonylated products.

In 2019, Lee, Ball, and Sammis employed SO_2F_2 as a fluorosulfonylating reagent of (hetero)aryl and alkyl magnesium salts (see Table 1).[46]

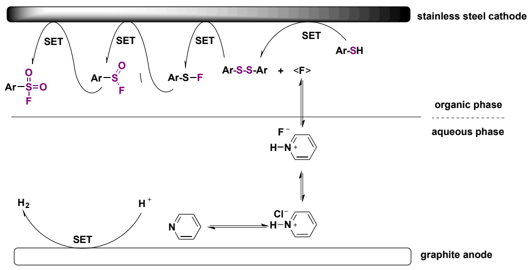
Laudadio, Nöel and colleagues[47] utilized aromatic sulfides or disulfides in inexpensive graphite/stainless steel electrodes to obtain fluorosulfonylated aromatic compounds. The electrochemical reaction involved the addition of pyridine (1 equiv.) as electron mediator or phase transfer catalyst, KF as fluorine source and electrolyte (5 equiv.) in a CH_3CN / 1 M HCl biphasic reaction mixture. The scope of the transformation is illustrated in Scheme 9.



Scheme 9. Scope of the electrochemical fluorosulfonylation of thiols

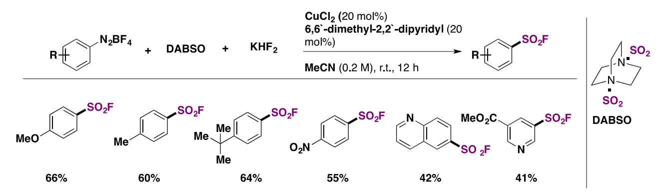
Electron neutral, donating and withdrawing groups attached to the aryl sulfide provided the respective fluorosulfonylated products in good yields. Also, it was noticed that steric congestion in the *ortho* positions of the aryl sulfides afforded products in good yields as well. The synthesis of pyridine-2-sulfonyl fluoride (Scheme 9, second row of products), also known as PyFluor (a deoxyfluorination reagent), could be accomplished in excellent yields.[22] The authors[47] rehearsed aliphatic thiols as well for the electrochemical fluorosulfonylation reaction (not shown) affording excellent yields of fluorosulfonylated aliphatic products.

The authors[47] investigated the reaction mechanism. Anodic oxidation of aryl sulfide to disulfide was confirmed by kinetic experiments. Oxidation of disulfide results in the radical cation,[48] which reacts with fluoride to render sulfenyl fluoride (Ar-SF, nucleophilic fluorination). The addition of TEMPO or butylated hydroxytoluene as radical scavengers lowers the efficacy of the electrochemical event, purporting to a radical process. A sulfinyl fluoride (Ar-SOF) intermediate was also detected, but could not be isolated, being sulfonic acid the major side product. The mechanism is described in Scheme 10.



Scheme 10. Mechanism for the electrochemical fluorosulfonylation of sulfides

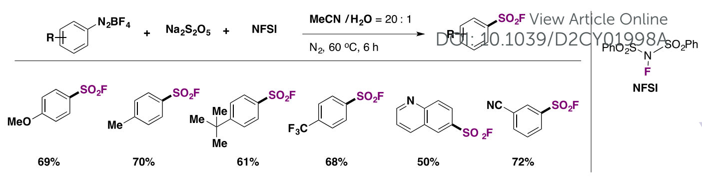
Arene diazonium salts have been employed since 2020 as aryl precursors for the syntheses of fluorosulfonylated arenes. Liu, Chen, Liu, and colleagues[49] proposed the use of DABSO as surrogate of SO_2, in the presence of KHF_2 and $CuCl_2$ salt and 6,6`-dimethyl-2,2`-dipyridyl as ligand to accomplish the fluorosulfonylation of tetrafluoroborate arene diazonium salts. Selected examples of the transformation are illustrated in Scheme 11.



Scheme 11. Selected examples for the fluorosulfonylation of aryldiazonium salts employing a Cu catalyst.

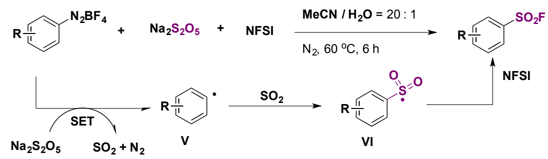
Both arenes with electron donating and withdrawing groups afforded the fluorosulfonylated products in good yields. The authors[49] investigated the reaction mechanism and concluded that the mechanistic pathways depended on the electronic nature of the arene. They also applied the SuFEx chemistry and obtained coupling products from aryl fluorosulfonates (sulphates, sulfonamides, etc.).

Liu, Qing, and colleagues[50] improved on the technique by Liu and co-workers[49] doing without the Cu catalyst and the costly DABSO reagent, replacing this latter with $Na_2S_2O_5$ as SO_2 source. However, the source of F is the more costly NFSI (*N*-fluorobenzenesulfonimide) rather than the inexpensive KHF_2 employed by Liu.[49] In Scheme 12, a brief scope of the fluorosulfonylation of arenediazonium salts is presented.



Scheme 12. Scope for the fluorosulfonylation of arenediazonium salts with $Na_2S_2O_5$ as source of SO_2 and NFSI as the F contributor

Comparing yields from identical products between the two methodologies described in Schemes 11 (Liu and colleagues`) and Scheme 12 (Qing and collaborators`), similar reaction efficacies are observed from 4-methoxybenzenediazonium, 4-methylbenzenediazonium, 4-*tert*-butylbenzenediazonium, and 6-(diazenyl)quinoline tetrafluoroborate salts. Qing[50] established a radical mechanism to account for product formation. Use of radical scavenger TEMPO inhibited product formation. A postulated mechanism includes the formation of an aryl radical by ET from the benzenediazonium tetrafluoroborate salt. Radical intermediate **V** (Scheme 13) reacts with $Na_2S_2O_5$ to generate radical intermediate **VI**, which by fluorine atom transfer from NFSI renders the product.



Scheme 13. Proposed reaction mechanism

Confronting the works of Liu and Qing, the former requires a transition metal catalyst (in sub-stochiometric quantities) and an expensive SO_2 surrogate (DABSO) but cheap fluorine source (KHF_2), while the work of Qing employs an inexpensive source of SO_2 ($Na_2S_2O_5$) but a rather costly source of fluorine (NFSI). From an environmental perspective, the protocol by Qing allows aqueous MeCN mixtures to be employed in the reactions.

At the same time that appeared the report by Qing, Liu and colleagues[51] introduced a variant of the work of Qing, this time employing $K_2S_2O_5$ as source of SO_2, NFSI as F atom provider, in MeCN / H_2O / HOAc and benzenediazonium tetrafluoroborates as starting substrates. The reactions were carried out at room temperature, for 6 h, and yields of products were comparable to the other two methodologies.[49,50] After this report, the group of Liu,[52] informed the one-pot strategy to obtain fluorosulfonyl arenes directly from anilines.

Zhong, Weng and colleagues,[53] also in 2020, informed the fluorosulfonylation of arene tetrafluoroborate salts employing $Na_2S_2O_5$ as source of SO_2, Selectfluor as the F atom provider, in methanol as solvent, at 70 ºC, for 9 h. The yields of the respective fluorosulfonylated arenes are high.

Louvel, Tlili, and collaborators,[54] reported the photocatalyzed substitution of aryldiazonium salts with SO_2F group employing DABSO as source of SO_2, KHF_2 as source of F, in MeCN as solvent and an organic photocatalyst, 2,4,6-*tris*(diphenylamino)-5-fluoro*iso*phthalonitrile (3DPAFIPN),

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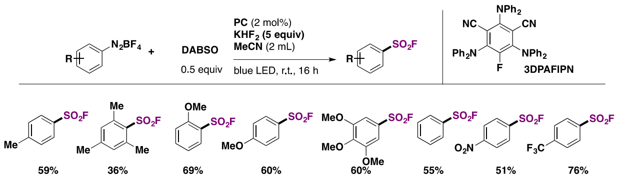
irradiating with blue LEDs. A scope of the transformation is illustrated in Scheme 14.



Scheme 14. Selected examples for the 3DPAFIPN-photocatalyzed fluorosulfonylation of aryl diazonium salts

Bui, Tran and Kim[55] have very recently developed a visible-light mediated methodology for the synthesis of sulfonyl fluorides starting from aryl azo sulfones. In this report, $K_2S_2O_5$ and NFSI were used as sulfonyl and fluorine sources respectively. All the reactions were carried out at room temperature, in aqueous mixtures to obtain the desired products in 60-85% yields.

All the methodologies available to synthesize aromatic fluorosulfonylated products are displayed in Table 1.

C.- Aliphatic Fluorosulfonylations

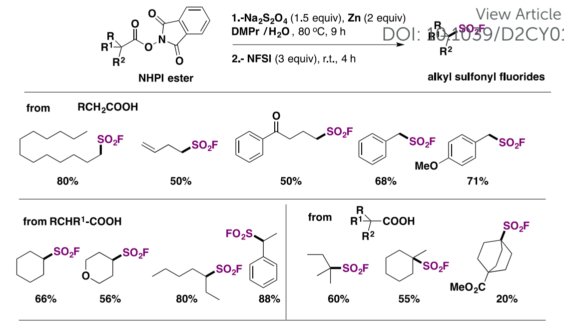
C.1.-Syntheses of Alkyl Sulfonyl Fluorides

Alkyl sulfonyl fluorides bear relevance in different fields, such as chemical biology, medicinal chemistry, and synthetic organic chemistry. Aliphatic sulfonyl fluorides have significant relevance as peptide-type inhibitors.[56–58]

Typical methods for the syntheses of aliphatic sulfonyl fluorides involve classical Cl / F exchange from the corresponding chlorides,[14] or starting from alkyl halides, thiols or disulfides and performing Cl / F exchange, or the addition of SO_2F Michael acceptors such as ESF.[59–61] Synthetic methods via radical sulfur dioxide insertion/fluorination also provide aliphatic sulfonyl fluorides.[62–65]

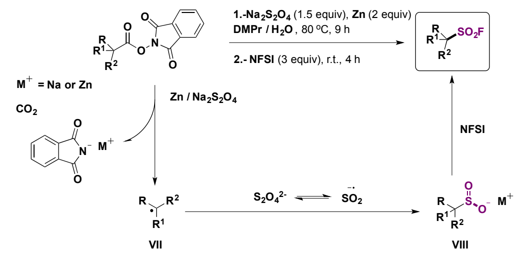
In 2016, the group of Shavnya[66] converted alkyl bromides into alkyl sulfonyl fluorides utilizing rongalite (hydroxymethylsulfinate), NFSI in reasonably good yields (see Table 2).[67]

Ma, Ma, Liu and collaborators[68] have recently achieved the direct syntheses of aliphatic sulfonyl fluorides, starting from *N*-hydroxyphthalimide (NHPI) esters (Scheme 15) in the presence of $Na_2S_2O_4$, Zn, in a mixture of *N,N*-dimethylpropionamide (DMPr) / H_2O (5 : 1 v/v) as reaction medium, under Ar-atmosphere, at 80 ºC , for 9 h, then NFSI at room temperature for additional 4 h. The scope of the transformation is illustrated in Scheme 15.



Scheme 15. Selected examples for the radical fluorosufonylation of NHPI esters

Scheme 15 shows that the current protocol[68] can convert primary, secondary and tertiary carboxylic acids into their respective sulfonyl fluorides through the NHPI ester derivatives. The authors also proposed a reaction mechanism to account for product formation, according to Scheme 16.



Scheme 16. Proposed reaction mechanism

The authors[68] performed some control experiments with radical scavengers (TEMPO) and radical clocks (the NHPI ester derived from 2-cyclopropylacetic acid) which indicated the presence of free radicals. On the basis of experimental results, a reductive decarboxylation of NHPI ester employing $Na_2S_2O_4$ / Zn generates the corresponding alkyl radical intermediate (**VII**, Scheme 16), which is subsequently trapped by SO_2 radical anion to form the alkyl sulfinate (**VIII**). Electrophilic fluorination by NFSI afforded the product.

Nie and collaborators[69] reported on a photocatalytic methodology for accessing aliphatic sulfonyl fluorides based on a visible light-mediated photocatalyzed decarboxylative fluorosulfonylation of aliphatic NHPI esters. Optimized reaction conditions were achieved when $Ir[(dF(CF_3)ppy]_2(dtbbpy)PF_6$ ($[Ir^{III}]$) was employed as photocatalyst, *N*-ethyldi*iso*propylamine (DIPEA) as sacrificial reductant, DABSO as SO_2 source, in *iso*propanol as solvent and under blue light irradiation in Ar atmosphere. Then NFSI was allowed to react with the sulphonyl radical previously formed, affording the aliphatic sulfonyl fluoride in very good to excellent yields. The methodology proved to work very satisfactorily with a variety of primary, secondary, and tertiary carboxylic acid NHPI esters, including derivatives of pharmacologically active drugs such as *Oxaprozin* and *Flubiprofen*, among others (Scheme 17). Regarding the reaction mechanism, the authors[69] proposed a reductive photocatalytic cycle mediated by the $[Ir^{III}]$ photocatalyst. Upon light excitation, the exited $[Ir^{III}]^*$ undergoes a single electron transfer process with DIPEA affording the $[Ir^{II}]$ specie and $DIPEA^{\bullet +}$. Subsequently, the NHPI ester is reduced by $[Ir^{II}]$

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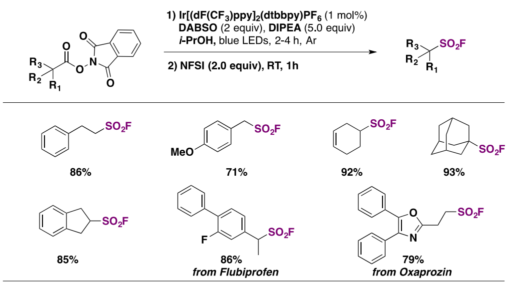
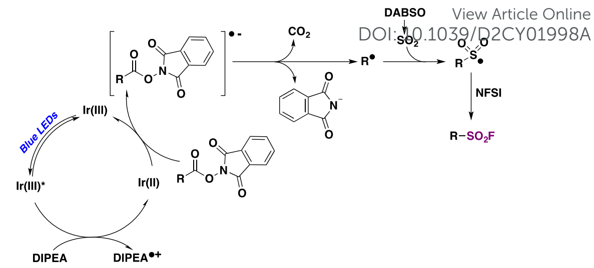
affording the alkyl radical (R•) and regenerating the [Ir^{III}] photocatalyst. The reaction of SO_2 (released from DABSO) with the R• gives rise to a sulphonyl radical which is captured by NFSI, through fluorine atom transfer, affording the aliphatic sulfonyl fluoride product (Scheme 18).

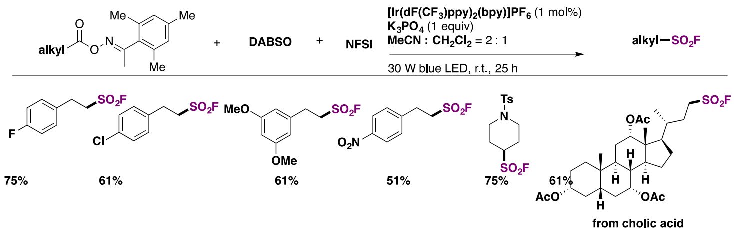


Scheme 17. Selected examples for the photocatalytic fluorosulfonylation of aliphatic carboxylic acids NHPI esters



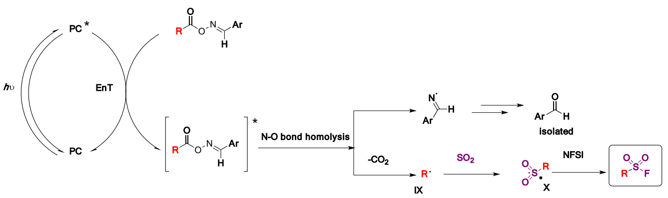
Scheme 18. Proposed reaction mechanism

In 2022, Chen, Weng, and colleagues[65a] achieved the photocatalytic decarboxylative[65b] direct fluorosulfonylation of oxime esters by energy transfer, in the presence of DABSO and NFSI reagents to yield alkyl-fluorosulfonylated products. The scope of the transformation is illustrated in Scheme 19.



Scheme 19. Scope of the Ir-photocatalyzed decarboxylative direct fluorosulfonylation of oxime esters by energy transfer (EnT), in the presence of DABSO and NFSI reagents to yield alkyl-fluorosulfonylated products

The authors[65] investigated the reaction mechanism. They obtained evidence of the N-O bond scission in oxime esters that generated the iminyl radicals. To commence with, irradiation from blue LEDs generates the triplet excited state of the photocatalyst (E_T = 60.42 Kcal/mol), which transfers its triplet energy to the oxime ester (E_T = 49.78 Kcal/mol), undergoing, this latter N-O bond homolysis to produce iminyl radicals and alkyl radicals, after releasing CO_2. Subsequently, the alkyl radical (**IX**) is trapped by DABSO to yield the alkylsulfonyl radical (**X**), which by F transfer from NFSI affords the alkylfluorosulfonylation product (Scheme 20).



Scheme 20. Proposed reaction mechanism

Weng and collaborators[70] developed two different copper-catalyzed *direct* decarboxylative fluorosulfonylation methodologies of aliphatic carboxylic acids and made the resulting alkyl radicals react with a SO_2 / fluorine sources to render the fluorosulfonylated alkyl derivative. These strategies are very attractive because they do not require previous derivatization of the carboxylic acid functionality. In the first methodology, limited only to 3-arylpropionic acids, a Cu/*N*-fluorobenzenesulfonimide (NFSI) catalytic system is employed to perform the decarboxylative fluorosulfonylation, where NFSI is both used as fluorine source and hydrogen atom transfer (HAT) agent, assisting on the homolytic cleavage of carboxylic acid O-H bonds.

The second and more appealing strategy, which presents a much wider substrate scope, utilizes 9-mesitylacridine (Acr) as photocatalyst, DABSO as SO_2 source, Selectfluor as fluorine donor, in dichloromethane as solvent and in the presence of Cu and 5,5'-dimethyl-2,2'-bipyridine (L2) under 400 nm LEDs irradiation and N_2 saturation conditions.[70] Regarding the substrate scope, the reaction performed well with a range of primary, secondary, and tertiary carboxylic acids, affording the corresponding sulfonyl fluorides in moderate to good yields (Scheme 21). The authors[70] proposed a reaction mechanism initiated by hydrogen abstraction of the carboxylic acid O-H bond by the exited photocatalyst (Acr*). The resulting carboxyl radical undergoes CO_2 loss affording an alkyl radical (R•) that reacts with SO_2, generated by DABSO decomposition, affording a sulphonyl radical. A L2Cu^{I} complex abstracts a fluorine atom from Selectfluor yielding a L2Cu^{II}F adduct and Selectfluor radical dication. Then, the sulfonyl radical abstracts a fluorine atom from the L2Cu^{II}F adduct giving rise to the aliphatic sulfonyl fluoride product and regenerating the L2Cu^{I} complex. On the other hand, Selectfluor radical dication abstracts a hydrogen atom from AcrH regenerating the photocatalyst and closing the catalytic cycle (Scheme 22).

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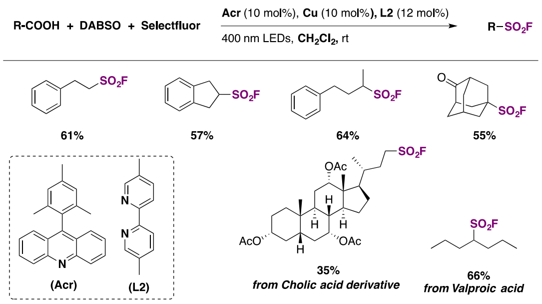
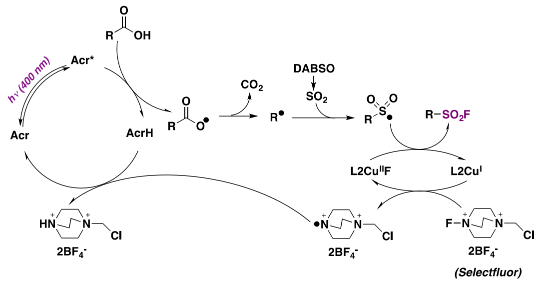
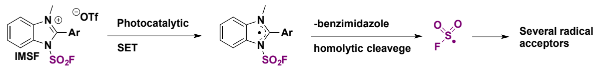


Scheme 21. Selected examples for the photocatalytic fluorosulfonylation of aliphatic carboxylic acids



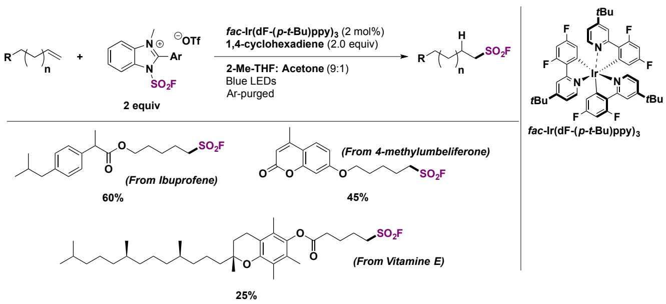
Scheme 22. Proposed reaction mechanism

Wang and colleagues[71] employed the redox-active solid imidazolium fluorosulfonyl salt (IMSF) to carry out the late-stage radical hydrofluorosulfonylation of drug molecules and natural products. This reagent reacted through a single electron transfer process and generated the fluorosulfonyl radical under visible light photocatalytic conditions (Scheme 23).



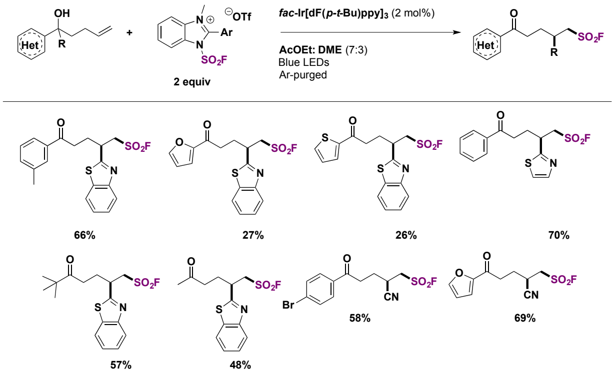
Scheme 23. Fluorosulfonyl radical formation with an Imidazolium fluorosulfonate salt

Selected examples for the use of IMSF in relevant substrates are illustrated in Scheme 24. Using an Iridium photocatalyst, 1,4-ciclohexadiene as hydrogen atom donor and the IMSF salt under visible light irradiation, terminal alkene derivates of drug molecules such as *ibuprofen* and 4-methylumbeliferone or natural products (vitamin E) were obtained with good regioselectivity.



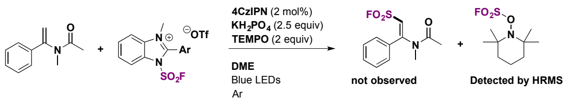
Scheme 24. Selected examples of the radical hydrofluorosulfonylation

An alternative use of the IMSF salt[71] was also presented for the difunctionalization of alkenes. Employing unsaturated tertiary alcohols, the reaction proceeded through distal migration induced by the fluorosulfonyl radical. This protocol required an Iridium photocatalyst and several aryl groups were well tolerated, as shown in Scheme 25.



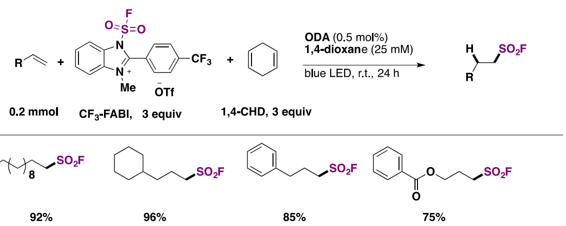
Scheme 25. Radical migration fluorosulfonylation: substrate scope

To explore the mechanistic aspect of the radical fluorosulfonylation protocol a control experiment was carried out using TEMPO under an alkenyl functionalization conditions. The addition of the fluorosulfonyl radical to the unsaturated substrate was completely inhibited, and only TEMPO-fluorosulfonyl adduct was detected by high resolution mass spectrometry (Scheme 26).



Scheme 26. Fluorosulfonylation of alkenes: control experiment with TEMPO

The hydro fluorosulfonylation of alkenes[72] was also recently accomplished by Wang, Liao, and colleagues.[73] The study was challenged by the fact that when $ClSO_2F$ was employed as SO_2F radical precursor, a chloro-fluorosulfonylated product (ATRA product) was obtained from the olefin under photocatalytic conditions in the presence of H atom donors (such as 1,4-CHD), due to the low BDE of Cl-SO_2F bond. The authors[73] developed 1-fluorosulfonyl 2-aryl benzoimidazolium triflate (CF_3-FABI, *vide infra*) as fluorosulfonyl radical precursor. The photocatalyst used was oxygen-doped anthracene (ODA), in 1,4-dioxane as solvent under irradiation with blue LEDs. A brief scope of the transformation is depicted in Scheme 27.

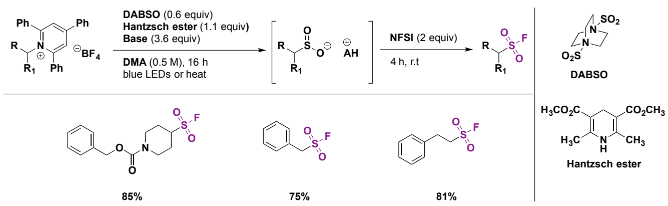


Scheme 27. Succinct examples for the oxygen-doped anthracene-photocatalyzed hydro fluorosulfonylation of alkenes with FABI

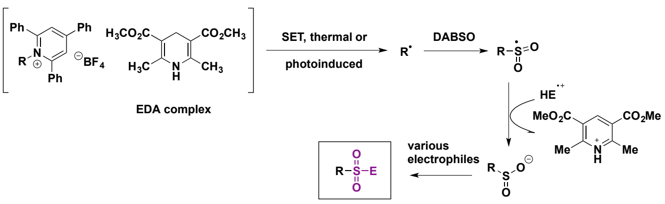
In a 2019 report, Andrews, Willis and colleagues[74] presented a protocol for the synthesis of alkyl sulfonyl derivates from readily available amines via Katritzky pyridinium salt intermediates. This strategy employed a primary or secondary

Katritzky salt, DABSO as SO_2 source, an organic base (Et_3N, 2,6-lutidine or piperidine) and the Hantzsch ester to prepare a sulfinate salt who could react with several electrophiles to generate the alkyl sulfonyl derivates or the fluorine sulfonyl compounds.

The reaction pathway is shown in Scheme 28. The radical species can be generated by photoinduced electron transfer from electron donor-acceptor complex (EDA) between Katrintzky salts and the Hantzsch ester. This very convenient catalyst-free strategy allows to generate the alkyl radical who reacts with a SO_2 source (DABSO) and produces the sulfonyl radical. Sulfonyl radical can undergo a hydrogen atom transfer (HAT) reaction from the Hantzsch ester, and an ulterior deprotonation to afford the sulfinate salt. Subsequently *in-situ* reaction with several electrophiles provided diverse sulfonyl-derivates.



Scheme 28. Catalyst-free deaminative synthesis of sulfonyl-derivates

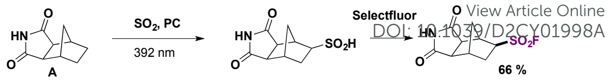


Scheme 29. Functionalization of Sulfinates salts employ NFSI

This methodology was successfully applied to the synthesis of > 60 examples of sulfones (from the corresponding secondary, benzylic and primary amines), sulfonamides and sulfonyl fluorides (Scheme 29). This reaction was carried out by a one-pot procedure and products could be obtained under bulk conditions (10 mmol of substrate) with very good yields.

The authors also performed UV-visible experiments from mixtures of Katritzky pyridinium salts and Hantzsch ester in DMA as solvent, showing a significant bathochromic shift when compared to the isolated components, strongly suggesting the formation of the EDA complex. They also attempted the reaction in the presence of TEMPO, where only the starting materials were observed, supporting the presence of radicals in the reaction mixtures.

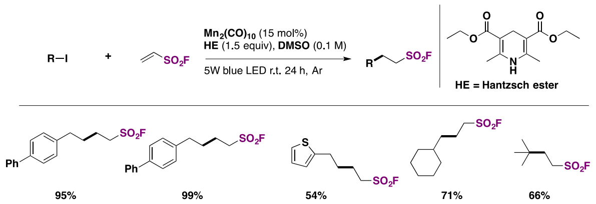
In 2021 MacMillan and co-workers reported the development of a decatungstate-catalyzed conversion of C(sp^3)-H bonds into the corresponding alkyl sulfinic acids.[75a] The authors[75a] employed this methodology for the synthesis of several organosulfur compounds. They performed the functionalization of the tricyclic imide **A** shown in Scheme 30. The sulfinic acid intermediate was converted to the corresponding sulfonyl fluoride using Selectfluor as fluorine source.



Scheme 30. A selected example for the Decatungstate-catalyzed conversion of C(sp^3)-H bonds into the corresponding alkyl sulfinic acids and ulterior fluorination

Indirect methods (those making use of fluorosulfonylated hubs such as ESF) to synthesize alkyl fluorosulfonyl compounds have also been developed.

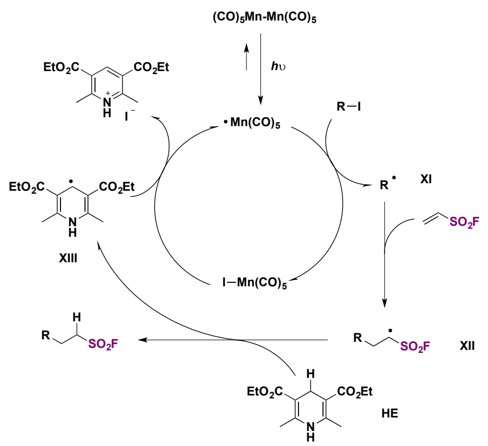
Zhang, Qin, and colleagues[60] achieved the syntheses of alkyl sulfonyl fluorides through photocatalysis, employing ESF[75b] (see section C.2.2.-), and an alkyl iodide with $Mn_2(CO)_{10}$ as photocatalyst, Hantzsch ester as reductant in DMSO as solvent, under blue LEDs illumination. The scope of the reaction is illustrated in Scheme 31.



Scheme 31. Selected examples for the photocatalyzed syntheses of fluorosulfonylated alkyl compounds from alkyl iodides

The authors[60] expanded the scope of the methodology by synthesizing potentially biological active alkyl sulfonyl fluorides from steroids, *zidovudine*, *chloramphenicol, thiamphenicol* and other pharmacophores, obtaining the respective alkyl-fluorosulfonylated-substituted compounds in good yields.

The authors investigated the reaction mechanism and made a proposal such as that depicted in Scheme 32. The photocatalyst is excited by illumination from the LED source producing the Mn-Mn homolytic cleavage affording $Mn(CO)_5$ radicals, which through I atom transfer from alkyl iodide, produce an alkyl radical intermediate (**XI**), and $Mn(CO)_5$-I. Alkyl radical intermediate **XI** adds to ESF to render intermediate **XII**, which abstracts a H atom from the Hantzsch ester **HE** to afford the product. In turn, the radical from **HE**, **XIII**, is oxidized and rearomatizes to a pyridinium iodide (Scheme 32).



Scheme 32. Proposed reaction mechanism

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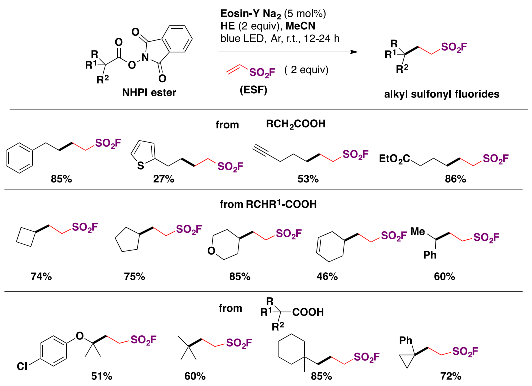
In 2019, Xu, Liao and colleagues[76a] carried out the indirect syntheses of alkyl-substituted sulfonyl fluorides by a photocatalyzed decarboxylative reaction of NHPI esters and ESF (section C.2.2.-) as source of sulfonyl fluoride, in the presence of Hantzsch ester (HE) in MeCN as solvent under irradiation with blue LEDs. A succinct scope of the transformation is illustrated in Scheme 33.



Scheme 33. Scope for the photocatalytic preparation of aliphatic sulfonyl fluorides from NHPI esters and ESF

Primary, secondary and tertiary carboxylic acids afforded good yields of the respective alkyl fluorosulfonylated products. All the methodologies available to synthesize alkyl-substituted fluorosulfonylated products are displayed in Table 2.

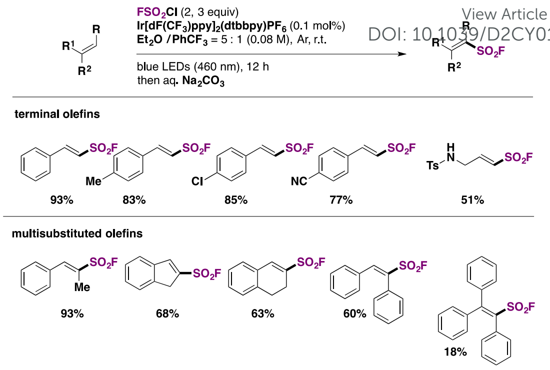
C.2.-Syntheses of Fluorosulfonylated Alkenes

Fluorosulfonylated alkenes[76b] can be synthesized either through direct fluorosulfonylation strategies (C.2.1.-) from olefins or alkynes, or by employing fluorosulfonylating hubs (pre-installed SO_2F moiety, C.2.2.-), such as ESF and its derivatives or by using SO_2 and NFSI.[63]

C.2.1.- Direct Strategies to Synthesize Fluorosulfonylated Alkenes

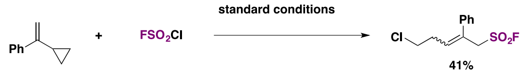
Direct fluorosulfonylation of alkenes, bypassing the use of installed FSO_2-containing hubs, has been lately developed, specially by radical methodologies.[36]

The difficulty of generation of FSO_2 radical has thwarted advances in the study of this unstable species.[77] The group of Liao[78] managed to generate the FSO_2 radical by photoredox conditions. The precursor of FSO_2 radical was FSO_2Cl, employing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 as photocatalyst under blue LEDs irradiation in Et_2O / $PhCF_3$ mixture of solvents. The scope of the transformation is depicted in Scheme 34.



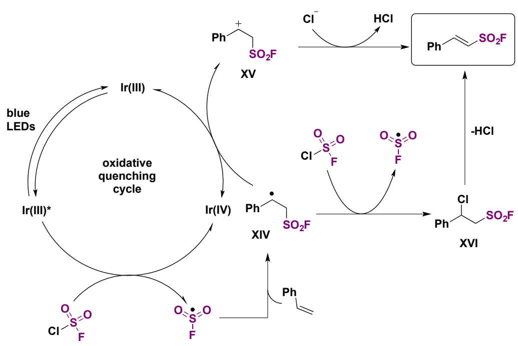
Scheme 34. Selected examples for radical fluorosulfonylation of alkenes

Both electron donating and electron-withdrawing substituted styryl systems afforded the respective fluorosulfonylated products in good yields (Scheme 34). Also, internal 1,2-disubstituted alkenes and trisubstituted alkenes afforded reasonable yields of the fluorosulfonylated olefins. The authors investigated the reaction mechanism[78] performing some radical probe experiments, such as the use of radical scavenger TEMPO. Under these latter conditions, a total inhibition of the fluorosulfonylated olefinic product was observed. A radical probe experiment with radical clock 1-phenyl-1-cyclopropyl ethylene afforded the ring opening product shown in Scheme 35.



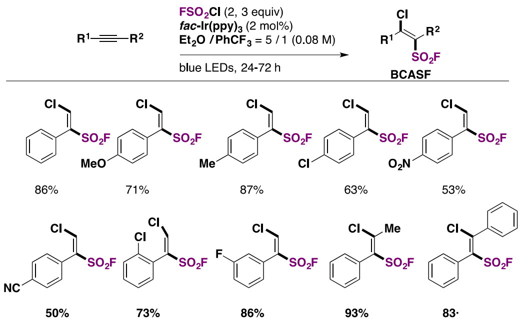
Scheme 35. Radical clock experiment with 1-phenyl-1-cyclopropyl ethylene

These latter experiments indicated the presence of free radicals in the reaction. Comparative DFT calculations between the CF_3SO_2 and FSO_2 radicals also showed that the latter has a more planar configuration and a more positive sulfur atom, consistent with the higher electronegativity of F compared to CF_3. The authors[78] postulated a reaction mechanism such as that shown in Scheme 36. The Ir(III) photocatalyst is excited to its triplet manifold by illumination from the blue LEDs, which by a SET reaction to FSO_2Cl renders the FSO_2 radical and chloride anion. FSO_2 radical readily reacts with the olefin to supply intermediate **XIV** (Scheme 36), which can either be oxidized by the upper oxidation state of the photocatalyst (i.e.: Ir(IV)) to render **XV**, which is deprotonated to yield the final product, or else **XIV** can suffer a chlorine atom transfer from $ClSO_2F$ to render **XVI**, which loses HCl to give the product (Scheme 36).



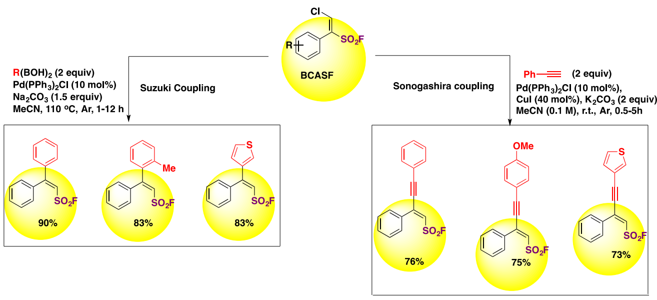
Scheme 36. Proposed reaction mechanism

Nie, Liao, and colleagues,[79] utilized FSO_2Cl as the chloro-fluorosulfonylating reagent, which under blue LEDs (λ_{max} = 460 nm) illumination in the presence of *fac*-Ir(ppy)$_3$ photocatalyst, an alkyne substrate in Et_2O/$PhCF_3$ mixture of solvents, afforded β-chloro alkenylsulfonyl fluoride (BCASF) in good yields. The scope of the reaction is illustrated in Scheme 37.



Scheme 37. Selected examples for the photocatalyzed syntheses of BCASFs

Both electron withdrawing and donating groups on the arylacetylenes rendered good yields of BCASF products. Also, internal alkynes are appropriate substrates for the reaction. β-Chloro alkenylsulfonyl fluoride (BCASF) hubs are powerful entities for introducing alkyl, alkenyl and alkynyl groups onto the β-position of BCASF through coupling reactions, affording β,β-disubstituted ethylenesulfonyl fluorides and ynenyl-sulfonyl fluorides (*vide infra*, Scheme 38). The authors[79] profited from the chlorine handle of the BCASFs substrates to perform coupling reactions. A Suzuki coupling with boronic acids and Sonogashira coupling with terminal alkynes. Some of these examples are depicted in Scheme 38.



Scheme 38. Suzuki- and Sonogashira-type couplings of BCASFs

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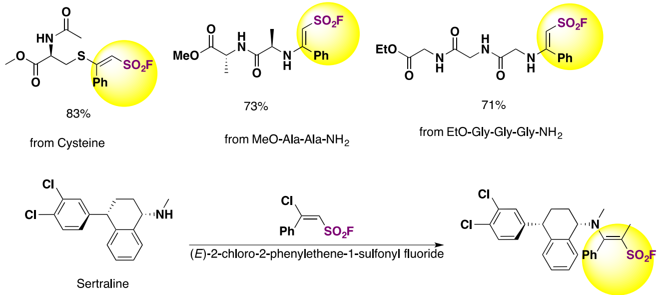
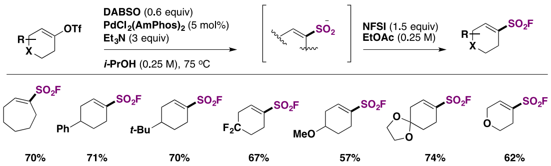
The authors[79] employed the BCASFs as sulfonyl carriers in amino acids, peptides and drugs. Cysteine and *N*-terminals of peptides were thus modified by (*E*)-2-chloro-2-phenylethene-1-sulfonyl fluoride (Ph-BCASF) to afford peptides shown in Scheme 39.



Scheme 39. Cysteine, *N*-terminals of peptides and drugs modified by (*E*)-2-chloro-2-phenylethene-1-sulfonyl fluoride (Ph-BCASF)

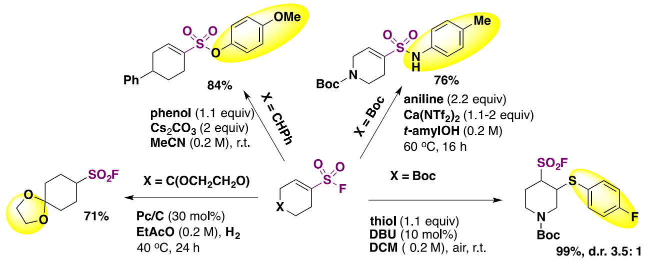
The authors[79] also attempted the *E* / *Z* isomerization of the BCASFs. *N,N*-di*iso*propylethyleneamine (DIPEA) was found effective for this goal.

Lou, Willis and collaborators[80] achieved the synthesis of fluorosulfonylated cycloalkenes through the use of DABSO, a Pd catalyst and NFSI as fluorine source. The scope for the syntheses of cyclic alkenyl sulfonyl fluorides is depicted in Scheme 40.



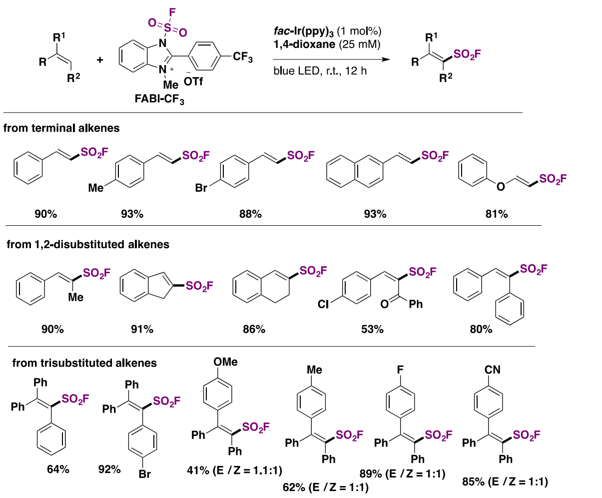
Scheme 40. Selected examples for the syntheses of cyclic alkenyl sulfonyl fluorides

The authors[80] investigated derivatization reactions. Substitution of alkenyl sulfonyl fluorides at the sulfur atom was done with 4-methoxyphenol, to form sulfonate esters, or with anilines to form sulfonamides (Scheme 41).



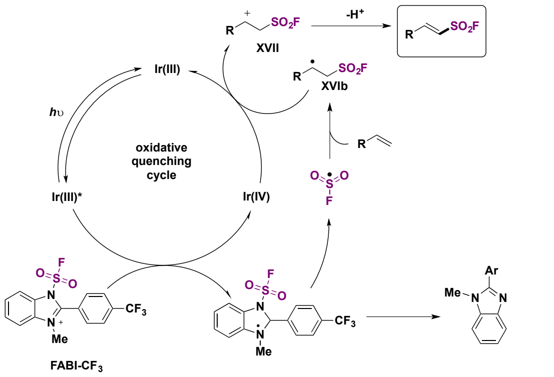
Scheme 41. Derivatization of alkenyl sulfonyl fluorides

In 2022, the group of Liao[81] developed a strategy for the synthesis of fluorosulfonylated alkenes, employing FABI-CF_3 (Scheme 42) as fluorosulfonyl radical precursor. Under *fac*-Ir(ppy)$_3$ photocatalysis, in 1,4-dioxane as solvent and under blue LEDs irradiation, fluorosulfonylated alkenes were obtained. Scheme 42 illustrates some examples of this transformation.



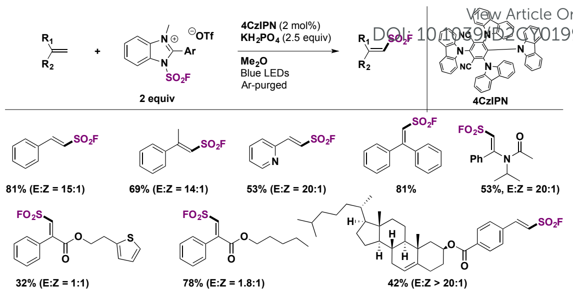
Scheme 42. Scope of the photocatalyzed fluorosulfonylation of alkenes

The authors investigated the reaction mechanism. A mechanistic proposal is depicted in Scheme 43. Irradiation of the photocatalyst $Ir(ppy)_3$ by blue LEDs generates the triplet excited state of Ir(III)* ($E_{1/2\ Ir(IV)/Ir(III)*}$ = -1.73 V vs SCE), undergoing a SET to FABI-CF_3 ($E_{1/2\ red}$ = -1.07 V vs SCE), which suffers a homolytic cleavage of the N-S bond to render FSO_2 radicals. In turn, FSO_2 radicals add to the styrene affording intermediate **XVIb** (Scheme 43). **XVIb** is oxidized by the upper redox state of the photocatalyst affording **XVII**, which can deprotonate to furnish the fluorosulfonylated alkene. (Scheme 43)



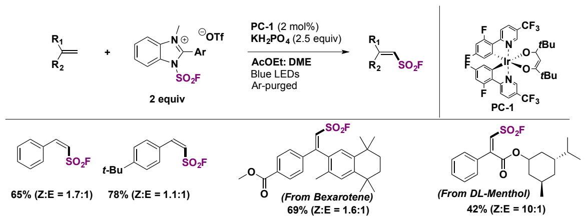
Scheme 43. Proposed reaction mechanism

In a very recent report, Zhang, Wang, and colleagues[71] explored the stereoselective radical fluorosulfonylation of several alkenes. The optimized reaction conditions for the synthesis of *E*-fluorosulfonyl alkenes are shown in Scheme 44. This protocol employed 4CzIPN as photocatalyst (Scheme 44) and KH_2PO_4 as base under visible light irradiation at room temperature. Under these conditions, several examples of unsaturated hydrocarbons were functionalized in good yields with high regio- and stereo-selectivity. They also reported the reaction of two natural derivatized alkenes from cholesterol and estrone and obtained the corresponding products in moderate yields.



Scheme 44. Photocatalytic synthesis of *E*-fluorosulfonyl alkenes

The authors[71] modified the reaction conditions to obtain the less thermodynamically stable *Z*-products. With a different solvent mixture and employing a different photocatalyst (PC-1, Scheme 45) the reaction was extended to produce several *Z*-alkenyl sulfonyl fluorides including derivates from the bioactive compounds *DL*-menthol and *bexarotene* (Scheme 45).



Scheme 45. Photocatalytic synthesis of *Z*-fluorosulfonyl alkenes

C.2.2- Use of Ethylene Fluorosulfonylating Hubs for Increasing Molecular Diversity

The fluorosulfonylation of multiple bonds has contributed with relevant "fluorosulfonylating hubs" such as ESF,[20,78,82–88] an excellent Michael acceptor,[86] α-bromo ethylene sulfonyl fluoride (BESF) with an α–bromine handle,[31,59,89,90] β-chloro alkenylsulfonyl fluorides (BCASF, with a β-chlorine atom handle),[79] and but-3-ene-1,3-disulfonyl difluoride (BDF).[91] Substituted-alkynyl-1-sulfonyl fluorides (SASFs),[72,92] among the alkynyl-SO_2F "hubs" candidates have been employed in click chemistry and SuFEx reactions (*vide infra*). Saturated alkyl-substituted sulfonyl fluorides such as 2-azidoethane-1-sulfonyl fluoride (ASF)[93] and sulfonyl fluoride isocyanides[94] are also excellent candidates for SuFEx chemistry. These hubs can be employed as powerful SO_2F-carriers for the late-stage incorporation into peptides and pharmacophores under mild conditions. Due to their bis-electrophilic nature, the selective reactivity of the FSO_2, the ethylene groups, and the "halide handles", (substituted)-ethylene sulfonyl fluorides have been involved in numerous transformations where varying the reaction conditions either reactive site (double bond or SO_2F or the halogen handle attached) can ensue unique transformations enhancing the chemical diversity reservoir.

ESF, the primogenial hub, has been synthesized by fluorination of 2-chloroethane-1-sulfonyl chloride with KHF_2 and ulterior treatment with MgO.[14] It has been employed as dipolarophile in 1,3-dipolar cycloadditions to render fluorosulfonylated heterocycles.[95] When reacted with organic azides, ESF behaves as acetylene equivalent affording 1,2,3-triazoles with elimination of SO_2F.[96] However, ESF reacts with

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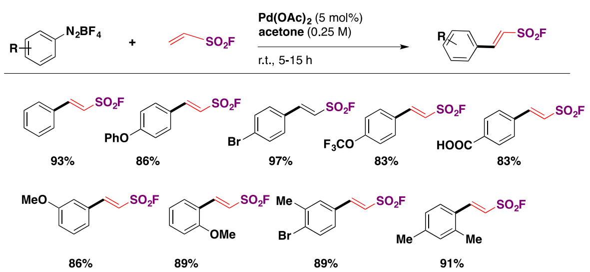
diazoalkanes such as diazomalonate, affording fluorosulfonylated heterocycles and cyclopropanes, depending on the reaction conditions.[97]

ESF has also been employed in conjugate addition reactions,[98] palladium-catalyzed Heck-type couplings using aryl iodides,[20] diazonium salts,[99] boronic acids,[61,84,90] Pd-catalyzed alkenylation,[86] and rhodium-catalyzed C-H activation.[61,100] Also, the photocatalyzed fluorosulfonylethylations of aryl iodides (*vide supra*, section B),[60] and the photocatalyzed decarboxylative fluoroethylsulfonylation of *N*-hydroxyphthalimide esters[76] (*vide supra*, section C.1.-) have been recently described with ESF reagent.

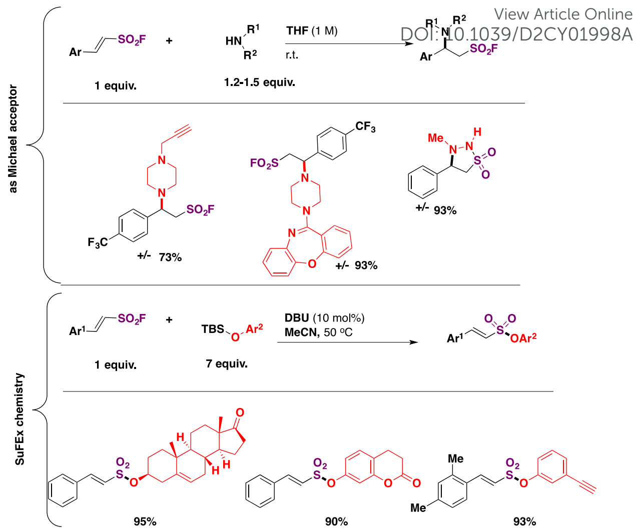
In 2016, Qin, Wu, Sharpless and colleagues[99] reported the synthesis of β-arylethenesulfonyl fluorides[101] directly from aryldiazonium salts and ESF, via a Heck-type β-C-H arylation pathway through the Heck-Masuda process.[102,103] The standard procedure involved the freshly prepared benzenediazonium tetrafluoroborate, treated with ESF[14] and $Pd(OAc)_2$ in acetone, at room temperature. The *E*-stereoisomers from β-phenylethenesulfonyl fluorides were obtained exclusively. The scope of the reaction is represented in Scheme 46.



Scheme 46. Selected examples for the scope of the synthesis of β-arylethenesulfonyl fluorides from aryldiazonium salts and ESF

Both electron releasing and withdrawing groups on the benzenediazonium salts rendered the respective β-arylethenesulfonyl fluorides in good yields (Scheme 46). Benzenediazonium salts substituted at the *meta* and *ortho* positions, as well as 3,4-, and 2,3-disubstituted-benzenediazonium salts, afforded the respective β-arylethenesulfonyl fluorides in reasonably good yields.

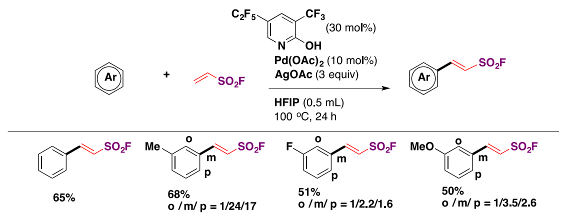
Both the olefin moiety and the sulfonyl fluoride group in β-arylethenesulfonyl fluorides can function as electrophiles. The reaction of β-arylethenesulfonyl fluorides with secondary cyclic amines afforded the Michael addition product as opposed to the substitution at sulfur atom, whereas the reaction with *tert*-butyldimethylsilyl (TBS) ether in acetonitrile, using DBU as base, afforded the alkenylsulfonates via SuFEx chemistry (Scheme 47).



Scheme 47. β-arylethenesulfonyl fluorides as bis-electrophiles: Michael addition and SuFEx chemistry

The strong preference for the Michael addition[86] of secondary amines to ESF over the substitution at S is quite remarkable. However, for β-arylethenesulfonyl fluorides, the reactivity is somewhat diminished, since only electron poor or neutral aromatic moieties are reactive towards the amines (Scheme 47).[101]

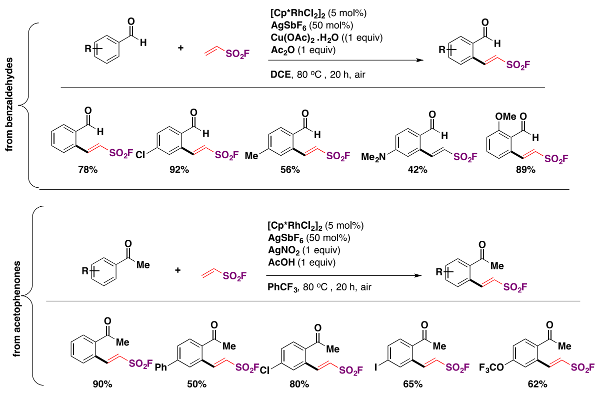
Then Chen, Wang, Yu and colleagues[86] informed a variant of the Pd catalysis to achieve a homolytic aromatic substitution of arenes with ESF for the synthesis of aryl ethenesulfonyl fluorides. A succinct display of the scope of the reaction is illustrated in Scheme 48.



Scheme 48. Selected examples for the HAS of arenes with ESF

The homolytic substitution is poorly regioselective and necessitates harsh reaction conditions.[86]

In 2018, the group of Qin[88,100] reported the Rh-catalyzed *ortho*-substitution of benzaldehydes and acetophenones with ESF group to achieve the fluorosulfovinylation of aryl C(sp^2)-H bonds from aromatic aldehydes and ketones. A brief scope of the transformation is illustrated in Scheme 49.



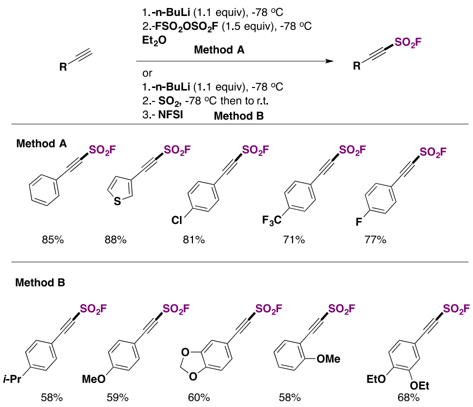
Scheme 49. Selected examples for the Rh-catalyzed *ortho*-substitution of benzaldehydes and acetophenones with ESF

From Scheme 49, it is observed that both benzaldehydes and acetophenones of diverse electronic nature are good candidates for the Rh-catalyzed incorporation of ESF.

However, the major drawback of ESF and its derivatives is the inherent structural limitation to ethyl or ethylene moieties present in the final products. There are also some concerns with the use of ESF related to the high toxicity (oral LD50 is 50 mg/Kg for rats) and being a severe lachrymator.[35] Its preparation from the toxic 2-chloroethane-1-sulfonyl chloride is also a concern. All the methodologies available to synthesize alkenyl-substituted fluorosulfonylated products are displayed in Table 3.

C.3.- Syntheses of Alkynyl Sulfonyl Fluorides

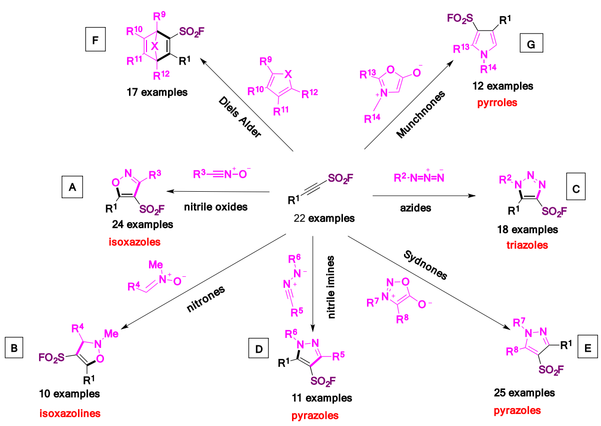
As recently as 2020, Smedly, Sharpless, Moses and colleagues,[92] synthesized 2-substituted-alkynyl-1-sulfonyl fluorides (SASFs), which bear both an alkyne functionality (ready for a click reaction with azides) and the SO_2F SuFExable group. The syntheses of SASFs were readily accomplished by reaction of terminal alkynes with *n*BuLi and FSO_2OSO_2F (or gaseous SO_2 and NFSI afterwards, as the source of F) at -78 ºC in Et_2O (or THF when SO_2 gas is used). The authors uncovered that the method employing the fluorosulfonic acid anhydride (i.e.: FSO_2OSO_2F) (Method A, Scheme 50) worked well with electron poor substrates, while the method utilizing SO_2 and NFSI (Method B, Scheme 50) worked satisfactorily with electron -rich substrates. Scheme 50 depicts the syntheses of a series of SASFs substrates.



Scheme 50. Selected examples for the syntheses of SASFs

These SASFs were later applied to construct a very interesting diverse set of heterocyclic compounds bearing SO_2F moiety taking advantage of the click chemistry. The authors[92] combined the classic click chemistry reaction concept between an alkyne and an azide group[104,105] to render triazole-type products with the SuFEx reaction which is associated with the fluorosulfonyl group. This new click associative chemistry was coined *Diversity Oriented Clicking* (DOC), a methodology which encompasses two-in-one click chemistry sequential protocols with the aim of building on the diversity of scaffolds by click processes using 2-substituted-alkynyl-1-sulfonyl fluorides (SASFs) as starting substrates.

In order to put into practice the DOC methodology, SASFs were made to react with dipoles and cyclic dienes as coupling partners. The 1,3-nitrogen dipoles included nitrile oxides (Scheme 51A), nitrones (Scheme 51B), azides (Scheme 51C), nitrile imines (Scheme 51D), Sydnones (Scheme 51E), dienes (Scheme 51F), and pyrroles (Scheme 51G), among others. The reaction click products of these dipoles with SASFs are illustrated in Scheme 51.



Scheme 51. Selected general examples of dipoles reacting with SASFs

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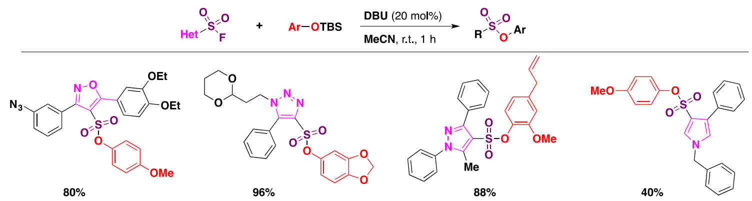
In this manner, a series heteroaromatic compounds bearing the fluorosulfonic anchor such as isoxazoles, isoxazolines, pyrazoles, triazoles, and pyrroles could be obtained. It is to be pointed out the high selectivity of the reactions, since single regioisomers in each case were obtained (a recent synthesis of 2,4,5-trisubstituted oxazoles sulfonyl fluorides was proposed by H.-L. Qin[106] without the employment of SASFs, although through the Rh-catalyzed heterocycloaddition of nitriles with 2-diazo-2-(fluorosulfonyl)acetate).

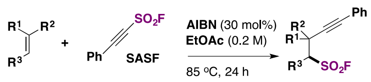
In order to apply the SuFEx click chemistry on the fluorosulfonyl heterocyclic compounds synthesized (Scheme 51), the authors[92] constructed a DOC library. A brief panorama of the scope of the reaction is illustrated for the syntheses of sulfonates in Scheme 52.



Scheme 52. Examples of SuFEx click chemistry reactions from isoxazole, triazole, pyrazole and pyrrole fluorosulfonyl derivatives

Competition experiments indicated that the reactivity for the SuFEx reaction followed the order triazole > pyrazole > isooxazoline = isoxazole.

Frye, Studer and colleagues[72] have employed a SASF reagent (2-substituted-alkynyl-1-sulfonylfluoride) to synthesize a β-alkynyl-fluoro sulfonyl alkane. An excerpt of the reaction is illustrated in Scheme 53.

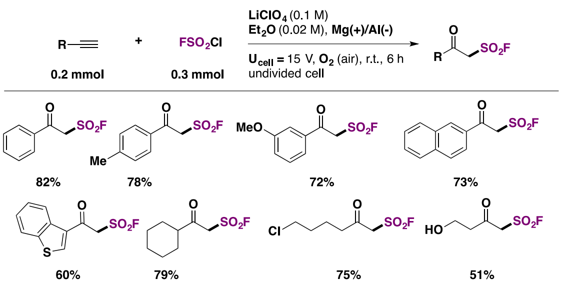


Scheme 53. General strategy for the syntheses of β-alkynyl-fluoro sulfonyl alkanes

B.4- Syntheses of β-keto Sulfonyl Fluorides

β-Ketosulfonyl fluorides were recognized as analogs to β-ketoesters, in terms of versatile reactivity. The only known method to synthesize β-ketosulfonyl fluorides used gaseous SF_5Cl reagent.[107]

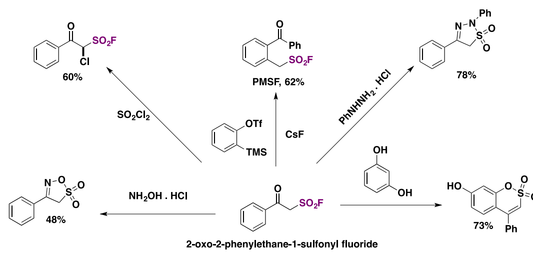
Chen, Huang, Liao and colleagues[108] achieved the electrochemical syntheses of β-ketosulfonyl fluorides using a sacrificial anode of magnesium and an aluminum cathode in Et_2O as solvent, with $LiClO_4$ as electrolyte. The scope of the transformation is illustrated in Scheme 54.



Scheme 54. Selected examples for the electrochemical syntheses of β-keto sulfonyl fluorides

Aryl and heteroaryl acetylenes afforded good yields of the respective β-keto sulfonyl fluorides. Aliphatic acetylenes such as cyclohexylacetylene, 6-chlorohexyne, 1-hydroxy-3-butyne gave good yields of fluorosulfonylated products as well. Changing the reaction conditions (THF, instead of Et_2O, $LiClO_4$ 0.2 M, and U cell = 10 V) the authors[108] obtained the α-chloro-β-keto sulfonyl fluorides from phenylacetylenes.

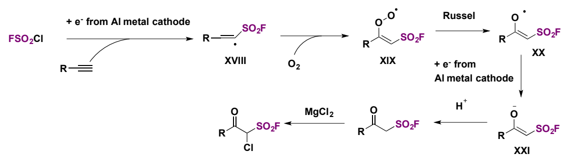
Interestingly, the authors examined the transformation of 2-oxo-2-phenylethane-1-sulfonyl fluoride into derivatives. Scheme 55 depicts some of these relevant transformations.



Scheme 55. Transformations of 2-oxo-2-phenylethane-1-sulfonyl fluoride into derivatives into derivatives

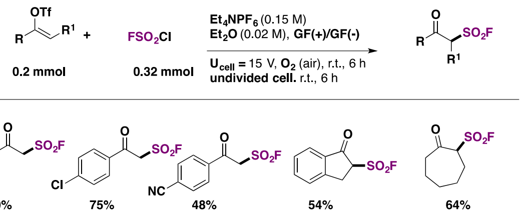
The inhibitor PMSF[18,19] (Scheme 55, upper center) is obtained in very good yield. The reaction of 2-oxo-2-phenylethane-1-sulfonyl fluoride with hydroxylamine hydrochloride produced a novel heterocycle "oxathiazole" in reasonably good yield (Scheme 55, lower left side).

Based on radical probe experiments, and the necessity of both electrical current and electrolyte in order to accomplish product formation, the authors postulated a plausible reaction mechanism such as that depicted in Scheme 56. By cathodic reduction, FSO_2Cl produced FSO_2 radicals and chloride anion. FSO_2 radicals add to the terminal phenylacetylene carbon to produce intermediate **XVIII**, which in the presence of air generates intermediate **XIX**. By a Russel mechanism, intermediate **XX** is formed, which is reduced in situ to intermediate **XXI**, which upon protonation renders the product in Et_2O. In THF, chlorination of the β-keto sulfonyl fluorides by $MgCl_2$ affords the α-chloro-β-keto sulfonyl fluorides (Scheme 56).



Scheme 56. Proposed reaction mechanism.

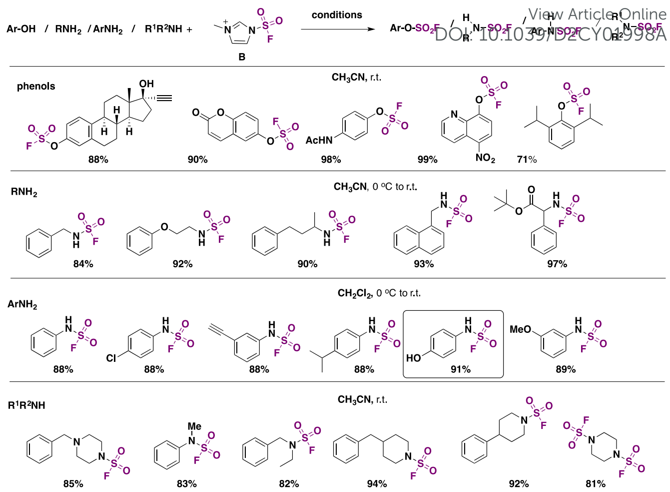
In 2022, Feng, Huang, and colleagues[109] introduced a modification of the electrochemical syntheses of β-keto sulfonyl fluorides through the radical fluorosulfonylation of vinyl triflates. The authors[109] used graphite felt (GF) as electrodes to generate FSO_2 radicals from FSO_2Cl, in diethyl ether as solvent, with Et_4NPF_6 as electrolyte. The scope of the transformation is illustrated in Scheme 57.



Scheme 57. Selected examples for the radical fluorosulfonylation of vinyl triflates

B.5.- Syntheses of fluorosulfonylamines and the fluorosulfonylation of phenols

In 2018, Guo, Sharpless, Dong, and colleagues[6] developed an electrophilic fluorosulfonyl donor capable of fluorosulfonylating alcohols, phenols, primary and secondary amines in excellent yields. The reagent is fluorosulfuryl imidazolium triflate **B** (Scheme 58), which was observed to be much more reactive and stable than the classic SO_2F_2 reagent.[110] **B** Was examined in its ability to fluorosulfonylate a range of phenols, primary and secondary amines, according to Scheme 58.



Scheme 58. Scope of the fluorosufonylation of phenols, primary aliphatic amines, primary aromatic amines and secondary amines

Reagent **B** was prepared from 2-methylimidazole and SO_2F_2. Phenols were converted to their respective fluorosulfates in the presence of triethylamine (Scheme 58). Even sterically hindered phenols were transformed to their respective fluorosulfates in very good yields. Unlike SO_2F_2, **B** reacted readily with primary and secondary amines, as shown in Scheme 58, affording the corresponding sulfamoyl fluorides without the presence of additives, as opposed to when reagent SO_2F_2 is used, which necessitates the presence of triethylamine and additives (such as DMAP or DABSO) to afford sulfamoyl fluorides. Both aliphatic and aromatic primary amines reacted under the conditions shown in Scheme 58. Even the less reactive secondary amines provided good yields of products. This represents one of the few protocols to prepare and isolate products bearing the sulfamoyl fluoride group.

It is to be observed that the amine site preferentially reacts in the presence of the phenol function, as depicted in Scheme 58 for aromatic primary amines, in sharp contrast to the SO_2F_2 reagent, which prefers the phenol reactivity over the amine site.

D.-Conclusions

The profound impact attributed to organic compounds bearing the $-SO_2F$ functionality has traversed fields, from organic chemistry to biological applications, from drug discovery to material sciences, most probably driven by the seminal paper by Sharpless in 2014 with the introduction of SuFEx click chemistry reaction. This constantly growing and expanding area of fluorosulfonylated compounds has demanded a significant need for alternative methods (one-pot procedures) to synthesize aromatic and aliphatic sulfonyl fluorides, that allow the simultaneous incorporation of both SO_2 and F groups, without the requirement of previously installed SO_2 or F functionalities.

In this review, we critically discussed, from the organic chemist´s perspective, new methodologies for the syntheses and some applications of (hetero)aromatic-, alkyl-, alkenyl-, alkynyl- sulfonyl fluorides, β-keto-sulfonyl fluorides, and the syntheses of compounds with N-SO_2F and O-SO_2F bonding.

Besides the classical Cl / F exchange from the corresponding chlorides, the syntheses of alkyl-substituted sulfonyl fluorides can be carried out by direct or indirect methods. Synthetic direct methods via radical sulfur dioxide insertion/fluorination provide aliphatic sulfonyl fluorides in good yields or the visible light-photocatalyzed addition of SO_2F radicals from newly developed SO_2F-reagents affords excellent yields of aliphatic saturated fluorosulfonyl substrates. Indirect methods can resort to the addition of SO_2F- Michael acceptors such ESF and derivatives. The drawback with the employment of ESF (and derived hubs) is the use of toxic and hygroscopic starting 2-chloroethane-1-sulfonyl chloride substrate for their syntheses. Also, the synthesis of the precursors for radical fluorosulfonylating reagents derived from benzimidazolium salts necessitates $ClSO_2F$ reagent, which is costly (U$D 10955/mol).

Fluorosulfonylated alkenes can also be synthesized either through direct fluorosulfonylating radical strategies from olefins or alkynes as substrates, or else by employing fluorosulfonylating hubs such as ESF and its derivatives. Direct radical fluorosulfonylating reagents to accomplish the syntheses of fluorosulfonylated alkenes involve $ClSO_2F$, and FSO_2-substituted benzimidazolium salts precursors, which share limitations concerned with handling and costs.

On the other hand, the syntheses of fluorosulfonylated (hetero)arenes, other than the classical Cl / F exchange in aryl sulfonyl chlorides, can contemplate the use of disulfides with Selectfluor to obtain the sulfonyl fluoride in high yields. Aryl sulfonamides, sulfonylhydrazides and arylsulfinates can also be used as starting substrates for the synthesis of aryl sulfonyl fluorides. Direct methods, namely those that do not require pre-synthesized/installed sulfur-containing substrates, can employ aryl iodides, aryl bromides, aryl boronic acids, and aryl diazonium salts as starting materials, DABSO, $Na_2S_2O_5$ as sources of SO_2, and a fluorinating reagent (Selectfluor, NFSI, or KHF_2). Probably, these latter methods are the more amicable in terms of reagents handling and costs. However, to date, no direct radical fluorosulfonylating reagents, such as FSO_2-substituted benzoimidazolium salts, have been employed for the incorporation of the SO_2F group onto (hetero)aromatic compounds, although radical methods to fluorosulfonylate aromatic substrates are already in place.

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Among the catalytic methodologies established for the fluorosulfonylation of aliphatic and aromatic compounds, metal-mediated methods, thermal techniques, and more recently photocatalytic and electrochemical protocols have been informed. However, the application of flow system methodologies has not been reported for fluorosulfonylation reactions, which could be conveniently applied in the photocatalyzed protocols so far informed. This area will probably witness an expansion in the near future.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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Table 1. Methods to synthesize (hetero)aromatic sulfonyl fluorides Ar-SO_2

N⁰	Starting substrate	Product	Reagents & Reaction conditions	Ref
1	**$ArSO_2NHNH_2$**	**$ArSO_2F$**	**Selectfluor** H_2O, 60 ºC	43a
2	**Ar-SO_2Na**	**$ArSO_2F$**	**Selectfluor** H_2O, 60 ºC	43a
3	**Ar-SO_2NH_2**	**$ArSO_2F$**	Pirylium bromide $MgCl_2$, **KF**, MeCN, then H_2O	42
4	**Ar-N=N-SO_2Me**	**$ArSO_2F$**	**$K_2S_2O_5$, NFSI,** MeCN:H_2O, blue LEDs, r.t., 4 h	55
5	**Ar-I**	**$ArSO_2F$**	1) $Pd(OAc)_2$ **DABSO**	4

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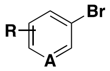
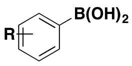
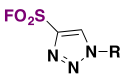
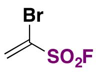
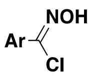
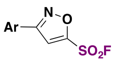
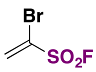
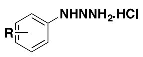
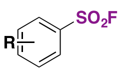
			PAd_2Bu, *i*PrOH 75 °C, 16 h. 2) **Selectfluor**	
6		**(Het)SO$_2$F**	1)**DABSO**, $PdCl_2(AmPhos)_2$, Et_3N ,*i*-PrOH 75 °C, 24 h 2)**NFSI**	32
7	**(TMS)ArOTf**	**ArSO$_2$F**	NHR^1R^2, **SO$_2$F$_2$**, KF, 18-crown-6 THF	44
8		**ArSO$_2$F**	1) $NiBr_2$ (glyme), Tmphen, **DABSO**, LiO*t*-Bu DMI,100 °C,16 h 2) **NFSI,** DIPEA	45
9	**(Het)Aryl-SH or (Het)Aryl-SS-Aryl(Het)**	**(Het)Aryl-SO$_2$F**	Batch electrocell, (C / Fe) **KF**, Pyridine, CH_3CN / HCl, 20 mA, r.t., 6-48 hr	47
10	**ArN$_2$BF$_4$**	**ArSO$_2$F**	**DABSO**, **KHF$_2$,** $CuCl_2$, 6,6`-dimethyl-2,2`-dipyridyl, MeCN, r.t., 12 h	49
11	**ArN$_2$BF$_4$**	**ArSO$_2$F**	**Na$_2$S$_2$O$_5$, NFSI**, MeCN / H_2O = 20 : 1 N_2, 60 °C, 6 h	50
12	**ArN$_2$BF$_4$**	**ArSO$_2$F**	**DABSO**, 3DPAFIPN **KHF$_2$**, MeCN,blue LED, r.t., 16 h	54
13	**ArN$_2$BF$_4$**	**ArSO$_2$F**	**K$_2$S$_2$O$_5$, NFSI,** MeOH/H_2O/AcOH, r.t., 6h	51,52
14	**ArN$_2$BF$_4$**	**ArSO$_2$F**	**Na$_2$S$_2$O$_5$, NFSI, Selectfluor**,MeOH,70 °C,9 h	53
15	**(Het)Ar-MgX**	**(Het)Ar-SO$_2$F**	**SO$_2$F$_2$**, THF, 23 °C, 1h	46
16	**R-N$_3$**		DMF, 50 °C, 14h 	59
17			$N(Pr)_3$ ^{t}BuOH, r.t. 	31
18			DABSO, NFSI, base, [Cu], MeCN, 40 °C, 2 h	43b

Table 2. Methods to synthesize alkyl sulfonyl fluorides Ar-SO_2F

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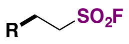
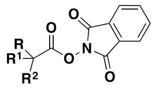
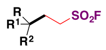
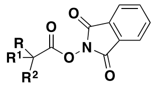
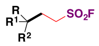
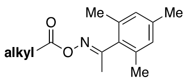
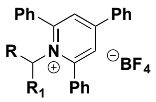
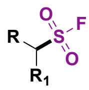
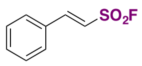
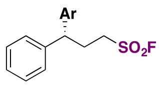
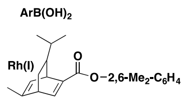
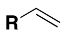
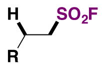
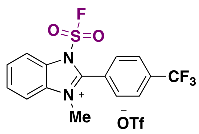
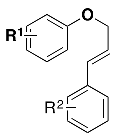
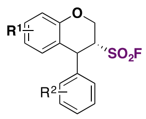
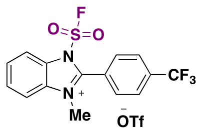
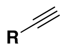
Entry	Starting substrate	Product	Reagents & Reaction Conditions	References
1	R-Br	R-SO_2F	1.-**Rongalite,** DMSO, r.t. 2.-H_3PO_4 3.-DIPEA, **NFSI**	66
2	R—I		 $Mn_2(CO)_{10}$, HE, DMSO 5W blue LED r.t. 24 h, Ar	60
3	RCOOH	R–SO_2F	**$Na_2S_2O_5$, NFSI**, Cu, Na_2HPO_4, MeCN:H_2O, r.t.	70
4			 Eosin-Y Na_2, HE, MeCN blue LED, Ar, r.t., 12-24 h	76
5			1.-**$Na_2S_2O_4$**, Zn, DMPr / H_2O, 80 °C, 9 h 2.- **NFSI**, r.t., 4 h	68
6		alkyl–SO_2F	**DABSO, NFSI** $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ K_3PO_4, MeCN : CH_2Cl_2 30 W blue LED, r.t., 25 h	65
7			1.- **DABSO**, HE, Base DMA, 16 h, blue LEDs or heat 2.- **NFSI**, 4 h, r.t	74
8			 CsF, EtOAc, 50 °C, 12 h	61
9			 **(FABI)** ODA, CHD, 1,4-dioxane blue LED, r.t., 24 h	73
10			 ODA, 1,4-dioxane blue LED, r.t., 24 h	111
11			Method A 1.-n-BuLi, -78 °C 2.-**FSO_2OSO_2F**, -78 °C Et_2O Method B 1.-n-BuLi, -78 °C 2.- **SO_2**, -78 °C then to r.t. 3.- NFSI	92

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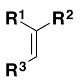
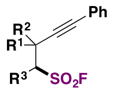
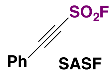
12			 AIBN, EtOAc 85 °C, 24 h	72

Table 3. Syntheses of alkenyl fluorosulfonylated compounds

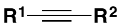
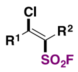
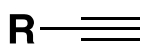
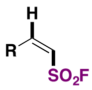
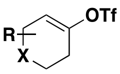
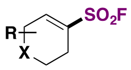
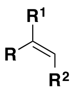
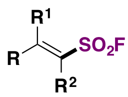
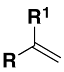
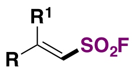
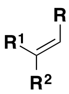
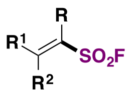
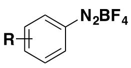
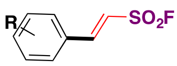
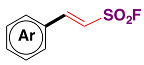
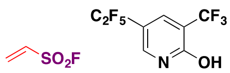
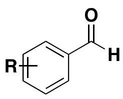
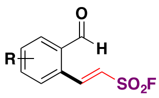
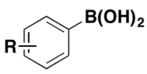
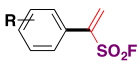
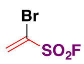
Entry	Starting substrate	Product	Reagents & Reaction Conditions	References
1		 **BCASF**	**FSO_2Cl,** *fac*-Ir(ppy)$_3$, Et_2O / $PhCF_3$ blue LEDs, 24-72 h	79
2			**(FABI)** ODA, $(TMS)_3SiH$, 1,4-dioxane blue LED, r.t., 24 h	73
3			1) **DABSO,** $PdCl_2(AmPhos)_2$, Et_3N, *i*-PrOH, 75 °C 2) **NFSI** EtOAc	80
4			**FABI** *fac*-Ir(ppy)$_3$, 1,4-dioxane blue LED, r.t., 12 h	81
5			**IMSF,** 4CzIPN, KH_2PO_4, DME, blue LED	71
6			**FSO_2Cl** $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ Et_2O / $PhCF_3$, Ar, r.t. blue LEDs (460 nm), 12 h then aq. Na_2CO_3	78
7			 $Pd(OAc)_2$, acetone r.t., 5-15 h	99
8			 $Pd(OAc)_2$, AgOAc, HFIP 100 °C, 24 h	86
9			 $[Cp^*RhCl_2]_2$, $AgSbF_6$ $Cu(OAc)_2 .H_2O$, Ac_2O DCE, 80 °C, 20 h, air	88,100
10			 $Pd(dba)_3$, Ligand, K_3PO_4, toluene, 50 °C, 24 h	90

Table 4. Synthesis of β-keto-sulfonyl flluorides, fluorosulfamoyl (NR_2-SO_2F), and fluorosulphate (ArO-SO_2F) compounds

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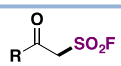
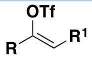
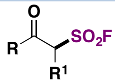
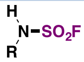
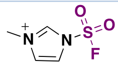
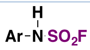
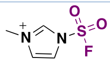
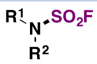
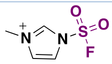
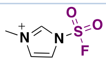
Entry	Starting substrate	Product	Reagents & Reaction Conditions	References
1	R—≡		**FSO_2Cl** $LiClO_4$,Et_2O, Mg(+)/Al(-) U_{cell} = 15 V, O_2 (air), r.t., 6 h undivided cell	108
2			**FSO_2Cl** Et_4NPF_6,Et_2O, GF(+)/GF(-) U_{cell} = 15 V, O_2 (air), r.t., 6 h undivided cell. r.t., 6 h	109,112
3	**RNH_2**		 **(IMSF)** CH_3CN, 0 °C to r.t.	6
4	**$ArNH_2$**		 **(IMSF)** CH_2Cl_2, 0 °C to r.t.	6
5	**R^1R^2NH**		 **(IMSF)** CH_3CN, r.t.	6
6	**RR^1NH**	**RR^1NSO_2F**	**AISF, DBU, THF, r.t. 10min**	5
7	**Ar-OH**	**Ar-O-SO_2F**	 **(IMSF)** CH_3CN, r.t.	6

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