Review

# Recent Advances of S−[18]F Radiochemistry for Positron Emission Tomography

Xiaoyun Deng and Xiaohua Zhu*

Cite This: *ACS Omega* 2023, 8, 37720−37730

Read Online

ACCESS | 📊 Metrics & More | 📖 Article Recommendations

**ABSTRACT:** The click chemistry of sulfur(VI) fluoride exchange (SuFEx) has facilitated the widespread application of sulfur−fluoride compounds such as sulfonyl fluorides, fluorosulfates, and sulfamoyl fluorides in various fields, especially in the development of ^{18}F ligands for PET (positron emission tomography) imaging. In recent years, the prominent progress of sulfur−[18]fluoride compounds has been achieved through the combination of ^{18}F and sulfur−fluoride chemistry. These compounds serve as potential ^{18}F tracers, ^{18}F synthons, and reagents for ^{18}F-fluorination, thereby complementing the range of ^{18}F ligands, typically C−[18]F structures, used in PET studies. This review aims to provide an overview of S−[18]F labeling reactions through examples of relevant ^{18}F compounds and highlight the advancements and breakthroughs achieved in the past decade.
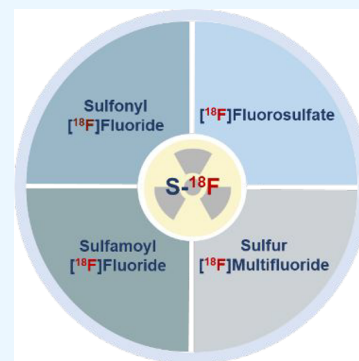
## 1. INTRODUCTION

The extensive clinical use of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) in cancers, cardiovascular diseases, and neurological disorders has established ^{18}F as the most commonly used PET nuclide.[1,2] Most developed ^{18}F probes for PET imaging are obtained by C−[18]F formation, including aliphatic and aromatic ^{18}F-fluorination with nucleophilic [^{18}F]fluoride as well as electrophilic ^{18}F-fluorination with [^{18}F]F$_2$ and [^{18}F]F$_2$-derived reagents.[3,4] Over the past few decades, the rapid advancement of ^{18}F radiochemistry has led to the establishment of various noncanonical ^{18}F labelings involving bond formation with elements such as sulfur, boron, silicon, aluminum, and gallium. Among these radiolabeled hetero-^{18}F compounds, the S−[18]F molecules represent significant building blocks and imaging agents for PET studies.[5] In the S−[19]F chemistry, the compounds containing an SO$_2$F group have garnered considerable focus in the fields of chemistry and biology owing to the balanced stability and reactivity of these molecules under physiological systems. These functionalities have demonstrated potential in various applications, such as serving as potent protease inhibitors, biological probes, and covalent modifiers of proteins.[6−11] However, the standard synthetic methods used to obtain such compounds have relied mainly on Cl/F exchange from the corresponding chlorides.[12−14] Following the introduction of the concept of "sulfur(VI) fluoride exchange" (SuFEx) as a potent reaction for click chemistry[15,16] by Sharpless and colleagues in 2014, considerable efforts have been devoted to developing alternative pathways for the synthesis of SO$_2$F compounds that have a wide range of functional group tolerance and can be obtained from readily

accessible starting materials. Apart from the rapidly developing SO$_2$F chemistry, the preparation of sulfonimidoyl fluorides was disclosed several decades ago.[17] Additionally, certain sulfur multifluorinated compounds are frequently produced to be employed as fluorinating reagents.[18] In the S−[18]F radiochemistry, since [^{18}F]fluoride is predominantly produced through the [18]O(p,n)[18]F nuclear reaction from a cyclotron in high radioactivity and high specific activity,[3] the present methods of S−[18]F formation frequently employ the [^{18}F]-fluoride as the primary source of fluorine-18. Herein, we mainly focus on and summarize the synthesis and applications of S−[18]F compounds. Specifically, the synthetic methods of ^{18}F-labeled aryl/alkenyl sulfonyl fluorides, fluorosulfate, sulfamoyl fluorides, and sulfur multifluorides are concisely summarized. Furthermore, to gain a more comprehensive understanding of the recent research progress, this paper extensively covers the reaction scopes, applications, and limitations.

## 2. SULFONYL [18]FLUORIDE

Sulfonyl-based functional groups, including sulfones, sulfinic acids, and sulfonamides, have found widespread use in various fields, such as acting as active ingredients in pharmaceuticals[19] and agrochemicals,[20] playing a critical role as intermediates in

complex chemical syntheses,[21,22] and being utilized as specialty materials and food additives.[23] In general, the synthesis of these functional groups is based on the classic reactivity patterns of sulfides.[24] The arrangement of the $SO_2$ group is what links all functional groups that are derived from the sulfonyl fragment. This implies that direct introduction of the $SO_2$ group is a simple approach to produce these molecules, which has been proved by the utilization of the $SO_2$ surrogates, such as $K_2S_2O_5$, $Na_2S_2O_5$, and 1,4-diazabicyclo[2.2.2]octane-1,4-diium-1,4-disulfinate (DABSO).[25] These $SO_2$ sources have been widely used to introduce the $SO_2$ group through metal catalysis.[26−31] In particular, Willis and colleagues demonstrated the application of this catalytic system in the synthesis of (hetero)arenesulfonyl fluorides using DABSO as a $SO_2$ source and corresponding (hetero)aryl bromides as precursors.[32] Subsequently, various synthetic methods employing $SO_2$ surrogates have been developed to convert electrophiles, such as aryl iodides, alkenyl triflates, or arenediazonium salts, into their corresponding arenesulfonyl fluorides.[33−37] Studies have also been conducted on the use of aryl nucleophiles as aryl sources in catalytic protocols. Examples include the Cu(I)- or Ni(II)-catalyzed synthesis utilizing DABSO and aryl boronic acid,[30,31] as well as the Bi-catalyzed system with $SO_2$ gas and (hetero)aryl boronic acids.[38] In addition, an electrochemical method was reported to directly convert conventional precursors of thiols into sulfonyl fluorides using KF as a cost-effective, safe, and readily available fluoride source.[39]
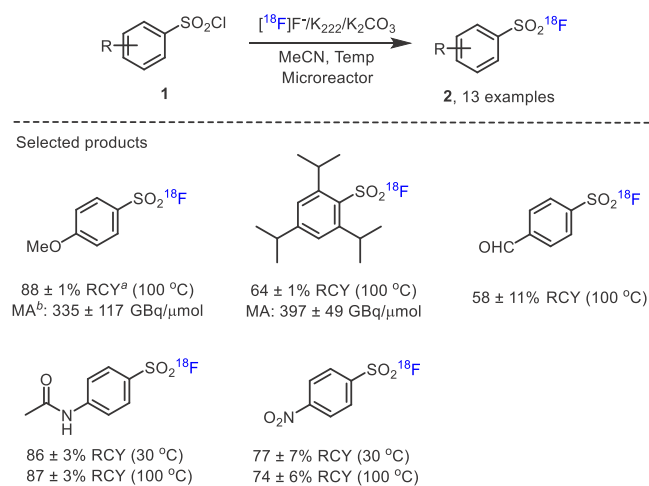
In radiochemistry, [18F]-labeled arenesulfonyl fluorides were usually synthesized from the precursors of sulfonyl chlorides 1 (Scheme 1), except that [18F]tosyl fluoride was identified as a

### Scheme 1. General Radiosynthesis of [18F]-Labeled Arenesulfonyl Fluorides
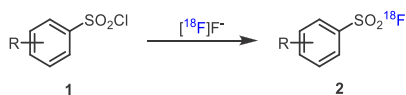


side product in the preparation of [18F]-labeling synthons of [18F]fluoromethyl tosylate[40] and [18F]fluoromethyl-$d_2$ tosylate[41] from methylene bis(4-methylbenzenesulfonate) and methylene-$d_2$ bis(4-methylbenzenesulfonate), respectively. The chloride precursors could be obtained by direct chlorosulfonylation[42] with chlorosulfonic acid or sulfonylation followed by chlorination using cyanuric chloride.[43] In 2013, Fraser and co-workers developed a highly effective approach to get [18F]-labeled arenesulfonyl fluorides using an Advion Nano-Tek Microfluidic Synthesis System (Scheme 2).[44] Another microfluidic platform, which is called magnetic droplet microfluidics (MDM), was processed to synthesize [18F]-labeled arenesulfonyl fluoride via the manipulation of microliter-scale liquid droplets using magnetic particles.[45] Even though these methods could shorten the reaction time and the [18F] products were synthesized with excellent radiochemical yields (RCYs) and molar activities (MAs), sulfonyl chlorides were still used as the labeling precursors and the reaction was typically accomplished by nucleophilic substitution with [18F]fluoride. There have been no novel labeling approaches with readily available precursors to obtain [18F]-labeled arenesulfonyl fluorides in the recent decades. The difficulties in the preparation of the complicated drug-like $SO_2{}^{18}F$ compounds limited the PET studies using tracers containing the $SO_2{}^{18}F$ group.
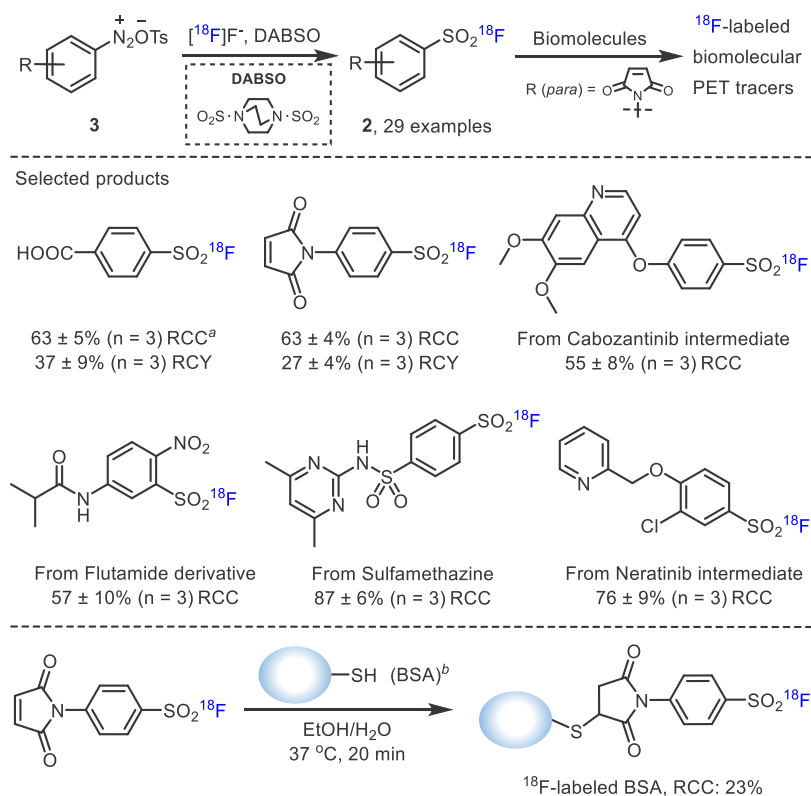
### Scheme 2. Radiosynthesis of [18F]-Labeled Arenesulfonyl Fluorides Using Microfluidics



Selected products

88 ± 1% RCY[a] (100 °C)
MA[b]: 335 ± 117 GBq/μmol

64 ± 1% RCY (100 °C)
MA: 397 ± 49 GBq/μmol

58 ± 11% RCY (100 °C)

86 ± 3% RCY (30 °C)
87 ± 3% RCY (100 °C)

77 ± 7% RCY (30 °C)
74 ± 6% RCY (100 °C)

[a]RCY, radiochemical yield. [b]MA, molar activity.

Recently, our group developed a novel strategy to directly construct carbon−$SO_2$−[18F] from arenediazonium tosylates with an $SO_2$ source (DABSO) and [18F]fluoride (Scheme 3).[46] A broad range of substrates is compatible with this approach, allowing for the synthesis of [18F]-labeled pharmaceutically relevant compounds by late-stage [18F]-fluorination, including [18F] products derived from the corresponding substrates of flutamide (an antiandrogen drug), neratinib (an anticancer drug) intermediate, cabozantinib (an anticancer drug) intermediate, and sulfamethazine (an antibacterial drug). Additionally, the utilization of a reactive [18F]-labeling synthon, containing a prosthetic group based on maleimide, facilitated the production of two [18F]-labeled temperature-sensitive biomolecules that featured cysteine residues by maleimide−cysteine chemistry.[47] Achieving multiple bond formations in a single reaction to obtain [18F]-labeled products proves challenging within [18F] radiochemistry.[48−50] This difficulty arises due to the utilization of only trace amounts of [18F]fluoride (in nanomoles), which significantly limits the compatibility of forming [18F]-included "multibond" compounds. Remarkably, the successful direct aryl−$SO_2$−[18F] two-bond formation showcased favorable compatibility in this regard. Based on these advantages, this [18F]-fluorosulfonylation method represented a notable advancement in radiosynthesizing the [18F]-labeled arenesulfonyl fluorides.

The [18F]-labeled sulfonyl fluorides containing bifunctional groups have been developed in the past decade and successfully coupled to the biological molecules that are not easily labeled with [18F] directly. As shown in Scheme 4, a sufficiently stable [18F]-labeled arenesulfonyl fluoride (5) bearing a formyl group was prepared as an [18F] synthon and reacted with the 9-amino acid bombesin analogue (6, BBN-ONH$_2$) to give [18F]BBN-OX-MESIT-$SO_2F$ (7) through oxime formation with an acceptable yield.[51] In PBS (10% DMSO), this radiolabeled biomolecule was observed to remain stable for a duration of 2 h at 37 °C. However, in murine serum, it underwent extensive conversion to radiolabeled metabolites in less than 15 min. Thus, the stability of the biomolecules containing a $SO_2{}^{18}F$ group should be considered when constructing $SO_2{}^{18}F$ compounds as the labeling reagents.[52]
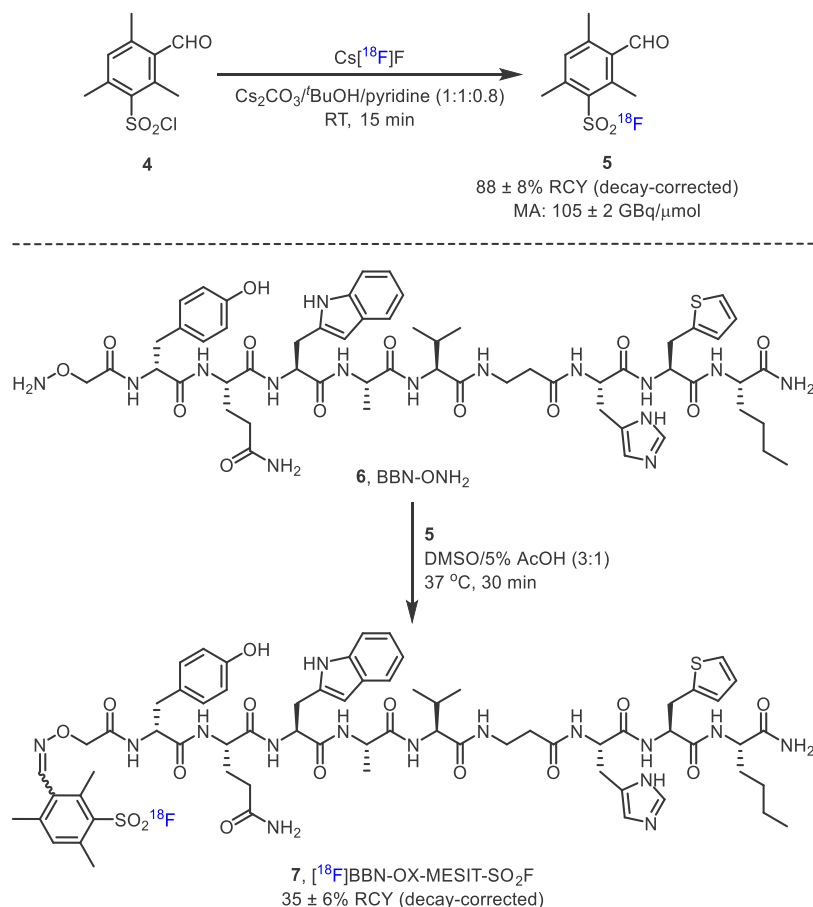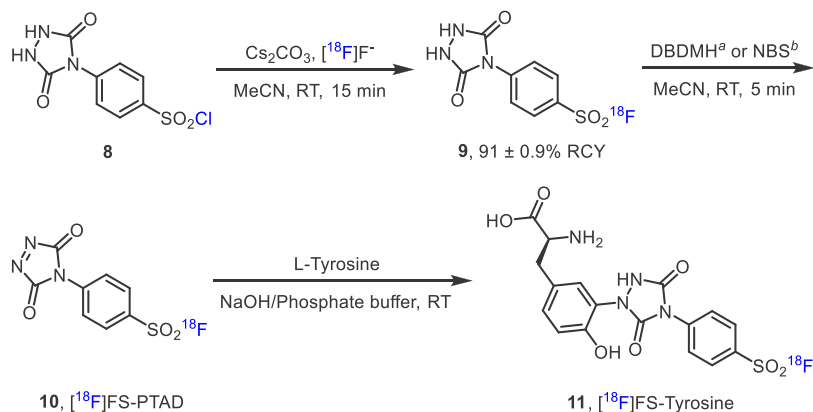
**Scheme 3. Radiosynthesis of $^{18}$F-Labeled Arenesulfonyl Fluorides from Arenediazonium Tosylates**



Selected products

63 ± 5% (n = 3) RCC[a]
37 ± 9% (n = 3) RCY

63 ± 4% (n = 3) RCC
27 ± 4% (n = 3) RCY

From Cabozantinib intermediate
55 ± 8% (n = 3) RCC

From Flutamide derivative
57 ± 10% (n = 3) RCC

From Sulfamethazine
87 ± 6% (n = 3) RCC

From Neratinib intermediate
76 ± 9% (n = 3) RCC

$^{18}$F-labeled BSA, RCC: 23%

[a]RCC, radiochemical conversion. [b]BSA, bovine serum albumin.

Another SO$_2$$^{18}$F synthon (**10**, [$^{18}$F]FS-PTAD) comprising a cyclic diazodicarboxamide group was prepared in a high RCY by two steps, starting from $^{18}$F-fluorination of the precursor 4-[4-(chlorosulfonyl)phenyl]urazole (**8**) followed by complete conversion with the oxidizing agent (Scheme 5).[53] Immediately, an ene-like reaction (the tyrosine click reaction here)[54,55] of [$^{18}$F]FS-PTAD with L-tyrosine could afford an $^{18}$F-labeled tyrosine derivative [$^{18}$F]FS-tyrosine (**11**). This rapid and efficient labeling methodology with multiple steps was demonstrated to be suitable to yield $^{18}$F-labeled tyrosine derivatives as potential ligands for use in PET studies, even though only a slight accumulation of the labeling product **11** was found in two primary human glioblastoma cell lines and F98 rat glioma cell by cell uptake experiments.

In addition to acting as labeling synthons, $^{18}$F-labeled sulfonyl fluorides could also be used for $^{18}$F-fluorination in certain cases.[56] As shown in Scheme 6, the reaction of 2-pyridinesulfonyl chloride (**12**) with [$^{18}$F]KF/K$_{222}$ afforded the fluorinating agent [$^{18}$F]PyFluor (**13**) in an excellent radiochemical conversion (RCC). With this SO$_2$$^{18}$F compound in hand, deoxy-radiofluorination of an aliphatic hydroxyl compound (**14**) was realized as the aliphatic C–$^{18}$F bond was formed under mild conditions, generating $^{18}$F compound **15** in 15% RCC. The traditional approach to convert alcohols into alkyl–$^{18}$F compounds involves a two-step sequence that consists of forming leaving groups, such as –OTs or –OMs, from alcohols, followed by aliphatic $^{18}$F-fluorination. This "one-pot" direct deoxy-radiofluorination using [$^{18}$F]PyFluor represents a breakthrough in $^{18}$F-labeling of alkyl compounds since the unstable tosylate precursors of conventional radiofluorination[3,4,57] limits the preparation of $^{18}$F-labeled alkyl fluorides.

Unlike $^{18}$F-labeled arenesulfonyl fluorides, the $^{18}$F-labeled alkenesulfonyl fluorides showed good reactivity without bearing additional highly reactive functional groups.[58,59] In 2018, Fraser and co-workers reported the first radiochemical synthesis of [$^{18}$F]ethenesulfonyl fluoride (**20**, [$^{18}$F]ESF) and its conjugation with amino acids and proteins through Michael addition (Scheme 7).[58] The synthesis was performed in a microfluidic reactor system via a $^{18}$F/$^{19}$F isotopic exchange method with nonradiolabeled ESF (**17**) or treatment of the precursor 2,4,6-trichlorophenylethenesulfonate (**19**, TCPE) with [$^{18}$F]fluoride (Scheme 7, M1 or M2). Both of these methods did not require chromatographic purification and could be operated in a straightforward way to obtain [$^{18}$F]ESF in good radiochemical yields. As shown in Scheme 7, the addition of [$^{18}$F]ESF to compounds containing amino groups can produce $^{18}$F-labeled alkyl sulfonyl fluorides (**21**) through Michael conjugation. Nevertheless, it has been observed that these radiolabeling products exhibit instability in both injectable formulation and rat serum. Encouragingly, [$^{18}$F]ESF has shown exceptional performance in $^{18}$F-fluorinating reactions.[60] Unlike deoxy-radiofluorination of alcohols with the reagent [$^{18}$F]PyFluor, this radiofluorination strategy could be implemented in a wide variety of scopes, including aromatic chloride, nitro, ammonium, boronic acid, and iodonium ylide compounds as well as aliphatic tosylate, p-nitrobenzenesulfonate, and trifluoromesylate precursors. Comparable radiofluorinating RCYs to those using a conventional [$^{18}$F]fluoride source in most cases provided the alternative possibility to produce $^{18}$F radiopharmaceuticals. In addition, it significantly minimizes the required reaction equipment, potentially reducing it to just a heating/stirring aluminum block and disposable vials in the simple setup.

**Scheme 4. Radiosynthesis of the $^{18}$F-Labeled Arenesulfonyl Fluoride (5) and [$^{18}$F]BBN-OX-MESIT-SO$_2$F Peptide**



5
88 ± 8% RCY (decay-corrected)
MA: 105 ± 2 GBq/μmol

6, BBN-ONH$_2$

5
DMSO/5% AcOH (3:1)
37 °C, 30 min

7, [$^{18}$F]BBN-OX-MESIT-SO$_2$F
35 ± 6% RCY (decay-corrected)

**Scheme 5. Radiosynthesis of [$^{18}$F]FS-PTAD and [$^{18}$F]FS-Tyrosine**



8

Cs$_2$CO$_3$, [$^{18}$F]F$^-$
MeCN, RT, 15 min

9, 91 ± 0.9% RCY

DBDMH$^a$ or NBS$^b$
MeCN, RT, 5 min

10, [$^{18}$F]FS-PTAD

L-Tyrosine
NaOH/Phosphate buffer, RT

11, [$^{18}$F]FS-Tyrosine

$^a$DBDMH, 1,3-dibromo-5,5-dimethylhydantoin. $^b$NBS, N-bromosuccinimide.

Apart from [$^{18}$F]ESF, the Liang and Xiao groups reported a novel method to get $^{18}$F-labeled alkenesulfonyl fluorides (**28**) by a three-step reaction[61] (Scheme 8), including Cu-catalyzed addition of Cl/SO$_2$OCF$_2$H to alkenes (**24**), dehydrochlorination, and $^{18}$F-labeling of SO$_2$OCF$_2$H precursor (**27**) with [$^{18}$F]fluoride. The unique reactivity exhibited by alkenyl SO$_2$OCF$_2$H compounds allowed for the convenient radiosynthesis of $^{18}$F-labeled alkenesulfonyl fluorides. The strategy described enabled the $^{18}$F labeling of a diverse array of substrates in RCCs between 58% and 92%. Two of these $^{18}$F compounds were isolated and purified in moderate decay-corrected

radiochemical yields. However, the molar activities needed to be further improved since $^{18}$F/$^{19}$F exchange happened during the labeling process.

## 3. [$^{18}$F]FLUOROSULFATE

The OSO$_2$F unit can serve as either an effective leaving group or a robust connecting building block in organic synthesis, contingent upon the specific characteristics of the substituted aryl and alkyl compounds involved. These applications encompassed various processes such as metal-mediated couplings, sulfur(VI) fluoride exchange (SuFEx) reactions,

## Scheme 6. Radiosynthesis of [$^{18}$F]PyFluor and Its Application of Deoxy-Radiofluorination
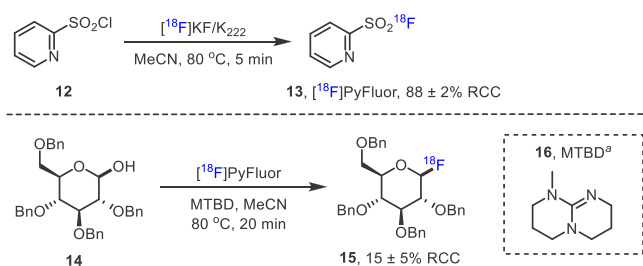


$^a$MTBD, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

carbonylation, involvement in alkylation and acylation reactions, hydrolysis, alcoholysis, and fluorinations.[62] For the radio-chemistry, Blower and co-workers reported the preparation and application of the potassium [$^{18}$F]fluorosulfate (**30**),[63] which represented the first example for PET imaging using a probe bearing an S—$^{18}$F bond. The production of potassium [$^{18}$F]fluorosulfate is shown in Scheme 9; the reaction of [$^{18}$F]KF/K$_{222}$ with a Lewis acid—base SO$_3$—pyridine complex (**29**) yielded the radio product with a moderate decay-corrected RCY of $31.6 \pm 9.5\%$ and a high molar activity of $48.5 \pm 13.4$ GBq/$\mu$mol. In both in vitro and in vivo experiments, this uncomplicated and inorganic $^{18}$F-labeled radiopharmaceutical showed specific uptake of the sodium—iodide symporter (NIS). Notably, PET/CT imaging conducted on normal mice within the initial hour postinjection displayed noticeable uptake of the potassium [$^{18}$F]fluorosulfate at locations known to exhibit NIS expression. The radiosignal was blocked by coinjection of sodium perchlorate, a known NIS inhibitor,[64−66] thus demonstrating the remarkable potential of potassium [$^{18}$F]-fluorosulfate as an outstanding PET tracer for NIS.

Aryl fluorosulfates, which are widely used OSO$_2$F compounds, can be easily obtained through reactions involving phenols or alcohols with sulfuryl fluoride, sulfuryl chloride fluoride, fluorosulfonic acid, and fluorosulfonic anhydride as well as a solid fluorosulfuryl imidazolium triflate.[62] They are more stable than arenesulfonyl fluorides in reports of sulfur(VI) fluoride exchange (SuFEx),[11,15,67,68] which attracted researchers

to investigate the radiosynthetic strategies and PET imaging applications of $^{18}$F-labeled aryl fluorosulfates. In 2020, Chun, Hong, and co-workers reported the pioneering research of the direct radiosynthesis of $^{18}$F-labeled aryl fluorosulfates utilizing phenols or aryl imidazole sulfonates (**34**, imidazylates) (Scheme 10).[69] They devised two strategies both from phenols for this $^{18}$F-radiosynthesis. The first mode involved one-pot [$^{18}$F]-fluorosulfurylation of phenols deploying 1,1′-sulfonyldiimidazole (**33**, SDI) and [$^{18}$F]fluoride. The second was realized by [$^{18}$F]fluorination of imidazylate precursors derived from phenols. The [$^{18}$F]fluorosulfurylated products with moderate to high RCYs were prepared by both methods, while Mode 2 afforded higher RCYs in most cases. The substrate scope of this [$^{18}$F]fluorosulfurylation strategy was tolerated with various functional groups, such as carbonyl, azide, hydroxy, formyl, alkenyl, and alkynyl moieties. Some drug-relevant compounds and natural products were also labeled with $^{18}$F by this methodology in good RCYs.

Based on SuFEx reactions,[11,15,67,68] Sharpless, Yang, Wu, and co-workers bridged click chemistry and $^{18}$F-radiosynthesis, developing an ultrafast process to synthesize $^{18}$F-labeled aryl fluorosulfates (Scheme 11).[70] Within a brief duration of just 30 s at room temperature, the conversion of [$^{18}$F]fluoride using nonradioactive aryl fluorosulfates (**36**), obtained from phenols and sulfuryl fluoride, was effectively and successfully achieved. Subsequently, a rapid (<1 min) C18-cartridge separation process was employed to isolate the $^{18}$F-labeled aryl fluorosulfates. Interestingly, the precursors of aryl fluorosulfates have been reported as intermediates for a deoxyfluorination protocol producing aryl fluorides from phenols.[71] In this radiolabeling strategy, using the fluorosulfate precursors that possess extensive structural and functional diversity enabled the $^{18}$F labeling to get the corresponding radioproducts in excellent RCYs of 83−100% and high molar activities. PET imaging of a healthy mouse using one particular $^{18}$F-labeled product revealed the absence of a nonspecific radiosignal in the bones, thereby indicating the good stability of [$^{18}$F]arenefluorosulfate without $^{18}$F-defluorination in vivo. For further investigations, a specific olaparib analog incorporating an aryl fluorosulfonyl component was labeled with $^{18}$F and then employed for PET imaging in a xenograft model of a human breast cancer, which was

## Scheme 7. Radiosynthesis of [$^{18}$F]ESF and Its Applications
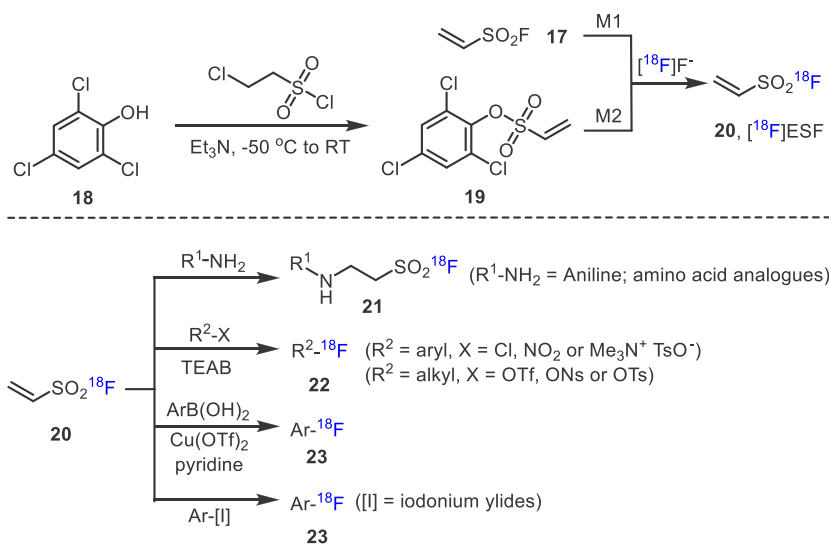
**Scheme 8. Radiosynthesis of $^{18}$F-Labeled Alkenesulfonyl Fluorides from Alkenes**
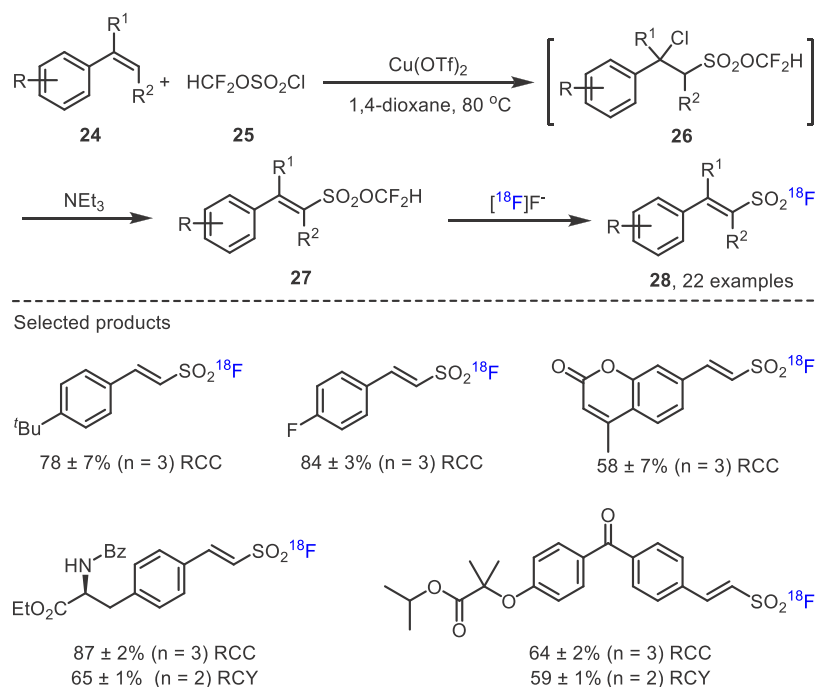


**Scheme 9. Radiosynthesis of $[^{18}F]KSO_3F$ from $SO_3^{3-}$ Pyridine Complex**
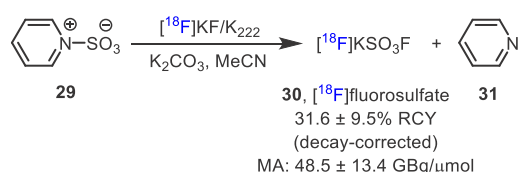


established using the MCF-7 cell line known for its elevated expression of PARP1. Additionally, in order to evaluate the specificity of the probe, blocking experiments were conducted by administering a preinjection of excess olaparib, a well-established PARP1 inhibitor. As a result, accumulation of the $^{18}$F-labeled olaparib analog in blocking experiments decreased obviously in tumors compared with that in nonblocking imaging studies, which supported this probe a potential PARP1-specific ligand for PET imaging.

## 4. SULFAMOYL [$^{18}$F]FLUORIDE

In the S−F chemistry, the sulfamoyl fluoride stands out as a highly stable yet efficient synthetic precursor or synthon for various valuable compounds, such as sulfamides[15] and azide derivatives[72] obtained by substitution and click chemistry, respectively. For the radiochemistry, Chun, Hong, and co-workers developed the radiosynthesis of $^{18}$F-labeled sulfamoyl fluorides (**39**) from the precursors of cold sulfamoyl fluorides,[73] generated from corresponding amines, by $^{18}$F/$^{19}$F isotopic exchange methodology (Scheme 12). This $^{18}$F-labeling strategy was performed efficiently with sulfamoyl precursors produced from aromatic and aliphatic secondary amines as well as primary amines that possessed mono- or bis-SO$_2$F moieties. They also attempted the direct $^{18}$F-fluorosulfurylation of amines based on their initial method[69] to produce $^{18}$F-labeled aryl fluorosulfates from phenols using 1,1′-sulfonyldiimidazole (SDI) and [$^{18}$F]-

fluoride. Unfortunately, despite their efforts, the desired radioproduct could not be obtained.

Recently, they successfully achieved the direct radiofluorosulfurylation for synthesizing $^{18}$F-labeled sulfamoyl fluorides from amines (Scheme 13).[74] This approach involved the in situ generation of an [$^{18}$F]FSO$_2^+$ transfer species by eluting the $^{18}$F-trapped QMA cartridge with an acetonitrile−water solution containing the imidazolium salt **42**, which has been used to synthesize the aryl fluorosulfates and sulfamoyl fluorides.[16] Mechanistic analysis conducted by using $^{19}$F NMR unveiled the formation of [$^{18}$F]FSO$_2^+$ as a mixture comprising [$^{18}$F]SO$_2$F$_2$ and [$^{18}$F]fluorosulfuryl imidazolium salt. The eluted [$^{18}$F]FSO$_2^+$ exhibited reactivity toward various amine substrates, including primary aliphatic and aromatic amines as well as secondary aliphatic and aromatic amines. This method enabled the synthesis of $^{18}$F-labeled sulfamoyl fluorides without the need of cryptand or strictly anhydrous conditions for the $^{18}$F-labeling process. In addition, it is also applicable to diverse phenolic substrates, which can be converted into $^{18}$F-labeled fluorosulfates (Scheme 13). Compared to previous methods (Schemes 10 and 11), this approach allows for the direct $^{18}$F labeling of fluorosulfates using phenols to obtain $^{18}$F-labeled fluorosulfates. However, it requires the prior preparation of $^{18}$F-labeling reagents, resulting in an additional radio reaction step.

## 5. SULFUR [$^{18}$F]MULTIFLUORIDE

Compared to the previous categories of S−$^{18}$F compounds, progress in the development of sulfur [$^{18}$F]multifluorides has been comparatively sluggish. Diethylaminosulfur trifluoride (DAST) was typically recognized for its utility in deoxyfluorination reactions of hydroxyl and carbonyl oxygens.[75] This reactive fluorinating reagent has found applications in the field of radiochemistry. After introduction of $^{18}$F into DAST with hydrogen [$^{18}$F]fluoride via $^{18}$F/$^{19}$F exchange, [$^{18}$F]DAST (**44**) was generated with more than 80% of the available activity incorporated (Scheme 14).[76] Deoxy-radiofluorination of several uncomplicated alcohols using this reactive agent could yield $^{18}$F-

**Scheme 10. Radiosynthesis of $^{18}$F-Labeled Aryl Fluorosulfates from Phenols or Aryl Imidazole Sulfonates (Imidazylates)**
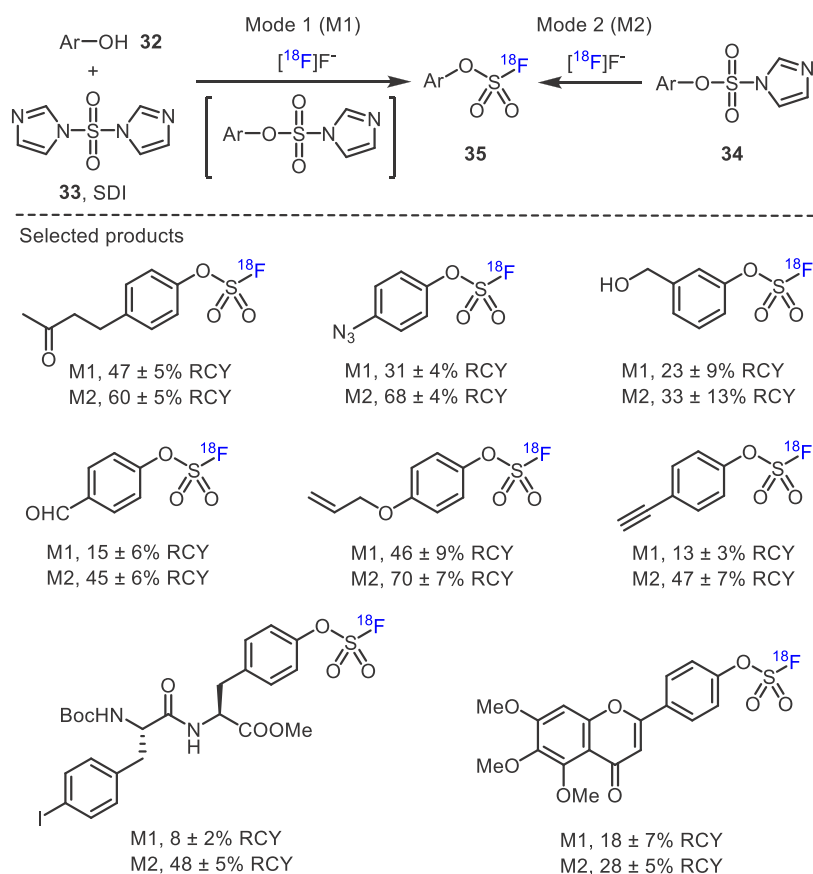


**Scheme 11. [$^{18}$F]SuFEx of Aryl Fluorosulfates**
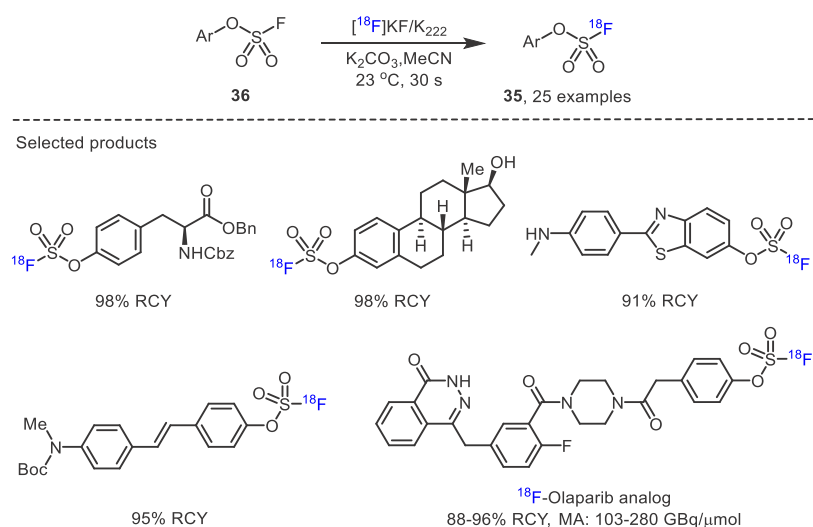


labeled fluoroalkyl compounds (**45−47**). However, in the early years, no $^{18}$F/$^{19}$F exchange was observed for sulfur hexafluoride (SF$_6$), a gas of another sulfur multifluoride, when it was treated with hydrogen [$^{18}$F]fluoride.[77] Afterward, a small yield of [$^{18}$F]SF$_6$ was formed during the production of recoil [$^{18}$F]-fluoride atoms[78] by the $^{19}$F(n,2n)$^{18}$F nuclear reaction[79] in the presence of SF$_6$.[80,81] A long time later in 2016, Llop and co-workers reported a readily automatable method for the preparation of [$^{18}$F]SF$_6$,[82] which involved an ion-beam-induced isotopic exchange reaction on the basis of the $^{19}$F(p,pn)$^{18}$F

nuclear reaction. As SF$_6$ has been used as fluorinated gas to evaluate lung ventilation by magnetic resonance imaging (MRI),[83] the radiolabeled [$^{18}$F]SF$_6$ was employed to investigate lung ventilation by PET imaging in a rat model of acute lung inflammation induced by administering lipopolysaccharide (LPS) via intratracheal nebulization.[84] Successful identifications of the hypoventilated lung regions with [$^{18}$F]SF$_6$ showed promise for clinical translation. In comparison to conventional imaging strategies for lung ventilation, PET imaging utilizing [$^{18}$F]SF$_6$ offers several advantages, including enhanced

**Scheme 12. Radiosynthesis of $^{18}$F-Labeled Sulfamoyl Fluorides through $^{18}$F/$^{19}$F Isotopic Exchange**
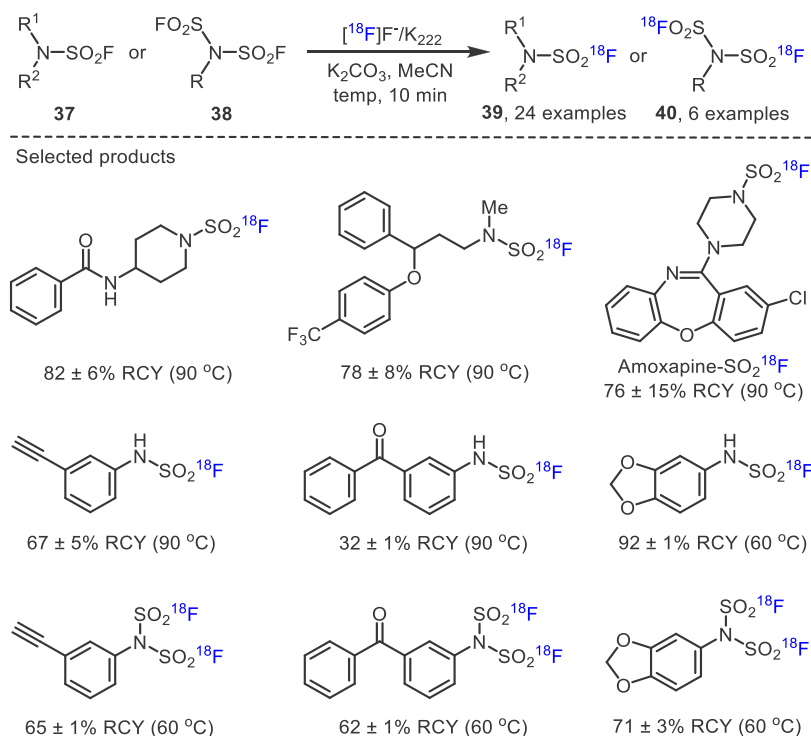


**Scheme 13. Radiosynthesis of $^{18}$F-Labeled Sulfamoyl Fluorides and Aryl Fluorosulfates from Amines and Phenols, Respectively**
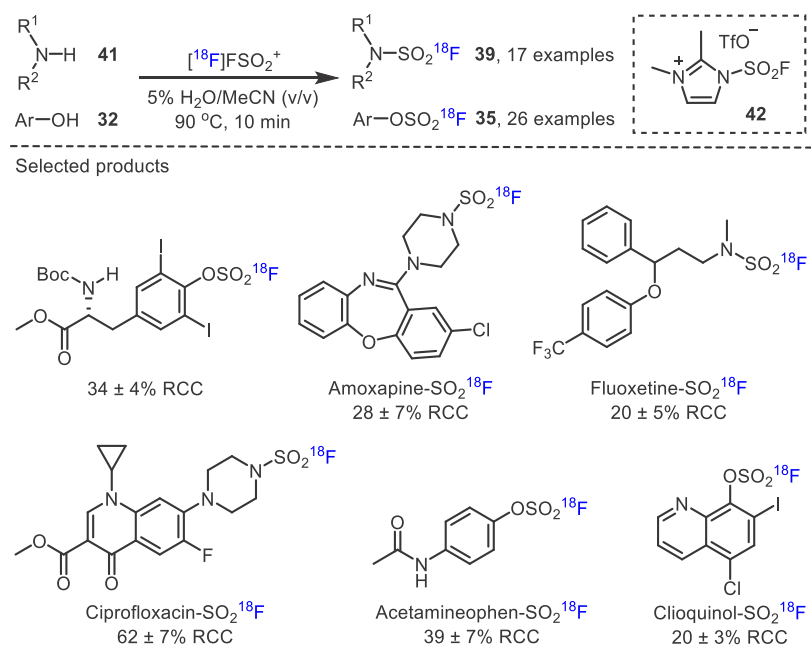


sensitivity, improved spatiotemporal resolution, and the ability to provide quantitative images of lung ventilation defects.

## 6. CONCLUSIONS AND PERSPECTIVES

Over the past decade, we have witnessed a remarkable advancement in S–$^{18}$F radiochemistry for positron emission tomography. As SuFEx has progressed rapidly, it is our expectation that these endeavors will establish a vital link between radiofluorination and SuFEx chemistry. The utilization of simple precursors and fast labeling reactions for S–$^{18}$F constructions has emerged as particularly noteworthy for

meeting the demands of $^{18}$F probe production. The application of these S–$^{18}$F compounds extends beyond PET tracers alone, and they can also be deployed as $^{18}$F synthons for the synthesis of biomolecules, as well as the $^{18}$F-fluorinating reagents for the radiolabeling of PET ligands.

When both the main part and the S–$^{18}$F fragment of the radiolabeled compound exhibit good stability, it is possible to consider the direct synthesis of S–$^{18}$F probes for PET tracers. Although this method for PET imaging studies has always been a focal point of research for scientists, the development of SO$_2$$^{18}$F synthons is also an important area of focus in S–$^{18}$F

**Scheme 14. Radiosynthesis of $[^{18}F]$DAST and Its Application of Deoxy-Radiofluorination**
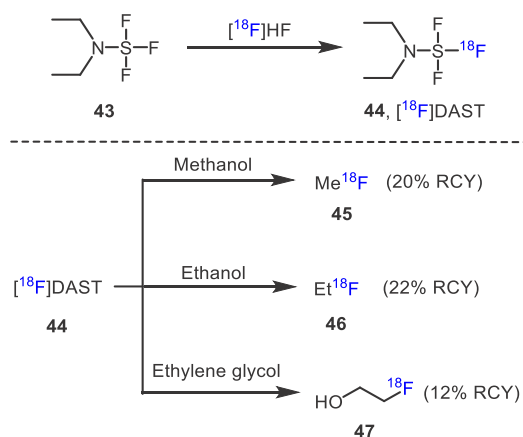


radiochemistry since many temperature-sensitive or water-soluble biomolecules cannot be directly labeled with $^{18}F$. An indirect labeling method conducted with the $SO_2^{18}F$ synthon provides a possibility for $^{18}F$ labeling of these biomolecular compounds. In general, whether these $S—^{18}F$ compounds can be used for clinical translation depends on various factors such as their in vivo stability, pharmacological activity, toxicity, and other relevant imaging aspects. Furthermore, the development of moderately stable $SO_2^{18}F$ compounds as fluorinating agents is also a key consideration in late-stage $^{18}F$-fluorination chemistry. Such $SO_2^{18}F$ compounds often possess a certain level of stability and reactivity. It is believed that in the near future more novel and convenient methods to obtain $S—^{18}F$ compounds will be developed, which will be ingeniously applied in the investigation of $^{18}F$ probes for PET imaging.

## ■ AUTHOR INFORMATION

### Corresponding Author

**Xiaohua Zhu** − *Department of Nuclear Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China;* ⊙ orcid.org/0000-0003-0495-9510; Email: evazhu@vip.sina.com

### Author

**Xiaoyun Deng** − *Department of Nuclear Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China;* ⊙ orcid.org/0000-0002-2276-3143

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.3c05594

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

## ■ REFERENCES

(1) Gambhir, S. S.; Czernin, J.; Schwimmer, J.; Silverman, D. H. S.; Coleman, R. E.; Phelps, M. E. A Tabulated Summary of the FDG PET Literature. *J. Nucl. Med.* **2001**, *42*, 1S−93S.

(2) Shankar, L. K.; Hoffman, J. M.; Bacharach, S.; Graham, M. M.; Karp, J.; Lammertsma, A. A.; Larson, S.; Mankoff, D. A.; Siegel, B. A.; Abbeele, A. V. d.; Yap, J.; Sullivan, D. Consensus Recommendations for the Use of 18F-FDG PET as an Indicator of Therapeutic Response in Patients in National Cancer Institute Trials. *J. Nucl. Med.* **2006**, *47*, 1059−1066.

(3) Deng, X.; Rong, J.; Wang, L.; Vasdev, N.; Zhang, L.; Josephson, L.; Liang, S. H. Chemistry for Positron Emission Tomography: Recent Advances in 11C-, 18F-, 13N-, and 15O-Labeling Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 2580−2605.

(4) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. Synthesis of 11C, 18F, 15O, and 13N Radiolabels for Positron Emission Tomography. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998−9033.

(5) Pascali, G.; Matesic, L.; Zhang, B.; King, A. T.; Robinson, A. J.; Ung, A. T.; Fraser, B. H. Sulfur - fluorine bond in PET radiochemistry. *EJNMMI Radiopharm. Chem.* **2017**, *2*, 9.

(6) Brouwer, A. J.; Jonker, A.; Werkhoven, P.; Kuo, E.; Li, N.; Gallastegui, N.; Kemmink, J.; Florea, B. I.; Groll, M.; Overkleeft, H. S.; Liskamp, R. M. J. Peptido Sulfonyl Fluorides as New Powerful Proteasome Inhibitors. *J. Med. Chem.* **2012**, *55*, 10995−11003.

(7) Shannon, D. A.; Gu, C.; McLaughlin, C. J.; Kaiser, M.; van der Hoorn, R. A. L.; Weerapana, E. Sulfonyl Fluoride Analogues as Activity-Based Probes for Serine Proteases. *ChemBioChem.* **2012**, *13*, 2327−2330.

(8) Gu, C.; Shannon, D. A.; Colby, T.; Wang, Z.; Shabab, M.; Kumari, S.; Villamor, J. G.; McLaughlin, C. J.; Weerapana, E.; Kaiser, M.; Cravatt, B. F.; van der Hoorn, R. A. L. Chemical Proteomics with Sulfonyl Fluoride Probes Reveals Selective Labeling of Functional Tyrosines in Glutathione Transferases. *Chem. Biol.* **2013**, *20*, 541−548.

(9) Grimster, N. P.; Connelly, S.; Baranczak, A.; Dong, J.; Krasnova, L. B.; Sharpless, K. B.; Powers, E. T.; Wilson, I. A.; Kelly, J. W. Aromatic Sulfonyl Fluorides Covalently Kinetically Stabilize Transthyretin to Prevent Amyloidogenesis while Affording a Fluorescent Conjugate. *J. Am. Chem. Soc.* **2013**, *135*, 5656−5668.

(10) Narayanan, A.; Jones, L. H. Sulfonyl fluorides as privileged warheads in chemical biology. *Chem. Sci.* **2015**, *6*, 2650−2659.

(11) Zheng, Q.; Woehl, J. L.; Kitamura, S.; Santos-Martins, D.; Smedley, C. J.; Li, G.; Forli, S.; Moses, J. E.; Wolan, D. W.; Sharpless, K. B. SuFEx-enabled, agnostic discovery of covalent inhibitors of human neutrophil elastase. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 18808−18814.

(12) Davies, W.; Dick, J. H. CCLXXXVI.—Aromatic sulphonyl fluorides. A convenient method of preparation. *J. Chem. Soc.* **1931**, *0*, 2104−2109.

(13) Bianchi, T. A.; Cate, L. A. Phase transfer catalysis. Preparation of aliphatic and aromatic sulfonyl fluorides. *J. Org. Chem.* **1977**, *42*, 2031−2032.

(14) Patel, C.; André-Joyaux, E.; Leitch, J. A.; de Irujo-Labalde, X. M.; Ibba, F.; Struijs, J.; Ellwanger, M. A.; Paton, R.; Browne, D. L.; Pupo, G.; Aldridge, S.; Hayward, M. A.; Gouverneur, V. Fluorochemicals from fluorspar via a phosphate-enabled mechanochemical process that bypasses HF. *Science* **2023**, *381*, 302−306.

(15) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry. *Angew. Chem., Int. Ed.* **2014**, *53*, 9430−9448.

(16) Guo, T.; Meng, G.; Zhan, X.; Yang, Q.; Ma, T.; Xu, L.; Sharpless, K. B.; Dong, J. A New Portal to SuFEx Click Chemistry: A Stable Fluorosulfuryl Imidazolium Salt Emerging as an "F−SO2+" Donor of Unprecedented Reactivity, Selectivity, and Scope. *Angew. Chem., Int. Ed.* **2018**, *57*, 2605−2610.

(17) Johnson, C. R.; Bis, K. G.; Cantillo, J. H.; Meanwell, N. A.; Reinhard, M. F. D.; Zeller, J. R.; Vonk, G. P. Preparation and reactions of sulfonimidoyl fluorides. *J. Org. Chem.* **1983**, *48*, 1−3.

(18) Ni, C.; Hu, M.; Hu, J. Good Partnership between Sulfur and Fluorine: Sulfur-Based Fluorination and Fluoroalkylation Reagents for Organic Synthesis. *Chem. Rev.* **2015**, *115*, 765−825.

(19) Harrak, Y.; Casula, G.; Basset, J.; Rosell, G.; Plescia, S.; Raffa, D.; Cusimano, M. G.; Pouplana, R.; Pujol, M. D. Synthesis, Anti-Inflammatory Activity, and in Vitro Antitumor Effect of a Novel Class of Cyclooxygenase Inhibitors: 4-(Aryloyl)phenyl Methyl Sulfones. *J. Med. Chem.* **2010**, *53*, 6560−6571.

(20) Xu, W.-M.; Han, F.-F.; He, M.; Hu, D.-Y.; He, J.; Yang, S.; Song, B.-A. Inhibition of Tobacco Bacterial Wilt with Sulfone Derivatives Containing an 1,3,4-Oxadiazole Moiety. *J. Agric. Food Chem.* **2012**, *60*, 1036−1041.

(21) Vogel, P.; Turks, M. r.; Bouchez, L.; Marković, D.; Varela-Álvarez, A.; Sordo, J. Á. New Organic Chemistry of Sulfur Dioxide. *Acc. Chem. Res.* **2007**, *40*, 931−942.

(22) El-Awa, A.; Noshi, M. N.; du Jourdin, X. M.; Fuchs, P. L. Evolving Organic Synthesis Fostered by the Pluripotent Phenylsulfone Moiety. *Chem. Rev.* **2009**, *109*, 2315−2349.

(23) Ager, D. J.; Pantaleone, D. P.; Henderson, S. A.; Katritzky, A. R.; Prakash, I.; Walters, D. E. Commercial, Synthetic Nonnutritive Sweeteners. *Angew. Chem., Int. Ed.* **1998**, *37*, 1802−1817.

(24) Liu, N.-W.; Liang, S.; Manolikakes, G. Recent Advances in the Synthesis of Sulfones. *Synthesis* **2016**, *48*, 1939−1973.

(25) Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. DABCO-Bis(sulfur dioxide), DABSO, as a Convenient Source of Sulfur Dioxide for Organic Synthesis: Utility in Sulfonamide and Sulfamide Preparation. *Org. Lett.* **2011**, *13*, 4876−4878.

(26) Nguyen, B.; Emmett, E. J.; Willis, M. C. Palladium-Catalyzed Aminosulfonylation of Aryl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 16372−16373.

(27) Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. Palladium-Catalyzed Sulfination of Aryl and Heteroaryl Halides: Direct Access to Sulfones and Sulfonamides. *Org. Lett.* **2013**, *15*, 6226−6229.

(28) Emmett, E. J.; Hayter, B. R.; Willis, M. C. Palladium-Catalyzed Synthesis of Ammonium Sulfinates from Aryl Halides and a Sulfur Dioxide Surrogate: A Gas- and Reductant-Free Process. *Angew. Chem., Int. Ed.* **2014**, *53*, 10204−10208.

(29) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. One-pot three-component sulfone synthesis exploiting palladium-catalysed aryl halide aminosulfonylation. *Chem. Sci.* **2014**, *5*, 222−228.

(30) Chen, Y.; Willis, M. C. Copper(i)-catalyzed sulfonylative Suzuki−Miyaura cross-coupling. *Chem. Sci.* **2017**, *8*, 3249−3253.

(31) Lo, P. K. T.; Chen, Y.; Willis, M. C. Nickel(II)-Catalyzed Synthesis of Sulfinates from Aryl and Heteroaryl Boronic Acids and the Sulfur Dioxide Surrogate DABSO. *ACS Catal.* **2019**, *9*, 10668−10673.

(32) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. One-pot palladium-catalyzed synthesis of sulfonyl fluorides from aryl bromides. *Chem. Sci.* **2017**, *8*, 1233−1237.

(33) Tribby, A. L.; Rodríguez, I.; Shariffudin, S.; Ball, N. D. Pd-Catalyzed Conversion of Aryl Iodides to Sulfonyl Fluorides Using SO2 Surrogate DABSO and Selectfluor. *J. Org. Chem.* **2017**, *82*, 2294−2299.

(34) Lou, T. S.-B.; Bagley, S. W.; Willis, M. C. Cyclic Alkenylsulfonyl Fluorides: Palladium-Catalyzed Synthesis and Functionalization of Compact Multifunctional Reagents. *Angew. Chem., Int. Ed.* **2019**, *58*, 18859−18863.

(35) Zhong, T.; Pang, M.-K.; Chen, Z.-D.; Zhang, B.; Weng, J.; Lu, G. Copper-free Sandmeyer-type Reaction for the Synthesis of Sulfonyl Fluorides. *Org. Lett.* **2020**, *22*, 3072−3078.

(36) Liu, Y.; Yu, D.; Guo, Y.; Xiao, J.-C.; Chen, Q.-Y.; Liu, C. Arenesulfonyl Fluoride Synthesis via Copper-Catalyzed Fluorosulfonylation of Arenediazonium Salts. *Org. Lett.* **2020**, *22*, 2281−2286.

(37) Louvel, D.; Chelagha, A.; Rouillon, J.; Payard, P.-A.; Khrouz, L.; Monnereau, C.; Tlili, A. Metal-Free Visible-Light Synthesis of Arylsulfonyl Fluorides: Scope and Mechanism. *Chem. Eur. J.* **2021**, *27*, 8704−8708.

(38) Magre, M.; Cornella, J. Redox-Neutral Organometallic Elementary Steps at Bismuth: Catalytic Synthesis of Aryl Sulfonyl Fluorides. *J. Am. Chem. Soc.* **2021**, *143*, 21497−21502.

(39) Laudadio, G.; Bartolomeu, A. d. A.; Verwijlen, L. M. H. M.; Cao, Y.; de Oliveira, K. T.; Noël, T. Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride. *J. Am. Chem. Soc.* **2019**, *141*, 11832−11836.

(40) Neal, T. R.; Apana, S.; Berridge, M. S. Improved synthesis of [18F]fluoromethyl tosylate, a convenient reagent for radiofluoromethylations. *J. Labelled Compd. Rad.* **2005**, *48*, 557−568.

(41) Wang, J.; Qu, X.; Shoup, T. M.; Yuan, G.; Afshar, S.; Pan, C.; Zhu, A.; Choi, J.-K.; Kang, H. J.; Poutiainen, P.; El Fakhri, G.; Zhang, Z.; Brownell, A.-L. Synthesis and Characterization of Fluorine-18-Labeled N-(4-Chloro-3-((fluoromethyl-d2)thio)phenyl)picolinamide for Imaging of mGluR4 in Brain. *J. Med. Chem.* **2020**, *63*, 3381−3389.

(42) Cremlyn, R.; Nunes, R. Reactions of N-(p-Chlorosulfonylphenyl)Maleimide. *Phosphorus Sulfur* **1987**, *31*, 245−254.

(43) Blotny, G. A new, mild preparation of sulfonyl chlorides. *Tetrahedron Lett.* **2003**, *44*, 1499−1501.

(44) Matesic, L.; Wyatt, N. A.; Fraser, B. H.; Roberts, M. P.; Pham, T. Q.; Greguric, I. Ascertaining the Suitability of Aryl Sulfonyl Fluorides for [18F]Radiochemistry Applications: A Systematic Investigation using Microfluidics. *J. Org. Chem.* **2013**, *78*, 11262−11270.

(45) Fiel, S. A.; Yang, H.; Schaffer, P.; Weng, S.; Inkster, J. A. H.; Wong, M. C. K.; Li, P. C. H. Magnetic Droplet Microfluidics as a Platform for the Concentration of [18F]Fluoride and Radiosynthesis of Sulfonyl [18F]Fluoride. *ACS Appl. Mater. Interfaces* **2015**, *7*, 12923−12929.

(46) Deng, X.; Wang, Z.; Zhou, H.; Liu, J.; Yu, B.; Zhu, X. Radiosynthesis of 18F-Labeled Arenesulfonyl Fluorides through Two-Bond Construction with [18F]Fluoride. *Org. Lett.* **2023**, *25*, 1969−1973.

(47) Ravasco, J. M. J. M.; Faustino, H.; Trindade, A.; Gois, P. M. P. Bioconjugation with Maleimides: A Useful Tool for Chemical Biology. *Chem. Eur. J.* **2019**, *25*, 43−59.

(48) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. A broadly applicable [18F]trifluoromethylation of aryl and heteroaryl iodides for PET imaging. *Nat. Chem.* **2013**, *5*, 941−944.

(49) Rühl, T.; Rafique, W.; Lien, V. T.; Riss, P. J. Cu(i)-mediated 18F-trifluoromethylation of arenes: Rapid synthesis of 18F-labeled trifluoromethyl arenes. *Chem. Commun.* **2014**, *50*, 6056−6059.

(50) Zheng, J.; Wang, L.; Lin, J.-H.; Xiao, J.-C.; Liang, S. H. Difluorocarbene-Derived Trifluoromethylthiolation and [18F]-Trifluoromethylthiolation of Aliphatic Electrophiles. *Angew. Chem., Int. Ed.* **2015**, *54*, 13236−13240.

(51) Inkster, J. A. H.; Liu, K.; Ait-Mohand, S.; Schaffer, P.; Guérin, B.; Ruth, T. J.; Storr, T. Sulfonyl Fluoride-Based Prosthetic Compounds as Potential 18F Labelling Agents. *Chem. Eur. J.* **2012**, *18*, 11079−11087.

(52) King, A. T.; Matesic, L.; Keaveney, S. T.; Jamie, J. F. An Investigation into the In Vitro Metabolic Stability of Aryl Sulfonyl Fluorides for their Application in Medicinal Chemistry and Radiochemistry. *Mol. Pharmaceutics* **2023**, *20*, 1061−1071.

(53) Al-Momani, E.; Israel, I.; Buck, A. K.; Samnick, S. Improved synthesis of [18F]FS-PTAD as a new tyrosine-specific prosthetic group for radiofluorination of biomolecules. *Appl. Radiat. Isot.* **2015**, *104*, 136−142.

(54) Ban, H.; Gavrilyuk, J.; Barbas, C. F., III Tyrosine Bioconjugation through Aqueous Ene-Type Reactions: A Click-Like Reaction for Tyrosine. *J. Am. Chem. Soc.* **2010**, *132*, 1523−1525.

(55) Ban, H.; Nagano, M.; Gavrilyuk, J.; Hakamata, W.; Inokuma, T.; Barbas, C. F., III Facile and Stabile Linkages through Tyrosine: Bioconjugation Strategies with the Tyrosine-Click Reaction. *Bioconjugate Chem.* **2013**, *24*, 520−532.

(56) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent. *J. Am. Chem. Soc.* **2015**, *137*, 9571−9574.

(57) Ametamey, S. M.; Honer, M.; Schubiger, P. A. Molecular Imaging with PET. *Chem. Rev.* **2008**, *108*, 1501−1516.

(58) Zhang, B.; Pascali, G.; Wyatt, N.; Matesic, L.; Klenner, M. A.; Sia, T. R.; Guastella, A. J.; Massi, M.; Robinson, A. J.; Fraser, B. H. Synthesis,

bioconjugation and stability studies of [18F]ethenesulfonyl fluoride. *J. Labelled Compd. Rad.* **2018**, *61*, 847−856.

(59) Klenner, M. A.; Pascali, G.; Zhang, B.; Ciancaleoni, G.; Massi, M.; Fraser, B. H. Effect of Rhenium(I) Complexation on Aza-Michael Additions to 5-Amino-1,10-Phenanthroline with [18F]Ethenesulfonyl Fluoride towards PET Optical Tracer Development. *Aust. J. Chem.* **2019**, *72*, 288−294.

(60) Zhang, B.; Fraser, B. H.; Klenner, M. A.; Chen, Z.; Liang, S. H.; Massi, M.; Robinson, A. J.; Pascali, G. [18F]Ethenesulfonyl Fluoride as a Practical Radiofluoride Relay Reagent. *Chem. Eur. J.* **2019**, *25*, 7613−7617.

(61) Zhang, W.; Deng, X.; Zhang, F.-X.; Lin, J.-H.; Xiao, J.-C.; Liang, S. H. Synthesis and 18F Labeling of Alkenyl Sulfonyl Fluorides via an Unconventional Elimination Pathway. *Org. Lett.* **2022**, *24*, 4992−4997.

(62) Revathi, L.; Ravindar, L.; Leng, J.; Rakesh, K. P.; Qin, H.-L. Synthesis and Chemical Transformations of Fluorosulfates. *Asian J. Org. Chem.* **2018**, *7*, 662−682.

(63) Khoshnevisan, A.; Chuamsaamarkkee, K.; Boudjemeline, M.; Jackson, A.; Smith, G. E.; Gee, A. D.; Fruhwirth, G. O.; Blower, P. J. 18F-Fluorosulfate for PET Imaging of the Sodium−Iodide Symporter: Synthesis and Biologic Evaluation In Vitro and In Vivo. *J. Nucl. Med.* **2017**, *58*, 156−161.

(64) De Groef, B.; Decallonne, B. R.; Van der Geyten, S.; Darras, V. M.; Bouillon, R. Perchlorate versus other environmental sodium/iodide symporter inhibitors: Potential thyroid-related health effects. *Eur. J. Endocrinol.* **2006**, *155*, 17−25.

(65) Dohán, O.; Portulano, C.; Basquin, C.; Reyna-Neyra, A.; Amzel, L. M.; Carrasco, N. The Na$^+$/I$^-$ symporter (NIS) mediates electroneutral active transport of the environmental pollutant perchlorate. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 20250−20255.

(66) Tran, N.; Valentín-Blasini, L.; Blount, B. C.; McCuistion, C. G.; Fenton, M. S.; Gin, E.; Salem, A.; Hershman, J. M. Thyroid-stimulating hormone increases active transport of perchlorate into thyroid cells. *Am. J. Physiol.-Endoc. M.* **2008**, *294*, E802−E806.

(67) Chen, W.; Dong, J.; Li, S.; Liu, Y.; Wang, Y.; Yoon, L.; Wu, P.; Sharpless, K. B.; Kelly, J. W. Synthesis of Sulfotyrosine-Containing Peptides by Incorporating Fluorosulfated Tyrosine Using an Fmoc-Based Solid-Phase Strategy. *Angew. Chem., Int. Ed.* **2016**, *55*, 1835−1838.

(68) Chen, W.; Dong, J.; Plate, L.; Mortenson, D. E.; Brighty, G. J.; Li, S.; Liu, Y.; Galmozzi, A.; Lee, P. S.; Hulce, J. J.; Cravatt, B. F.; Saez, E.; Powers, E. T.; Wilson, I. A.; Sharpless, K. B.; Kelly, J. W. Arylfluorosulfates Inactivate Intracellular Lipid Binding Protein(s) through Chemoselective SuFEx Reaction with a Binding Site Tyr Residue. *J. Am. Chem. Soc.* **2016**, *138*, 7353−7364.

(69) Kwon, Y.-D.; Jeon, M. H.; Park, N. K.; Seo, J. K.; Son, J.; Ryu, Y. H.; Hong, S. Y.; Chun, J.-H. Synthesis of 18F-Labeled Aryl Fluorosulfates via Nucleophilic Radiofluorination. *Org. Lett.* **2020**, *22*, 5511−5516.

(70) Zheng, Q.; Xu, H.; Wang, H.; Du, W.-G. H.; Wang, N.; Xiong, H.; Gu, Y.; Noodleman, L.; Sharpless, K. B.; Yang, G.; Wu, P. Sulfur [18F]Fluoride Exchange Click Chemistry Enabled Ultrafast Late-Stage Radiosynthesis. *J. Am. Chem. Soc.* **2021**, *143*, 3753−3763.

(71) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. Nucleophilic Deoxyfluorination of Phenols via Aryl Fluorosulfonate Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 1452−1455.

(72) Meng, G.; Guo, T.; Ma, T.; Zhang, J.; Shen, Y.; Sharpless, K. B.; Dong, J. Modular click chemistry libraries for functional screens using a diazotizing reagent. *Nature* **2019**, *574*, 86−89.

(73) Jeon, M. H.; Kwon, Y.-D.; Kim, M. P.; Torres, G. B.; Seo, J. K.; Son, J.; Ryu, Y. H.; Hong, S. Y.; Chun, J.-H. Late-Stage 18F/19F Isotopic Exchange for the Synthesis of 18F-Labeled Sulfamoyl Fluorides. *Org. Lett.* **2021**, *23*, 2766−2771.

(74) Kim, M. P.; Cho, H.; Kayal, S.; Jeon, M. H.; Seo, J. K.; Son, J.; Jeong, J.; Hong, S. Y.; Chun, J.-H. Direct 18F-Fluorosulfurylation of Phenols and Amines Using an [18F]FSO2+ Transfer Agent Generated In Situ. *J. Org. Chem.* **2023**, *88*, 6263−6273.

(75) Middleton, W. J. New fluorinating reagents. Dialkylaminosulfur fluorides. *J. Org. Chem.* **1975**, *40*, 574−578.

(76) Straatmann, M. G.; Welch, M. J. Fluorine-18-Labeled Diethylaminosulfur Trifluoride (DAST): An F-for-OH Fluorinating Agent. *J. Nucl. Med.* **1977**, *18*, 151−158.

(77) Rogers, M. T.; Katz, J. J. Fluorine Exchange Reactions between Hydrogen Fluoride and the Halogen Fluorides. *J. Am. Chem. Soc.* **1952**, *74*, 1375−1377.

(78) Colebourne, N.; Wolfgang, R. Some Gas-Phase Reactions of Hot and Thermal Atomic Fluorine. *J. Chem. Phys.* **1963**, *38*, 2782−2783.

(79) Smail, T.; Rowland, F. S. Insertion reactions of mono- and difluorocarbene with hydrogen halides. *J. Phys. Chem.* **1970**, *74*, 1866−1871.

(80) Williams, R. L.; Rowland, F. S. Addition of fluorine-18 atoms to acetylene. *J. Am. Chem. Soc.* **1972**, *94*, 1047−1051.

(81) Smail, T.; Iyer, R. S.; Rowland, F. S. Competitive addition of near-thermal fluorine-18 atoms to olefins. *J. Am. Chem. Soc.* **1972**, *94*, 1041−1046.

(82) Gómez-Vallejo, V.; Lekuona, A.; Baz, Z.; Szczupak, B.; Cossío, U.; Llop, J. Ion beam induced 18F-radiofluorination: straightforward synthesis of gaseous radiotracers for the assessment of regional lung ventilation using positron emission tomography. *Chem. Commun.* **2016**, *52*, 11931−11934.

(83) Schreiber, W. G.; Eberle, B.; Laukemper-Ostendorf, S.; Markstaller, K.; Weiler, N.; Scholz, A.; Bürger, K.; Heussel, C. P.; Thelen, M.; Kauczor, H.-U. Dynamic 19F-MRI of pulmonary ventilation using sulfur hexafluoride (SF6) gas. *Magn. Reson. Med.* **2001**, *45*, 605−613.

(84) Passannante, R.; Gómez-Vallejo, V.; Cossío, U.; Ruiz-Cabello, J.; Lekuona, A.; Salinas, V.; Amado-Rodríguez, L.; Albaiceta, G. M.; Martín, A.; Rejc, L.; Llop, J. Assessment of Regional Lung Ventilation with Positron Emission Tomography Using the Radiofluorinated Gas [18F]SF6: Application to an Animal Model of Impaired Ventilation. *Mol. Imaging Biol.* **2023**, *25*, 413−422.