Synthesis M. P. Kim et al. Short Review

The First Decade of SuFEx Chemistry: Advancements in SuFEx Polymerization, Non-Canonical SuFEx Reactions, and SuFEx Radiochemistry

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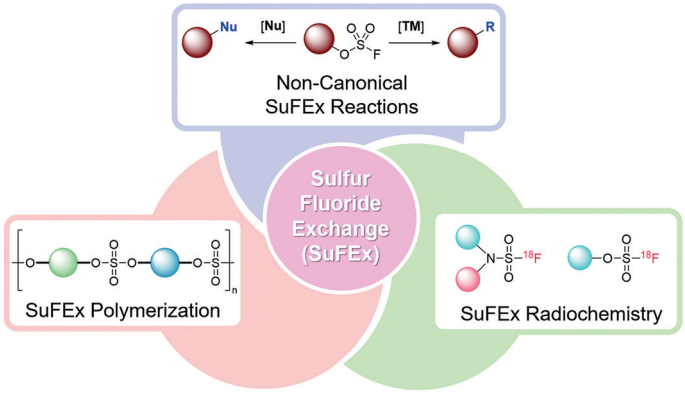

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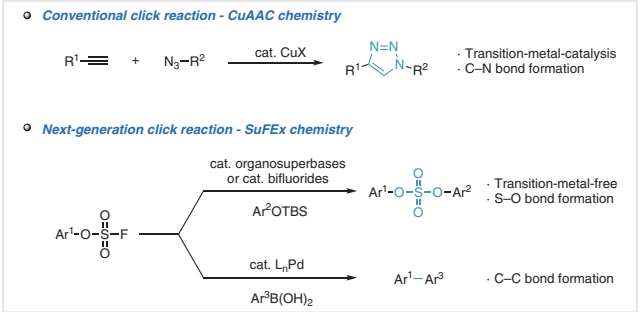
Abstract This year marks the 10th anniversary of SuFEx chemistry, a field that has witnessed significant advancements over the past decade. These include efficient synthetic strategies toward polymerization via the SuFEx approach leading to diverse polymers, alongside the discovery of new SuFExable hubs and coupling conditions. Non-canonical reactions, such as deoxyfluorination and on-water reactions, have also emerged. Furthermore, there have been substantial strides in the radiosynthesis of [^{18}F] SuFExable hubs. This review provides an overview of these developments, focusing on polymerization, non-canonical reaction, and radiochemistry in SuFEx chemistry.

1 Introduction
2 SuFEx Polymerization
3 Non-Canonical SuFEx Reactions
4 Fluorine-18 SuFEx Radiochemistry
5 Conclusions and Outlook

Key words SuFEx chemistry, polymerization, polymer degradation, deoxyhalogenation, radiofluorination

1 Introduction

Sulfur fluoride exchange (SuFEx) chemistry celebrates its 10th anniversary this year, originating from the seminal paper by the Sharpless group published in *Angewandte Chemie* in 2014.[1] SuFEx chemistry, regarded as next-generation click chemistry, enables the formation of stable organosulfur-based linkages promoted by organosuperbases or bifluorides (Scheme 1).[1–3] Notably, SuFEx reactions can be performed under ambient conditions, without the need for moisture-sensitive techniques such as glovebox or Schlenk line setups.[1–3] While copper-catalyzed azide–alkyne cycloaddition (CuAAC), among metal-catalyzed AAC reactions, forms triazole-based linkages, SuFEx chemistry facilitates the facile formation of sulfur–heteroatom linkages, such as S–O and S–N bonds, via nucleophilic substitution.[1–6] Furthermore, SuFExable hubs can be also employed in transition-metal-catalyzed cross-coupling reactions to form carbon–heteroatom linkages (e.g., C–O, C–N, and C–F), thus expanding the versatility of synthetic strategies.[7–10]



Scheme 1 Comparison of CuAAC and SuFEx reactions.

Common SuFExable hubs, including sulfonyl fluorides, fluorosulfates, sulfamoyl fluorides, and iminosulfur oxydifluorides, exhibit distinct physical and chemical properties.[1,11–13] For example, sulfonyl fluorides demonstrate higher thermal stability, better resistance to redox reactions, and greater tolerance to acidic conditions compared to the more commonly used sulfonyl chlorides.[1] Through the use of orthogonal reactivity, SuFEx coupling reactions have been applied to the formation of complex oligomeric and

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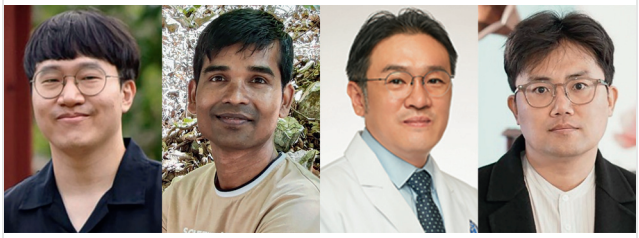


Min Pyeong Kim (left) earned his B.S. degree in 2017 from Ajou University. Then, he moved to LG Chem for industrial experience as a chemical engineer from 2018 to 2019. He has been a combined M.S./Ph.D. student at UNIST under the guidance of Prof. Sung You Hong since 2019. He is interested in the utilization of SuFExable hubs.

Manoj Kumar Sahoo (second left) obtained his Ph.D. degree in 2018 from CSIR-National Chemical Laboratory supervised by Prof. Balaraman Ekambaram. After completing his doctoral studies, he moved to the Chang group at Korea Advanced Institute of Science and Technology, Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science and worked there as a postdoctoral fellow from 2019 to 2022. Since 2022, he has been a Senior Researcher in the Hong group. His current research work is focused on transition-metal-catalyzed reactions using SuFExable hubs.

Joong-Hyun Chun (second right) received his Ph.D. degree under the supervision of Prof. Gerald F. Koser at University of Akron in 2005. After a short stay as a postdoc at Kent State University in the Laali group, he continued to pursue a postdoctoral experience at National Institutes of Health (NIH) with Dr. Victor Pike from 2007 to 2012. In 2013, he took up a position as a research associate at Wolfson Brain Imaging Centre at the University of Cambridge, UK. He moved to Yonsei University in 2015 as an assistant professor, and currently is an associate professor. His research interests focus on methodology development for radiochemistry along with hypervalent compounds.

Sung You Hong (right) earned his B.S. degree with *summa cum laude* honors from Seoul National University in 2002. He completed his doctoral studies in organic chemistry at the University of Oxford from 2005 to 2009 under the supervision of Prof. Benjamin G. Davis (co-advisor: Prof. Malcolm L. H. Green). Following his D.Phil., he conducted postdoctoral research with Prof. Peter H. Seeberger at the Max Planck Institute. In late 2010, he began his independent academic career at UNIST. His research focuses on SuFEx chemistry and nickel catalysis.

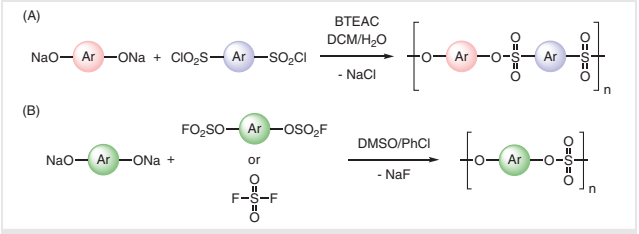
polymeric structures.[14–17] Additionally, they have been applied in bioconjugation chemistry.[18,19] Moreover, SO_2F-containing compounds have garnered attention because the –SO_2F moiety can serve both as a covalent inhibitor and as a chemical probe.[20] To meet the high demand for versatile imaging agents, stable aryl fluorosulfates have been identified as effective fluorine-18 based radiotracers.[21] Furthermore, electrolyte additives incorporating SO_2F bearing compounds or their derivatives have successfully improved electrochemical performances.[22,23] Since several excellent review articles on SuFEx chemistry have been previously introduced,[24–28] this review aims to cover the progress made in SuFEx chemistry over the past decade, focusing on three specific topics: polymerizations, non-canonical reactions, and radiochemistry.

2 SuFEx Polymerization

2.1 Synthesis of SuFEx Polymers

2.1.1 Polysulfonates and Polysulfates

Polysulfonates and polysulfates emerged in the 1960s and 1970s.[29,30] Particularly, the simple condensation polymerization process between aromatic disulfonyl chlorides and disodium bisphenoxides was employed to produce polysulfonates with the aid of benzyltriethylammonium chloride (BTEAC) (Scheme 2A).[30] In addition, polysulfates were synthesized from bisfluorosulfates and disodium bisphenoxides during that period (Scheme 2B).[29] However, the polymerizations of polysulfonates and polysulfates face limitations due to the noncatalytic nature of the polycondensation and the use of stoichiometric amounts of sodium phenoxide monomers. The basic conditions can lead to the degradation of polymeric main chains through alcoholysis, which hinders efficient polymerization.



Scheme 2 Early works of noncatalytic polymerization methods: (A) polysulfonates (Herweh, 1968); (B) polysulfates (Firth, 1972)

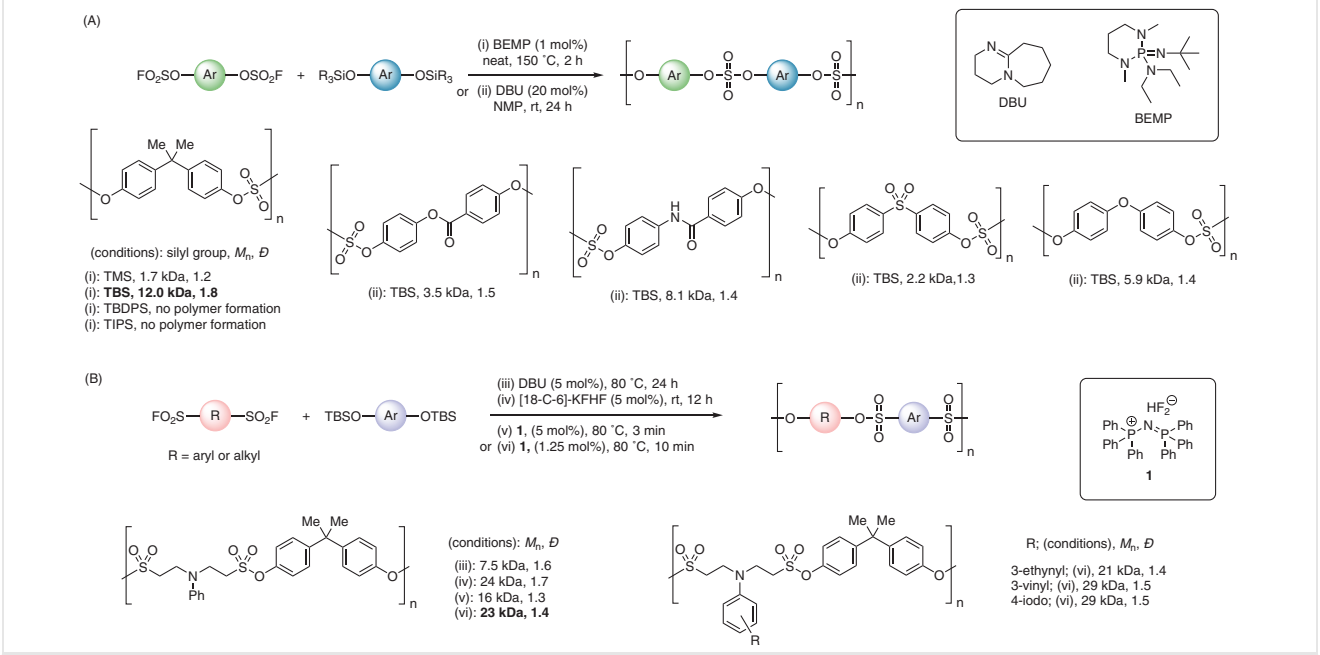
In 2014, Sharpless and Fokin introduced an organosuperbase-catalyzed polymerization method for polysulfates (Scheme 3A).[31] The Gembus group previously reported the synthesis of sulfonates using sulfonyl fluorides and silyl ethers with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[32] The reaction between aryl fluorosulfates/sulfonyl fluorides and silyl ethers produces *tert*-butyldimethylfluorosilane (TBSF) as a byproduct. Due to the strong bonding nature of Si–F, the formation of TBSF can provide the thermodynamic driving force of the reaction. Even though silyl fluorides are not completely intact against nucleophiles,[33] TBSF does not significantly interrupt the reaction. Compared to the noncatalytic classical polymerization, the improvement allows for the use of only 20 mol% of DBU or 1 mol% of 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) as catalysts, while allowing high molecular weights on the polymerization.[31] Additionally, they evaluated the effect of different silyl ethers. Among trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBS), *tert*-butyldiphenylsilyl (TBDPS), and triisopropylsilyl (TIPS) groups, TBS was found to be the best silyl group in the presence of 1 mol% BEMP. This catalytic condensation polymer-

ization is compatible with various functional groups, producing polymers with high molecular weights and moderate polydispersity ($Đ = M_w/M_n$).

In 2017, Sharpless and Wu introduced bifluoride-catalyzed polysulfonates polymerization (Scheme 3B) instead of the use of organosuperbases.[34] They evaluated various bifluoride catalysts for polysulfonates. Interestingly, using 5 mol% of KFHF alone does not lead to polymerization. However, with the addition of 18-crown-6 as a phase transfer agent (PTA) along with KFHF, the desired polysulfonate was successfully synthesized.[34,35] The use of 1.25 mol% of $[Ph_3P{=}NPPh_3]^+ FHF^-$ **1** was found to be optimum bifluoride catalyst compared to other bifluoride salts. While the previous synthesis of polysulfonates were limited to rigid aromatic backbones,[30] this limitation was overcome by utilizing ethenesulfonyl fluoride (ESF)–amine derived monomers, allowing the creation of aliphatic polysulfonate chains.

The bifluoride-catalyzed polymerization was also applied to polysulfates, and the impact of cations for polysulfates polymerization was investigated (Scheme 4A).[36] The polymerization efficiency was evaluated various cationic bifluorides such as sulfonium, guanidium, phosphonium, and ammonium salts. Among them, tris(dimethylamino)sulfonium bifluoride (**2**) enables a 20-fold improvement in turnover number (TON) compared to the previous polysulfate synthesis using 1 mol% BEMP. Additionally, the $Đ$ and molecular weight were fine-tunable by using a monosubstituted fluorosulfate **3** or silyl ether **4** as a molecular weight modifier (Scheme 4B). Also, they also applied the examination of this catalytic polymerization to polysulfonate synthesis (Scheme 4C). When aliphatic bissulfonyl fluorides were used as monomers in the above study, molecular weights ranging from 21 to 39 kDa were obtained.[34] Similarly, in this work, the polysulfonate polymerization yields a low molecular weight (10–25 kDa) with 5 mol% of high catalyst loading with the aliphatic monomers. On the other hand, the polymerization with aromatic disulfonyl fluorides requires only 0.5 mol% of catalyst and accomplish a high molecular weight (>60 kDa). Taking all these into account, the aromatic monomeric units are more favorable approach than aliphatic congeners in SuFEx polymerization.

Polysulfate synthesis has been largely focused on AA/BB-type step-growth polycondensation. Advancing beyond this approach, a chain-growth polycondensation approach was introduced using iminosulfur oxydifluoride initiator in 2021.[37] SuFExable hubs exhibit reactivity in the following order of $-N{=}SOF_2$ >> $-SO_2F$ > $-OSO_2F$.[38] This reactivity pattern allows for controlled sequential reactions even when they coexist within the reaction mixture. While 20 mol% DBU is typically used in step-growth polymerization,[31] only 2 mol% DBU is sufficient to achieve this chain-growth polymerization within 1 hour when 2 mol% of (4-nitrophenyl)sulfurimidoyl difluoride (**5**) was added as an initiator (Scheme 5A). Notably, the molecular weight is controllable by changing the monomer/initiator ratio. This method also showed typical chain-growth polymerization behavior, where M_n increased with monomer conversion, while $Đ$ remains consistent (Scheme 5B). Block copolymer-



Scheme 3 Contemporary revival of SuFEx polymerizations: (A) organosuperbase-catalyzed polysulfate synthesis (Fokin and Sharpless, 2014); and (B) bifluoride-catalyzed polysulfonate synthesis (Wu and Sharpless, 2017)

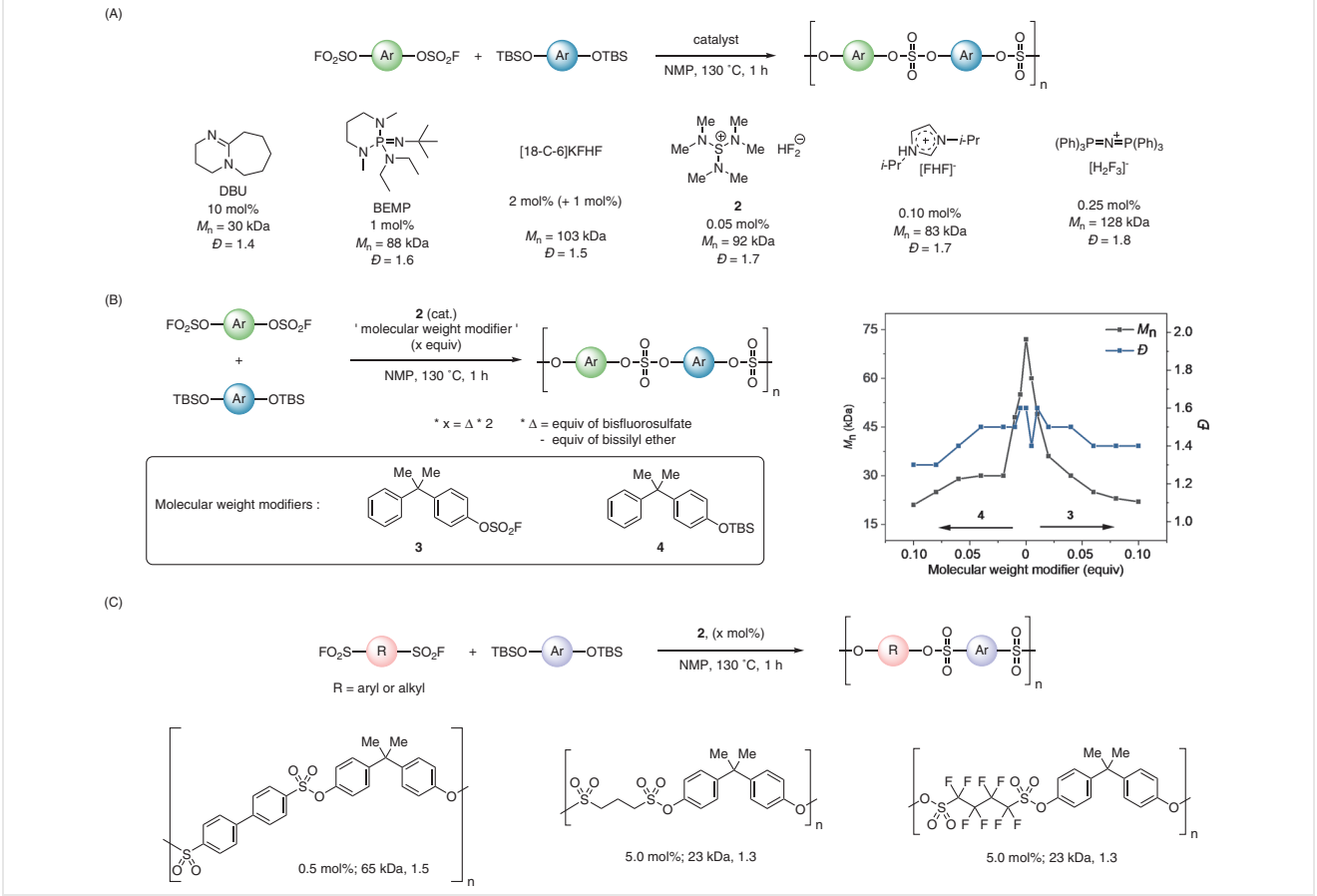
ization was achieved by initial homo-extension using dihydroxyphenol derivative monomers capped with –TBS and –SO_2F, before introducing a different monomer (Scheme 5C). Subsequently, our group expanded this to a periodic copolymerization approach by homologation method.[39] An iterative approach to synthesize the sequence-regulated oligosulfate homologues was conducted in a multidirectional manner, enabling the generation of oligomeric bisfluorosulfates **6** with verified sequences (Scheme 5D). These sequence-regulated bisfluorosulfates were used to polymerize polysulfate periodic copolymer **7** with bissilyl ethers (Scheme 5E). The polymerization showed similar molecular weight and *Đ* to previously reported polysulfate polymerizations, meaning that monomers of oligomeric bisfluorosulfate also could attain efficient polymerization.

2.1.2 Polysulfamides

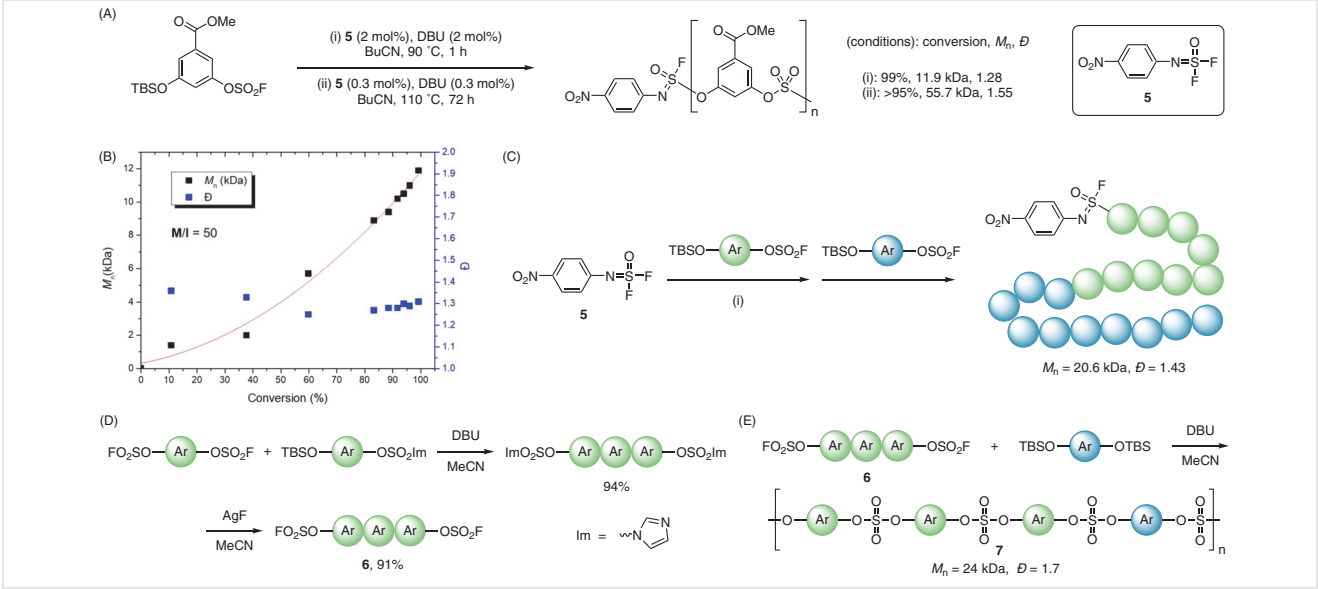
In 2020, the Michaudel group reported a SuFEx polymerization between bissulfamoyl fluorides and bisamines to afford polysulfamides (Scheme 6A).[40] This method provides both aliphatic and aromatic polysulfamides. The prepared polymers exhibited good thermal stability, with thermal decomposition occurring in the temperature range of 200 to 260 °C. While the polysulfate synthesis through SuFEx polymerization produces TBSF as a byproduct, it does not interfere with the catalytic role of DBU. This polysulfamide synthesis generates HF, and its removal inevitably requires the use of a stoichiometric amount of base. As a result, the molecular weights of the polymers obtained through this method tend to be low (2.9–8.7 kDa). Polysulfamide synthesis was further expanded to include utilization of AB-type monomers bearing NHBoc and sulfamoyl fluoride moieties (Scheme 6B).[41] The Boc group of the monomeric unit was in situ deprotected by trifluoroacetic acid (TFA), and the polymerization was subsequently carried out with 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base. This method showcased an improved molecular weight (4–17 kDa).

2.1.3 Polysulfluoridoimidates and Polysulfonimidates

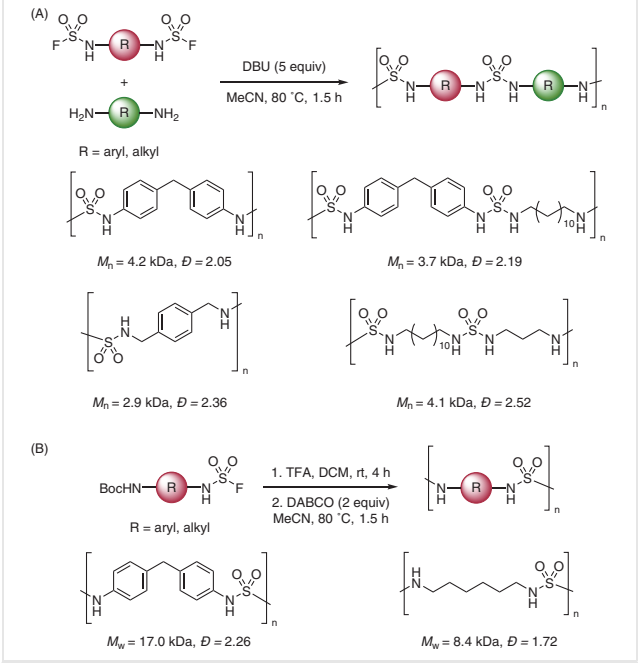
Polysulfluoridoimidates emerged as SuFEx polymers in 2021, synthesized from bissulfurimidoyl difluoride and



Scheme 4 Bifluoride-catalyzed SuFEx polymerization: (A) evaluation of cation effects of bifluoride catalysts for polysulfates synthesis; (B) modulation of M_n and *Đ* by molecular weight modifiers; (C) bifluoride **2** catalyzed polysulfonates polymerization (Sharpless, Wu, and Dong 2017)



Scheme 5 Diversified polymerization strategies of polysulfates; (A) chain polycondensation of polysulfates with iminosulfur oxydifluoride initiator **5**; (B) changes in M_n and Đ acquired from the corresponding conversion (C) block copolymerization of polysulfate (Wu and Sharpless, 2021); (D) iterative SuFEx approach to trimeric bisfluorosulfate; and (E) synthesis of polysulfate periodic copolymer using sequence-regulated trimeric bisfluorosulfate (Hong, Yu, and Chun, 2024). Diagram in (B) reprinted with permission from the author, as referenced in ref. 37.

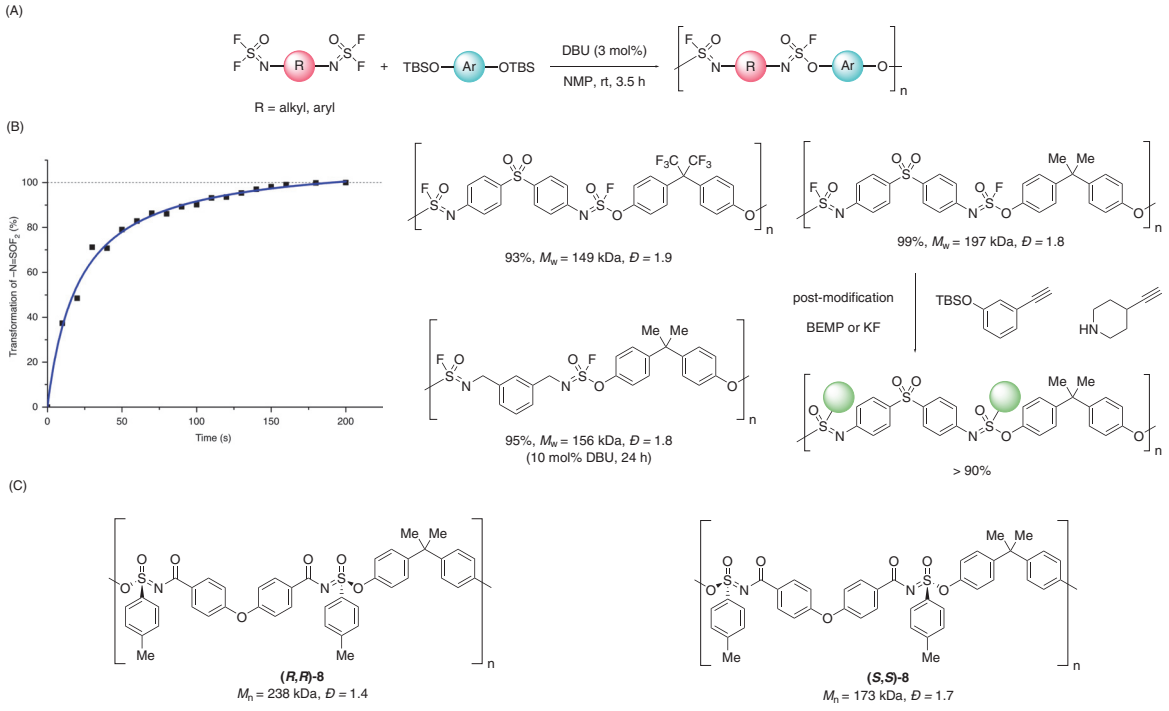


Scheme 6 SuFEx strategies to various polysulfamides; (A) synthesis of polysulfamides with AA/BB-type monomers (Michaudel, 2020); (B) polysulfamide polymerization using AB-type monomers (Michaudel, 2023)

bissilyl ether monomers (Scheme 7A).[42] One of the main features of this polymerization is the use of a single fluorine within the –N=SOF_2 moiety. As a result, polysulfluoridoimidates bear fluorines within the polymeric backbone, which facilitates opportunities for forthcoming modifications. By utilizing the rapid SuFEx coupling enabled by a highly reactive –N=SOF_2 component,[38] it is possible to synthesize high molecular weight polymers exceeding 100 kDa, which possess helical polymeric backbones (Scheme 7B).[42] Molecular modeling revealed that helicity can occur not only in homochiral polymers but also in heterochiral polymers with varying chiral centers. Moreover, experimental studies on the racemization of the enantiomerically pure compounds suggest that chirality inversion may occur in the polymer backbone, specifically leading to the formation of a thermodynamically stable structure. Subsequently, the Zuilhof group developed a polymerization method for polysulfonimidates (Scheme 7C).[43] Chirality was imparted to polysulfonimidates by employing enantiopure bissulfonylimidoyl fluorides. Using (*R*,*R*) and (*S*,*S*) monomers, configurationally chiral polysulfonimidates were prepared. Both chiral polymers **8** showed a symmetric circular dichroism spectra.

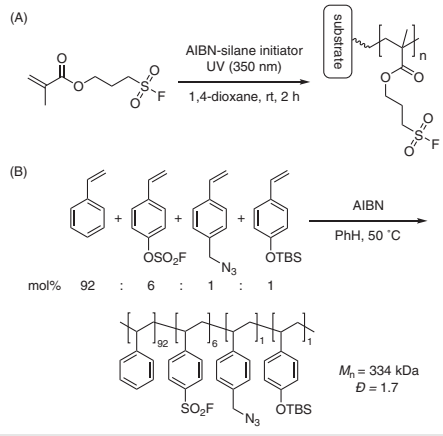
2.1.4 Postpolymerization Modification

In 2015, the Locklin group reported a polymer brush bearing sulfonyl fluorides on its side chains (Scheme 8A).[44] UV-initiated radical polymerization gave the desired prod-



Scheme 7 SuFEx polymers with sulfurimidoyl fluoride derivatives: (A) synthesis of polysulfluoridoimidates; (B) polymerization kinetic profile (Sharpless, Moses, Zuilhof, and Wu, 2021); (C) synthesis of polysulfonimidates. (Zuilhof, 2022). (B) is reprinted with permission from ref. 42. Copyright 2021 Springer Nature Limited.

uct from 3-(fluorosulfonyl)propyl methacrylate. Sulfonyl fluorides showed good tolerance to this radical polymerization, and subsequent postmodification proved to be efficient. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was found to be more efficient than DBU as a organosuperbase catalyst in this system. Following this work, the Fokin group developed a functional polystyrene from *para*-fluorosulfate, *para*-azido, and *para*-TBS bearing styrene derivatives as monomers along with a simple styrene monomer (Scheme 8B).[45] These functional groups on the polymer backbone were subsequently modified with dyes through SuFEx coupling and CuAAC reactions. Interestingly, the Lu group reported side-chain-type polysulfates, through radical polymerization using vinyl monomers including diaryl sulfates.[46] In 2023, the Hobbs group demonstrated ring-opening metathesis polymerization to give sulfonyl fluoride decorated polynorbornenes.[47] The catalyst used in this polymerization was 3rd generation Grubbs catalyst, and [M]/[I] ratio was proportional to the molecular weight. In 2023, the Liao group disclosed organocatalytic atom transfer radical polymerization and Cu-catalyzed atom transfer radical polymerization using 4-vinylbenzenesulfonyl fluoride (VBSF) to afford poly(VBSF).[48]



Scheme 8 Postpolymerization modification of SuFEx polymers: (A) polymer brush (Locklin, 2015); and (B) postclickable functional polystyrene (Fokin, 2016)

2.2 Degradation of SuFEx Polymers

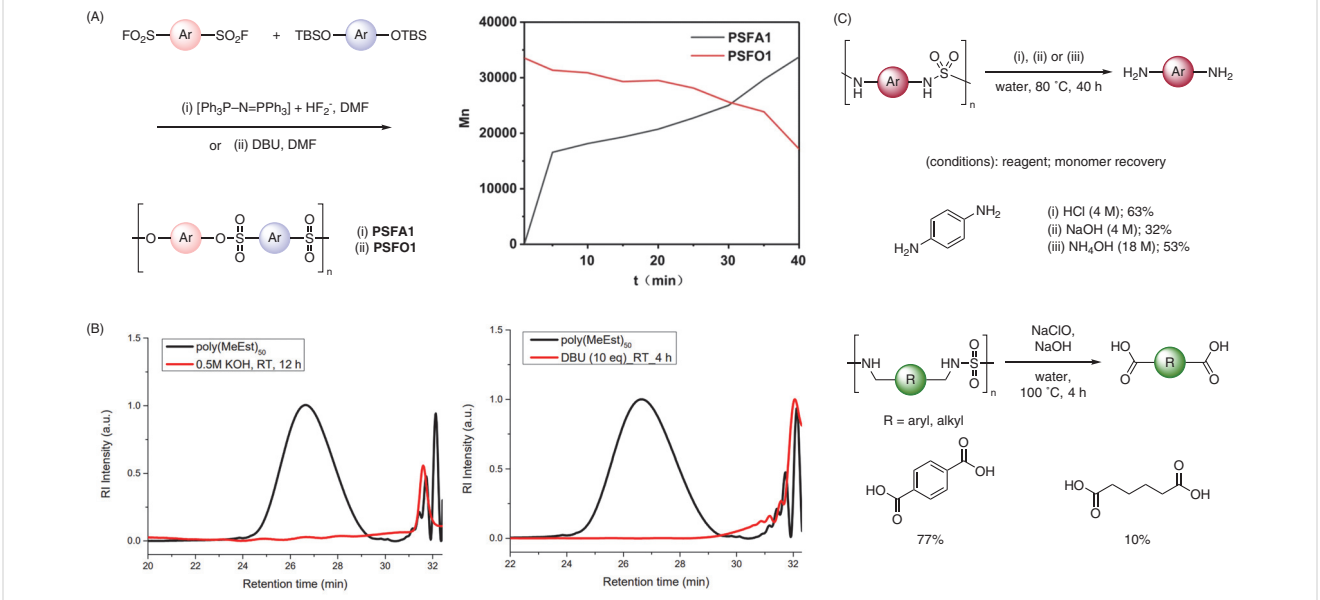
Plastic pollution has been considered one of the most endangering issues for maintaining a sustainable society. Countless commercial plastics have been disposed, buried, and accumulated in landfills; the recycling rate of plastics remains low.[49] To address this environmental issue, the degradation methods of plastics via pyrolysis, hydrolysis, and photolysis have garnered attention. For newly developed polymers, it is crucial to understand how they degrade, irrespective of the polymerization process used. In

2020, the Lu group reported the degradation behavior of polysulfonates.[50] In monitoring the molecular weight, Lu and co-workers found the reversible degradation of polysulfonates in the presence of DBU (Scheme 9A); Na_2CO_3, pyridine, and 4-(dimethylamino)pyridine (DMAP) were also evaluated, but there was no significant change in the GPC chromatogram. The strong nucleophilicity of organosuperbases is presumed to cause this difference. Also, in this transformation, DBU functions as a transesterification catalyst as well as a degradation catalyst. They demonstrated the transesterification of sulfonate linkages in small molecules, which was similarly reported in 1965.[51]

Wu and Sharpless showcased the chemical degradation of polysulfate (Scheme 9B).[37] They conducted the stability test across different pH ranges and found that polysulfates are stable in the pH range from 5 to 7, but degradation occurs at pH higher than 7 or lower than 5. Polysulfates were found to be degraded readily at high temperatures when exposed to organosuperbases, such as DBU and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG), similar to the case of polysulfonates. Moreover, DBU can induce the degradation at even room temperature. Unlike polysulfonates, pyridine is comparatively effective in the degradation of polysulfates. KOH in THF/water causes the chemical degradation. Our group also reported that sequenced polysulfates were degraded by alkaline hydrolysis in DMF at elevated temperature.[39]

In 2014, Sharpless and Fokin conducted chemical degradation experiment on polysulfates, while revealing its stability.[31] In addition, the hydrolytic stability of polysulfonates was demonstrated under the harsh conditions (e.g., Na_2CO_3, NaOH, and HCl in ethanol/water).[34] However, the cleavage of sulfate linkages within small molecules has been well established.[52,53] The hydrolysis of an organosulfur linkage in the polymer can depend on its solubility. Water uptake is one of the important parameters in polymer degradation through hydrolysis.[54,55] Both ethanol and water act as anti-solvents for polysulfates and polysulfonates, preventing water from penetrating between the polymer chains. In addition, the reactivity of polymers is generally lower than that of small molecules due to the limited reaction site.[54] It was also found that the polymer modification reaction is restricted when the corresponding polymers are insoluble.

The degradation of polysulfamides was demonstrated by the Michaudel group (Scheme 9C) using HCl, NH_4OH, and NaOH.[40,41] When HCl was used, the monomer recovery reached 74% isolated yield. In contrast, degradation under basic conditions using NaOH resulted in 42% monomer recovery. Sulfonamides, which have a similar structure to sulfamides, show stability under basic conditions. However, they relatively easily undergo hydrolysis under acidic conditions.[56,57] Interestingly, the degradation of polysulfamides can be carried out in aqueous solutions in the absence of organic solvents, presumably due to their moderate water solubility.[58] Therefore, it is expected that sulfamide moieties facilitate interactions between the polymer backbone with water, thereby promoting degradation. In 2023, the oxidative cleavage of polysulfamides using NaClO to afford monomers was reported.[41] The effective monomer recovery



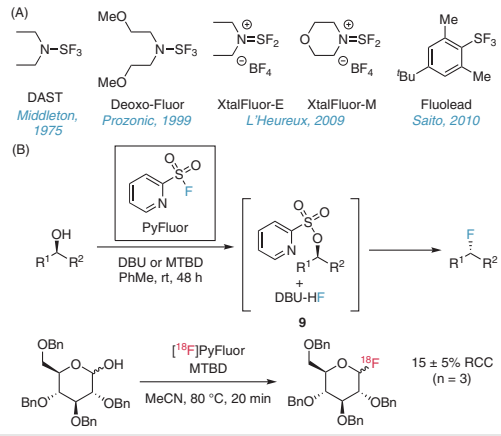
Scheme 9 Degradation of SuFEx polymers: (A) polymerization progresses using bifluoride (**PSFA1**) or DBU (**PSFO1**) (Lu, 2020); (B) GPC chromatograms of polysulfate degradation (Wu and Sharpless, 2021); (C) acid and alkaline hydrolysis (top), and deaminative oxidation (bottom) of polysulfamides (Michaudel, 2020 and 2023). The right figure of (A) was adapted with permission from ref. 50. Copyright 2020 Royal Society of Chemistry. Diagrams in (B) reprinted with permission from the author, as referenced in ref. 37.

suggests the feasibility of the transformation of polysulfamides into polycarbonates. In case of polysulfluoridoimidates, DBU was found to promote hydrolysis of the main linkages.[42] The Zuilhof group degraded polysulfonimidates through transesterification using phenols in the presence of DBU.[59] This process was exemplified through small-scale reactions with a broad substrate scope. During polymer degradation, fragments were analyzed by liquid chromatography-mass spectrometry (LC-MS).

2.3 Properties and Applications

The thermal and mechanical properties of polysulfonates were studied in the 1960s.[30] For instance, polysulfonate film can be produced due to its amorphousness, it exhibits thermal decomposition at around 350 °C. Polysulfonates have superior tensile strength and modulus compared to Lexan, well-established engineering plastics.[30] In 2014, the physical properties of polysulfates were compared to Lexan.[31] Polysulfates show better tensile modulus and similar yield stress. The polysulfate thin film was obtained by compression molding. The opaque and yellowish film formed from the molding has lower oxygen permeability than Lexan.[31]

Since 2018, polysulfates have been applied as functional materials by several groups. The Lu group presented functional polysulfates having side chains of pyrazolinyl and phthalimide moieties.[60] These functional polymers showed nonvolatile flash memory behavior, suggesting the potential use in electronic devices. Subsequently, the Yang group demonstrated a polysulfate featuring an ester linkage having flexible aliphatic backbones.[61] They prepared this polymer for liquid crystal applications and observed nematic and smectic phases. In 2020, the Lu group reported aggregation-induced emission (AIE) type polysulfates.[62] Monomers were prepared with tetraphenylethylene and naphthylamide groups, which are common moieties that exhibit AIE properties; the synthesized polymers showed the fluorescence emission in the solid and solution state. Subsequently, they showcased polysulfate crosslinked polymers using tris(fluorosulfate) and tris(silyl ether) monomers.[63] The crosslinked polymer can adsorb pyridine effectively, becomes gelatinous and swells up almost 10-fold. They demonstrated the entrapment of iodomethane vapor within the gelatinous matrix. In 2022, the An group fabricated polysulfate hollow fiber membrane.[64] The polysulfate hallow fiber shows sandwich membrane structure. The fluorene-based polysulfates, developed by Liu, Wu, Sharpless, and co-workers, facilitate the utilization of highly efficient polymer dielectrics.[65] The electrochemical performances of the dielectrics were evaluated by the fabrication of nanocomposite film with Al_2O_3.



Scheme 10 Deoxyfluorination reagents and proposed mechanism; (A) representative deoxyfluorination reagents; and (B) deoxyfluorination of alcohols-mediated by PyFluor and its extension to ^{18}F-aliphatic radiofluorination (Doyle, 2015)

3 Non-Canonical SuFEx Reactions

3.1 Metal-Free Strategies for Deoxyhalogenation Reactions

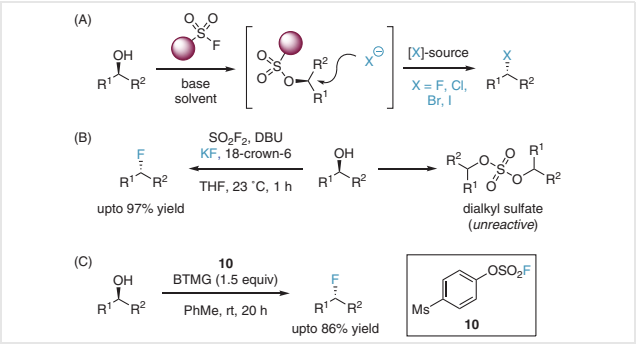
3.1.1 Deoxyhalogenation of Alcohols Activated by SuFExable Hubs

Organofluorine compounds are key molecules in the pharmaceutical industry.[66] The incorporation of fluorine atoms in pharmaceutically active molecules can improve the lipophilicity, metabolic stability, or binding affinity.[67] The common deoxyfluorinating agents include gaseous SF_4, diethylaminosulfur trifluoride (DAST), bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor), and their analogous chemicals (Scheme 10A).[68–71] However, the use of these reagents comes with significant limitations. For instance, DAST exhibits poor thermal stability and can be explosive at elevated temperatures. Additionally, it lacks chemoselectivity, resulting in undesired side pathways including an elimination reaction.[72]

In 2015, the Doyle group developed a method for the deoxyfluorination of alcohols using a low-cost and benchstable reagent, 2-pyridinesulfonyl fluoride (PyFluor) with better selectivity.[73] The reaction proceeds in two steps: first, alcohol activation by PyFluor to give a sulfonate ester intermediate **9**. Second, the fluoride ion is released from the intermediate to give a deoxygenated product. The group has also demonstrated fluorine-18 incorporation on aliphatic substrates by using [^{18}F]PyFluor reagent with 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (Scheme 10B).

Deoxyhalogenation reactions typically involve the activation of an alcoholic –OH group prior to nucleophilic substitution reaction by a halide ion (Scheme 11A). In 2021, the Sammis group developed a nucleophilic fluorination method by activating alcohols with SO_2F_2 gas (Scheme 11B);[74] 1°

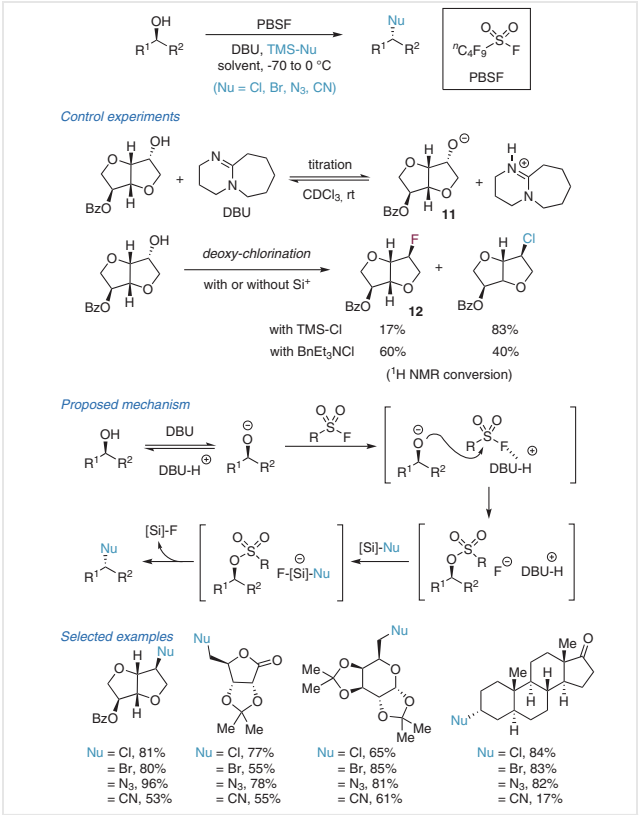
and 2° aliphatic alcohols with functional groups, including Br, NO_2, esters, alkenes, and alkynes, were tolerated to give the corresponding fluoroalkylated product. This reaction only required 1 h to complete without any sign of elimination side product. However, this reaction produced dialkyl sulfate as a side product. Therefore, this reaction requires large excess of base and reagents.



Scheme 11 Deoxyfluorination via SuFEx approach: (A) general mechanism of deoxyfluorination; (B) deoxyfluorination of alcohols using SO_2F_2 gas (Sammis, 2021); and (C) fluorosulfate-mediated deoxyfluorination of alcohols with BTMG (Hu, 2021)

The Hu group reported another method for one-pot deoxyfluorination of alcohols using SuFEx reagent 4-(methylsulfonyl)phenyl fluorosulfate (**10**) (Scheme 11C).[75] The rationale behind exploring SuFExable hubs as deoxyfluorinating reagents is to find readily available, bench-stable, and easy-to-handle fluorinating reagents compared to gaseous SO_2F_2. They screened several aryl fluorosulfates and found that **10** is the most efficient reagent in giving a high yield of the desired product. Compound **10** activates the alcohol for the substitution reaction and supplies the fluoride ion for concomitant fluorination in the presence of BTMG. Next, the activated alcohol undergoes substitution with the fluoride ion to give the product. Notably, various 1°, 2°, and benzyl alcohols with sensitive functional groups, including iodo, nitro, cyano, aldehyde, ketone, olefins, alkyne, ester, amine, and amide, were tolerated and produced the corresponding fluorinated compounds in high yields, which was previously not achievable.

Recently, the Kim group developed an interesting one-pot protocol for deoxygenative nucleophilic substitution of alcohols (Scheme 12). A commercially available SuFEx reagent, perfluorobutanesulfonyl fluoride (PBSF), was used for alcohol activation.[76] First, the alcohol becomes activated by the SuFEx reagent, assisted by DBU, and releases a fluoride ion. The released fluoride ion then activates the trimethylsilyl group attached nucleophile for substitution to form a strong Si–F bond. They conducted a series of control experiments to understand the reaction mechanism. Without a base, the reaction did not give any desired product. Similarly, by mixing an equimolar ratio of DBU and PBSF, no change was observed in ^{1}H and ^{19}F NMR analysis. However, the reaction of DBU (2 equiv) with alcohol resulted in an upfield shift of the ^{1}H NMR signals from alcohol, suggesting the formation of alkoxide ions **11** via deprotonation.

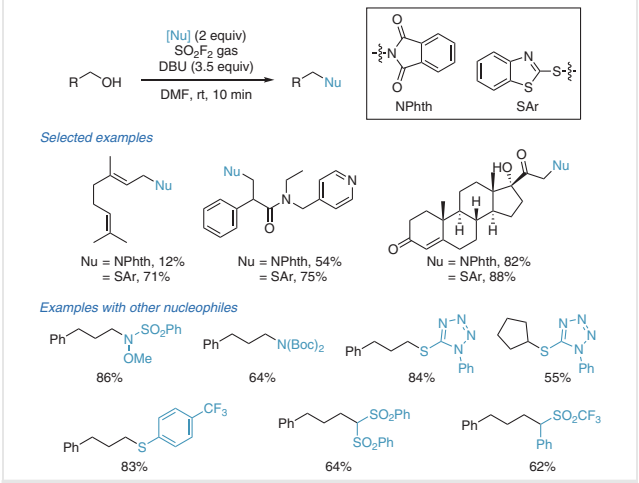


Scheme 12 Deoxyhalogenation and nucleophilic substitution and proposed mechanism (Kim, 2024)

Moreover, in the absence of TMSCl, a higher amount of deoxyfluorinated products **12** was observed (Scheme 12), which strongly supports the role of silicon as a fluoride scavenger. Based on the control experiments, they proposed that the base-assisted alcohol activation and the subsequent substitution by the activated silyl nucleophile proceeds through a transition state in an S_N2 fashion giving the final product. Inversion of configuration was observed to give a single isomer when a chiral alcohol was involved in the reaction. With a broad scope of alcohols and nucleophiles, such as Cl, Br, N_3, and CN, this method is a significant advancement in deoxygenative halogenation and the concurrent nucleophilic substitution reactions. Under optimal conditions, alcohols derived from natural products, biomolecules, and sugar molecules reacted smoothly to give the corresponding substitution products with a suitable nucleophile in moderate to excellent yields without the formation of elimination products.

3.1.2 Deoxygenative Nucleophilic Substitution of Alcohols

Deoxygenative nucleophilic substitution of unactivated free alcohols has been a challenging task due to high C–O bond dissociation energy and acidic O–H bond. Thus, preactivation of the alcoholic hydroxyl group is necessary. The Sammis group applied this strategy and reported substitution reactions by different nitrogen and sulfur-bearing nucleophiles after activating the –OH group with SO_2F_2 gas (Scheme 13).[77] This method has advantages, such as mild reaction conditions and easier product purification, compared to the classical Mitsunobu reaction. It has a broad scope for several primary and secondary alcohols with phthalimides, aromatic thiols, and other nucleophiles like di-*tert*-butyl iminodicarboxylates, and sulfones. Alcohols with sensitive functional groups, such as ketone, alkene, alkyne, chloro, bromo, and nitro groups, were tolerated to give the desired product. Under the optimal conditions, side products from deoxyfluorination or elimination reactions were not observed, although highly reactive alkyl fluorosulfate intermediates were involved in this reaction.

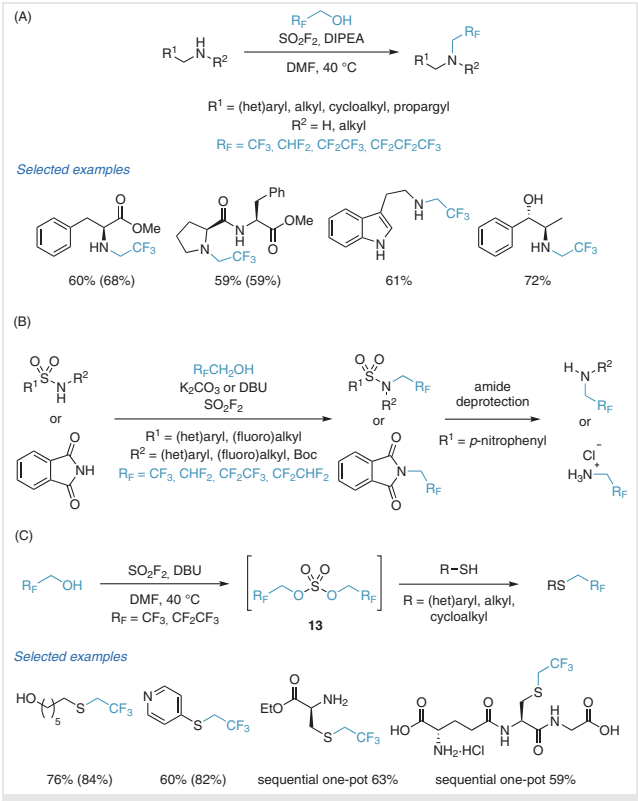


Scheme 13 Deoxygenative nucleophilic substitution reaction of alcohols using SO_2F_2 gas (Sammis, 2020)

3.1.3 Synthesis of Fluoroalkylated Amines and Fluoroalkylated Thioethers

Various biologically active molecules and marketed drug candidates contain one or more nitrogen atoms in functional groups like amines, anilines, amides, sulfonamides, and imines in their core structures. Similarly, *N*-fluoroalkyl amines are also important motifs in bioactive molecules.[78] The synthesis of *N*-fluoroalkyl-substituted amine derivatives needs expensive fluoroalkyl halides, triflates, sulfonates, or tosylates, and the reaction of amines with these reagents is always problematic and gives low product yields. Additionally, fluoroalkyl halides are volatile compounds known for ozone layer depletion, restricting their uses. These limitations of fluoroalkyl electrophiles inspired many researchers to investigate organic fluorosulfates derived from fluorinated alcohols as a promising alternative to these fluoroalkyl compounds.

In 2018, a metal-free method for the direct synthesis of valuable 1,1-dihydrofluoroalkyl amines was developed by the Sammis group (Scheme 14A).[79] This method exclusively produced monoalkylated amine derivatives using low molecular weight fluorinated alcohols as alkylating reagents. The reaction proceeds with selective one-pot activation of alcohols by SO_2F_2 gas followed by S_N2 reaction with an amine to give the desired product. This reaction is a major advancement in synthesizing 1,1-dihydrofluoroalkyl amines under transition-metal-free conditions. It also enables easy access to electronically diverse 1,1-dihydrofluoroalkyl amines, such as primary, secondary, cyclic, heterocyclic, and benzylic, from inexpensive starting materials under ambient conditions. However, anilines and sterically hindered amines were not reactive enough to give the desired product. Reaction rate measurement by studying in situ reaction progress using infrared (IR) spectroscopy showed that trifluoroethanol and morpholine had similar



Scheme 14 SO_2F_2-mediated functionalization: (A) synthesis of 1,1-dihydrofluoroalkyl amines (Sammis, 2018); (B) *N*-fluoroalkylation of sulfonamides, phthalimides, and carbamates (Leroux, 2023); and (C) 1,1-dihydrofluoroalkylation through sulfur-based nucleophiles (Sammis, 2019)

reaction rates with SO_2F_2 gas. Again, the formation rate of trifluoroethyl fluorosulfate is approximately four times faster than the rate of its reaction with morpholine, suggesting the accumulation of the former intermediate in the reaction medium. From these reaction rate studies, the authors proposed that the selective reactivity of SO_2F_2 towards fluorinated alcohols over amines arises simply by controlling the different reaction parameters.

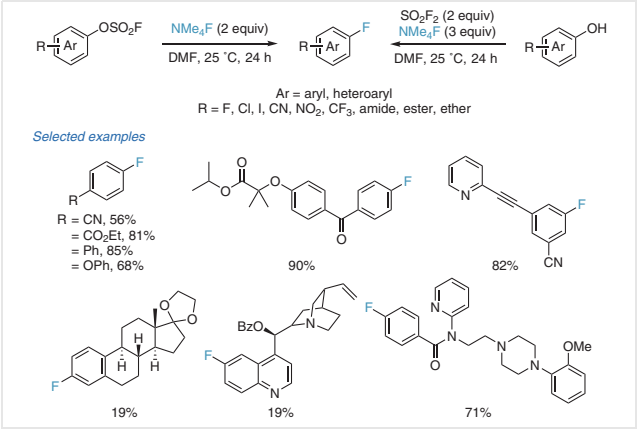
The Leroux group reported an *N*-fluoroalkylation method for sulfonamides, phthalimides, and carbamates using fluorinated alcohols activated by SO_2F_2 (Scheme 14B).[80] Notably, electron-rich heterocyclic amines gave good to excellent yields of the corresponding *N*-alkylated products, whereas electron-poor heterocyclic amines or sulfonamides only afforded the expected products in poor yields. They have also shown that the 4-nitrobenzenesulfonyl (nosyl) protected *N*-fluoroalkylated sulfonamides can be easily deprotected to the corresponding free amines via S_NAr reaction under mild conditions using thioglycolic acid and K_2CO_3 in DMF. Similarly, under optimal conditions, *N*-fluoroalkylation of phthalimide was completed within 30 min at room temperature when DBU was used as a base in DMAc. Phthalimide deprotection of these compounds resulted in the corresponding *N*-fluoroalkyl amines as hydrochloride salts.

The 1,1-dihydrofluoroalkylation is not only limited to *N*-nucleophiles, but also, sulfur-based nucleophiles can be employed to access 1,1-dihydrofluoroalkyl sulfides by reacting a thiol with an activated fluorinated alcohol. A thorough study by the Sammis group disclosed that the bis(1,1-dihydrofluoroalkyl) sulfate intermediate **13** formed in the presence of a strong base like DBU exclusively reacted with a thiol to give the corresponding thioether product (Scheme 14C).[81] Similarly, the trifluoroethyl fluorosulfate formed in the presence of weak bases like triethylamine or *N*,*N*-diisopropylethylamine (DIPEA) did not react with a thiol but selectively reacted with an amine.[79] Except with amines, the bis(1,1-dihydrofluoroalkyl) sulfates remained unreactive towards other competing nucleophiles, like alcohols and carboxylic acids, in their optimized conditions. Aliphatic, aromatic, and heteroaromatic thiols with various functional groups were well tolerated under optimal conditions giving the desired products.

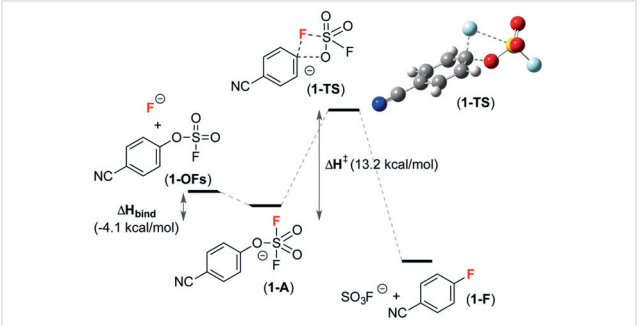
3.1.4 Deoxygenative Fluorination of Phenols

The development of transition-metal-free deoxygenative fluorination of phenolic compounds is challenging. 1,3-Bis(2,6-diisopropylphenyl)-2,2-difluoro-4-imidazoline (PhenoFluor) reported by the Ritter group is excellent deoxyfluorinating reagent.[82] The reaction involves a straightforward activation of the –OH group of phenol with PhenoFluor, which then reacts with the fluoride source to deliver the product. This reagent can efficiently activate phenolic compounds to deliver fluoroarenes in one step and is well-suited for late-stage modification of complex molecules. However, its synthesis involves a multistep procedure, thus making PhenoFluor an expensive reagent. Again, its high molecular weight produces stoichiometric urea as a by-product and is problematic in product isolation. To overcome these limitations, the scientific community is keen on developing new reagents and novel methods for deoxyfluorination reactions.

In 2017, the Sanford group reported a metal-free nucleophilic fluorination strategy to prepare fluoroarenes from phenol-derived aryl fluorosulfates using commercially available tetramethylammonium fluoride (Me_4NF) as a fluoride source (Scheme 15).[83] This reaction proceeds under mild conditions giving fluoroarenes in moderate to excellent yields. Various substituted and electronically biased (hetero)arylfluoro compounds were prepared under the optimal conditions. This method shows good functional group compatibility with alkenes, amines, ketones, esters, and amides. Moreover, the reaction can be carried out in a one-pot fashion; it is scalable and applicable to the late-stage modification of different drug candidates.

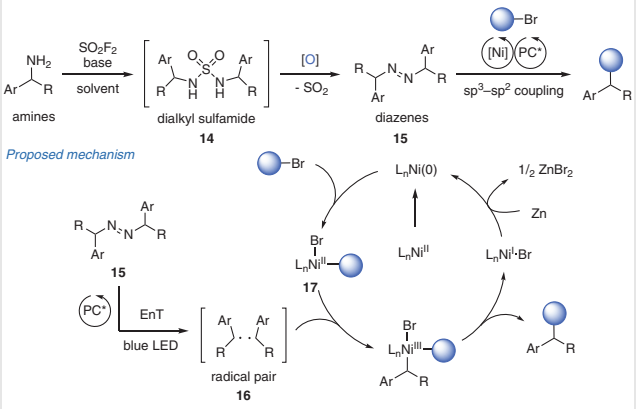


Scheme 15 Deoxyfluorination of aryl fluorosulfate with NMe_4F (Sanford, 2017)



Scheme 16 Calculated energy profile of the reaction between 1-OFs and fluoride (Sanford, 2017). Reprinted with permission from ref. 83. Copyright 2017 American Chemical Society.

Based on ab initio calculations, they proposed that the reaction proceeds with the formation of the favorable pentacoordinate intermediate **1-A** followed by transition state **1-TS** with 13.2 kcal/mol of activation enthalpy ($\Delta H^{\ddagger}$), where concerted C–O bond cleavage and C–F bond formation takes place to provide the desired product (Scheme 16). Subsequently, they reported a systematic mechanistic investigation on the deoxyfluorination of aryl fluorosulfates.[84] This mechanistic study also suggests the formation of a similar pentacoordinate intermediate as proposed in their earlier work.



Scheme 17 Dual photoredox-nickel catalyzed deaminative arylation of benzyl amines activated by SO_2F_2 gas (Michaudel, 2023)

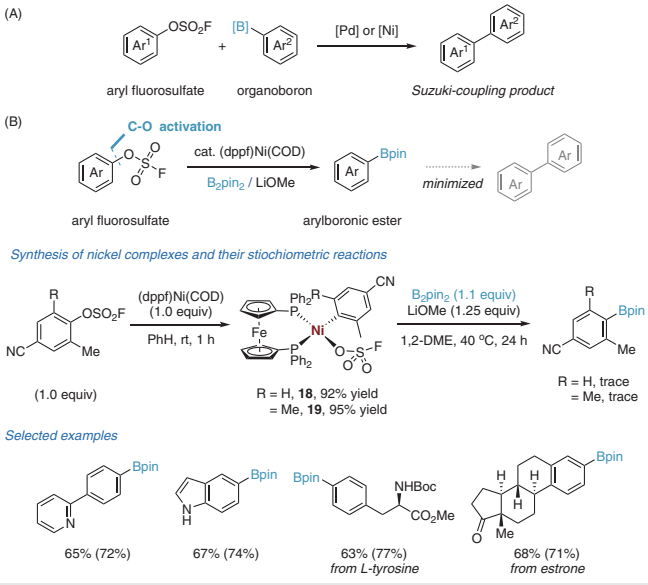
3.2 Dual Photoredox–Nickel-Catalyzed Deaminative Arylation of Amines

Recently, the Michaudel group developed a novel strategy to utilize benzylic amines as a potential alkylating reagent in the deaminative arylation of bromoarenes (Scheme 17).[85] For amine activation, they used the straightforward SuFEx chemistry. First, an amine was reacted with SO_2F_2 gas to produce *N*,*N*′-disubstituted sulfamides **14**, which further oxidized to give a diazene derivative **15**. Next, a visible-light-activated photocatalyst undergoes energy transfer efficiently with the diazene molecule to generate alkyl radicals with concomitant release of molecular nitrogen. Finally, the alkyl radical **16** was intercepted by the nickel(aryl) complex **17**, which then undergoes reductive elimination to generate the desired product. This reaction proceeded smoothly under ambient conditions and has broad substrate scope.

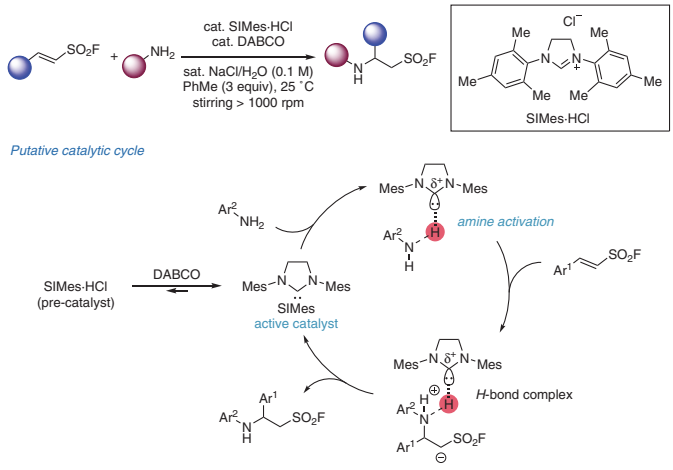
3.3 Borylation of Aryl Fluorosulfates under Nickel Catalysis Guided by Mechanistic Understanding

Creating organoboron compounds using transition metal catalysis with electrophilic coupling partners and diboron reagents is consistently difficult task to achieve. These reactions are inherently associated with the formation of Suzuki-type homocoupling side products. Sharpless and Henley independently have shown that aryl fluorosulfates can be employed as one of the electrophilic coupling partners in Suzuki reactions (Scheme 18A).[86,87]

With our continuous effort to expand SuFEx chemistry, we developed a nickel-catalyzed borylation of aryl fluoro-



Scheme 18 Non-canonical SuFEx reactions: (A) Suzuki cross-coupling reaction; and (B) nickel-catalyzed borylation of aryl fluorosulfates via C–O bond activation (Hong, 2024)



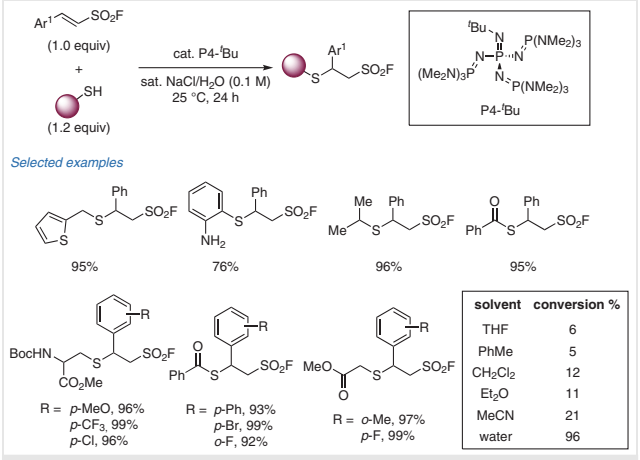
Scheme 19 NHC-catalyzed, on-water aza-Michael addition of amines and ESF derivatives (Bae, 2022)

sulfates via C–O bond activation (Scheme 18B).[88] This reaction was developed and guided by detailed mechanistic understanding through the synthesis, isolation, and characterization of well-defined intermediate complexes. Two intermediate nickel complexes **18** and **19** were synthesized by reacting electronically and sterically balanced aryl fluorosulfates with 1,1′-bis(diphenylphosphino)ferrocene-ligated nickel(0) complex in an equimolar ratio in good isolated yields (Scheme 18). These intermediate nickel complexes were fully characterized by ^{1}H, ^{19}F, and ^{31}P NMR spectra along with mass spectrometry and single-crystal X-ray analysis.

3.4 On-Water SuFEx Reactions

Organic reactions using water as a medium have advantages from a green chemistry perspective. Water has adequate availability and low-cost, it is nontoxic and nonflammable and has a relatively high boiling point; these features make water a near ideal medium for sustainable chemical processes. Recently, the Bae group has expanded the chemistry of SuFExable hubs and developed several reactions using water as a reaction medium. In 2022, his group reported an NHC-catalyzed aza-Michael addition of amines with β-aryl-substituted ESFs to give β-aminosulfonyl fluorides (Scheme 19).[89] Water saturated with NaCl was used as the reaction medium. Also, water significantly accelerated the reaction rate and gave excellent chemo- and site-selective products. As the reactants are insoluble in water, vigorous stirring is required to accelerate the reaction. This reaction has broad substrate scope and wide functional group compatibility.

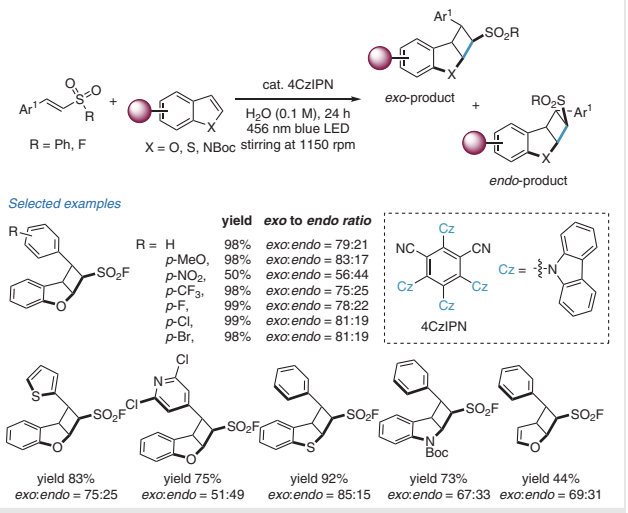
Subsequently, they reported a thia-Michael addition reaction by reacting ESFs with different thioethers catalyzed by the organosuperbase P4-^{t}Bu (Scheme 20).[90] This reaction was also successfully achieved on water. A low catalyst loading of P4-^{t}Bu (0.01 mol%) is sufficient to drive the reaction to completion under mild conditions. They measured the reaction rate by conducting this reaction on water and in other typical organic solvents. This study shows superior activity on water compared to other solvents. They suggest that high reactivity might be due to the hydrophobic hydration of the reactant molecules. A typical Micheal-type addition reaction mechanism was proposed for this reaction. This reaction exemplifies a broad substrate scope and tolerates various sensitive functional groups, such as halide, amine, and ester, to give the desired product in excellent yields.



Scheme 20 Organosuperbase-catalyzed, on water, thia-Michael addition of thiols and ESF derivatives (Bae, 2022)

Recently, the Bae group developed an on water dearomative [2+2] cycloaddition under visible light photocatalytic conditions (Scheme 21).[91] Organic photocatalyst 4CzIPN in low loading (only 2 mol%) completes the reaction in 24 h and delivers the product in excellent yields. This reaction proceeded under mild and ambient conditions under blue light irradiation. The two coupling partners of this reaction

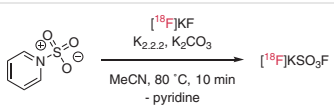
are (hetero)arylated ESFs and heteroaromatic compounds to provide heterocyclic alkyl SuFExable hubs as the final product. The reaction proceeded smoothly with different ESFs and electronically biased heteroaromatics showing broad functional group compatibility. The reaction resulted in high product yields and a high preference for *exo* selectivity. In this reaction, the water medium plays an important role and substantially accelerates the rate by creating a biphasic protecting layer and developing a high-pressure-like environment around the reactant molecules.



Scheme 21 On-water, visible-light-photocatalyzed dearomative [2+2] cycloaddition reaction (Bae, 2024)

4 Fluorine-18 SuFEx Radiochemistry

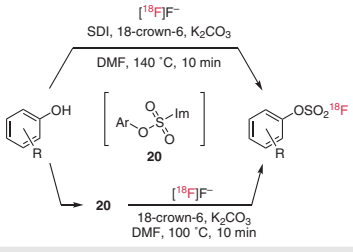
Fluorine-18 is by far the most utilized radioisotope in positron emission tomography (PET) imaging modality due to its low positron energy, short positron range, and a relatively longer half-life compared to that of carbon-11, oxygen-15, and nitrogen-13.[92,93] In line with the popularity of SuFEx chemistry, the advancement in fluorine-18-based PET radiotracer development is being actively sought together with the study of S–^{18}F SuFEx radiochemistry.[21] Unlike using SuFExable hubs that provide sulfate linkage by the displacement of fluorine and incoming nucleophiles, the investigation of the stable S–^{18}F bond to be utilized in physiological environments is being actively sought which functions as a fluorine-18 label for PET imaging purposes. This has led to the identification of stable S–^{18}F-containing SuFEx compounds, which led the development of SO_2F-functionalized PET radiopharmaceuticals. Among the ^{18}F-SuFEx molecules, aryl fluorosulfates have been extensively explored due to their easy preparation from existing phenols in pharmaceutical compounds. In 2017, the synthesis of [^{18}F]fluorosulfates was reported from the reaction of pyridine-SO_3 complex and [^{18}F]KF with $K_{2.2.2}$ and K_2CO_3 in MeCN enables the synthesis of [^{18}F]KSO_3F in 65% radiochemical yield (RCY) under optimized condition (Scheme 22).[94] ^{18}F-SO_3F^- demonstrated specific uptake in the human sodium iodide importer (hNIS), making it valuable for PET imaging of thyroid-related diseases.



Scheme 22 Synthesis of [^{18}F]KSO_3F from pyridine trioxide complex (Blower, 2017)

4.1 Direct Radiofluorosulfurylation

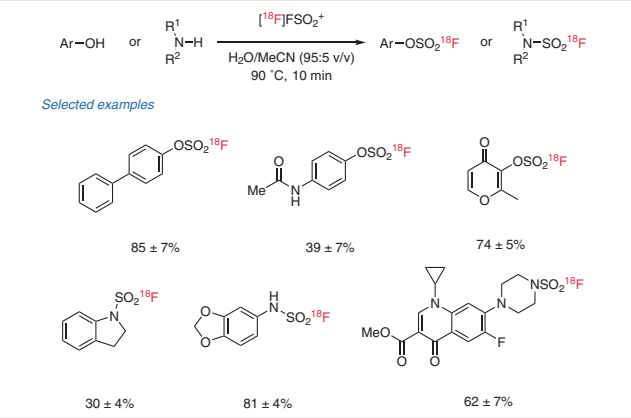
Two distinct methods for radiofluorosulfurylation were introduced in 2020, enabling the direct conversion of phenols into aryl [^{18}F]fluorosulfates (Scheme 23).[95] The first one is the nucleophilic fluorination of an isolated aryl imidazylate (imidazolylsulfonate) **20** ($ArOSO_2Im$, Im = imidazole), which is prepared from phenol and 1,1-sulfonyldiimidazole (SDI). The second one is the direct, one-pot radiofluorosulfurylation from phenols via an in situ generated imidazylate intermediate. In most cases, the radiochemical conversion (RCC) of the latter was lower than that of the former approach; however, RCCs up to 77% were achievable with a molar activity exceeding 40 GBq/μmol. The electronic effect and the position of the substituent on the phenyl ring did not have a notable impact on the RCC. Drug relevant substances like acetaminophen and coumarin were successfully radiofluorinated using a commercial, automated radiosynthesizer, resulting in radiochemical yields in a range from 28% to 60%.



Scheme 23 Radiofluorosulfurylation of phenols and radiofluorination of aryl imidazylate to [^{18}F]fluorosulfates (Chun and Hong, 2020)

Subsequently, a novel radiofluorosulfurylating technique was developed using in situ generated [^{18}F]FSO_2^+ species from 1-(fluorosulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (SuFEx-IT) (Scheme 24).[96] The key [^{18}F]FSO_2^+ species was generated by the elution of SuFEx-IT through the ^{18}F-trapped quaternary methyl ammonium (QMA) cartridge, obviating the need for azeotropic drying and the use of cryptand to proceed with radiofluorination. The direct use of cartridge-generated [^{18}F]FSO_2^+ donors provided diverse ^{18}F-labeled fluorosulfate derivatives from phenols and amines even in hydrous organic solvents.

The mechanistic analysis accompanied by ^{19}F NMR investigation revealed the disappearance of the ^{19}F signals from the SuFEx-IT and fluoride. Notably from the QMA elution media, the fluorosulfurylating agent is found to be composed of an admixture of $[^{18}F]$SuFEx-IT and $[^{18}F]SO_2F_2$, which contributed to the radiofluorosulfurylation of phenols and amines.

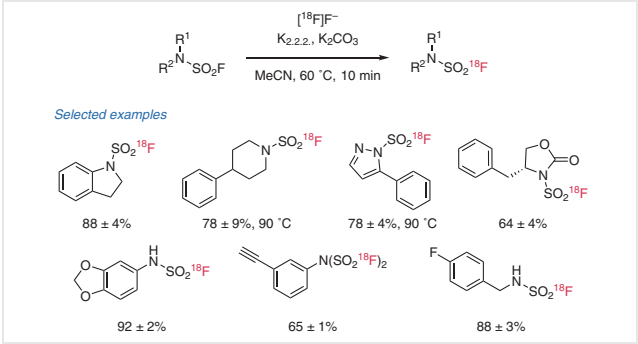


Scheme 24 Radiofluorosulfurylation of phenols and amines by $[^{18}F]FSO_2^+$ from $[^{18}F]F^-$ treated SuFEx-IT (Chun and Hong, 2023)

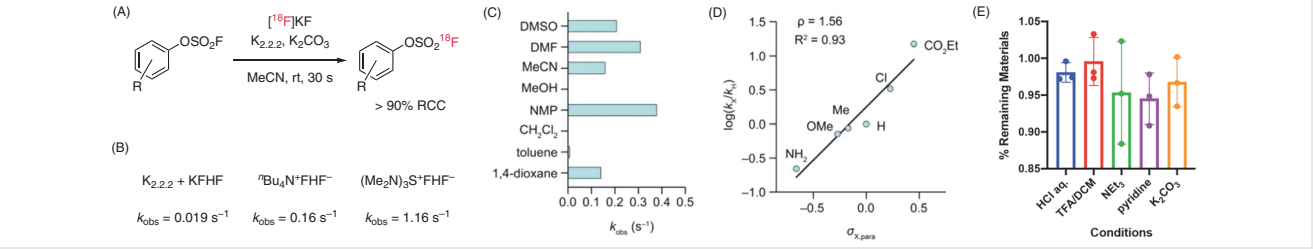
4.2 Late-stage $^{19}F/^{18}F$ Isotope Exchange (IEx)

The isotopic exchange (IEx) between fluorine-18 and fluorine-19 also highlighted the promise to access ^{18}F-SuFEx radiochemistry. Wu, Yang, and Sharpless developed an efficient method for the synthesis of aryl $[^{18}F]$fluorosulfates via late-stage isotopic exchange from nonradioactive fluorosulfates with ^{18}F-radioisotope. (Scheme 25A).[12] Strikingly, this isotopic exchange between ^{19}F and ^{18}F underwent very rapidly (~30 sec) at room temperature. Irrespective of the molecular complexity, remarkably high RCCs were attained with heavily functionalized aryl fluorosulfates. In their study on reaction rates, they demonstrated that the KFHF alone was unable to initiate the exchange process. However, an increase in the rate was observed upon the addition of the proper PTA (Scheme 25B). Using tetrabutylammonium (TBA) as the cationic core resulted in a faster reaction rate compared to employing other cryptands like 18-crown-6 or $K_{2.2.2}$ as PTAs. Also, the rate constant is high with polar aprotic solvents such as MeCN, DMF, and NMP (Scheme 25C). By comparing phenyl fluorosulfate with different *para*-substituents on fluorosulfates, the Hammett analysis indicated that the exchange reaction builds negative charge ($\rho = 1.56$) (Scheme 25C). Extensive experiments were conducted to assess the stability of ^{18}F-aryl fluorosulfates under a wide range of chemical conditions, including exposure to acids, bases, aqueous solutions, amino acids, redox reactions, and different nucleophilic and electrophilic environments, in order to assess their potential as PET radiotracers. Moreover, the chemical stability of aryl fluorosulfates was assessed in various medicinal chemistry reactions. In 2023, the Herth group developed a method to create highly reactive ^{18}F-labeled tetrazines using isotopic exchange of ^{18}F-aryl fluorosulfate, specifically for bioorthogonal purposes.[97]

The radiosynthesis of sulfamoyl $[^{18}F]$fluorides using isotopic exchange was described by Chun and Hong (Scheme 26).[98] Unlike the direct radiofluorosulfurylation of phenolic substrates, sulfamoyl $[^{18}F]$fluorides were inaccessible directly from amine precursors. In contrast to IEx using aryl fluorosulfates, these amine derivatives need slightly elevated temperatures to achieve high RCCs. The optimized conditions for the isotopic exchange of sulfamoyl fluoride from secondary aliphatic amine boded well for primary, secondary, mono-SO_2F-, and bis-SO_2F sulfamoyl fluorides. When



Scheme 26 Late-stage $^{18}F/^{19}F$ isotope exchange of sulfamoyl fluorides (Chun and Hong, 2021)



Scheme 25 (A) Late-stage $^{18}F/^{19}F$ isotope exchange of fluorosulfates; (B) PTA and counterion effects; (C) solvent effects; (D) Hammett plot; and (E) stability of fluorosulfates in various acids and bases (Wu, Yang and Sharpless, 2021). Diagrams in (C), (D), and (E) reprinted with permission from ref. 12. Copyright 2021 American Chemical Society.

prepared ^{18}F-AISF was used to radiofluorosulfurylate the amine, only 2% RCC of the desired sulfamoyl [^{18}F]fluoride was obtained.

5 Conclusions and Outlook

In the last 10 years, SuFEx chemistry has witnessed remarkable developments across diverse research fields. In particular, SuFEx polymerization is one of the areas achieving rapid progress. Organosuperbase-catalyzed polymerization using DBU and BEMP has been widely utilized in the synthesis of polysulfates and polysulfonates. Polysulfamides and polysulfluoridoimidates have been also introduced in the SuFEx community from bissulfamoyl fluoride and bissulfurimidoyl difluoride monomers. Moreover, the homopolymerization of polysulfate has been further expanded to the copolymerization of alternating, block, and periodic copolymers. The side-chain type of SuFEx polymers, where fluorosulfates and sulfonyl fluorides are placed on the branch, have also been studied. Additionally, the mechanical properties of polysulfates and polysulfonates have been examined compared to polycarbonates. In the case of polysulfate, especially, various applications, such as membranes, polymer dielectrics, and liquid crystals, have been proposed.

Transition-metal-free deoxygenation reactions of alcohols using SuFExable hubs have been largely reported with halide-, sulfur-, or nitrogen-based nucleophiles. Since these reactions do not rely on ligand-ligated transition metal catalysts, they can be more cost-effective and environmentally benign. In addition, fluoroalkylation reactions have been developed, which are valuable for pharmaceutical chemistry and materials science. By utilizing SuFEx chemistry under the ambient conditions, synthetic chemists can explore unconventional reaction mechanisms in a practical and versatile manner.

As a part of the growing expansion in the SuFEx field, the radioisotopic activation methods of S–F bonds have been widely investigated. Aryl [^{18}F]fluorosulfates can be synthesized through direct radiofluorosulfurylation of phenolic precursors or by using an isotopic exchange method. When dealing with sulfamoyl [^{18}F]fluoride, the isotopic exchange method is the only viable option due to the unavailability of stable intermediates. In situ generated [^{18}F]FSO_2^+ overcomes the restriction issues associated with the amine precursor. QMA-eluted [^{18}F]FSO_2^+ transferring agent can be directly applied to both phenols and amines to produce ^{18}F-labeled aryl fluorosulfates and sulfamoyl fluorides, respectively. Operational simplicity and tolerance of hydrous conditions are additional benefits of using the [^{18}F]FSO_2^+ method to produce ^{18}F-SuFEx molecules.

Despite rapid advancements in this field, there is still a lot of remaining work waiting for the SuFEx community. Even though diverse SuFEx polymers have been emerged, their synthetic methods for achieving higher architectures have not been extensively reported. For example, the expansion took place on only a few polymers, and more attention should be given to sequence-regulated SuFEx polymers. The development of various methods, including copolymerization, will enrich the diversity of mechanical properties. In terms of sustainability, the recycling technology to transform SuFEx polymers into monomers and precursors for easy conversion is essential. Also, biocompatible SuFEx polymers can be considered.

The future application of SuFExable hubs in organic reactions is expected to expand, as they provide versatile platforms that enhance the toolbox of chemical space. Their orthogonal reactivity and compatibility with ambient reaction conditions offer distinct advantages over other reagents. As researchers continue to develop synthetic methods using these hubs, they can be applied to organotransition metal catalysis and radical chemistry.

The development of PET radiotracers containing SO_2F functionality is a growing area of interest. Currently, the main focus lies on ^{18}F-labeled fluorosulfates and sulfamoyl fluorides, while ongoing efforts are made to uncover additional SuFEx-compatible molecules for biological purposes. For the rigorous application in the field of biomedical science, the physiological stability of each SuFEx drug candidate should be guaranteed before advancement to the desired medical use. The radiolabeling simplicity of S–F congeners opens up the new possibility of active research in drug repurposing with SO_2F-functionalized molecules. Overall, numerous beneficial characteristics will expedite the progress of the SuFEx field in advancing the development of novel drug compounds, including radiopharmaceuticals.

Conflict of Interest

The authors declare no conflict of interest.

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