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Sulfur-based organofluorine reagents for selective fluorination, fluoroalkylation, and fluoroolefination reactions

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ABSTRACT

A good partnership between "soft" sulfur and "hard" fluorine creates a rich chemistry for the introduction of structurally diverse fluorine or fluoroalkyl groups into organic molecules. The combination of sulfur and fluorine chemistry enables the synthesis of bench-stable sulfur-based fluorination reagents, fluoroalkyl sulfones, sulfoximine, sulfoxides, sulfinate, and sulfides. Notably, the reactivity of these reagents could be well-tuned by the incorporation of different substituents on sulfur, or changing the number of fluorine atoms (fluoroalkyl groups) in sulfur-based organofluorine reagents under different reaction conditions. Thus, a series of valuable fluorination, fluoroalkylation, fluoroolefination, fluoroalkanesulfonylation, fluoroalkanesufinylation, and fluoroalkanethiolation reactions *via* nucleophilic, electrophilic, and radical modes have been realized. The present review encompasses and highlights the polarity transduction, different C – S bond cleavages, radical fluoroalkylation reactions, and unique fluorine effects of sulfur-based organofluorine reagents.

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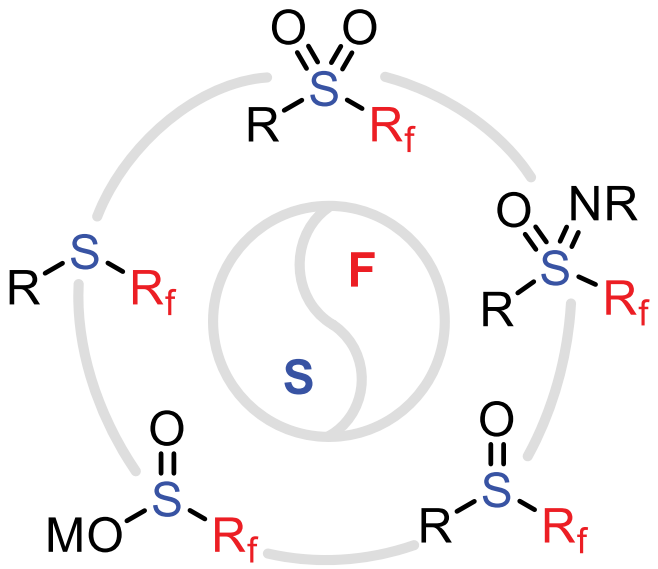
KEYWORDS
Sulfur; fluorine; fluorination; fluoroalkylation; fluoroolefination

GRAPHICAL ABSTRACT



Introduction

Organofluorine compounds have received increasing attention due to their unique physicochemical properties, which rendered them with wide applications in pharmaceuticals, agrochemicals, and advanced materials.[1] The tremendous growth of organofluorine chemistry is largely attributed to the development of new fluorination, fluoroalkylation and fluoroolefination reagents. Among them, sulfur-based reagents are recognized as one of the most widely used and powerful reagents due to the rich-chemistry of sulfur.[2a] The combination of "soft" sulfur with "hard" fluorine rendered the readily transferring of fluorine or fluoroalkyl functionalities into organic molecules,[2b–2d] arising from the high polarity of C – S bonds and the formation of strong S – O bonds.[2e] Previously, we have summarized the sulfur-based fluorination, fluoroalkylation, and fluoroolefination reagents as well as their related reactions from 1958 to 2014.[2f] Herein, we wish to update our work on sulfur-based organofluorine reagents in selective fluorination,

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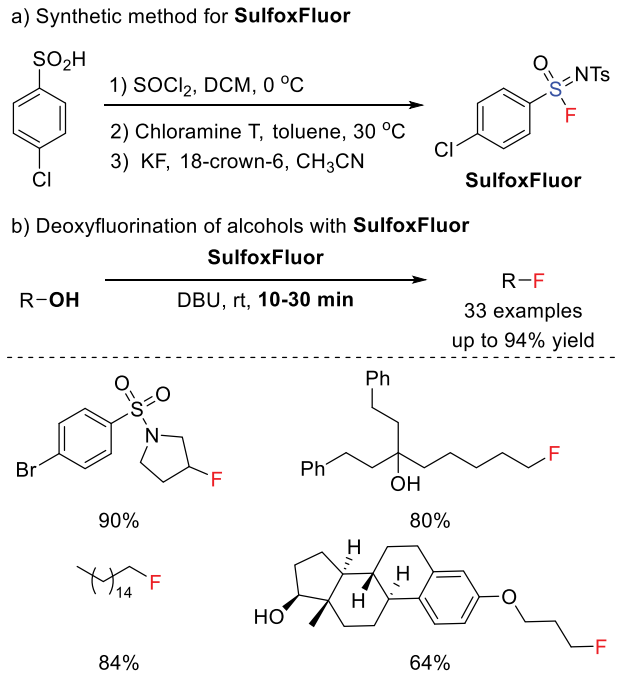


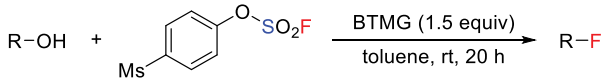
Scheme 1. Synthetic applications of SulfoxFluor as a fluorination reagent. (a) Synthetic method for SulfoxFluo. (b) Deoxyfluorination of alcohols with SulfoxFluo.

fluoroalkylation, and fluoroolefination from 2015 to February 2023.

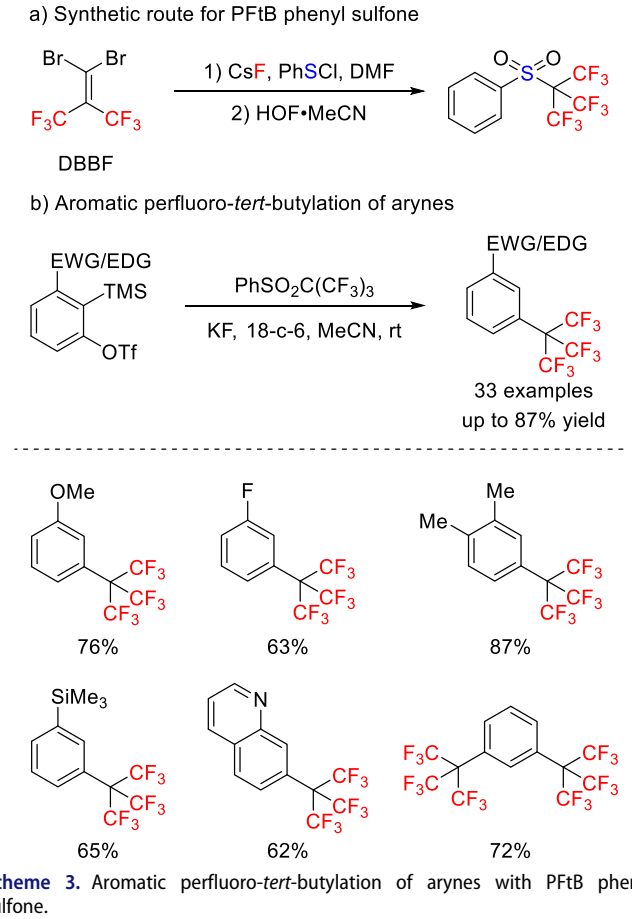
Sulfur-based fluorination reagents

N-Tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor) as a bench-stable, scalable, fluorine-economical, and highly reactive fluorination reagent has been developed by Hu and coworkers (Scheme 1). The hectogram scale of SulfoxFluor could be easily prepared *via* direct amidation of 4-chlorobenzenesulfonyl chloride and chloramine-T trihydrate, and subsequent chlorine-fluorine exchange after simple purification techniques (Scheme 1a).[3] Notably, SulfoxFluor shows superior activity and selectivity in deoxyfluorination of alcohols at room temperature within 30 min.[4] Structurally diverse primary and secondary monoalcohols are smoothly converted into the corresponding alkyl fluorides in moderate to excellent yields. Hydroxyl groups at the sterically less hindered positions from multiple alcohols are selectively transformed into monofluorination products. This is the first example of sulfonimidoyl fluorides acting as fluorination reagents and being used for the late-stage modification of biomolecules and their derivatives (Scheme 1b).

Aryl fluorosulfonates, as one of the analogs of sulfonyl fluoride in deoxyfluorination of alcohols with 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG), features bench-stability, readily availability, low-cost and high fluorination/elimination selectivity (Scheme 2).[5] This is the novel function of aryl fluorosulfonates as a fluorination reagent,[5a] rather than an alternative electrophile to an aryl triflate or a sulfate connector used in click chemistry.[5b,5c]



Scheme 2. Aryl fluorosulfonate as the fluorination reagent.

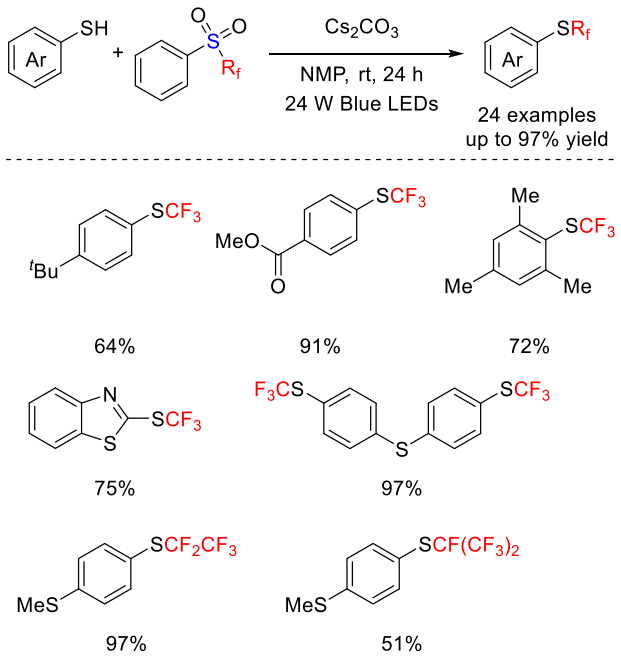


Scheme 3. Aromatic perfluoro-*tert*-butylation of arynes with PFtB phenyl sulfone.

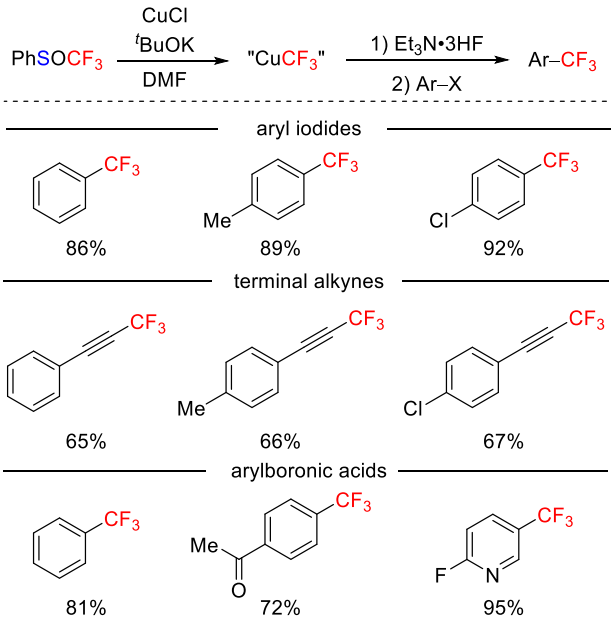
Sulfur-based fluoroalkylation reagents

For perfluoroalkylation

Perfluoro-*tert*-butyl group (PFtB) possesses large structural bulkiness and the strong electron-withdrawing capability, showing potential applications in molecular sensing and imaging. However, reliable methods for the synthesis of perfluoro-*tert*-butylated compounds are rare, due to the unavailability of PFtB-containing reagents. Encouraged by the generation of PFtB anion through the reaction of 1,1-dibromo-2,2-bis(trifluoromethyl)ethylene and CsF, PFtB phenyl sulfone has been designed and synthesized *via* the oxidation of PFtB phenyl sulfide (Scheme 3a).[6] PFtB phenyl sulfone is found to be readily activated by fluoride anion and successfully applied in the aromatic perfluoro-*tert*-butylation of arynes (Scheme 3b).[7] Using PFtB phenyl sulfone as the PFtB source provides efficient access to perfluoro-*tert*-butylated arenes in a *meta*-regioselectivity manner. The experimental results and density functional theory calculations reveal that the *meta*-regioselectivity arises from the extraordinary steric bulkiness of the PFtB group. The superior resolving ability of the PFtB group could be well



Scheme 4. S-perfluoroalkylation of thiophenols with perfluoroalkyl phenyl sulfones.



Scheme 5. Cu-mediated trifluoromethylation using $PhSOCF_3$.

used as a ^{19}F-labeled probe to detect various biologically relevant analytes.

Readily available trifluoromethyl phenyl sulfone ($PhSO_2CF_3$) had been conventionally used as a nucleophilic trifluoromethyl anion,[8] its application as a trifluoromethyl radical precursor is generally difficult due to its relatively low reduction potential. Fortunately, S-trifluoromethylation of thiophenols using $PhSO_2CF_3$ was realized *via* a visible-light-promoted intramolecular single electron transfer process (Scheme 4).[9] The formation of an electron donor-acceptor (EDA) complex *via* a 1:1 ratio of the electron-poor $PhSO_2CF_3$ and electron-rich thiophenolate anion was supported by the color change of their mixed DMAc solution as well as a bathochromic shift in UV/vis absorption spectroscopy. S-pentafluoroethylation and S-perfluoroisopropylation of thiophenols also proceeded successfully with corresponding perfluoroalkyl phenyl sulfones.

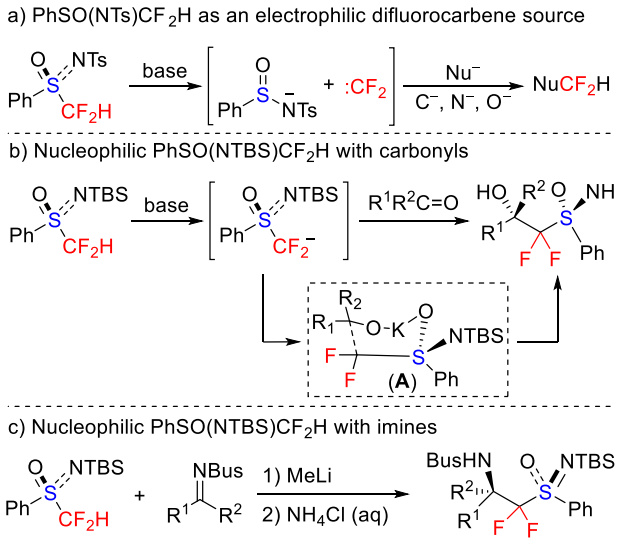
Trifluoromethyl phenyl sulfone ($PhSO_2CF_3$) was also evaluated in copper-mediated trifluoromethylation of aryl iodides by the generation of trifluoromethylcopper ("$CuCF_3$"), however, "$CuCF_3$" could not form efficiently under a series of reaction conditions. Using phenyl trifluoromethyl sulfoxide ($PhSOCF_3$) instead of $PhSO_2CF_3$, a 99% total yield of "$CuCF_3$" was detected. Notably, the competing reaction to produce CF_3H with $PhSO_2CF_3$ was observed in most cases, while inhibited with $PhSOCF_3$. On the other hand, the higher reactivity of $PhSOCF_3$ than $PhSO_2CF_3$ for the formation of "$CuCF_3$" probably arises from the less steric hindrance during the nucleophilic attack by *t*BuOK. Thus, an efficient method to produce "$CuCF_3$" from CuCl, $PhSOCF_3$, and ^{t}BuOK was developed and well applied in the trifluoromethylation of aryl halides, terminal alkynes as well as arylboronic acids (Scheme 5).[10]

For difluoroalkylation

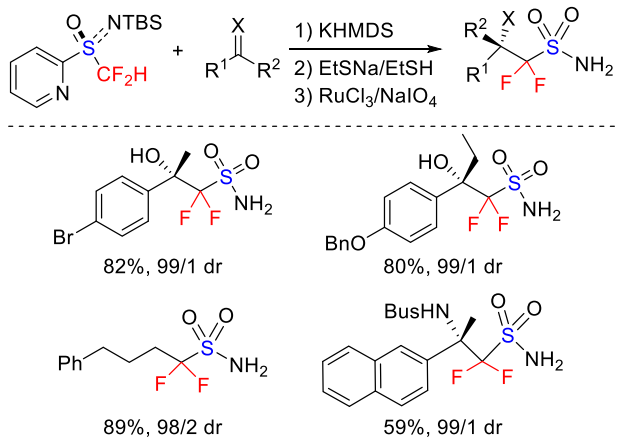
For nucleophilic difluoroalkylation

The combination of stereoselective nucleophilic difluoroalkylation reactions with difluoroalkylated sulfoximine is a straightforward strategy to afford valuable chiral difluoroalkylated skeletons, due to the high tunability of the sulfoximine functional group. The modulation of *p*-toluenesulfonyl (Ts) group to less electron-withdrawing substituent *tert*-butyldimethylsilyl (TBS) group decreases the nucleofugality of the sulfonimidoyl group, which switches the electrophilic difluoromethyl sulfoximine ($PhSO(NTs)CF_2H$, Scheme 6a)[11] to nucleophilic difluoromethyl sulfoximine ($PhSO(NTBS)CF_2H$). Moreover, the bulky group (TBS) on sulfoximine not only favors chiral induction, but remains inert under basic conditions to produce its carbanion $PhSO(NTBS)CF_2^-$. Different from the previous work on stereoselective difluoromethylation of carbonyls with chiral difluoromethyl phenyl sulfoximine ($PhSO(NTBS)CF_2H$) *via* a six-membered transition state **A** (Scheme 6b),[12] it was found that metal cation might be not involved in the transition state in the stereoselective difluoromethylation of imines with sulfoximine reagent (Scheme 6c).[13] A variety of highly stereoselective α-difluoromethyl amines were obtained in moderate to excellent yields, through the prior generation of $PhSO(NTBS)CF_2^-$ carbanion and subsequent nucleophilic addition to ketimines.

The modulation of the phenyl group ($PhSO(NTBS)CF_2H$) to the pyridyl group (2-$PySO(NTBS)CF_2H$) leads to the aromatic C – S cleavage instead of aliphatic C – S cleavage, which enables 2-$PySO(NTBS)CF_2H$ to act as an equivalent of $CF_2SO_2NH_2$. The difluoro(arylsulfoximidoyl)methyl group from 2-$PySO(NTBS)CF_2H$ reagent could be readily introduced into carbonyls, imines, and alkyl halides (Scheme 7).[14] This protocol provides an access to difluorosulfonamides with high stereoselectivity and chemoselectivity.



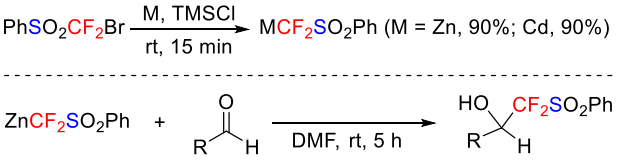
Scheme 6. Stereoselective difluoromethylation of imines with $PhSO(NTBS)CF_2H$.



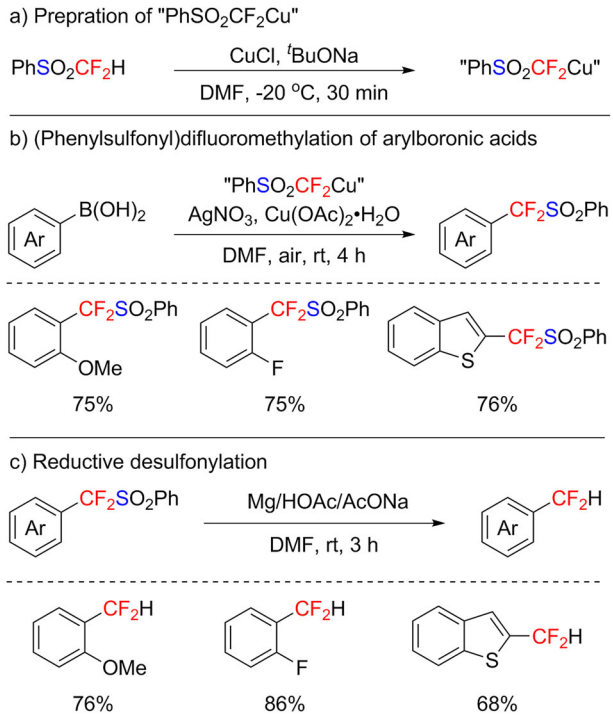
Scheme 7. Stereoselective difluoro(aminosulfonyl)methylation with 2-$PySO(NTBS)CF_2H$.

Difluoromethylzinc and cadmium reagents (HCF_2M, M = Zn or Cd) are fairly stable and only exhibit limited reactivity with highly reactive electrophiles such as allylic halides and propargyl halides. To improve the nucleophilicity of difluoromethyl anion, the phenylsulfonyl group is introduced to generate $PhSO_2CF_2MX$ (M = Zn or Cd) species *via* the corresponding metal insertion into the bromodifluoromethyl phenyl sulfone ($PhSO_2CF_2Br$). The formed $PhSO_2CF_2ZnX$ with a good balance of stability and reactivity react smoothly with both aryl and alkyl aldehydes (Scheme 8).[15]

More reactive (phenylsulfonyl)difluoromethyl organometallic reagent "$PhSO_2CF_2Cu$" was prepared in 96% total yield from the reaction of CuCl, $PhSO_2CF_2H$, and ^{t}BuONa in DMF at −20 °C for 30 min (Scheme 9a).[16] The application of "$PhSO_2CF_2Cu$" in (phenylsulfonyl)difluoromethylation of arylboronic acids was examined, and the addition of silver nitrate and $Cu(OAc)_2•H_2O$ could diminish the generation of side product aryl chloride and promote the formation of (phenylsulfonyl)difluoromethylated product (Scheme 9b). Furthermore, reductive desulfonylation of the target product by the treatment with Mg/HOAc/NaOAc gave difluoromethyl arenes in good yields (Scheme 9c).



Scheme 8. Nucleophilic difluoromethylation of aldehydes with (phenylsulfonyl)difluoromethylzinc reagent.

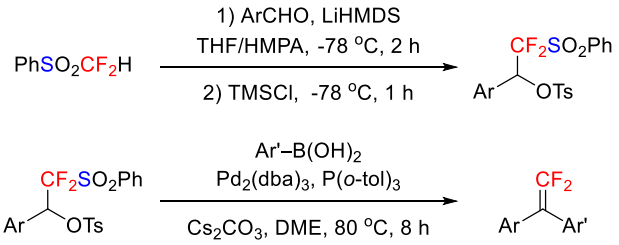


Scheme 9. Cu-mediated aerobic (phenylsulfonyl)difluoromethylation of arylboronic acids with $PhSO_2CF_2H$.

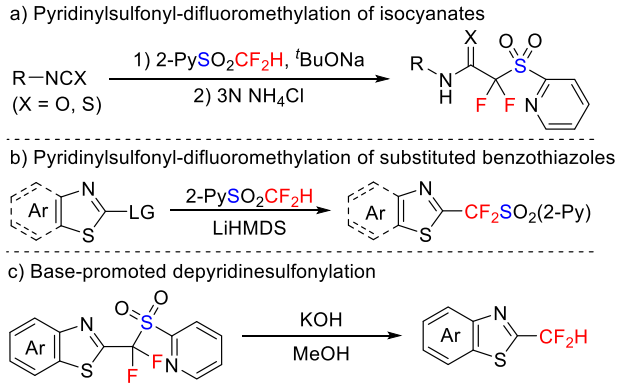
Nucleophilic (phenylsulfonyl)difluoro methylation of aldehydes could also proceed with difluoromethyl phenyl sulfone ($PhSO_2CF_2H$). α-[(Phenylsulfonyl) difluoromethyl]-benzyl tosylate could be further obtained by the following one-pot addition of tosyl chloride. Palladium-catalyzed dehydraosulfonylative cross-coupling reaction with arylboronic acids delivers a series of 2,2-diaryl-1,1-difluoroethenes (Scheme 10).[17]

Similar to the difluoroalkylated sulfoximine,[14] difluoromethylated sulfone bearing with pyridyl group (2-$PySO_2CF_2H$) rather than phenyl group ($PhSO_2CF_2H$) could be easily functionalized *via* desulfonylation under mild conditions. Several unexplored electrophiles including isocyanates (Scheme 11a)[18] and 2-substituted benzothiazoles (Scheme 11b)[19] have been examined in nucleophilic pyridinylsulfonyldifluoromethylation with 2-$PySO_2CF_2H$. Notably, changing the difluoromethyl source from 2-$PySO_2CF_2H$ to $TMSCF_2H$, the ring-opening S-difluoromethylation of 2-substituted benzothiazoles occurred, affording a wide range of difluoromethyl 2-isocyanophenyl sulfides. (Pyridinesulfonyl) difluoromethylated products could be further transformed into difluoromethylated compounds *via* the base-promoted depyridinesulfonylation (Scheme 11c).[19]

Other functionalizations of (pyridinesulfonyl)difluoromethylation products such as dipyridinative iodination of



Scheme 10. Synthetic application of (phenylsulfonyl)difluoromethylated product.

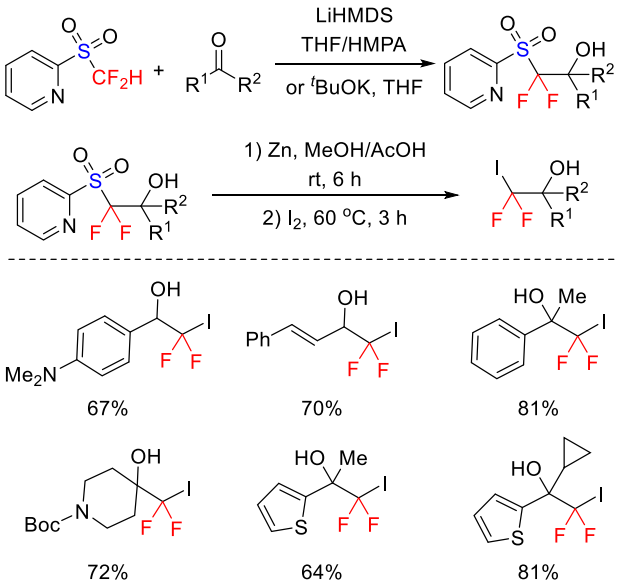


Scheme 11. Nucleophilic difluoromethylation with 2-$PySO_2CF_2H$.

(2-pyridyl sulfonyl)difluoromethylated carbinols could afford various iododifluoromethylated carbinols. An efficient method is established to produce difluorinated sulfinates *via* depyridination with Zn in MeOH/AcOH. Subsequently, the iodination of the *in-situ* formed difluorinated sulfinates with I_2 gives out the corresponding iododifluoromethylated carbinols (Scheme 12).[20] The whole nucleophilic iododifluoromethylation of carbonyl compounds with 2-$PySO_2CF_2H$ exhibit excellent functional-group tolerance under mild conditions.

For radical difluoroalkylation

Difluoroalkyl radical formed by photoredox catalysis. Radical fluoroalkylation using fluoroalkyl sulfones or their derivatives as fluoroalkyl radicals remain unexplored until 2016. Photoredox catalysts are proposed to generate highly reactive SET reductants to activate fluoroalkyl sulfones for radical fluoroalkylation. A series of fluoroalkyl sulfones show good radical reactivity using isocyanides as the model substrates, including monofluoromethylated, difluoromethylated, 1,1-difluoroethylated, (phenyl)difluoromethylated, (benzoyl)difluoromethylated, and trifluoromethylated sulfones (Scheme 13a).[21] Mechanistic studies demonstrated that $[Ru]^{2+}$ is irradiated by blue LEDs to form excited $[Ru]^{2+}$, which could be reduced by CO_3^{2-} to produce $[Ru]^{+}$. Single electron transfer from Ru^{+} to fluoroalkyl sulfone yields sulfinate ion, a fluoroalkyl radical, and regenerates $[Ru]^{2+}$. The addition of fluoroalkyl radical to isocyanide, intramolecular radical cyclization, then deprotonation provide the radical anion **A**. Further oxidation of radical anion **A** by excited $[Ru]^{2+}$ delivers product and photocatalyst $[Ru]^{+}$. Radical anion **A** could also be oxidized by the fluoroalkyl sulfone *via* a SET process to give desired product and fluoroalkyl radical (Scheme 13b).[21] Later, radical arylthiodifluoromethylation of various isocyanides with arylthiodifluoromethyl 2-pyridyl sulfone derivatives were also reported, affording phenanthridines and isoquinolines in good yields.[22]

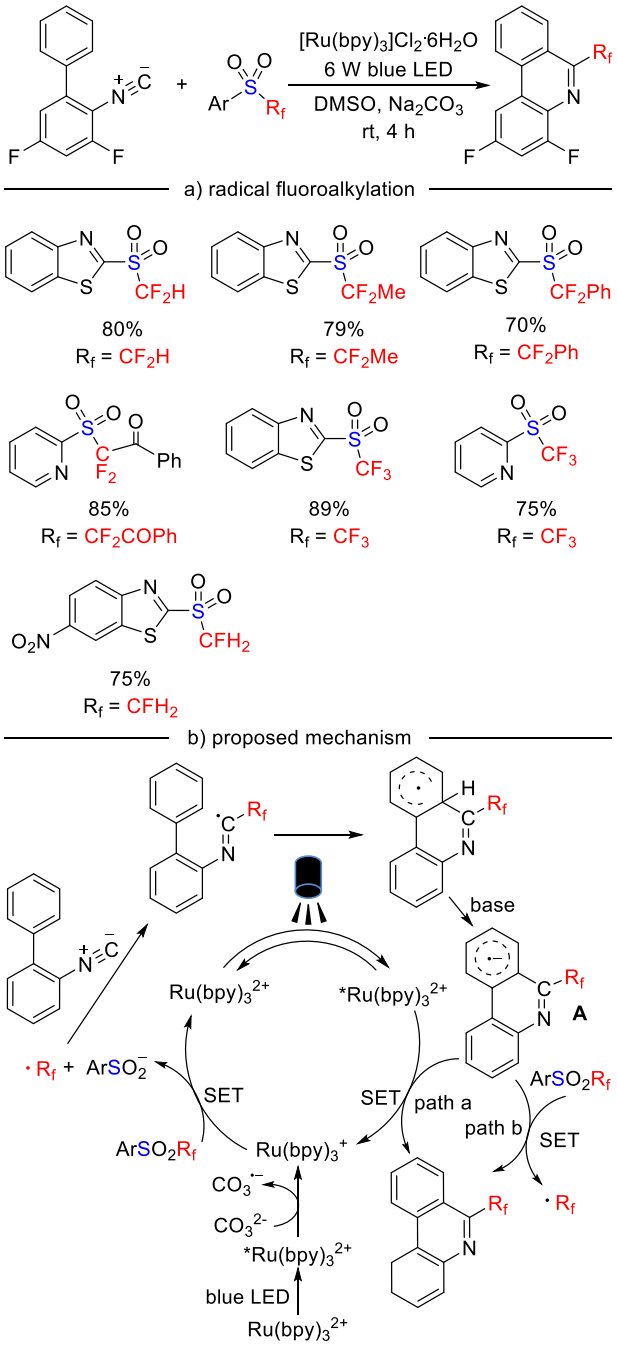


Scheme 12. Nucleophilic iododifluoromethylation of carbonyls with 2-$PySO_2CF_2H$.

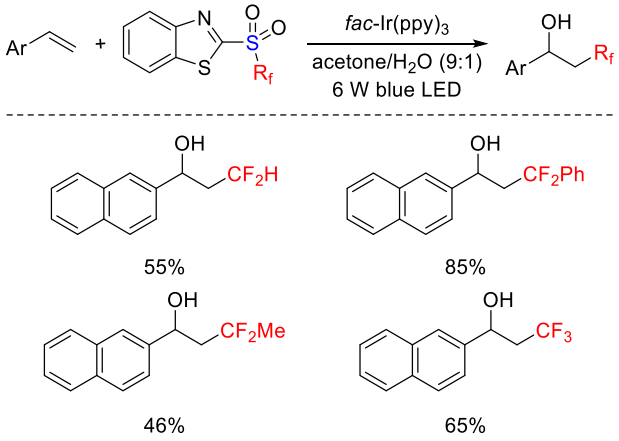
A logical extension of radical fluoroalkylation between aryl alkenes and fluorinated sulfones was also succeeded by visible-light photoredox catalysis. Various fluoroalkyl radicals containing difluoromethyl, (phenyl)difluoromethyl, 1,1-difluoroethyl, and trifluoromethyl radicals could be introduced into the styrene derivatives (Scheme 14).[23] Using *fac*-$Ir(ppy)_3$ instead of $[Ru(bpy)_3]Cl_2{\bullet}6H_2O$ avoids the addition of Na_2CO_3.

Difluoroalkyl radical formed by oxidation of difluoroalkyl anion. It is challenging to form $PhSO_2CF_2$ radical from $PhSO_2CF_2H$ *via* the homolytic cleavage of F_2C–H bond. Thus, the deprotonation of $PhSO_2CF_2H$ with subsequent oxidation of $PhSO_2CF_2^{-}$ by $PhI(OAc)_2$ using isocyanides as the radical acceptors were tested (Scheme 15).[24] The charging sequence of the oxidant and base allows their good compatibility in one system. The addition of Cs_2CO_3 and I_2 as the optimal additives could promote the generation of $PhSO_2CF_2$ radical from the hypervalent iodine intermediates, and inhibit homocoupling of the radical intermediate. With the $PhSO_2CF_2$-substituted phenanthridines in hand, a single electron transfer process with different nucleophiles such as alcoholates, phenols, thiolates, selenolates, salts of diethyl malonate derivatives, and salts of nitroalkanes have been systematically studied (Scheme 16).[25]

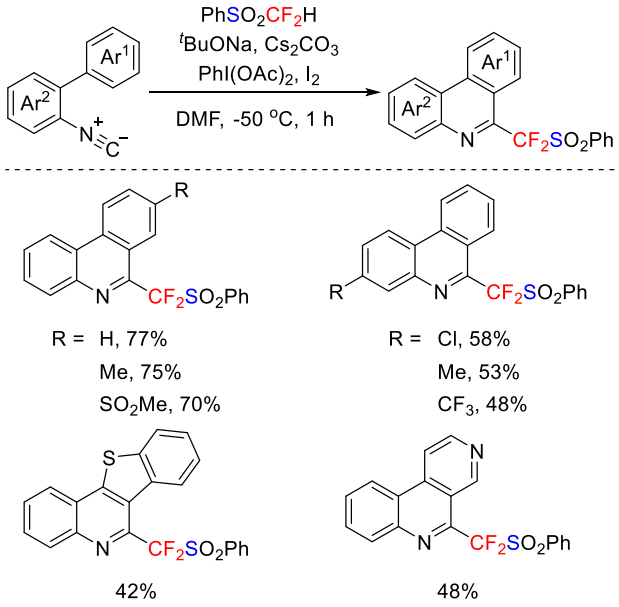
Readily available and scalable fluoroalkyl benzo[*d*]-thiazole-2-yl sulfone (2-$BTSO_2R_f$) could be further converted to fluoroalkyl sulfinate sodium ($NaSO_2R_f$).[26] The treatment of $NaBH_4$ and 2-$BTSO_2R_f$ in ethanol affords $NaSO_2CF_2H$ and $NaSO_2CF_2Ph$ and $NaSO_2CFH_2$ in 90%-97% yields on a large



Scheme 13. Radical fluoroalkylation of isocyanides with fluorinated sulfones by visible-light-promoted photoredox catalysis.



Scheme 14. Radical fluoroalkylation of styrenes with fluoroalkylated sulfones by visible-light photoredox catalysis.

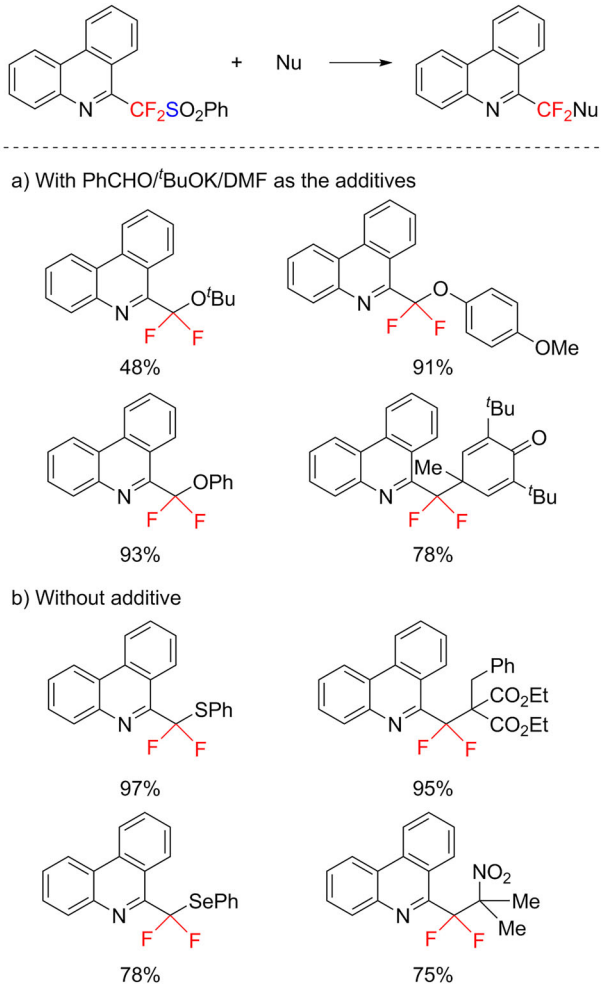


Scheme 15. Radical (phenylsulfonyl)difluoromethylation of isocyanides with $PhSO_2CF_2H$.

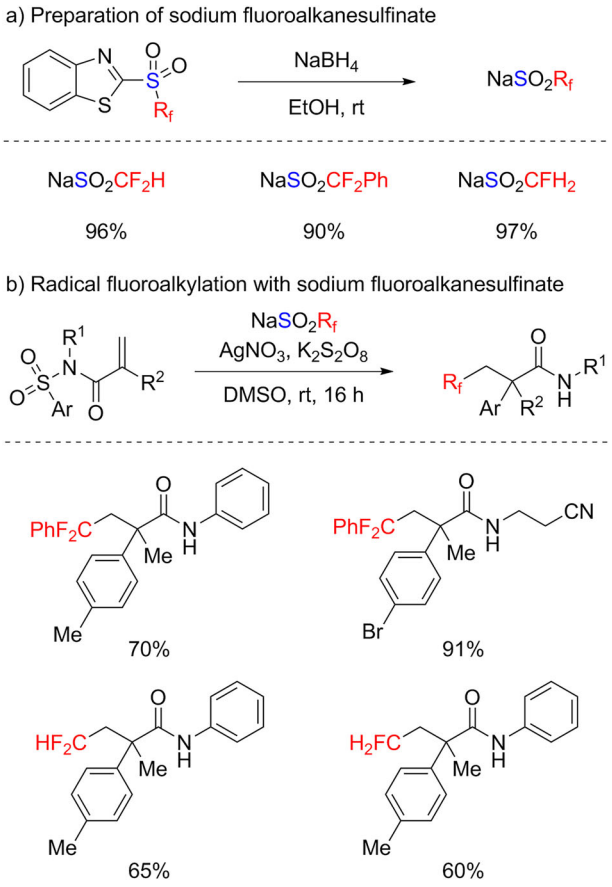
scale. The preparation and purification of $NaSO_2R_f$ are very simple and efficient (Scheme 17a). The utility of prepared sodium di- and monofluoroalkanesulfinates were employed in the radical Ag-catalyzed tandem fluoroalkylation/1,4-aryl migration/desulfonylation/hydrogen atom abstraction of conjugated *N*-arylsulfonylated amides to yield α-aryl-β-fluoroalkyl amides (Scheme 17b). The reactivity of $NaSO_2R_f$ in this transformation is $NaSO_2CF_2Ph > NaSO_2CF_2H > NaSO_2CFH_2$ from the results of competing experiments.

The replacement of the hydrogen atom of the sodium difluoromethylsulfinate ($NaSO_2CF_2H$) with a chlorine atom, the formed nucleophilic difluoromethyl radical could be readily reversed to an electrophilic chlorodifluoromethyl radical. Thus, highly selective and efficient radical chlorodifluoromethylation of electron-rich alkenes and heteroarenes was reported with $NaSO_2CF_2Cl$ (Scheme 18a).[27] Similar electrophilic fluoroalkyl radicals such as trifluoromethyl and phenylsulfonyldifluoromethyl radicals reacted well, while nucleophilic difluoromethyl and monofluoromethyl radicals showed poor results. The oncology candidate compound could be successfully prepared by the combination of radical chlorodifluoromethylation with $NaSO_2CF_2Cl$ and hydrodechlorination in the presence of a palladium catalyst (Scheme 18b).

Difluoroalkyl radical formed by the reduction by aryliron intermediates. The first iron-catalyzed difluoromethylation of arylzinc with 2-$PySO_2CF_2H$ *via* aliphatic C – S bond cleavage was reported in 2018 (Scheme 19).[28] Radical inhibition experiments by the addition of a single electron transfer inhibitor such as 2,2,6,6-tetramethylpiperidin-1-oxyl, 1,4-dinitrobenzene, and 1,4-benzoquinone (BQ) were conducted, no product was detected in these cases. Cyclized



Scheme 16. Fluoroalkylation of various nucleophiles with $PhSO_2CF_2$-substituted phenanthridines.



Scheme 17. Synthetic applications of fluoroalkyl sulfinate sodium. (a) preparation of fluoroalkyl sulfinate sodium.

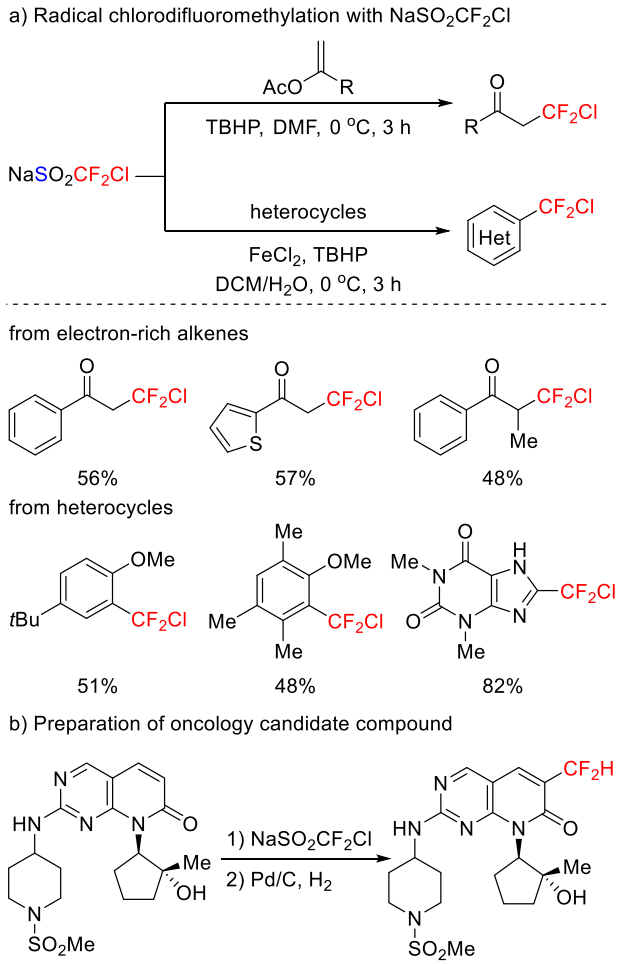
product was also obtained in the radical clock experiment, which all suggested that difluoromethyl radicals were generated by a SET pathway. This study not only shows the new reactivity of 2-$PySO_2CF_2H$ under inexpensive and environmentally benign iron catalysis but provides a novel method to construct difluoromethylated arenes.

Recently, the iron-catalyzed radical difluoroalkylation of lithium arylborates with various difluoroalkyl *N*-heteroalkyl sulfones was realized (Scheme 20a).[29] In this transformation, a sulfone with a lower reduction potential showed better radical reactivity than that with a higher reduction potential. And the yields of target products are more related to the structure of the *N*-heteroalkyl sulfones rather than their reduction potentials (Scheme 20b). Based on these results, the author proposed that the reduction potential limitation of sulfones probably was overcome by the coordination between the nitrogen atom of *N*-heteroaryl sulfones and iron catalyst, enabling the difluoroalkyl *N*-heteroaryl sulfones with low reduction potentials to undergo intermolecular SET process. This proposal was further proved by the observation of the deshielding effect caused by the coordination of *N*-heteroaryl sulfones and $FeCl_2$ in the NMR study. The proposed mechanism was shown in Scheme 20c. This work provides a new insight into SET chemistry.

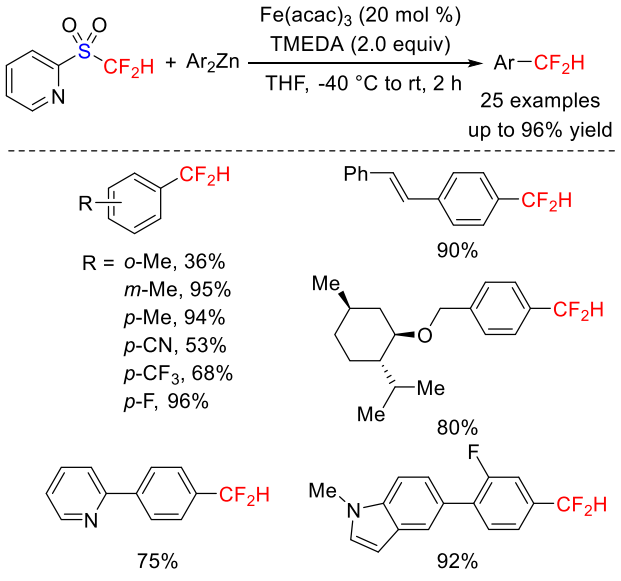
Difluoroalkyl radical formed by electrochemical reduction. Synthetic electrochemistry has emerged as a sustainable and green technique to produce radicals using electrons instead of stoichiometric amounts of chemical oxidants/reductants.[30] Therefore, radical fluoroalkylation under electrochemical conditions has attracted much attention. Encouraged by the excellent radical reactivity of fluoroalkyl sulfones under the visible-light photoredox catalysis, chemical oxidants, as well as transition-metal catalysis, the radical difluoroalkylation of alkenes with difluoroalkyl benzo[*d*]thiazol-2-yl (2-BT) sulfones by cathodic reduction was tested (Scheme 21).[31] This is the first example of electrochemistry-enabled radical difluoroalkylation of sulfones, which are compatible with a series of electron-deficient alkenes and difluoroalkyl *N*-heteroaryl sulfones.

For monofluoroalkylation

Highly diastereoselective nucleophilic monofluoroalkylation of aldehydes (Scheme 22a)[32] or *tert*-butanesulfinyl aldimines (Scheme 22b)[33] with α-fluoro-α-phenylthio-α-phenylsulfonyl-methane (FTSM) was developed, affording the corresponding *β*-fluorinated carbinols and α-monofluoromethyl amines, respectively. The high diastereoselectivity of these transformations attributes to fluorine substitution which results in the reversible nucleophilic addition of FTSM to aldehydes or *tert*-butanesulfinyl aldimines.

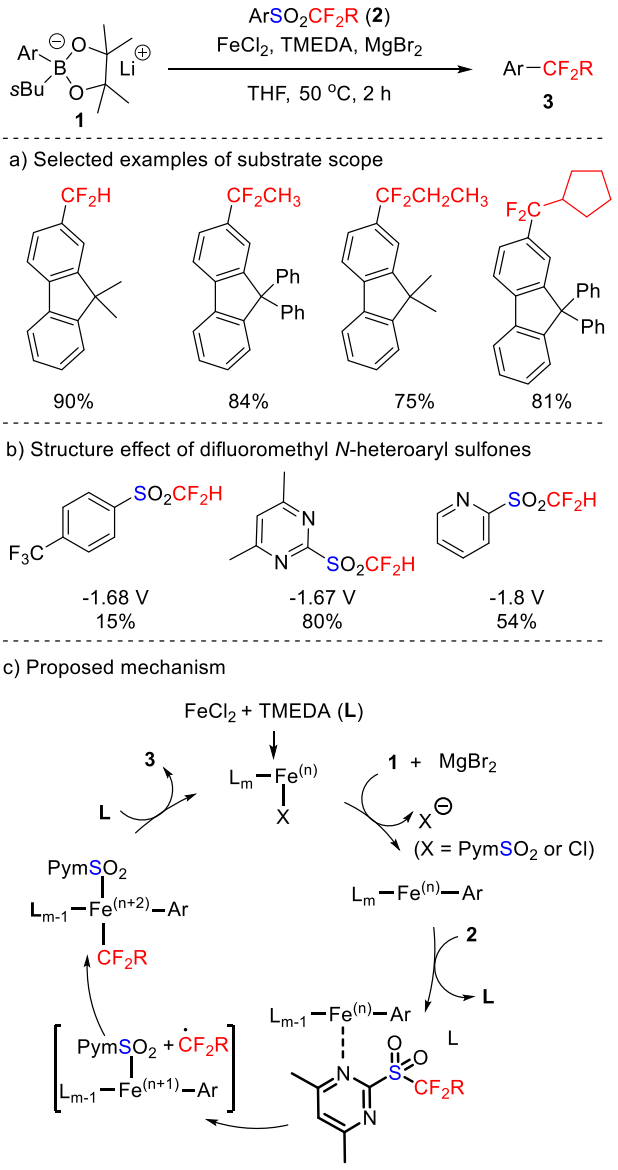


Scheme 18. Radical chlorodifluoromethylation with $NaSO_2CF_2Cl$.



Scheme 19. Iron-catalyzed radical difluoromethylation of arylzinc and 2-$PySO_2CF_2H$.

Highly stereoselective nucleophilic monofluoroalkylation of *N*-*tert*-butylsulfinyl ketimines with optically pure phenyl monofluoromethyl sulfoximine ($PhSO(NTBS)CFH_2$) was also investigated to produce *β*-fluorinated amines

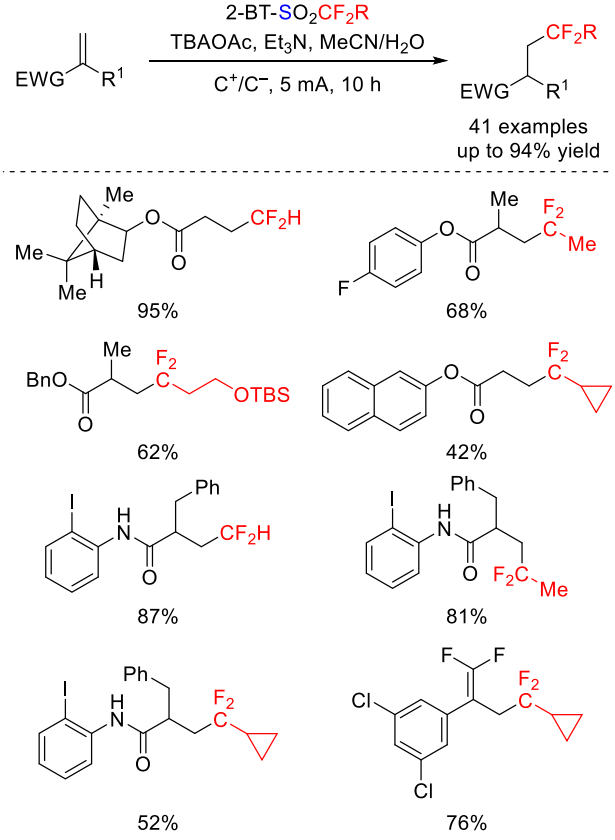


Scheme 20. Iron-catalyzed radical difluoroalkylation of lithium arylborates and difluoroalkyl *N*-heteroaryl sulfones.

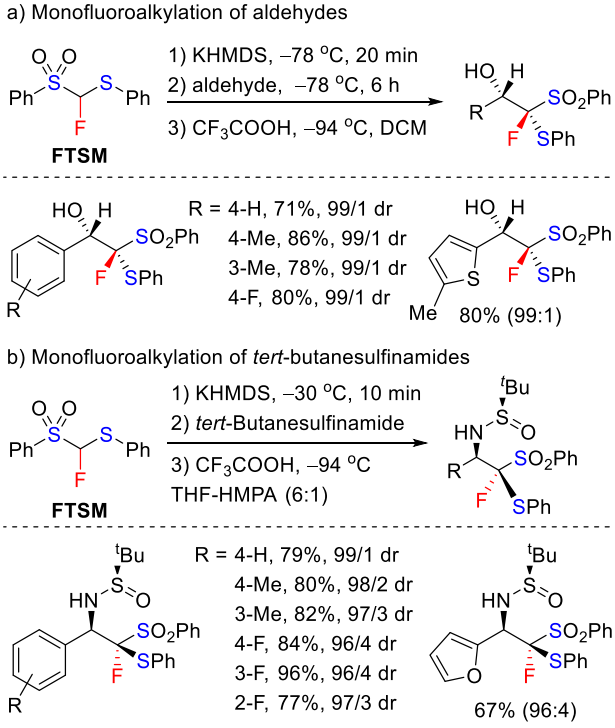
(Scheme 23).[34] Mechanistic studies demonstrated that the carbanions from $PhSO(NTBS)CFH_2$ in both R and S configurations were formed without selectivity. Different from the FTSM, the nucleophilic addition in this process is not reversible. Thus, the high stereoselectivity of this transformation was proposed to be enabled by the dynamic kinetic resolution of the monofluorinated carbanion.

Sulfur-based fluoroolefination reagents

Followed by the smoothly *gem*-difluoroolefination of carbonyls with difluoromethyl 2-pyridyl sulfone,[35] the monofluorinated 2-pyridyl benzyl sulfone was prepared using *N*-fluorobenzenesulfonimide (NFSI) (Scheme 24a) and successfully applied in the monofluoroolefination of aldehydes (Scheme 24b).[36] Initially, the mixture of Z- and E-sulfinate salts produced from Smiles rearrangement were obtained. Z-sulfinate salt was spontaneously and rapidly decomposed to Z-monofluoroalkene, while E-sulfinate salt was stable in the

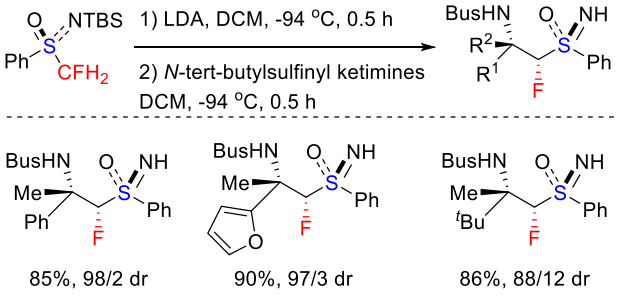


Scheme 21. Radical difluoroalkylation of alkenes under electrochemical conditions.

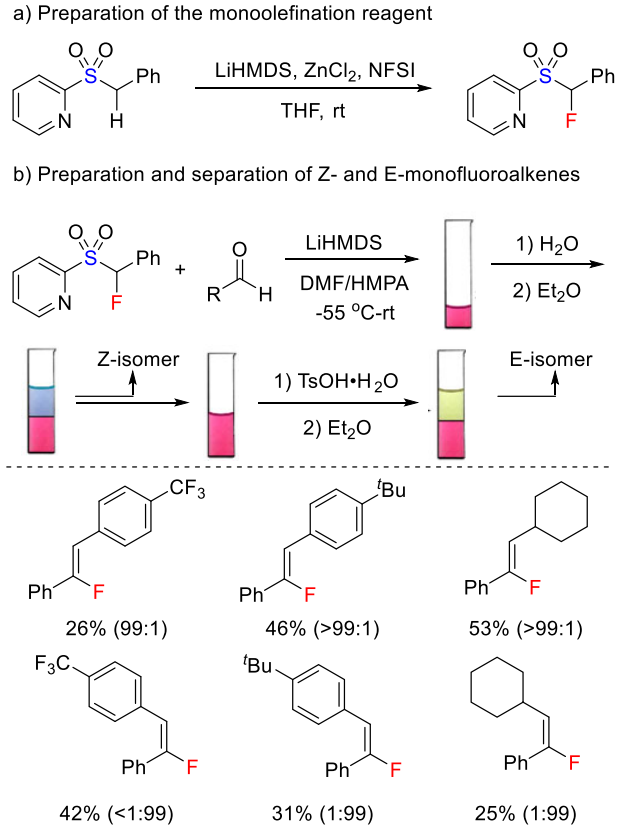


Scheme 22. Highly diastereoselective monofluoroalkylation of aldehydes or *tert*-butanesulfinamides with FTSM.

aqueous phase. The addition of diethyl ether could keep Z-monofluoroalkene in the organic phase, while the E-sulfinate salt is in the aqueous phase. Further addition of



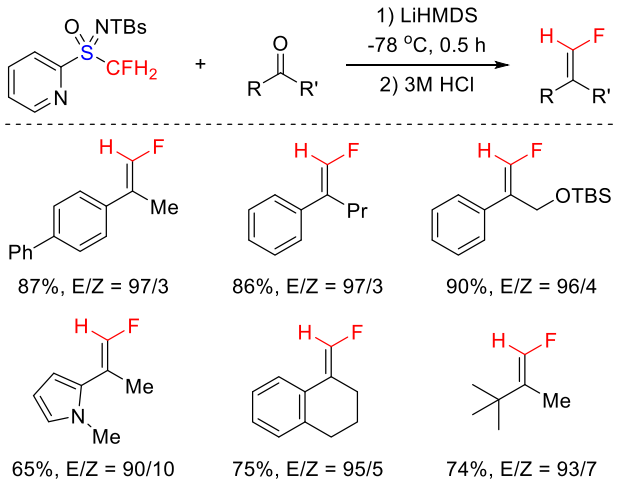
Scheme 23. Highly stereoselective monofluoroalkylation of amines.



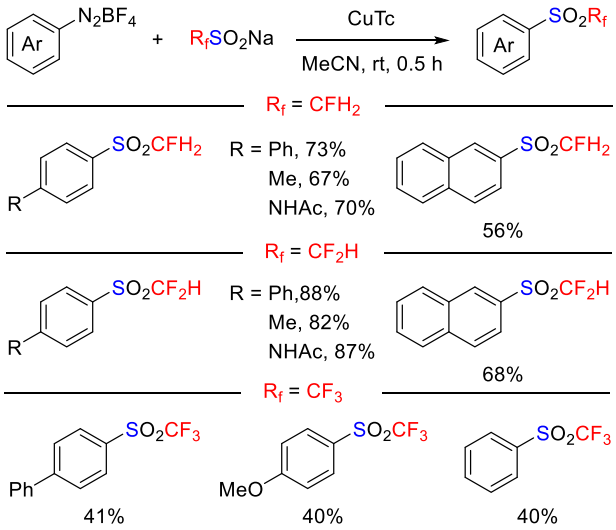
Scheme 24. Phase separation of Z- and E-monofluoroalkenes obtained *via* fluoroolefination of aldehydes with monofluorinated 2-pyridyl benzyl sulfone.

p-toluenesulfonic acid monohydrate as the acid in the aqueous phase afforded E-monofluoroalkene, which was separated by the addition of diethyl ether. This procedure is highly simplified and applied in the separation of fluorinated combretastatin, which cannot be separated by the preparative HPLC. Notably, no catalyst, additional reagent, or special solvent is required in this kinetic resolution and phase labeling/switching process.

Stereoselectivity of carbonyl olefination *via* Witting, Julia-Kocienski, or Horner-Wadsworth-Emmons reactions is difficult to control. The olefin metathesis only yields disubstituted terminal monofluoroolefins. Fortunately, a stereoselective Julia-Kocienski-type monofluoroolefination was realized using S-monofluoromethyl-S-(2-pyridyl)sulfoximine with carbonyls. The 2-pyridyl group was used to promote the olefination, and the sulfoximidoyl group could control the stereoselectivity. The present approach could convert a



Scheme 25. Stereoselective carbonyl olefination with fluorosulfoximines.



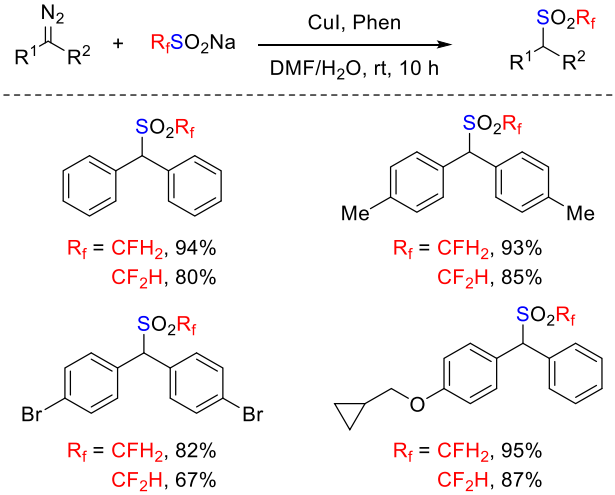
Scheme 26. Copper-mediated fluoroalkanesulfonylation of arenediazonium tetrafluoroborates.

series of ketones and aldehydes into di- and tri-substituted monofluoroalkenes (Scheme 25).[37]

Sulfur-based fluoroalkanesulfonylation/fluoroalkanesulfinylation/fluoroalkanethiolation reagents

For fluoroalkanesulfonylation

Without an external oxidant, sodium fluoroalkanesulfinate ($NaSO_2R_f$) cannot give fluoroalkyl radicals. In this case, $NaSO_2R_f$ acted as nucleophiles rather than radical fluoroalkyl precursors, which proceed fluoroalkanesulfonylation rather than radical fluoroalkylation. In CuTc-mediated di- and monofluoromethanesulfonylation of arenediazonium tetrafluoroborates (Scheme 26), the fluoroalkanesulfonylation reactivity of $NaSO_2R_f$ is in line with their nucleophilicity as the following order: $NaSO_2CFH_2 > NaSO_2CF_2H > NaSO_2CF_3$ without the consideration of the solubility of different sulfinates.[38] This trend is different from their reactivity in radical fluoroalkylation reactions.



Scheme 27. Copper-mediated cross-coupling of diazo compounds with fluoroalkyl sulfinates.

A similar trend is also observed in the copper-mediated cross-coupling reactions of diazo compounds with fluoroalkyl sulfinates, in which a reliable method was established for the synthesis of structurally diverse sulfones. In this transformation, the overall efficiency of these fluoroalkyl sulfinates is in line with their nucleophilicity as the following orders: $NaSO_2CFH_2 > NaSO_2CF_2H > NaSO_2CF_3$ (Scheme 27).[39]

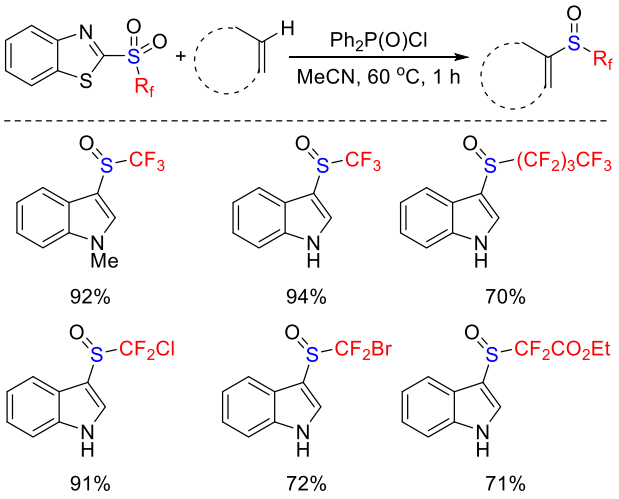
For fluoroalkanesulfinylation

Great advances in fluoroalkyl heteroaryl sulfones in nucleophilic and radical fluoroalkylation have been disclosed, however, their novel reactivity as an electrophile has been barely reported. Direct electrophilic fluoroalkanesulfinylation of electron-rich heteroarenes with fluoroalkyl heteroaryl sulfones proceeded in the presence of $Ph_2P(O)Cl$ *via* cleavage of C(het)−S and S = O bonds (Scheme 28).[40] It is the first example of fluoroalkyl heteroaryl sulfones as electrophilic fluoroalkanesulfinylation reagents. In this transformation, fluoroalkyl heteroaryl sulfones 2-$BTSO_2R_f$ with different R_f groups such as CF_3, $(CF_2)_3CF_3$, CF_2Br, and CF_2CO_2Et were well compatible.

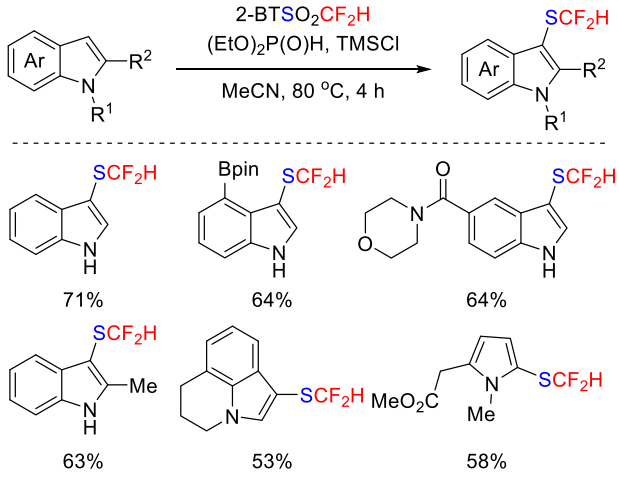
For fluoroalkanethiolation

For difluoromethanethiolation

Inspired by the success of fluoroalkyl heteroaryl sulfones as electrophilic fluoroalkanesulfinylation reagent, a similar strategy was employed to realize direct fluoroalkanethiolation of indoles with fluoroalkyl heteroaryl sulfones by the combination of $(EtO)_2P(O)H$ and TMSCl (Scheme 29).[41] Notably, the reactions of $(EtO)_2P(O)H$ with 2-$BTSO_2CF_3$ or 2-$BTSO_2CF_2H$ gave $(EtO)_2P(O)-O-S(O)CF_3$ and $(EtO)_2P(O)-O-S(O)CF_2H$, respectively. However, the $(EtO)_2P(O)-O-S(O)CF_3$ is favored to be attacked by indole to proceed trifluoroalkanesulfinylation, while $(EtO)_2P(O)-O-S(O)CF_2H$ is inclined to $O-S(O)CF_2H$ homolysis to generate $HS(O)CF_2H$. Finally, $ClSCF_2H$ derived



Scheme 28. Direct electrophilic fluoroalkanesulfinylation of heteroarenes with fluoroalkyl heteroaryl sulfones.



Scheme 29. Direct electrophilic difluoroalkanethiolation of indoles with 2-$BTSO_2CF_2H$.

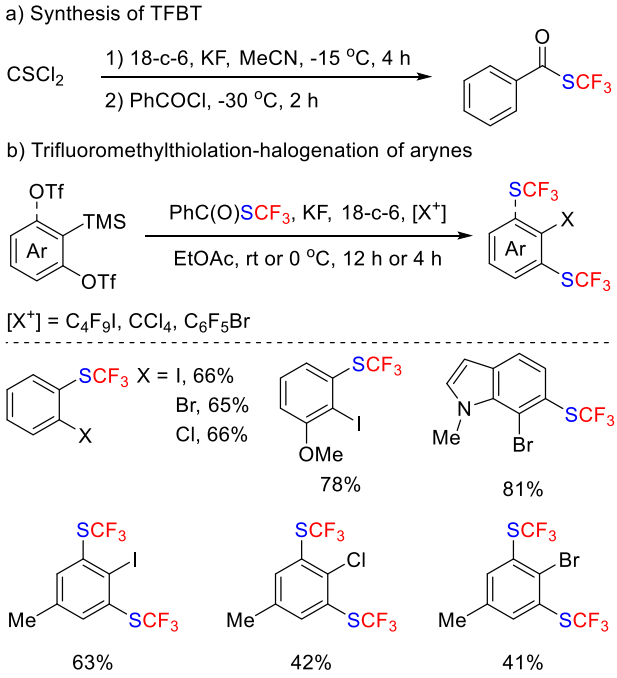
from the reaction of TMSCl and HF_2CSOH is proposed to be reactive species for the direct difluoromethanethiolation of indoles.

For trifluoromethylthiolation-halogenation

Very recently, a bench stable, low-cost, and easily scalable nucleophilic trifluoromethylthiolation reagent S-(trifluoromethyl)benzothioate (TFBT) was synthesized using KF as the only fluorine source (Scheme 30a).[42] It has been applied in 1,2-trifluoromethylthiolation iodination/bromination/chlorination, as well as 1,3-bis(trifluoromethylthiolation)-2-halogenation of arynes with an electrophilic halogenation reagent. (Scheme 30b).

Summary

In this review, we summarize our major efforts on sulfur-based organofluorine reagents in selective fluorination,



Scheme 30. Trifluoromethylthiolation-halogenation of arynes.

fluoroalkylation, fluoroolefination, fluoroalkanesulfonylation, fluoroalkanesufinylation, and fluoroalkanethiolation reactions. The synthetic method and reactivity of the corresponding fluorine-containing sulfones, sulfoximines, sulfoxides, sulfinates, and sulfides have been disclosed. With these sulfur-based organofluorine reagents in hand, a wide range of fluorine or fluoroalkyl groups such as perfluoroalkyl, difluoroalkyl, and monofluoroalkyl groups are introduced by nucleophilic, electrophilic, and radical modes.

Based on our recent investigation on sulfur-based organofluorine reagents, we are able to summarize the following aspects. (1) the polarity of sulfur-based organofluorine reagents could be transduced by the modulation of the functionalities of the sulfur or fluoroalkyl groups. For example, by changing the Ts group of $PhSO(NTs)CF_2H$ to TBS, the electrophilic difluoromethyl sulfoximine switches to nucleophilic difluoromethyl sulfoximine. Replacement of the hydrogen atom of $NaSO_2CF_2H$ with a chlorine atom, the nucleophilic CF_2H radical reverses to the electrophilic CF_2Cl radical. (2) The selective C – S bond cleavage of sulfur-based organofluorine reagents could be controlled by the modification of the heteroaryl groups. For example, using a pyridyl group ($2\text{-}PySO(NTBS)CF_2H$) instead of the phenyl group of $PhSO(NTBS)CF_2H$, the aromatic C – S bond is cleaved rather than the aliphatic C – S bond. (3) The studies of radical fluoroalkylation reactions profoundly enrich the chemistry of fluoroalkyl sulfones and sulfinates. Different modes to produce fluoroalkyl radicals including the reduction of fluoroalkyl sulfones *via* photoredox catalysis, electrochemistry, chemical reductants, and oxidation of fluoroalkyl sulfinates have been disclosed. In terms of fluoroalkyl sulfones with high reduction potentials, the formation of the EDA complex or the coordination with the transition-metal catalyst

could effectively decrease their reduction potentials to form the corresponding fluoroalkyl radicals. Notably, the same reagents could act as different synthons under different reaction conditions. For example, $NaSO_2R_f$ can generate fluoroalkyl radicals in the presence of external oxidants; in other cases, they serve as nucleophilic fluoroalkanesulfonylating agents. (4) The unique fluorine effect is probed in different transformations. For example, the reactivity of fluoroalkyl sulfinates in radical fluoroalkylation follows the order of $NaSO_2CF_2Ph > NaSO_2CF_2H > NaSO_2CFH_2$, while the reactivity in nucleophilic fluoroalkanesulfonylation is $NaSO_2CFH_2 > NaSO_2CF_2H > NaSO_2CF_3$. (5) Kinetic resolution and phase labeling/switching is an efficient and simplified approach to separate fluorinated combretastatin, which cannot be separated by the preparative HPLC.

Disclosure statement

The authors have no conflict of interest.

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