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The Development of New Reagents and Reactions for Synthetic Organofluorine Chemistry by Understanding the Unique Fluorine Effects

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1.1 Introduction

For a long period of time, fluorine chemistry research was deemed to be very dangerous, in part owing to the notorious fluorination reagents such as F_2 and HF, which are highly corrosive and reactive. In this context, synthetic organofluorine chemistry was only pursued by a handful of researchers for several decades after the first synthesis of F_2 by Moissan in 1886. However, great changes had taken place over the past decades. With the successful application of chlorofluorocarbons (although banned later owing to their ozone-depleting character by Montreal Protocol in 1987) as refrigerants, the development of high-performance fluorinated materials such as Teflon and the development of fluorinated pharmaceuticals and agrochemicals, organofluorine chemistry has become increasingly important in satisfying the huge demand for fluorinated molecules with diverse functions [1]. To date, organofluorine chemistry has become an indispensable branch of organic chemistry and enriched many aspects of related areas such as medicinal chemistry and materials science, among others. Perhaps the most prominent application of organofluorine compounds that has close relation with our everyday life is fluorinated drugs. For example, among the 59 drugs (39 of them are small molecule drugs) approved by FDA in 2018, 18 contain at least one fluorine atom; among the 48 drugs approved by FDA in 2019, 13 contain at least one fluorine atom [2]. Some representative fluorinated drugs approved in 2018 and 2019 are shown in Figure 1.1.

In spite of the importance of fluorinated molecules in modern society, naturally occurring organofluorine compounds are rare [3]. Basically, all the commercially supplied organofluorine compounds are manmade. Thus, the development of new reagents and reactions to introduce fluorine atoms or fluorine-containing moieties into organic molecules is one of the central goals in modern synthetic organofluorine chemistry.

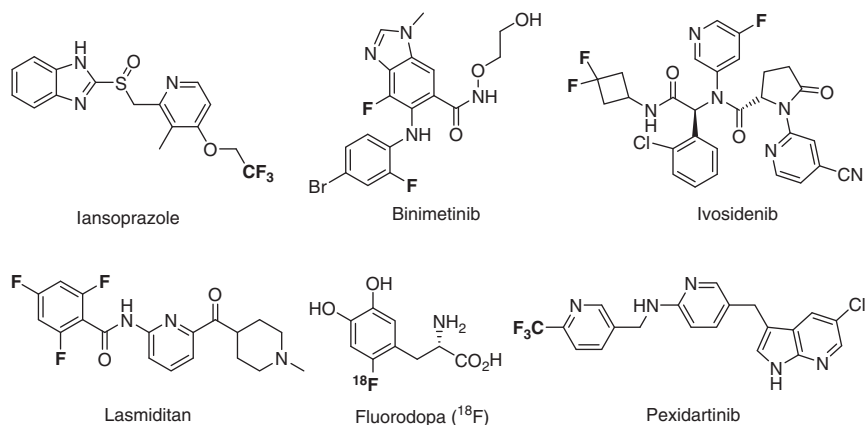


Figure 1.1 Fluorinated drugs newly approved by FDA in 2018 and 2019.

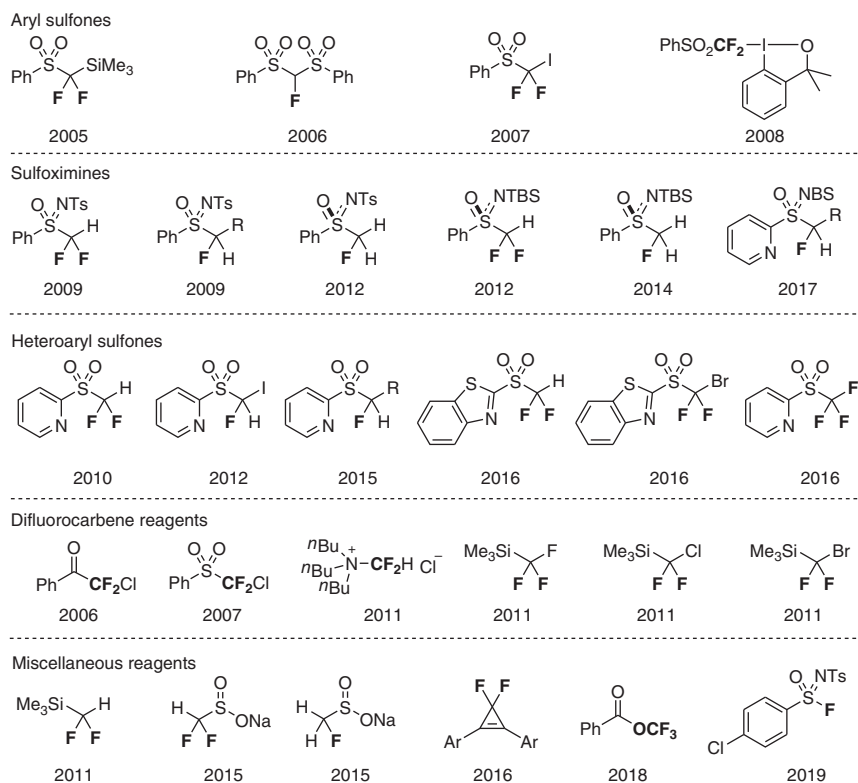


Figure 1.2 Organofluorine reagents developed or co-developed by us.

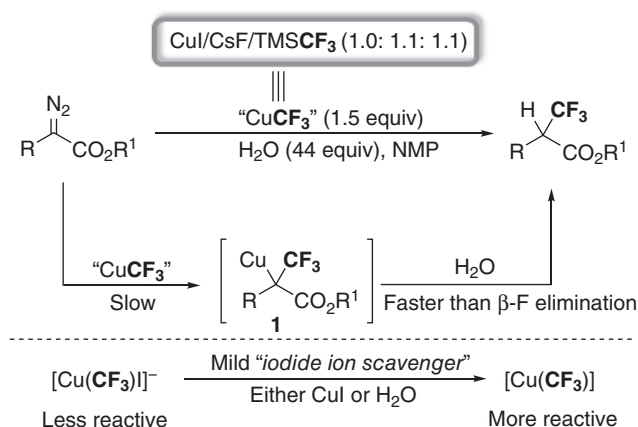
Over the past 15 years, our group has been interested in reaction mechanism-inspired synthetic organofluorine chemistry [4]. We have developed or co-developed a variety of reagents, including fluoroalkyl aryl sulfones [5], fluoroalkyl sulfoximines [6], fluoroalkyl heteroaryl sulfones [7], difluorocarbene reagents [8], fluorinated sulfinate salts [9], fluorinated esters [10], CpFluors [11], and SulfoxFluor [12], among others (for a review, see Ref. [4d]), for fluoroalkylation, fluoroolefination, and fluorination reactions (Figure 1.2). Our research program was triggered by two questions: (i) What are the unique features of organofluorine reactions (compared with regular organic reactions)? (ii) Is there any relationship among fluoroalkylation, fluoroolefination, and fluorination? In this review, we intend to answer these two questions by illustrating representative reagents and reactions developed (or co-developed) by us. In particular, understanding of the unique fluorine effects in organic reactions is helpful in addressing these two questions [4g].

1.2 The Unique Fluorine Effects in Organic Reactions

It is now gradually accepted that organofluorine reactions are usually distinct from regular organic reactions, and in many cases, fluorine substitution in an organic molecule imparts unique reactivity to the latter. As a result, direct application of the knowledge and experience acquired from regular organic reactions to organofluorine reactions often leads to failure or unexpected results. In this section, we provide some selected examples to highlight the unique features of organofluorine reactions. For more examples and discussions, one may refer to our recent tutorial review [4e].

1.2.1 Fluorine-Enabled Stability of “CuCF₃” in Water, and the Unusual Water-Promoted Trifluoromethylation

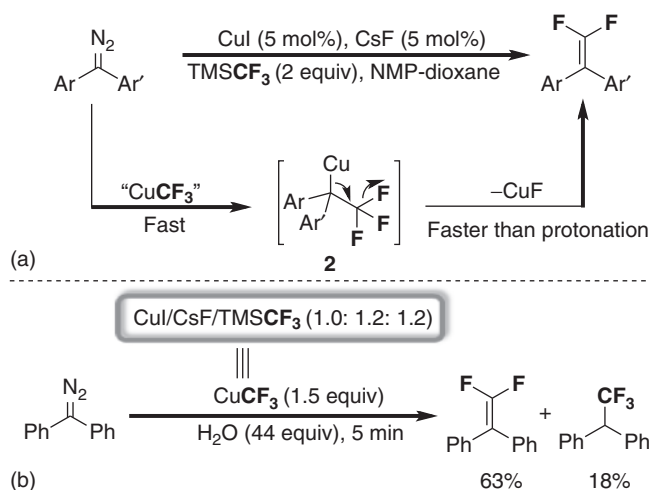
Organocopper reagents are widely used in organic synthesis [13]; however, these reagents are typically water sensitive. In 2012, we disclosed a water-promoted trifluoromethylation of α -diazo esters to access α -trifluoromethyl esters, representing the first example of fluoroalkylation of a non-fluorinated carbene precursor (Scheme 1.1) [14]. We found that “CuCF₃” (prepared from CuI/CsF/TMSCF₃) in *N*-methyl-2-pyrrolidone (NMP) is stable even in the presence of 66 equiv of water at room temperature within five hours and only about 5% of “CuCF₃” decomposed. Taking advantage of the unusual stability of “CuCF₃” in water (fluorine effect), we could therefore use water (CuI is also applicable) as the iodide scavenger to enhance the activity of “CuCF₃” prepared from CuI/CsF/TMSCF₃ significantly by changing “CuCF₃” in the form of [Cu(CF₃)I][−] to “ligandless” [Cu(CF₃)], which is more reactive toward α -diazo esters. From an organometallic chemistry point of view, water promotes the ligand exchange in “CuCF₃” by eliminating iodide, making the ligation of α -diazo esters to “CuCF₃” more favorable. The stability of “CuCF₃” toward water and the instability of alkylcopper intermediate **1** toward water ensure the success of this reaction.



Scheme 1.1 Water-promoted trifluoromethylation.

1.2.2 Fluorine Enables β -Fluoride Elimination of Organocopper Species

In the abovementioned water-promoted trifluoromethylation, a stoichiometric amount of copper is required and *gem*-difluoroolefin was found to be formed under strictly anhydrous conditions. Inspired by this fact, we developed a copper-catalyzed *gem*-difluoroolefination of diazo compounds, concisely [15] (Scheme 1.2a). In this catalytic reaction, diaryl diazomethanes were used instead of α -diazo esters for two reasons: (i) diaryl diazomethanes possess higher reactivity than α -diazo esters and can react with unactivated "CuCF₃" directly (without the need for eliminating ligated iodide in "CuCF₃"), making the addition of excess water or CuI as iodide scavenger no longer necessary, and (ii) diaryl-substituted alkylcopper intermediate

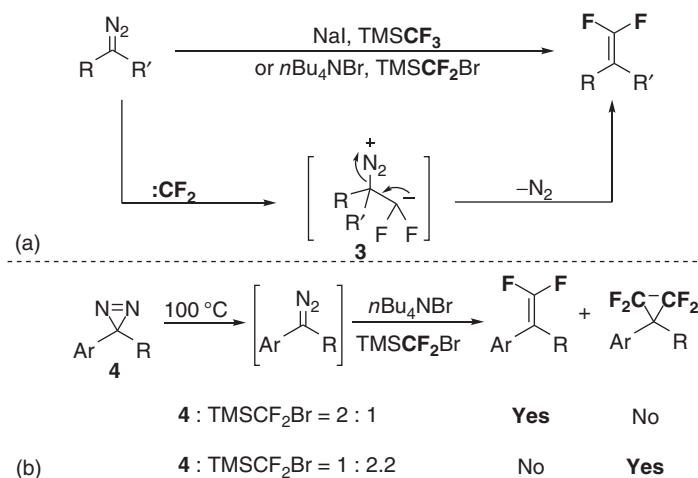


Scheme 1.2 Copper-catalyzed *gem*-difluoroolefination of diazo compounds.

2 readily undergoes β -fluoride elimination (even in the presence of excess amount of water) (Scheme 1.2b), which is critical to regenerate the copper catalyst and close the catalytic cycle.

1.2.3 The “Negative Fluorine Effect” Facilitates the α -Elimination of Fluorocarbanions to Generate Difluorocarbene Species

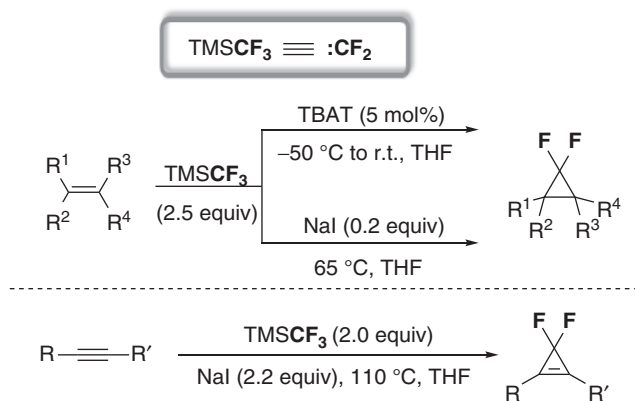
Based on the results described in Sections 1.2.1 and 1.2.2, we were able to achieve *gem*-difluoroolefination of diazo compounds under transition metal-free conditions via direct cross-coupling between a non-fluorinated carbene precursor from a diazo compound and difluorocarbene from TMSCF_3 or TMSCF_2Br (Scheme 1.3a) [16]. This reaction proceeds through nucleophilic addition of diazo compounds to difluorocarbene, followed by $\beta\text{-N}_2$ elimination from intermediate **3**, to form *gem*-difluoroolefins. The most significant feature of this protocol is the broad substrate scope (compared with our previous copper-catalyzed method of diazo compounds, which is only efficient for diaryl diazomethanes). α -Diazo acetates, diaryl diazomethanes, as well as diazirines are all suitable substrates. Moreover, by simply tuning the molar ratio of diazirines and TMSCF_2Br , either *gem*-difluoroolefins or tetrafluoropropanes can be obtained selectively (Scheme 1.3b). It should be noted that the *in situ* generation of difluorocarbene occurs via an α -elimination of fluoride ion from “ CF_3^- ” (in the case of TMSCF_3), or via an α -elimination of bromide ion from “ CF_2Br^- ” (in the case of TMSCF_2Br), which can be explained by the “negative fluorine effect (NFE),” that is, fluorine substitution on a carbanionic center will often have a negative (unfavorable) effect on the carbanion’s thermal stability and its nucleophilic reactions with many electrophiles.



Scheme 1.3 Transition metal-free *gem*-difluoroolefination of diazo compounds.

Alkylsilane reagents are useful in cross-coupling reactions. In the presence of a Lewis base, alkylsilane can act as “R[−]” donor to undergo alkylation under transition

metal catalysis [17]. In this context, fluoroalkylsilanes often serve as nucleophilic fluoroalkylation agents. For instance, (trifluoromethyl)trimethylsilane (TMSCF₃) has been recognized as an efficient “CF₃[−]” donor since 1989 [18] and has been studied extensively ever since [19]. However, because of the fluorine substitution, TMSCF₃ is not merely a “CF₃[−]” equivalent. In 2011, our group, in collaboration with the Prakash group, found that TMSCF₃ is also an efficient difluorocarbene precursor [8d]. By employing nonmetallic fluoride TBAT (tetrabutylammonium triphenyldifluorosilicate) as an initiator at low temperature (−50 °C to r.t.) or NaI as a promoter at higher temperature (65 or 110 °C), efficient synthesis of *gem*-difluorocyclopropa(e)nes can be achieved with TMSCF₃ (Scheme 1.4).

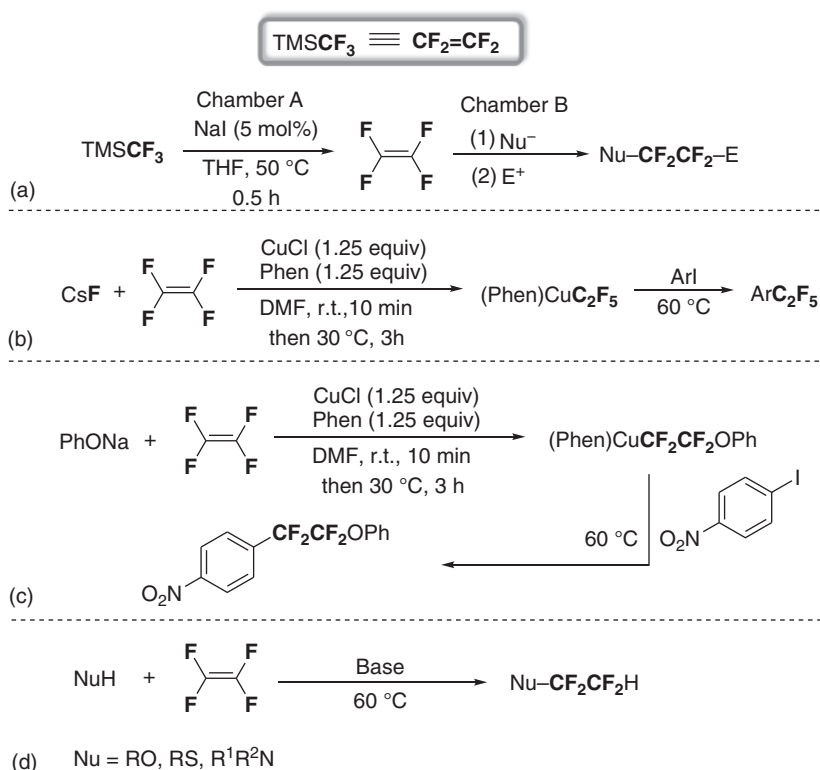


Scheme 1.4 TMSCF₃ as a difluorocarbene precursor for *gem*-difluorocyclopropa(e)nation.

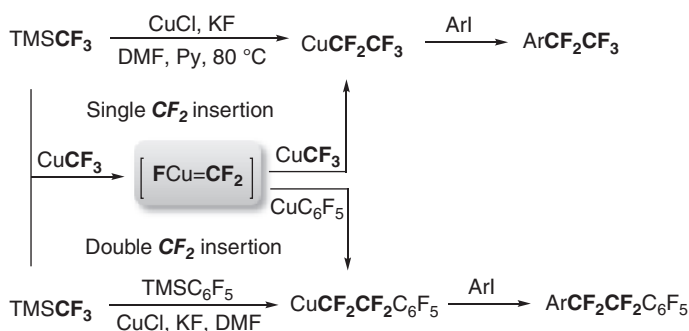
Difluorocarbene species derived from TMSCF₃ can dimerize to form tetrafluoroethylene (TFE) in an efficient and mild manner, providing a convenient and safe protocol for the generation and handling of TFE in academic laboratories (Scheme 1.5a) [20]. Previously, TFE was normally inaccessible for common laboratories due to its suspected carcinogenic and explosive nature. The application of on-site prepared TFE was demonstrated by the pentafluoroethylation and aryloxytetrafluoroethylation of aryl iodides and 1,1,2,2-tetrafluoroethylation of phenols, alcohols, thiophenols, and heterocyclic amines (Scheme 1.5b–d).

More recently, we also accomplished fluorocarbon chain elongation process with TMSCF₃ as a difluorocarbene source. Selective one-carbon elongation from trifluoromethyl to pentafluoroethyl [21], and two-carbon elongation from pentafluorophenyl to perfluorophenylethyl [22] were efficiently realized under copper-mediated conditions, providing a non-TFE pathway (Scheme 1.6). The key issue of this process is harnessing “CuCF₃” as a copper difluorocarbene (“Cu=CF₂”) equivalent.

TMSCF₂Br was developed by us as a privileged difluorocarbene reagent, which has been used to difluoromethylate a plethora of O-, S-, N-, P-, and C-nucleophiles as well as to cyclopropa(e)nate alkenes or alkynes [8e, f, 23] (Scheme 1.7). Because of the much better leaving ability of Br[−] than F[−], the life time of BrCF₂[−] is short enough

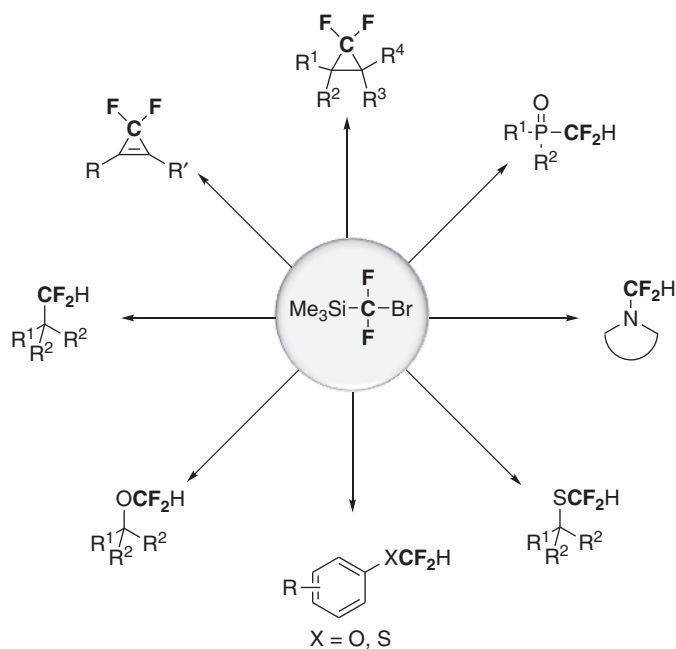


Scheme 1.5 TMSCF₃ as tetrafluoroethylene precursor.

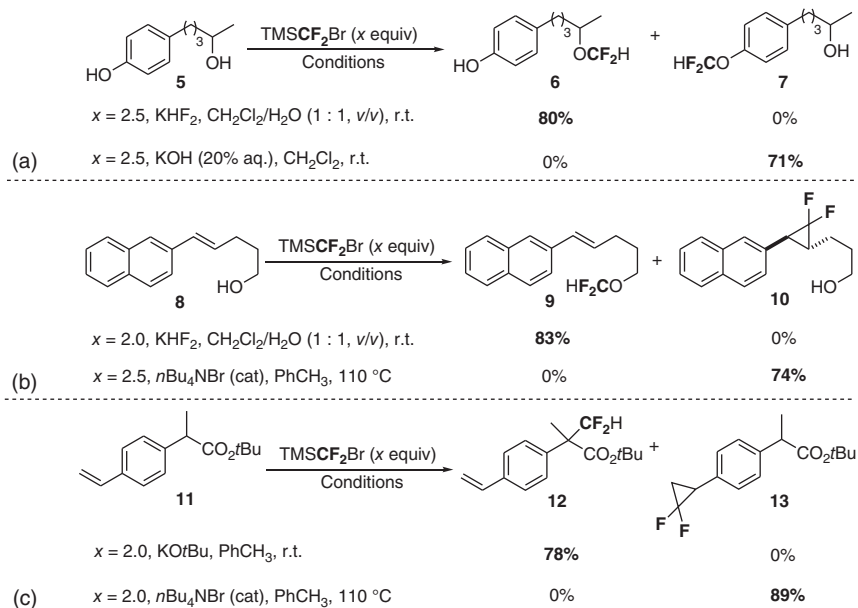


Scheme 1.6 TMSCF₃ for fluorocarbon elongation.

that it readily eliminates Br[−] to produce difluorocarbene even in the presence of large amount of water or acid. TMSCF₂Br can generate difluorocarbene under a wide range of conditions, ranging from strongly basic to weakly acidic, from aqueous to anhydrous, and from low temperatures to high temperatures [8e, f, 23, 24]. This unique feature renders TMSCF₂Br particularly versatile and makes its orthogonal reactions with ambident substrates possible [23] (Scheme 1.8).



Scheme 1.7 The application of TMSCF_2Br as a difluorocarbene reagent.



Scheme 1.8 Orthogonal reactivity of TMSCF_2Br with ambident substrates.

Let us take alkene-ester substrate **11** (see Scheme 1.8c) as an example to showcase the unusual orthogonal reactivity of TMSCF_2Br with different functional groups: in the presence of KO^tBu , the C—H bond α to the ester group could undergo deprotonation to generate the corresponding nucleophilic carbanion, which is highly reactive toward difluorocarbene, while the alkene group shows low reactivity toward difluorocarbene at room temperature because elevated temperature is required to conquer the substantial activation barrier for most alkenes (except the most electron-rich ones); when using $n\text{Bu}_4\text{NBr}$ to activate TMSCF_2Br at elevated temperature (in this case, 110°C), the alkene could efficiently react with the difluorocarbene, while the C—H bond α to the ester group is unreactive toward difluorocarbene in the absence of $n\text{Bu}_4\text{NBr}$ at high temperature.

1.2.4 Tackling the β -Fluoride Elimination of Trifluoromethoxide Anion via a Fluoride Ion-Mediated Process

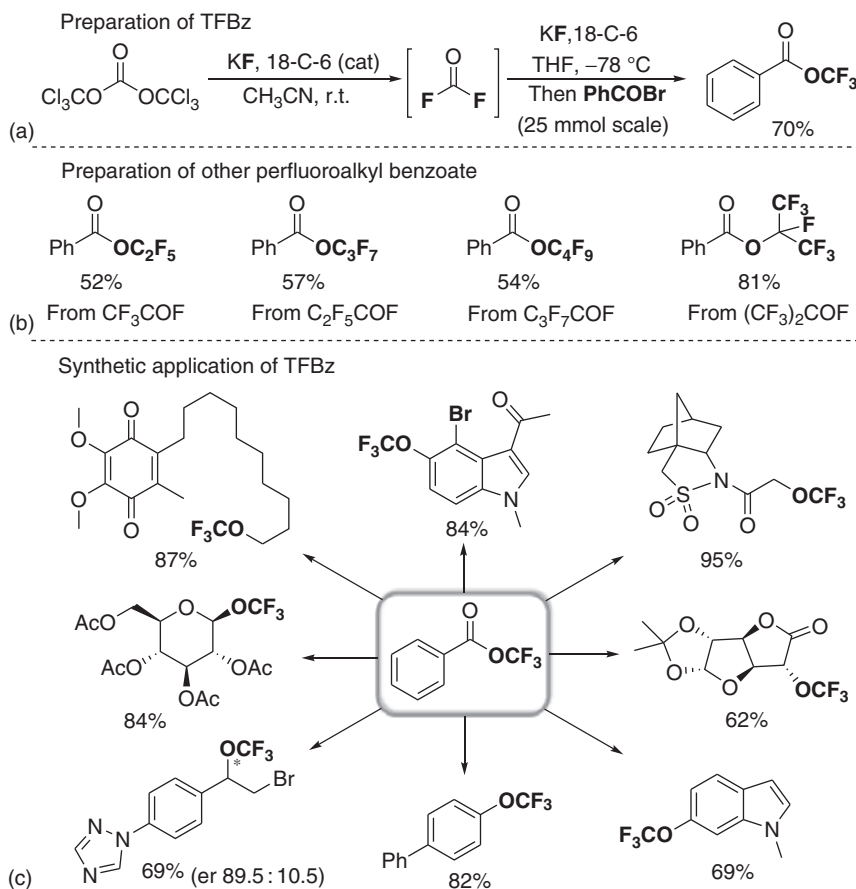
The trifluoromethoxy (CF_3O) group is increasingly important in drug development. Although methanol is definitely stable at room temperature, its perfluorinated analog, CF_3OH , is unstable at room temperature and decomposes (eliminating HF to form COF_2) even at -20°C [25]. Therefore, trifluoromethoxylation with CF_3OH is impractical and the development of new trifluoromethoxylation reagents is highly desired. In 2018, we developed trifluoromethyl benzoate (TFBz) as a new type of shelf-stable trifluoromethoxylation reagent [10]. TFBz can be readily prepared from triphosgene, KF, and PhCOBr , with COF_2 being an *in situ*-generated key intermediate (Scheme 1.9a). Notably, all the fluorine atoms in TFBz come from the cheap fluoride source KF. A variety of other perfluoroalkoxylation reagents can be obtained in a similar manner (Scheme 1.9b). The versatility of TFBz as a trifluoromethoxylation reagent was demonstrated by trifluoromethoxylation-halogenation of arynes, nucleophilic substitution of alkyl(pseudo)halides, cross-coupling with aryl stannanes, and asymmetric difunctionalization of alkenes (Scheme 1.9c).

1.3 The Relationships Among Fluoroalkylation, Fluoroolefination, and Fluorination

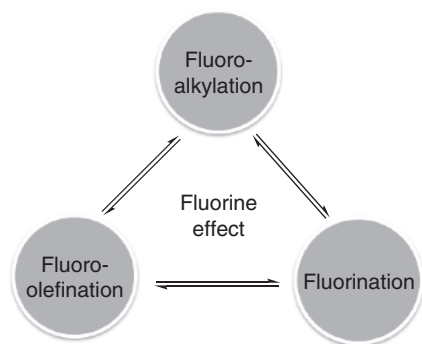
Although numerous fluoroalkylation, fluoroolefination, and fluorination methods have been elegantly established, the relationships among these three reactions have been ignored. As part of our longstanding interest in studying new fluoroalkylation, fluoroolefination, and fluorination reagents and reactions by probing the unique fluorine effects, we realized that there are close relationships among fluoroalkylation, fluoroolefination, and fluorination in many cases (Scheme 1.10). In this section, we intend to discuss these relationships by providing some examples.

1.3.1 From Fluoroalkylation to Fluoroolefination

A typical olefination reaction is started with a nucleophilic alkylation step (Scheme 1.11a). It is also true for fluoroolefination reactions. $\text{PhSO}_2\text{CF}_2\text{H}$ is a

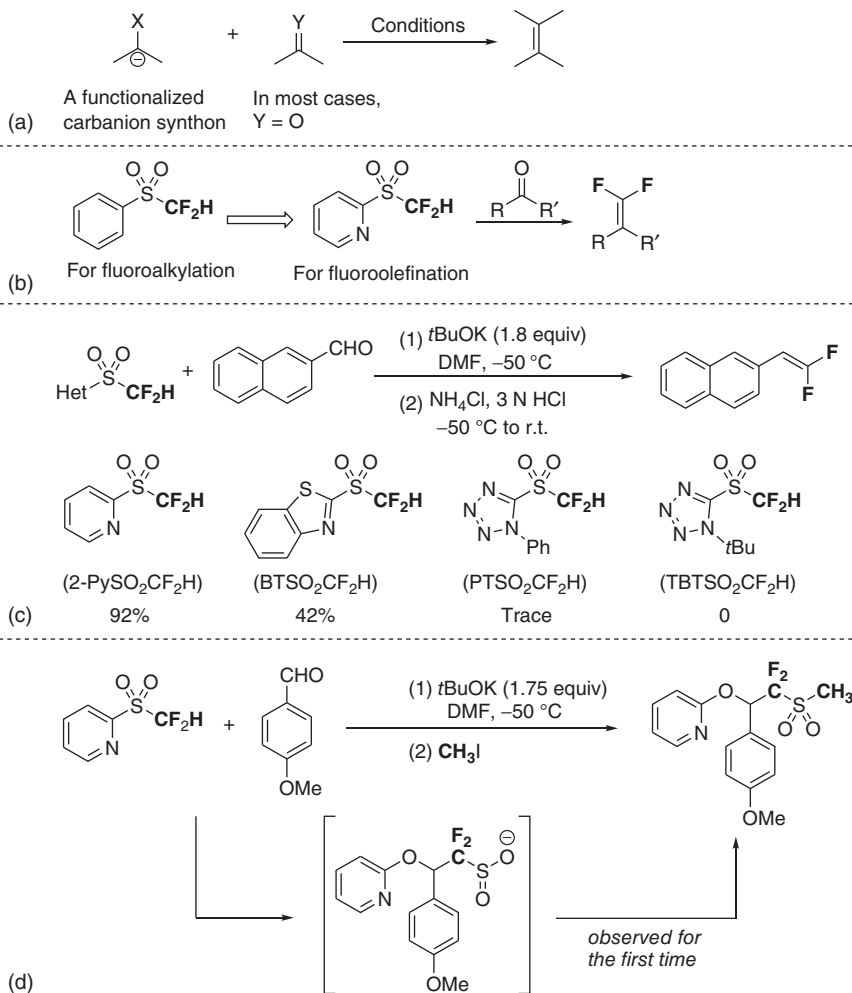


Scheme 1.9 Synthesis and application of TFBz as a new trifluoromethoxylation reagent.



Scheme 1.10 The relationships among fluoroalkylation, fluoroolefination, and fluorination.

powerful difluoromethylation reagent [26] and was studied extensively by us and others [5b, 27]. Inspired by the Julia–Kocienski reaction that uses heteroaryl sulfones for the synthesis of olefins [28], it is natural to envision whether a fluorinated version can be achieved for fluoroolefination. Indeed, by changing phenyl to 2-pyridyl, we developed difluoromethyl 2-pyridyl sulfone (2-PySO₂CF₂H) as a novel and efficient *gem*-difluoroolefination reagent [7a] (Scheme 1.11b).



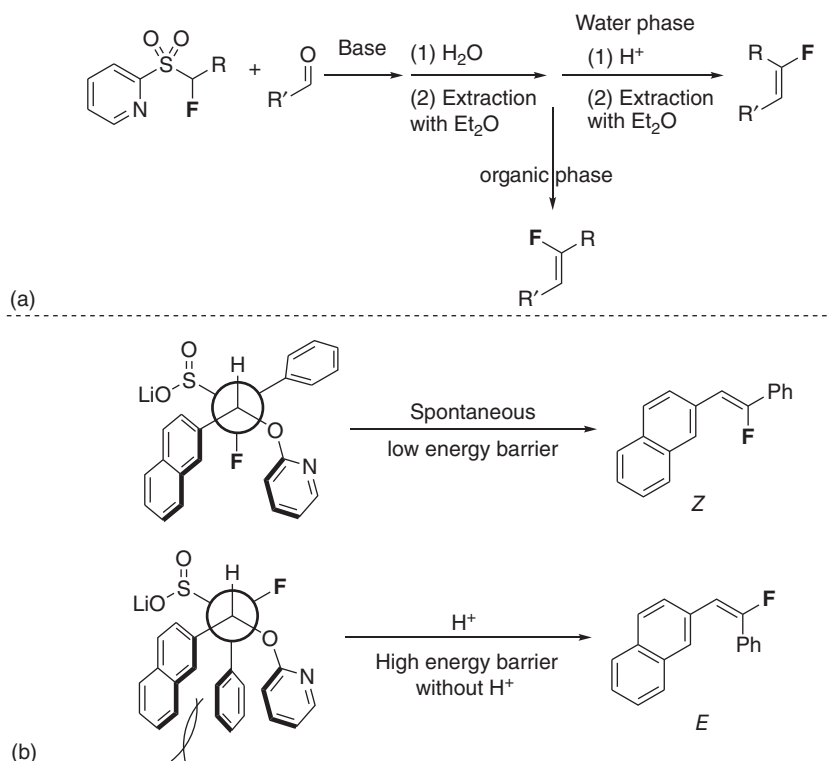
Scheme 1.11 The development of 2-PySO₂CF₂H for *gem*-difluoroolefination.

Notably, there is a unique fluorine effect in this olefination reaction. In non-fluorinated Julia–Kocienski olefination reactions, 2-pyridyl sulfones generally give lower yields of products than other heteroaryl sulfones, such as 1,3-benzothiazol-2-yl (BT), 1-phenyl-1*H*-tetrazol-5-yl (PT), and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) sulfones [28]. However, the Julia–Kocienski type difluoroolefination reaction shows unusual reactivity: 2-PySO₂CF₂H shows the highest reactivity,

but $\text{PTSO}_2\text{CF}_2\text{H}$ and $\text{TBTSO}_2\text{CF}_2\text{H}$ possess almost no reactivity (Scheme 1.11c). This sharp contrast between $2\text{-PySO}_2\text{CF}_2\text{H}$ and the other two reagents may be attributed to the much higher stability and better nucleophilicity of $2\text{-PySO}_2\text{CF}_2^-$ than other $\text{HetSO}_2\text{CF}_2^-$ anions. Another important feature of this reaction is that the sulfinate salt intermediate (Scheme 1.11d), which has never been observed in regular Julia–Kocienski reactions, was detected and captured by us for the first time, highlighting that organofluorine research enables intriguing insights into regular organic reactions.

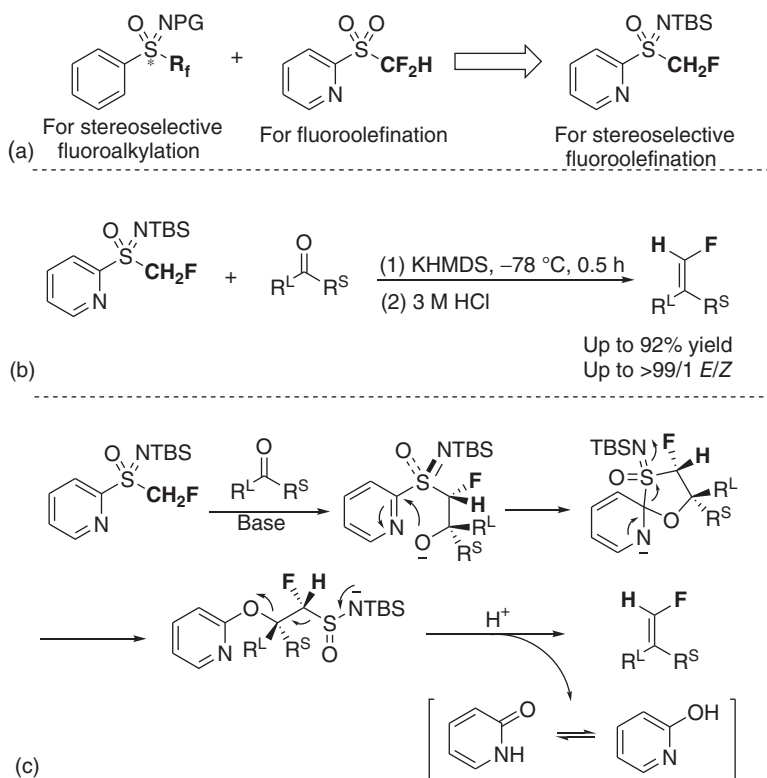
Although an efficient *gem*-difluoroolefination has been realized with $2\text{-PySO}_2\text{CF}_2\text{H}$, when it comes to monofluoroolefination, the issue of how to control the stereoselectivity arose.

In 2015, “a magic reaction” was discovered by us by the reaction of $2\text{-PySO}_2\text{CHFR}$ and aldehydes to prepare monofluoroalkenes [7c]. In this reaction, both *Z*- and *E*-isomers can be obtained and easily separated in an efficient and stereoselective manner (Scheme 1.12a). The key issue of this unique reaction is the significant stability difference between the two diastereoisomeric sulfinate salt intermediates (Scheme 1.12b), which enables spontaneous resolution and phase labeling of the two diastereoisomeric sulfinate salts, thus allowing separation of *Z*- and *E*-monofluoroalkenes by liquid–liquid extraction.



Scheme 1.12 Spontaneous resolution and phase separation to deliver *Z*- and *E*-monofluoroalkenes.

The synthesis of terminal monofluoroalkenes was regarded as a formidable challenge because of the minimal energy difference between the two stereoisomers. Encouraged by the excellent stereocontrol in the fluoroalkylation of carbonyl compounds with chiral sulfoximine reagents [6c–e] and the efficient fluoroolefination with 2-pyridyl sulfone reagents [7a] (Scheme 1.13a), we developed a novel heteroaryl sulfoximine reagent, *S*-monofluoromethyl-*S*-(2-pyridyl)sulfoximine, to access di- and trisubstituted terminal monofluoroalkenes with high stereoselectivity, concisely [6f] (Scheme 1.13b). The reaction proceeds through a highly diastereoselective addition of *S*-monofluoromethyl-*S*-(2-pyridyl)sulfoximine to carbonyls, followed by Smiles rearrangement and anti-1,2-elimination (Scheme 1.13c). The 2-pyridyl group plays a critical role in promoting the olefination, whereas the sulfoximidoyl group is pivotal for controlling the stereoselectivity.

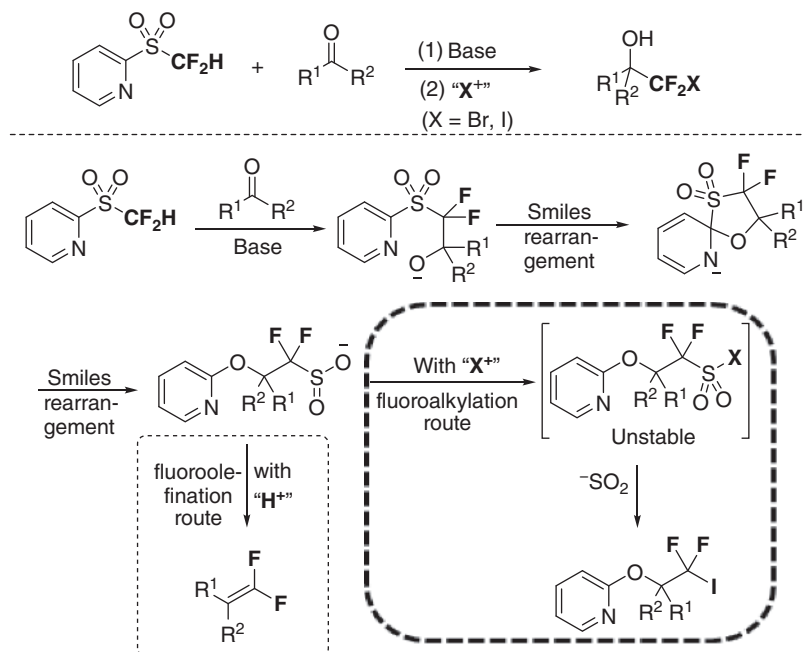


Scheme 1.13 The development of *S*-monofluoromethyl-*S*-(2-pyridyl)sulfoximine for stereoselective monofluoroolefination.

1.3.2 From Fluoroolefination to Fluoroalkylation

As mentioned in Section 1.3.1, 2-PySO₂CF₂H was developed as a new *gem*-difluoroolefination reagent and the sulfinate salt intermediate was found to be relatively stable and can be observed (see Scheme 1.11). Based on this fact, we realized a

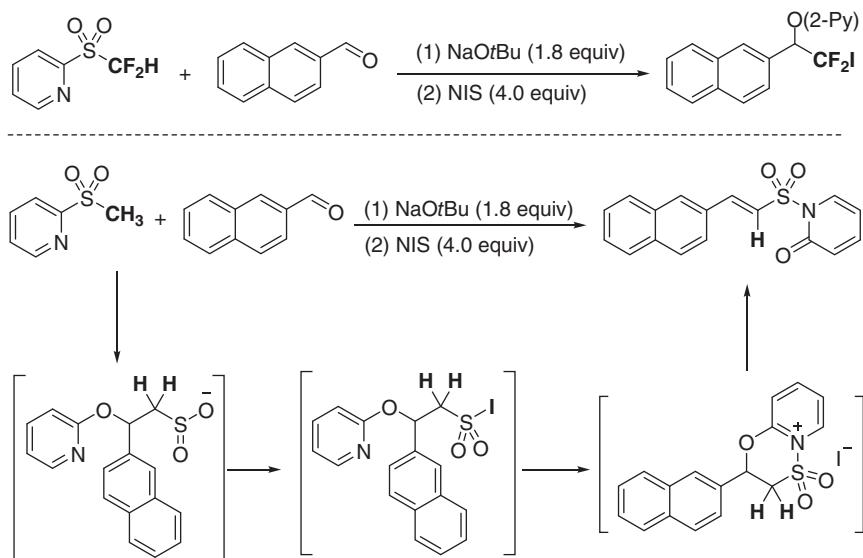
formal nucleophilic iodo- and bromodifluoromethylation of carbonyl compounds with 2-PySO₂CF₂H via *in situ* halogenation of the sulfinate salt intermediates delivered from Smiles rearrangement (Scheme 1.14). By simply using “X⁺” reagents to quench the reaction instead of “H⁺,” we could, therefore, tune the pathway from fluoroolefination to fluoroalkylation.



Scheme 1.14 Halodifluoromethylation with 2-PySO₂CF₂H.

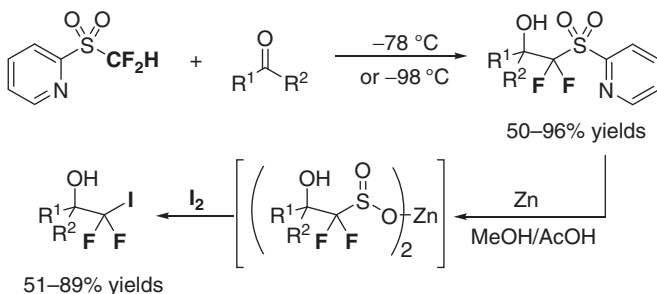
Remarkably, a unique fluorine effect was observed in this reaction [29]. Unlike the reaction between 2-PySO₂CF₂H and carbonyls (after a subsequent halogenation) giving formal nucleophilic halodifluoromethylated products, a similar reaction using non-fluorinated 2-PySO₂CH₃ results in a totally different kind of product, a *E*-alkene (Scheme 1.15). This product may be formed via intramolecular cyclization of the *in situ*-generated sulfonyl iodide intermediate produced from iodination of the sulfinate salt intermediate, followed by an elimination process. The change of reaction pathway using 2-PySO₂CH₃ is probably due to the different stability between the non-fluorinated sulfonyl iodide intermediate and the fluorinated ones.

As we can see from the mechanism shown in Scheme 1.14, Smiles rearrangement is one of the key steps in Julia–Kocienski *gem*-difluoroolefination reaction. In order to realize fluoroalkylation with 2-PySO₂CF₂H, inhibiting the Smiles rearrangement is a viable strategy. Indeed, by lowering the temperature to –78 or –98 °C and changing the solvent from DMF (*N,N*-dimethylformamide) to THF (tetrahydrofuran), the Smiles rearrangement can be inhibited and the nucleophilic addition products can be obtained in good yields [30] (Scheme 1.16). The obtained addition products can



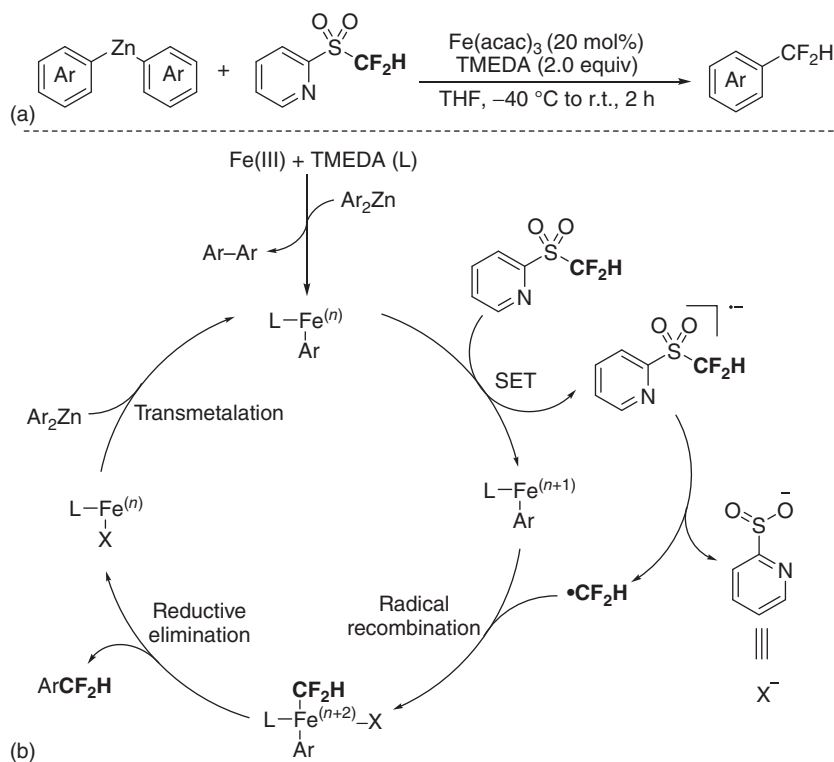
Scheme 1.15 Different reactivity of 2-PySO₂CF₂H and 2-PySO₂CH₃.

readily undergo depyridination to give sulfinate salts, which can be transformed to iododifluoromethylated products by treating with I₂.



Scheme 1.16 Direct nucleophilic addition of 2-PySO₂CF₂H to carbonyls for iododifluoromethylation via non-Smiles rearrangement pathway.

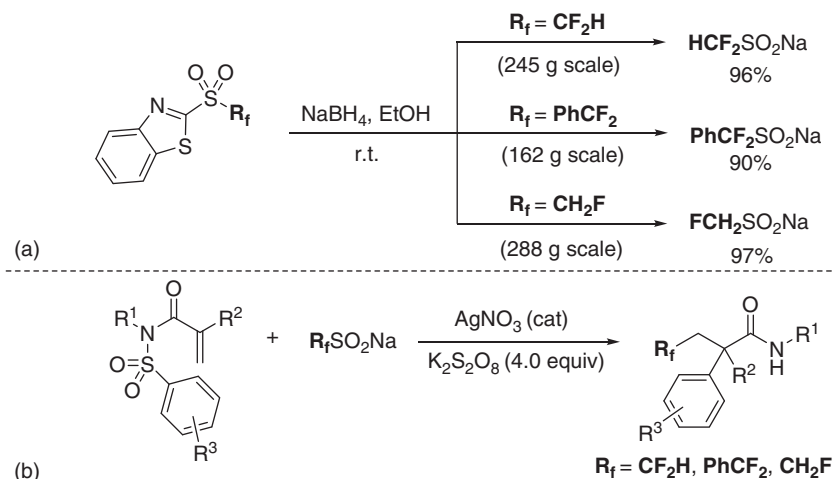
The abovementioned fluoroalkylation strategies with 2-PySO₂CF₂H are largely dependent on the nucleophilic 2-PySO₂CF₂[−] anion. However, difluoromethylation with 2-PySO₂CF₂H via direct CF₂H transfer is also possible. In 2018, we reported the first iron-catalyzed difluoromethylation of arylzincs with 2-PySO₂CF₂H, providing a facile method to structurally diverse difluoromethylated arenes at low temperature [31] (Scheme 1.17a). Mechanistic studies revealed that a difluoromethyl radical is involved in the reaction, and the direct transfer of CF₂H as a whole was supported by deuterium labeling experiment. A proposed catalytic cycle is shown in Scheme 1.17b.



Scheme 1.17 Iron-catalyzed difluoromethylation of arylzincs with 2-PySO₂CF₂H.

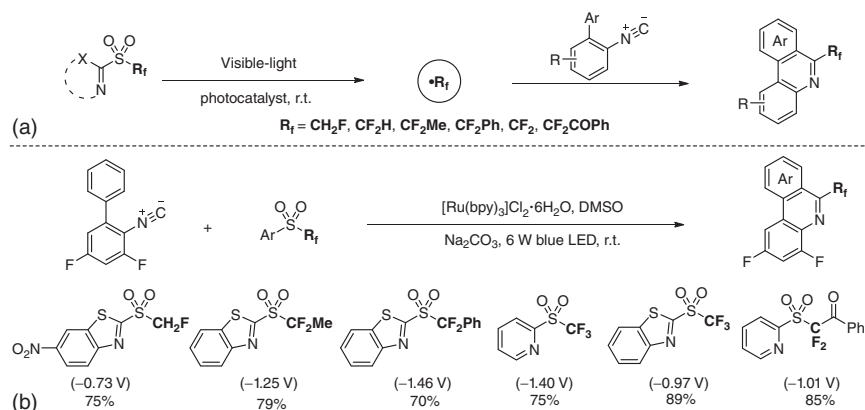
Except for 2-PySO₂CF₂H, many other fluorinated heteroaryl sulfones have been extensively investigated. As we can see from Scheme 1.11c, although BTSO₂CF₂H was found to be an inefficient fluoroolefination reagent, its use for radical fluoroalkylation is a great success. In 2015, we developed a novel method for the preparation of sodium fluoroalkanesulfonates by the reduction of the corresponding benzo[d]thiazol-2-yl sulfones (BTSO₂R_f) [9]. This method enables a highly efficient and rapid large-scale synthesis of sodium di- and monofluoromethanesulfonates (Scheme 1.18a). Synthetic application of these sulfonates in radical fluoroalkylation is exemplified by the silver-catalyzed cascade fluoroalkylation/aryl migration/SO₂ extrusion of conjugated *N*-arylsulfonylated amides (Scheme 1.18b).

The versatility of heteroaryl sulfones as fluoroalkyl radical precursors may be best illustrated by the readily tunable reactivity of heteroaryl sulfones that can generate a wide range of fluoroalkyl radicals such as monofluoromethyl, difluoromethyl, 1,1-difluoroethyl, phenyldifluoromethyl, benzoyldifluoromethyl, and trifluoromethyl radicals via visible light photoredox catalysis under mild conditions [7d]. The synthetic application of heteroaryl sulfones in radical fluoroalkylation of isocyanides was demonstrated to highlight the versatility of heteroaryl sulfones as fluoroalkyl radical precursors (Scheme 1.19a). The most prominent feature using heteroaryl sulfones as fluoroalkyl radical precursors is that they are



Scheme 1.18 The preparation and application of sodium fluoroalkanesulfonates.

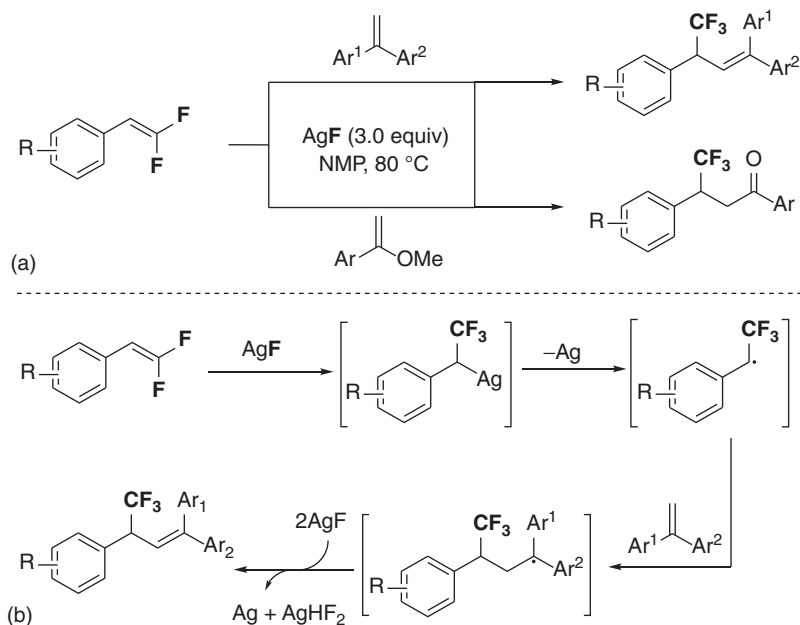
reactivity-tunable. By slightly changing the heteroaryl rings, the redox potential of fluorinated heteroaryl sulfones can be varied, ensuring the efficient generation of various fluoroalkyl radicals (Scheme 1.19b).



Scheme 1.19 Heteroaryl sulfones as fluoroalkyl radical precursors.

The combination of *gem*-difluoroolefination and fluorination can also be used as a good synthetic strategy for fluoroalkylation. In 2015, we reported an AgF-mediated fluorination of *gem*-difluoroolefination, followed by subsequent cross-coupling with a non-fluorinated olefin, to access α -CF₃ alkenes and β -CF₃ ketones [32] (Scheme 1.20a). Mechanistic studies revealed that α -CF₃-substituted benzyl radicals are involved, concluded by 2,2,6,6-tetramethylpiperidine 1-oxyl (TMEPO) trapping and radical clock experiments. A proposed mechanism is shown in Scheme 1.20b: addition of AgF to *gem*-difluoroolefination gives rise to α -CF₃-benzylsilver intermediate, which can undergo C—Ag bond homolysis to

give α -CF₃-substituted benzyl radical. Addition of this radical to non-fluorinated alkene generates a new radical, which is oxidized to a carbocation followed by deprotonation to afford α -CF₃ alkene.

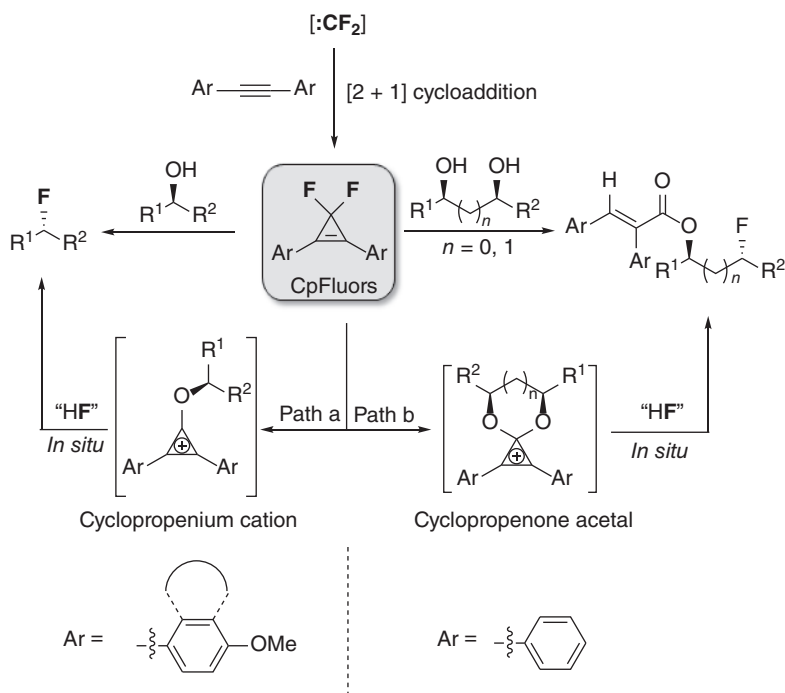


Scheme 1.20 AgF-mediated cross-coupling of *gem*-difluoroolefins and non-fluorinated olefins.

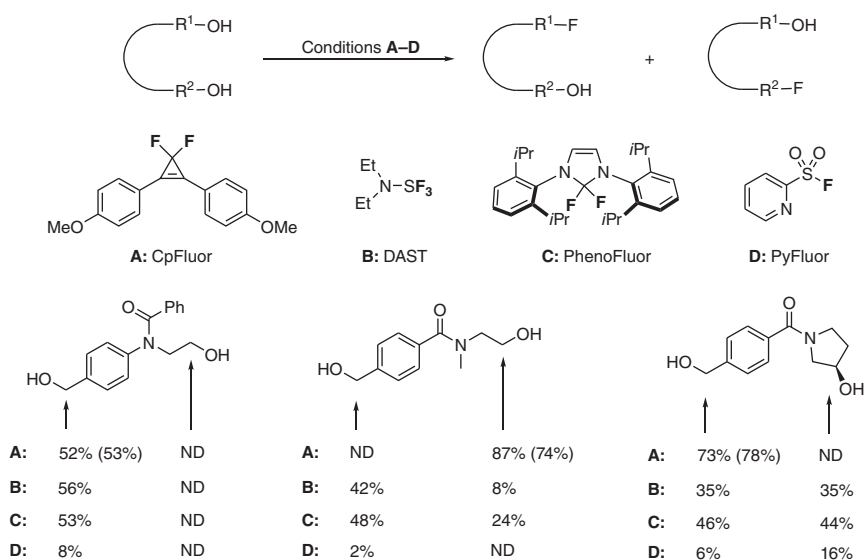
1.3.3 From Fluoroalkylation to Fluorination

3,3-Difluorocyclopropenes are readily available by the reaction of alkynes and difluorocarbene reagents, such as TMSCF₃, TMSCF₂Cl, and TMSCF₂Br [8d–f]. Based on the fact that 3,3-difluorocyclopropenes can be hydrolyzed to cyclopropanones in wet atmosphere and Lambert's elegant work in deoxychlorination of alcohols using 3,3-dichlorocyclopropenes [33], we successfully realized the use of safe and readily available difluorocarbene reagents for fluorination by means of 3,3-difluorocyclopropenes [11] (Scheme 1.21). To ensure the high efficiency of deoxyfluorination of aliphatic alcohols with 3,3-difluorocyclopropenes, the reaction should be carried out in a non-glass vessel because the *in situ*-generated HF will be consumed by the glassware (mainly SiO₂), thereby retarding the desired reaction.

The electronic nature of CpFluors is critical. For monoalcohols, utilizing electron-rich aryl substituent on CpFluors to stabilize the cyclopropenium cation intermediate is a key issue (Scheme 1.21, path a). However, for 1,2- and 1,3-diols, the reaction proceeds through cyclopropanone acetal intermediates, and is thus less dependent on the electronic nature of CpFluors (Scheme 1.21, path b). The most intriguing feature of CpFluors is that they are more sensitive to the electronic nature of alcohols than many other deoxyfluorination reagents; hence, selective



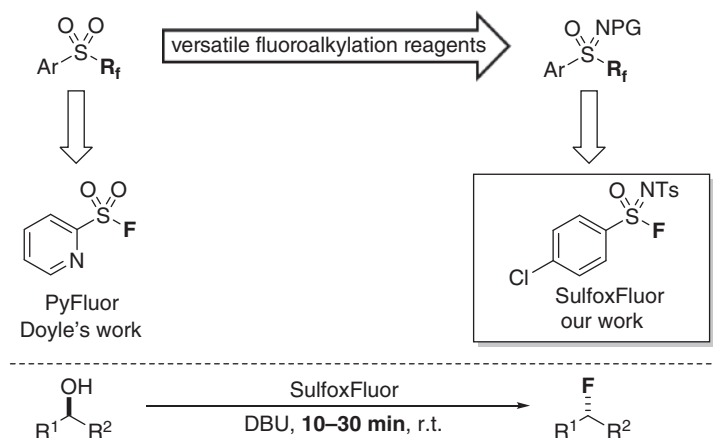
Scheme 1.21 Deoxyfluorination of alcohols with 3,3-difluorocyclopropenes.



Scheme 1.22 Selective deoxyfluorination of longer diols.

fluorination of electron-rich OH groups of longer diols (non-1,2- and 1,3-diols) can be realized (Scheme 1.22).

Based on our work on fluoroalkylation chemistry using fluorinated sulfones and sulfoximines, and also inspired by Doyle's work [34], we developed *N*-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor) as a new bench-stable and highly reactive deoxyfluorination reagent [12] (Scheme 1.23). The prominent features of SulfoxFluor include a rapid fluorination rate, fluorine economy, selective monofluorination at the least steric hindered site of diols, and high fluorination/elimination selectivity.



Scheme 1.23 Development of SulfoxFluor for deoxyfluorination.

1.4 Conclusions

Our efforts in the development of novel reagents for fluoroalkylation, fluoroolefination, and fluorination by probing the unique fluorine effects have been summarized. During our research work, we realized that (i) there are often unique fluorine effects in organic reactions, (ii) tackling the unique fluorine effect and unveiling the relationships among fluoroalkylation, fluoroolefination, and fluorination enable us to develop various reagents for synthetic organofluorine chemistry, and (iii) organofluorine reactions are not only practically useful but also provide fundamentally intriguing insights into generally organic reactions.

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