

## Good Partnership between Sulfur and Fluorine: Sulfur-Based Fluorination and Fluoroalkylation Reagents for Organic Synthesis

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Special Issue: 2015 Fluorine Chemistry

Received: May 1, 2014

Published: August 21, 2014

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## 1. INTRODUCTION

Fluorine, often called as “a small atom with a big ego”,<sup>1</sup> lies in the second row and the 17th column in the periodic table of the chemical elements. This unique position in the periodic table determines many intrinsic properties of fluorine, such as high electronegativity (4.0 in Pauling scale), small atomic radius ( $r_v = 1.47 \text{ \AA}$ ), and strong C–F bond strength (averages about 116 kcal/mol), among others.<sup>2</sup> More interestingly, the incorporation of fluorine atoms or fluorinated moieties into an organic molecule can often lead to profound changes of the latter’s physical, chemical, and biological properties.<sup>1–8</sup> However, although fluorine is the most abundant halogen and ranks number 13 among all elements in the earth’s crust, the naturally occurring organofluorine compounds (organic compounds bearing C–F bond) are rare.<sup>9,10</sup> Therefore, the development of efficient ways of introducing fluorine into organic compounds has become one of the hottest areas of organic synthesis these days.<sup>11–13</sup>

The synthesis of organofluorine compounds is largely based on the development of practical fluorination and fluoroalkylation reagents and reactions. In 1835, Dumas and Péligot described probably the first synthesis of an organofluorine compound (fluoromethane) using potassium fluoride and dimethyl sulfate.<sup>14,15</sup> Before 1960s, more attention was paid to the fluorination (C–F bond formation) reactions, and various inorganic fluorides (such as anhydrous HF,  $\text{SbF}_3$ , KF,  $\text{BF}_3$ , tetrafluoroborates,  $\text{F}_2$ , and  $\text{CoF}_3$ ) were used as fluorination reagents in the C–F bond forming reactions, including the well-recognized Swarts reaction, Balz-Schiemann reaction, Halex reaction, and Simons electrochemical fluorination.<sup>14–17</sup> During the past half century, various fluoroalkylation reagents

and reactions (such as perfluoroalkylation, trifluoromethylation, difluoromethylation, and monofluoromethylation) have been extensively investigated, while the more user-friendly fluorination reagents were also quickly developed during this period.<sup>2–8,11–14</sup> Two excellent reviews regarding the state-of-the-art of reagents and reactions in the synthetic organofluorine chemistry have been recently published.<sup>17</sup>

When looking into all these known fluorination and fluoroalkylation reagents, one may quickly realize an intriguing phenomenon—there are a long list of sulfur-based inorganic and organic compounds that serve as powerful fluorination and fluoroalkylation reagents (Figure 1). It is obvious that the combination of the “soft” sulfur and “hard” fluorine in these reagents,<sup>18</sup> along with the rich chemistry of sulfur-containing species,<sup>19</sup> make them ideal for transferring fluorine atoms or fluoroalkyl groups under different reaction conditions in organic synthesis. In retrospect, the first sulfur-based reagent in this series is sulfur tetrafluoride ( $\text{SF}_4$ ), which was disclosed as a robust deoxygenative nucleophilic fluorinating agent in 1958.<sup>20</sup> Thereafter, safer  $\text{SF}_4$ -derived fluorination reagents were discovered and commercialized, including *N,N*-diethylaminosulfur trifluoride (DAST),<sup>21,22</sup> bis(2-methoxyethyl)-aminosulfur trifluoride (Deoxo-Fluor),<sup>23</sup> and more recently 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead),<sup>24</sup> (diethylamino)difluorosulfonium tetrafluoroborate (XtalFluor-E) and difluoro(morpholino)sulfonium tetrafluoroborate (XtalFluor-M).<sup>25</sup> On the other hand, the first sulfur-based fluoroalkylation reagent is probably the perfluoroalkanesulfonyl chloride ( $R_3\text{SO}_2\text{Cl}$ ), which was used in free radical perfluoroalkylation of alkenes.<sup>26</sup> During the past decade, a variety of fluorinated sulfones, sulfoxides, sulfides, and sulfoximines have been extensively developed as either nucleophilic or electrophilic fluoroalkylation reagents. In this review, we wish to give an overview of the sulfur-based fluorination and fluoroalkylation reagents and related reactions for organic synthesis in a time frame from 1958 to June 2014.<sup>27</sup>

## 2. SULFUR-BASED FLUORINATION REAGENTS

Nucleophilic fluorination is one of the most effective approaches to synthesize organic fluorides, which not only provides various fluorinated building blocks (including fluoroalkylation reagents) for further elaborations, but also is able to directly introduce fluorine atom(s) to complex molecules that are of interest in pharmaceutical and agrochemical research and development.<sup>4,11a,21,28–33</sup> Among various nucleophilic fluorination reagents, the  $\text{SF}_4$ -derived reagents (see Figure 1), such as DAST and Deoxo-Fluor, are widely used deoxygenative fluorination reagents for alcohols, aldehydes, ketones, and carboxylic acids without preactivation, thus providing a streamline method to prepare organic fluorides from the readily available starting materials.<sup>22</sup> The driving force for this deoxygenative fluorination is the strong affinity of the sulfur atom toward oxygen (S–O bond 124 kcal/mol vs S–F bond 82 kcal/mol).<sup>34</sup> To date, the  $\text{SF}_4$ -based deoxygenative fluorination reagents have evolved for several generations,<sup>11k</sup> and the synthetic applications of  $\text{SF}_4$  and its derivatives DAST and Deoxo-Fluor have been extensively investigated by many research groups.<sup>22,28–33</sup> Recently, the  $\text{SF}_4$  derivatives XtalFluor-E and XtalFluor-M<sup>25</sup> as well as 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead)<sup>24</sup> have emerged as a new generation of selective fluorinating agents due to their relatively high thermal stability and robust fluorination ability. In addition, some other sulfur-based compounds, such as

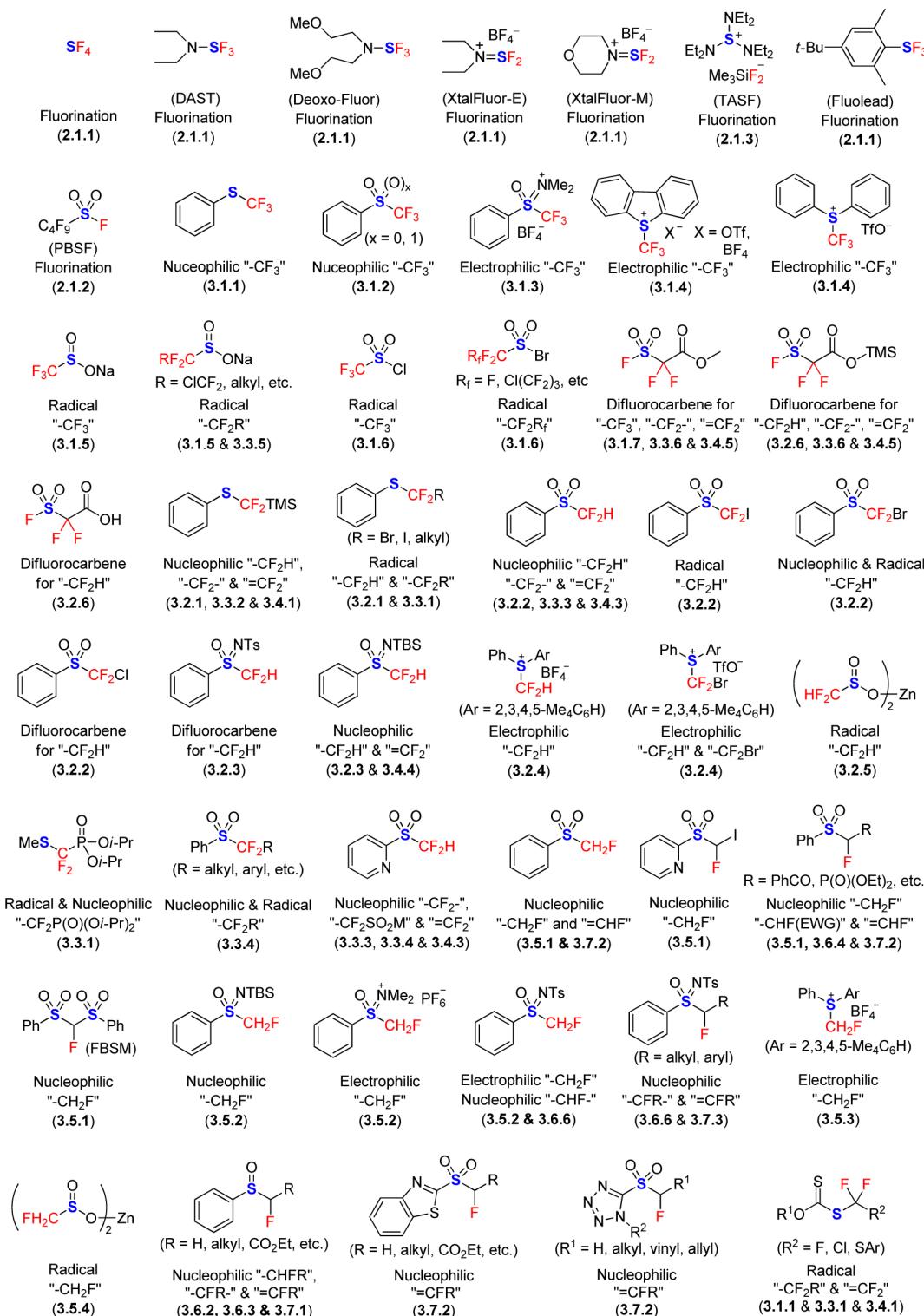


Figure 1. Sulfur-based fluorination and fluoroalkylation reagents.

perfluoroalkanesulfonyl fluorides ( $\text{R}_4\text{SO}_2\text{F}$ )<sup>35,36</sup> and tris-(dimethylamino)sulfonium difluorotrimethylsilicates (TASF),<sup>37</sup> have also been used as nucleophilic fluorination reagents, although they only have limited application in the formation of C–F bonds. Since many reviews on nucleophilic fluorination,<sup>4,22,28–33</sup> including the most recent one by Al-Maharik and O'Hagan,<sup>11</sup> have covered this topic, this section aims to only provide a brief introduction on the application of

various sulfur-based fluorination reagents in organic synthesis, particularly in the construction of C–F bonds.

## 2.1. For Fluorination

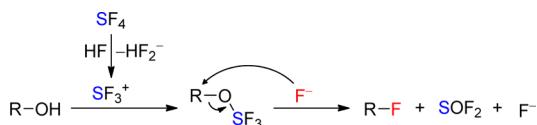
### 2.1.1. Sulfur Tetrafluoride Derivatives as Fluorination Reagents.

**2.1.1.1. Sulfur Tetrafluoride ( $\text{SF}_4$ ).** In 1958, a patent applied by Smith at DuPont disclosed the use of  $\text{SF}_4$  to replace the carbonyl oxygen with two fluorine atoms, which is the first example of using sulfur-based compounds in deoxygenative

fluorination reactions.<sup>20</sup> SF<sub>4</sub> has been successfully used to convert alcohols ( $-\text{OH}$ ), aldehydes ( $-\text{CHO}$ ), ketones ( $-\text{CO}-$ ), and carboxylic acids ( $-\text{CO}_2\text{H}$ ) to the corresponding deoxyfluorinated compounds ( $-\text{F}$ ,  $-\text{CHF}_2$ ,  $-\text{CF}_2-$ , and  $-\text{CF}_3$  or  $-\text{COF}$ ) respectively.<sup>20,28,29</sup>

A plausible reaction mechanism for a reaction between SF<sub>4</sub> and an alcohol is shown in Scheme 1. SF<sub>4</sub> is first activated by

Scheme 1



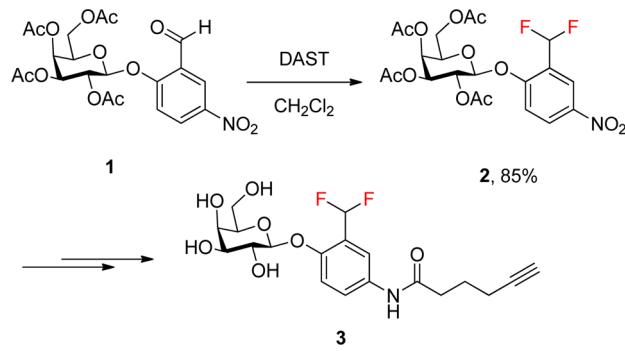
HF, which is either externally added or in situ generated via hydrolysis of SF<sub>4</sub> by adventitious water, to give the trifluorosulfonium cation. Then the alcohol (ROH) is activated to form the intermediate with a leaving group at the alcoholic carbon atom. Finally, the replacement of the leaving group by the fluoride ion affords the product (R-F), which proceeds through either an S<sub>N</sub>1 or S<sub>N</sub>2 pathway depending on the substrate structures.<sup>28,29</sup>

**2.1.1.2. DAST and Deoxo-Fluor.** Although SF<sub>4</sub> is capable of converting a series of oxygen-containing functional groups to corresponding fluorinated moieties, its gaseous character and high toxicity prevent its widespread application in laboratories.<sup>28,29</sup> Thus, the modification of the structure of SF<sub>4</sub> by replacing one of the fluorine atoms with a dialkylamino group has led to easy-to-handle reagents in liquid form.<sup>30</sup> In 1975, a pioneering work by Middleton and co-workers revealed that DAST is highly useful for converting both hydroxyl and carbonyl oxygen to fluorine atom(s) under mild conditions, which opens up new access to various fluorinated compounds with simple experimental procedures.<sup>21</sup> However, it was later found that DAST possesses relatively low thermal stability and often leads to detonation when heated to higher temperatures (such as above 50 °C), which is potentially dangerous for large scale fluorination processes.<sup>38</sup> Therefore, other SF<sub>4</sub>-derived reagents, such as morpholinosulfur trifluoride (MOST) and Deoxo-Fluor, have been identified as the safer reagents than DAST. Deoxo-Fluor, with two 2-methoxyethyl side chains at nitrogen, is found to have comparable (or sometimes even superior) reactivity to that of DAST.<sup>22,38c</sup> Currently, DAST and Deoxo-Fluor are probably the most widely used deoxygenative fluorination reagents.<sup>4,11k,32,33</sup>

Deoxygenative fluorination of aldehydes and ketones with (dialkylamino)sulfur trifluorides is a facile method to prepare difluoromethyl and difluoromethylene compounds, respectively.<sup>4,29,32</sup> For example, in a recent report, DAST was used to transform the aromatic aldehyde aglycone in acyl-protected glycosides, such as **1**, to difluoromethylphenyl aglycone, which is useful to design mechanism-based glycoside hydrolase profiling probes, such as **3** (Scheme 2).<sup>39</sup>

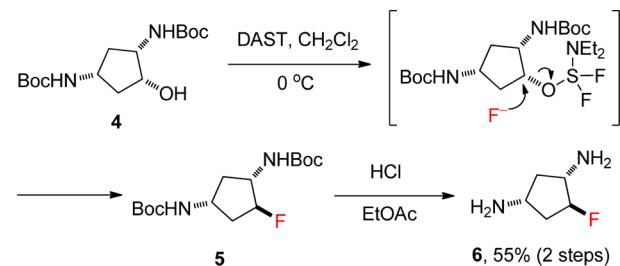
Among various fluorination reactions with DAST and Deoxo-Fluor, the dehydroxyfluorination of alcohols is particularly intriguing; the fluorination process can occur either via direct displacement of the hydroxyl group or via rearrangement followed by fluorination.<sup>29,32,33</sup> Recently, much attention has been paid to the stereoselective dehydroxyfluorination of various alcohols with DAST or Deoxo-Fluor to construct fluorine-bearing tertiary and quaternary stereogenic carbon centers.<sup>11k,33</sup> Commonly, the direct fluorine displacement of

Scheme 2



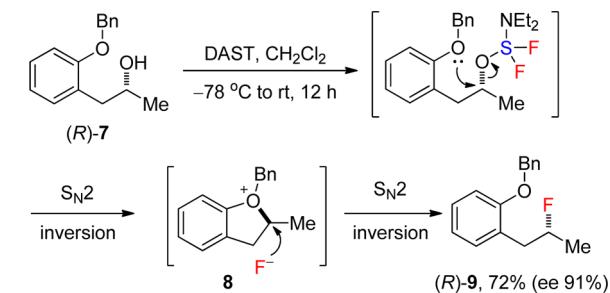
the hydroxyl group of secondary aliphatic alcohols with DAST or Deoxo-Fluor exhibits good stereocontrol, proceeding via S<sub>N</sub>2 mechanism with either inversion or retention of the configuration depending on whether there is a neighboring group participation.<sup>11k,32,33</sup> For instance, fluorination of enantiomerically enriched *cis*-diamidocyclopentanol **4** with DAST proceeds smoothly to afford fluorinated diaminocyclopentane **5** with inversion of configuration (Scheme 3),<sup>40</sup>

Scheme 3



whereas fluorination of enantiopure alcohol **7** gives the product **9** with retention of the configuration due to the participation of the neighboring benzyloxy group, probably via a five-membered oxonium intermediate **8** (Scheme 4).<sup>41</sup>

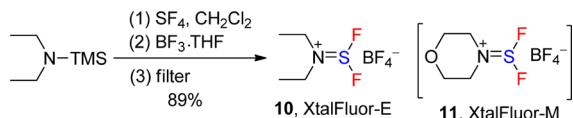
Scheme 4



**2.1.1.3. New Fluorination Reagents: XtalFluors and Fluolead.** Recently, (dialkylamino)difluorosulfonium tetrafluoroborates<sup>11d,25</sup> and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead)<sup>24</sup> have been developed as a new generation of sulfur-based fluorination reagents. These reagents are crystalline solids and featured by their enhanced thermal stability over dialkylaminosulfur trifluorides such as DAST and Deoxo-Fluor.<sup>11d,24,25</sup> Although (dialkylamino)difluorosulfonium salts have been known for a long time,<sup>42</sup> it is only in 2009 that Couturier and co-workers recognized diethylaminodifluorosul-

fonium tetrafluoroborate (XtalFluor-E) and morpholinodifluorosulfonium tetrafluoroborate (XtalFluor-M) as efficient deoxyfluorination reagents.<sup>25a</sup> XtalFluor-E (**10**) and XtalFluor-M (**11**) can be prepared from either SF<sub>4</sub> or the corresponding (dialkylamino)sulfur trifluorides DAST and MOST (Scheme 5).<sup>25</sup> However, the deoxygenative fluorination with XtalFluors

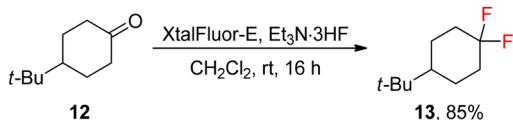
Scheme 5



usually needs an additional fluoride source (such as Et<sub>3</sub>N·3HF) or a base to promote the reaction, since the direct interaction between (dialkylamino)difluorosulfonium salts and an oxygen nucleophile can not produce a nucleophilic fluoride ion, which is in distinct contrast to the fluorination with (dialkylamino)sulfur trifluorides.<sup>11d,22</sup>

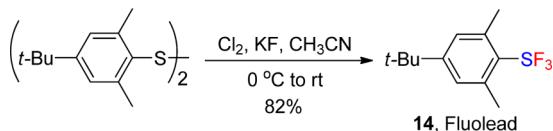
It has been found that in the fluorination of alcohols and carbonyl compounds, XtalFluors give less elimination byproducts than DAST and its analogues. For example, deoxyfluorination of ketone **12** with DAST/HF and Deoxo-Fluor/HF produced 33% and 16% yield of olefinic fluoride side products, respectively, whereas XtalFluor-E exhibited higher selectivity by giving 85% yield of *gem*-difluorides **13** along with only 4% yield of olefinic byproduct (Scheme 6).<sup>25a</sup>

Scheme 6



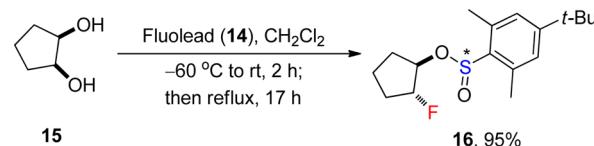
Following several earlier reports on fluorination with phenylsulfur trifluoride (PhSF<sub>3</sub>),<sup>43</sup> Umemoto and co-workers recently developed a more stable compound, 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead), as an alternative deoxyfluorination reagent to the commonly used (dialkylamino)sulfur trifluorides.<sup>24</sup> Fluolead can be readily prepared by chlorination of bis(4-*tert*-butyl-2,6-dimethylphenyl) disulfide with Cl<sub>2</sub> followed by halogen exchange with a fluoride salt such as KF (Scheme 7).<sup>24b,c</sup> Interestingly, Fluolead

Scheme 7



can selectively fluorinate diols to their monofluoride analogues of arylsulfonates. For example, the reaction of *cis*-1,2-diol **15** gives *trans*-2-fluoro-1-arylsulfinate **16** in 95% yield as a 95:5 mixture of two diastereomers based on the chiral sulfur center (Scheme 8).<sup>24c</sup> Umemoto and Singh also developed hexavalent sulfur compounds, arylsulfur chlorotetrafluorides (ArSF<sub>4</sub>Cl), as useful deoxygenative nucleophilic fluorination reagents. The ArSF<sub>4</sub>Cl reagents need preactivation with a reducing agent (such as pyridine) to in situ release the more reactive arylsulfur trifluorides.<sup>44</sup>

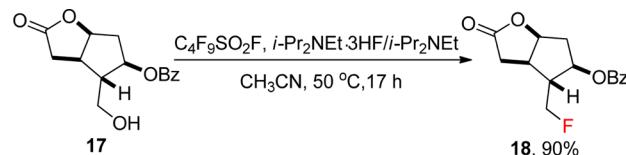
Scheme 8



### 2.1.2. Sulfonyl Fluorides as Fluorination Reagents.

Perfluorobutanesulfonyl fluoride (C<sub>4</sub>F<sub>9</sub>SO<sub>2</sub>F) has been used as a readily available reagent for the dehydroxyfluorination of alcohols. Initially, C<sub>4</sub>F<sub>9</sub>SO<sub>2</sub>F was reported to be capable of fluorinating alcohols under the action of DBU.<sup>35a,b</sup> In 2004, Yin and co-workers found that the fluorination can be promoted by the combination of an additional fluoride source and a tertiary amine.<sup>35c</sup> By using this protocol, primary, secondary, and tertiary alcohols were successfully transformed to the corresponding fluorinated products in high yields. For instance, the reaction of alcohol **17** gives the product **18** in 90% yield (Scheme 9).<sup>35c</sup>

Scheme 9



Tian and co-workers showed that other sulfonyl fluorides such as 5-*H*-3-oxa-1,1,2,2,4,4,5,5-octafluoropentanesulfonyl fluoride (HCF<sub>2</sub>CF<sub>2</sub>OCCF<sub>2</sub>CF<sub>2</sub>SO<sub>2</sub>F) can be used for the fluorination of peracetylated pyranose hemiacetals in the presence of DBU, giving the corresponding glycosyl fluorides in high yields (44~94%).<sup>36</sup>

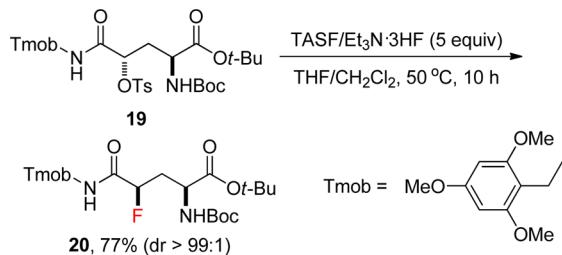
### 2.1.3. Sulfonium Fluorides as Fluorination Reagents.

Compared to the aforementioned sulfur-based deoxygenative fluorination reagents, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) is a highly nucleophilic and so-called “naked” fluoride ion source with a bulky noncoordinating sulfonium counterion, which can be prepared through the reaction of SF<sub>4</sub> with 3 equiv of (dimethylamino)trimethylsilane in a rigorously anhydrous form.<sup>37</sup> Since its introduction by Middleton in 1976,<sup>37</sup> TASF has become an excellent fluorination reagent for the preparation of alkyl fluorides, as well as a versatile activating agent in many transformations.<sup>45</sup> For example, in a recent report, TASF was used for the efficient synthesis of 4-fluorinated glutamines, such as **20**, from the corresponding tosylates, such as **19**. By adding Et<sub>3</sub>N·3HF to alleviate the basicity of TASF, the desired product **20** is obtained in 77% yield without epimerization at the C-2 position (Scheme 10).<sup>46</sup> It was found that other fluorination reagents including tetrabutylammonium triphenyldifluorosilicate (TBAT) are less effective in this reaction.

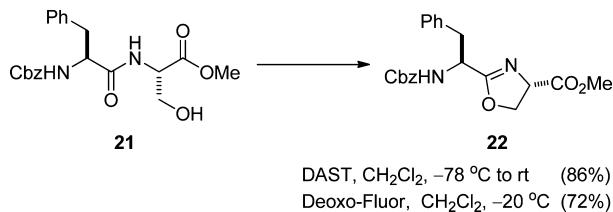
### 2.2. For Other Reactions

DAST and Deoxo-Fluor have been used as effective activating agents to synthesize many nonfluorinated compounds, such as amides and heterocycles.<sup>22c,47</sup> For example, dehydrative cyclization of peptide  $\beta$ -hydroxy amides such as **21** with the both reagents under mild conditions affords functionalized oxazolines, such as **22**, in high yields (Scheme 11).<sup>47b</sup> Very recently, this cyclization methodology has been used for the total synthesis of plantazolicin A, a new lead compound against

Scheme 10



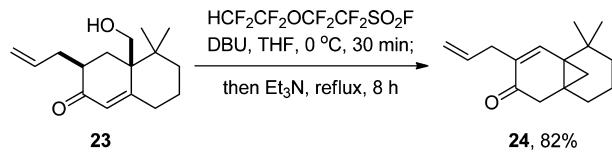
Scheme 11



anthrax infections.<sup>47c</sup> Recently, (dialkylamino)-difluorosulfonium tetrafluoroborates, such as XtalFluor-E, have been used to achieve similar transformations.

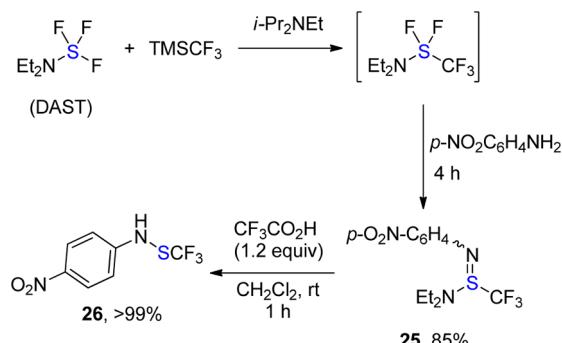
Poly(per)fluoroalkanesulfonyl fluorides are capable of inducing rearrangement reactions.<sup>49</sup> For example, using  $\text{HCF}_2\text{CF}_2\text{OCF}_2\text{CF}_2\text{SO}_2\text{F}$  as the reagent,  $\gamma$ -hydroxymethyl cyclohexenone **23** has been transformed into cyclopropyl enone **24** in 82% yield via tandem carbonium rearrangement (Scheme 12).<sup>49b</sup>

Scheme 12



It was found that, the reaction between DAST and Ruppert-Prakash reagent ( $\text{TMSCF}_3$ ) in the presence of *N,N*-diisopropylethylamine and a primary amine, such as 4-nitroaniline, is a useful method to prepare previously unknown trifluoromethanesulfonamidines (such as **25**) and trifluoromethanesulfanyl amides (such as **26**) (Scheme 13).<sup>50</sup> Moreover, trifluoromethanesulfanyl amides derived from aniline has been used to transfer trifluoromethylthio group to various electrophiles (see section 4).

Scheme 13



### 3. SULFUR-BASED FLUOROALKYLATION REAGENTS

#### 3.1. For Perfluoroalkylation (Including Trifluoromethylation)

Perfluoroalkyl groups, especially the trifluoromethyl group ( $\text{CF}_3$ ), are of great importance in agrochemicals, pharmaceuticals, and functional materials.<sup>6,7,9,17,51</sup> In recent years, the synthesis of trifluoromethylated compounds has become a hot research topic and numerous trifluoromethylations based on nucleophilic, electrophilic, free radical, and transition metal-mediated reactions have been achieved by using various perfluoroalkyl sources.<sup>12</sup> Among these sources, the sulfur-based reagents play very important roles—not only some conceptually new reactions, but also several practically attractive methods have been developed by using sulfur-based reagents. Although there have been numerous reviews on perfluoroalkylations,<sup>12</sup> to our knowledge, this is the first time a rather comprehensive survey has been made on the sulfur-based perfluoroalkylation reactions. In this section, we will provide a historical introduction on the development and application of sulfur-based perfluoroalkylation reagents, with an emphasis on the most recent development on their synthetic applications. This section is divided according to the reagents used (sulfides, sulfones, sulfoximines, sulfonium salts, sulfinate salts, sulfonyl halides, the tetrafluoroethane  $\beta$ -sultone derivatives, and some other less common reagents) and subdivided according to the reaction types. In this section,  $R_f$  is used to denote a perfluoroalkyl or polyfluoroalkyl group.

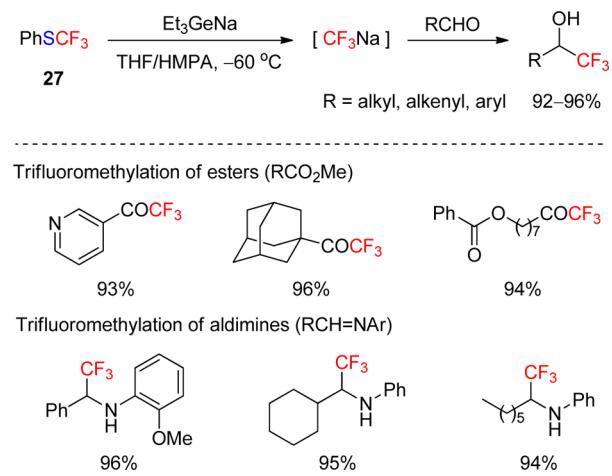
##### 3.1.1. Sulfides and Xanthates as Perfluoroalkylation Reagents

Per(poly)fluoroalkylation with the divalent sulfur compounds with the general formula  $R_f\text{SR}$  is underexplored; only sporadic examples have been reported.

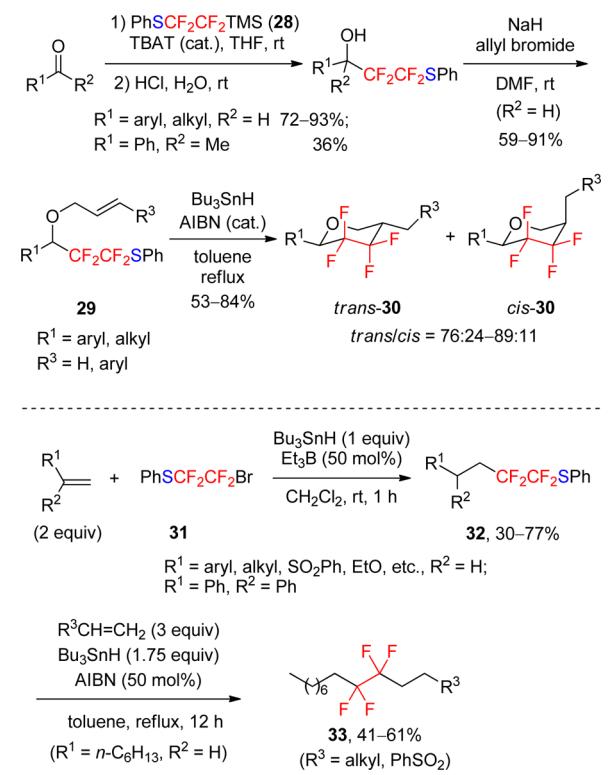
Trifluoromethyl phenyl sulfide ( $\text{PhSCF}_3$ , **27**) is a stable compound that can be easily prepared either from  $\text{PhSCH}_3$  via  $\alpha$ -trichlorination followed by a halogen-exchange reaction,<sup>52</sup> or from  $\text{PhSSPh}$  via trifluoromethylation with fluoroform.<sup>53</sup> Although reductive lithiation can activate the C–S bond of nonfluorinated sulfides to generate alkyllithiums for various transformations,<sup>54</sup> it is not applicable for trifluoromethylation due to the notoriously low stability of  $\text{CF}_3\text{Li}$ .<sup>55</sup> In addition, the sulfur atom in a sulfide is less electrophilic toward the common anionic species such as alkoxides than that in a sulfoxide or sulfone, thus the activation of the  $\text{CF}_3$ –S bond in a sulfide **27** for nucleophilic trifluoromethylation is far from trivial. In 1996, Yokoyama and Mochida<sup>56a</sup> showed that under the promotion of a germyl anion that has strong affinity to the sulfur atom, trifluoromethyl anion species could be formed from **27**. The in situ generated  $\text{CF}_3^-$  species from the combination of **27**/Et<sub>3</sub>GeNa reacted with both nonenolizable and enolizable aldehydes in THF/HMPA as the solvent at  $-60^\circ\text{C}$ , affording trifluoromethylated carbinols in excellent yields (Scheme 14).<sup>56</sup> However, the reaction is very sensitive to the steric hindrance and the counterion of the germyl anion; among possible promoters including PhEt<sub>2</sub>GeNa and Et<sub>3</sub>GeK, only Et<sub>3</sub>GeNa gives a high yield. The methodology has been extended to methyl esters<sup>56b</sup> and *N*-aryl aldimines,<sup>56c</sup> to give trifluoromethyl ketones and  $\alpha$ -trifluoromethyl amines, respectively (Scheme 14).

Polyfluoroalkyl sulfides have been used for both intra- and intermolecular radical fluoroalkylation reactions (Scheme 15).<sup>57</sup> By using [1,1,2,2-tetrafluoro-2-(phenylthio)ethyl]silane  $\text{PhSCF}_2\text{CF}_2\text{TMS}$  (**28**) as a tandem anion and radical tetrafluoroethylene equivalent, Beier and co-workers developed

### Scheme 14



### Scheme 15

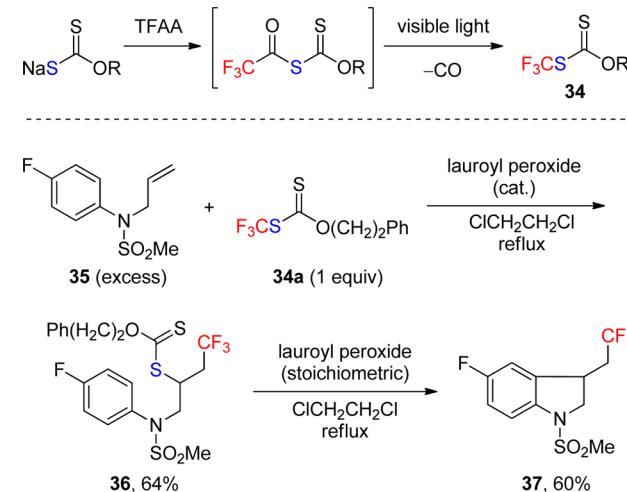


an intramolecular polyfluoroalkyl addition to alkenes.<sup>57a,b</sup> Fluoride-initiated nucleophilic additions of **28** to carbonyl compounds followed by allylation provides the corresponding allyl ether **29**. Reductive cleavage of the phenylthio group of **29** gives the 6-exo radical cyclization products **30** in good yields (53–84%). With 2-bromo-1,1,2,2-tetrafluoroethyl sulfide PhSCF<sub>2</sub>CF<sub>2</sub>Br (**31**) as a diradical synthon, the 1,1,2,2-tetrafluoroalkyl sulfide **32** obtained from the radical addition of **31** to alkenes can further react with another molecule of alkene to afford the tetrafluoroethylene-containing alkanes **33**.<sup>57c</sup>

Xanthates are extremely useful alkylation reagents for intermolecular radical addition reactions.<sup>58</sup> By taking advantage of the excellent radical chemistry of xanthates, Zard and co-workers in 2001 developed a lauroyl peroxide initiated atom transfer radical addition (ATRA) reaction for the introduction

of trifluoromethyl group into terminal alkenes with S-trifluoromethyl xanthates 34 (Scheme 16).<sup>59</sup> The xanthate

### Scheme 16

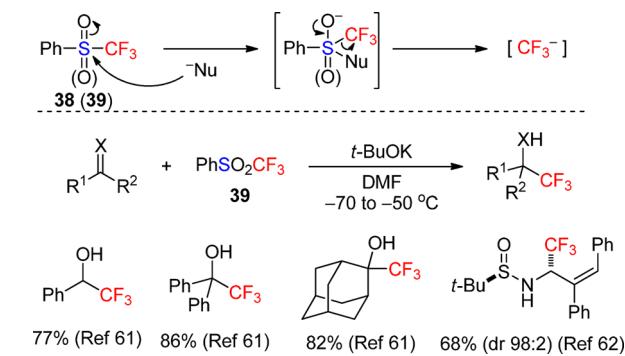


group in the adducts not only can be easily reduced off with hypophosphorus acid ( $H_3PO_2$ ) to give hydrotrifluoromethylation products,<sup>59b</sup> but also is possible to start another radical sequence.<sup>59a</sup> For example, the treatment of **36**, obtained from the addition of *O*-phenethyl xanthate **34a** to protected *N*-allyl aniline **35**, with stoichiometric quantity of lauroyl peroxide leads to the cyclization product **37**.<sup>59a</sup>

### 3.1.2. Sulfoxides and Sulfones as Perfluoroalkylation

**Reagents.** The oxidation of PhSCF<sub>3</sub> affords two new trifluoromethyl sources, PhSOCF<sub>3</sub> (38) and PhSO<sub>2</sub>CF<sub>3</sub> (39), in which the sulfur atoms readily undergo attack by a nucleophile to release trifluoromethyl anions.<sup>60</sup> In 2003, Prakash and co-workers reported an alkoxide-induced nucleophilic trifluoromethylation reaction with two equally effective reagents 38 and 39 (Scheme 17).<sup>61</sup> The driving force of this

### Scheme 17

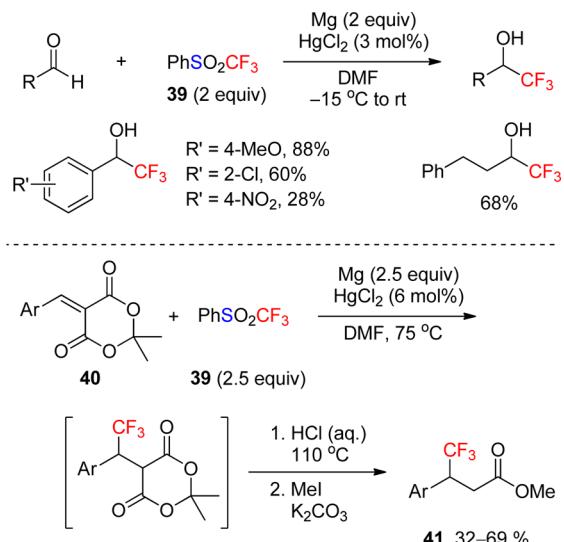


substitution reaction is the formation of a strong S–O bond and the high polarity of the C–S bonds of sulfoxide **38** and sulfone **39**. Using *t*-BuOK as a base, the reaction of nonenolizable carbonyl compounds and aldimines carried out in DMF as solvent affords  $\alpha$ -trifluoromethyl alcohols<sup>61</sup> and amines,<sup>62</sup> respectively, in good to excellent yields. It is worth noting that in the presence of CuI, the PhSO<sub>2</sub>CF<sub>3</sub>/*t*-BuOK system is also suitable for the generation of CF<sub>3</sub>Cu, a reactive intermediate that has found wide application in aromatic trifluoromethylation.<sup>12t</sup> Although the present reaction with

iodobenzene afforded  $\text{PhCF}_3$  in only 26% yield, it is believed that an optimization of the reaction conditions can make it to be a promising protocol for the synthesis of trifluoromethyl arenes.<sup>63</sup> Similarly, pentafluoroethylation has been achieved using  $\text{PhSO}_2\text{C}_2\text{F}_5$ ; in this case, the solvent THF is found to be superior to DMF.<sup>62</sup>

Compounds **38** and **39** are also good electron acceptors, and thus reduction with magnesium metal constitutes an alternative method to generate trifluoromethyl anion, which was first demonstrated in 2003 for the preparation of trifluoromethyl-trimethylsilane ( $\text{TMSCF}_3$ , also known as Ruppert-Prakash reagent) via a Barbier-type reaction with chlorotrimethylsilane ( $\text{TMSCl}$ ).<sup>64</sup>  $\text{TMSCl}$  used in the reaction not only serves as the reactant but also is an activator for magnesium. When catalytic quantities of mercury dichloride ( $\text{HgCl}_2$ ) are used to activate magnesium metal, the Barbier-type reaction between  $\text{PhSO}_2\text{CF}_3$  and aldehydes affords the trifluoromethylated carbinols (Scheme 18).<sup>65</sup> Due to the mildness of the reaction

Scheme 18

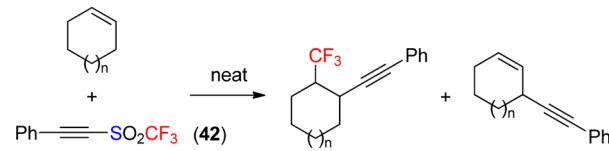


conditions, the  $\text{PhSO}_2\text{CF}_3/\text{Mg}/\text{HgCl}_2(\text{cat.})$  system very recently has been used for the trifluoromethylation of activated Michael acceptors such as arylidene Meldrum's acids **40**.<sup>66</sup>

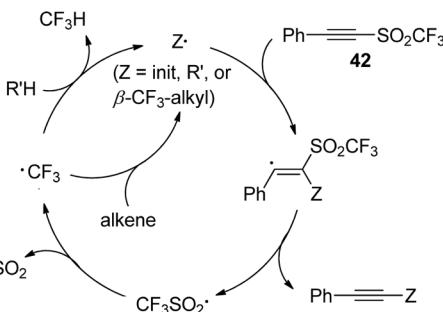
Although the use of sulfones in radical perfluoromethylation has been rare, the addition of alkynyl triflones to alkenes under the initiation of AIBN or upon irradiation with visible light is a synthetically useful method for the difunctionalization of alkenes, leading to trifluoromethyl-alkynylation products (Scheme 19).<sup>67,68</sup> In the initiation and propagation steps, the trifluoromethyl precursor,  $\text{CF}_3\text{SO}_2$  radical, is proposed to be generated through the addition of an alkyl radical to the  $\alpha$ -position of triflones, such as **42**, followed by an elimination reaction. The reaction of **42** with terminal alkenes, such as 1-octene, only afforded the addition products, whereas the reaction with cyclohexene provides substantial amounts of allylic alkynes resulting from the allylic hydrogen abstraction by the extremely electrophilic  $\text{CF}_3$  radical.<sup>67</sup> Fuchs and co-workers have systematically investigated the C–H hydrogen abstraction by a  $\text{CF}_3$  radical and used this chemistry in C–H functionalization with alkynyl,<sup>67,69</sup> vinyl,<sup>70</sup> and allyl triflones.<sup>68</sup>

**3.1.3. Sulfoximines as Perfluoroalkylation Reagents.** In contrast to perfluoroalkyl sulfones, which mainly serve as the nucleophilic perfluoroalkylation reagents, *S*-perfluoroalkyl

Scheme 19



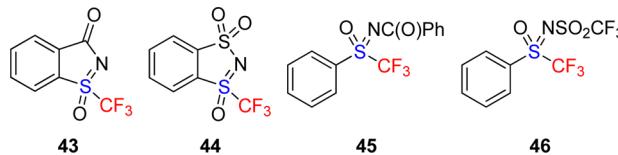
	n = 1	n = 2	
AIBN, reflux:	61%	37%	15%
$\text{hv}, 254\text{ nm}, 25^\circ\text{C}$ :	49%	79%	21%
			1%



sulfoximines can be modulated to electrophilic perfluoroalkylation reagents through functionalization of the nitrogen atom. Generally, perfluoroalkyl sulfoximines used as perfluoroalkylation reagents have been prepared by oxidative imination of the corresponding sulfoxides, such as  $\text{PhSOCl}_3$  (**38**),<sup>71</sup> followed by *N*-functionalization.<sup>72</sup> For details on their preparation, one can refer to recently published reviews on fluorinated sulfoximines.<sup>73</sup>

The first application of *S*-perfluoroalkyl sulfoximines in perfluoroalkylation was documented in a patent,<sup>74</sup> which claimed that two types of neutral sulfoximines (**43/44** and **45/46**), with the structures being shown in Scheme 20, could

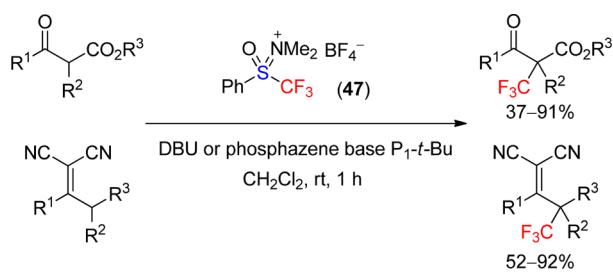
Scheme 20



react with nucleophiles such as Grignard reagents, alkynyl lithium, and sodium thiophenolates to give the corresponding trifluoromethylation products in low to moderate yields (13–73%).<sup>75</sup>

In 2008, Shibata and co-workers developed *N,N*-dimethyl-*S*-trifluoromethylsulfoximinium tetrafluoroborate (**47**), a trifluorinated analogue of Johnson's methylene transfer reagent, as a reagent for electrophilic trifluoromethylation of carbon nucleophiles (Scheme 21).<sup>72b</sup> Several carbon acids such as  $\beta$ -ketoesters and dicyanoalkylidenes have been trifluoromethylated under the action of an organic base. In 2011, Magnier and co-workers showed that the sulfoximinium cation of **47** with a triflate counterion is capable of trifluoromethylating alkynyl lithium reagents with low to moderate yields (2–53%).<sup>75</sup> However, compared to *S*-trifluoromethyl sulfonium salts, such as **50** and **51** (vide infra), the application of reagent **47** in transition metal-promoted trifluoromethylation reactions is still a challenge, as has been demonstrated in several publications.<sup>76</sup>

Scheme 21



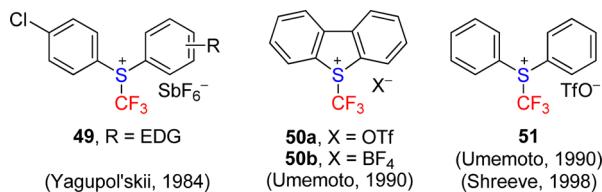
Interestingly, Hu and co-workers found that the treatment of *N*-tosyl sulfoximine **48** with sodium phenolate in the presence of an aldehyde, such as 4-bromobenzaldehyde, provides  $\alpha$ -trifluoromethyl alcohol as the product (Scheme 22), indicating that *S*-perfluoroalkyl sulfoximines can also serve as perfluoroalkyl anion sources under the action of a proper nucleophile.<sup>72a</sup>

Scheme 22



**3.1.4. Sulfonium Salts as Perfluoroalkylation Reagents.** Sulfonium salts, featured by a positively charged sulfur(IV) center, are good scaffolds for electrophilic transfer of a trifluoromethyl group. The first preparation and application of *S*-trifluoromethylsulfonium salts were accomplished by Yagupol'skii and co-workers in 1984,<sup>77</sup> when the sulfonium salts  $[p\text{-ClC}_6\text{H}_4\text{ArSCF}_3]^+(\text{SbF}_6)^-$  (**49**) (for structures, see Scheme 23), with two nonlinked aryl substituents, were obtained by

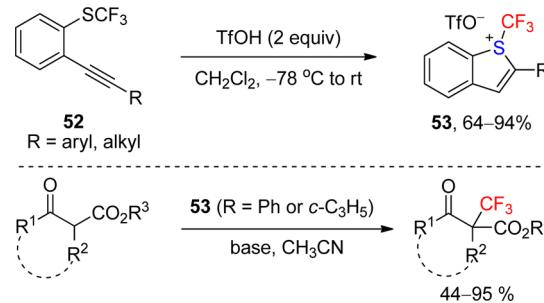
Scheme 23



treating *p*-chlorophenyl trifluoromethyl sulfoxide and an electron-rich arene with  $\text{SF}_4/\text{SbF}_5$ , and were found to react with thiolates to give the corresponding trifluoromethyl sulfides. However, these sulfonium salts have very limited application due to their low reactivity. To improve the trifluoromethylating capability, Umemoto and Ishihara in 1990 developed a series of *S*-heterocyclic sulfonium salts, that is, *S*-(trifluoromethyl)dibenzothiophenium salts, among which, the triflate and tetrafluoroborate salts with the simplest dibenzothiophenium skeleton (**50a** and **50b**, for structures, see Scheme 23) have found many applications in synthesizing  $\text{CF}_3$ -containing molecules and have been well-known as Umemoto reagents.<sup>12x,y,78</sup> Recently, the previously known but little used trifluoromethylidiphenylsulfonium triflate (**51**)<sup>78b,79</sup> has begun to be used as an effective electrophilic trifluoromethylation reagent<sup>76,80</sup> due to the development of a straightforward one-pot process to prepare it from

$\text{CF}_3\text{SO}_2\text{Na}^{81}$ . In addition to the aforementioned diarylsulfonium salts **49–51**, in 2010, Shibata and co-workers developed a new type of *S*-heterocyclic sulfonium salts **53** with a benzothiophene skeleton via intramolecular cyclization of *o*-(ethynyl)aryl trifluoromethyl sulfides **52** (Scheme 24).<sup>82</sup>

Scheme 24

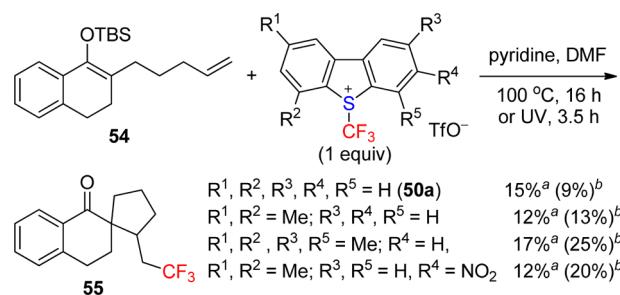


Although sulfonium salts **53** have comparable reactivity to sulfonium salts **50** in trifluoromethylation of carbon acids,<sup>82,83</sup> they are found to be more labile than the diarylsulfonium salts **50** and **51** under many conditions.<sup>84</sup> For details on the preparation of trifluoromethylated sulfonium salts, one can refer to two recent elegant reviews on electrophilic trifluoromethylation.<sup>12x,y</sup> In this subsection, we aim to present the progress on the synthetic application of trifluoromethylsulfonium salts since 2010. Parts of the material treated here have also been discussed in other general reviews.<sup>12m,x,y</sup>

**3.1.4.1. Transition Metal-Free Reactions.** Early research on the reaction of *S*-trifluoromethylsulfonium salts concentrated on the direct trifluoromethylation of nucleophiles such as various carbanionic species, silyl enol ethers, enamines, electron-rich arenes, and heteroatom nucleophiles (thioureas, thiolate salts, sulfinate salts, nitrite salts, phosphines, phosphinate salts, and iodide salts).<sup>12x,y,85</sup> However, the detailed mechanism for the transfer of a trifluoromethyl group has been under discussion for a long time.<sup>86</sup> In 2010, Mangier and co-workers provided a convincing proof for the involvement of a trifluoromethyl radical in the reaction of enol silyl ethers with *S*-trifluoromethylsulfonium salts.<sup>86</sup> By using a radical probe **54**, the formation of spirocyclic compound **55** is observed as the sole product, supporting a single-electron transfer (SET) pathway in this reaction (Scheme 25). This result also indicates a possible SET pathway in the reactions of soft nucleophiles such as  $\beta$ -ketoesters, ketones, enamines, and thiolates, which are the most frequent compounds capable of reacting directly with trifluoromethylated sulfonium salts.<sup>86</sup>

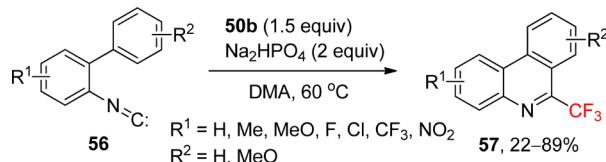
Very recently, Yu and co-workers developed a tandem transformation of isocyanides **56** with Umemoto reagent **50b**

Scheme 25



for the synthesis of trifluoromethylated phenanthridine derivatives **57**.<sup>87</sup> The reaction proceeds with  $\text{Na}_2\text{HPO}_4$  as proton scavenger, in the absence of any added oxidants or radical initiators, in *N,N*-dimethylacetamide (DMA) as solvent at 60 °C, furnishing cyclization products **57** in moderate to good yields (Scheme 26). As for the mechanism, although an

Scheme 26

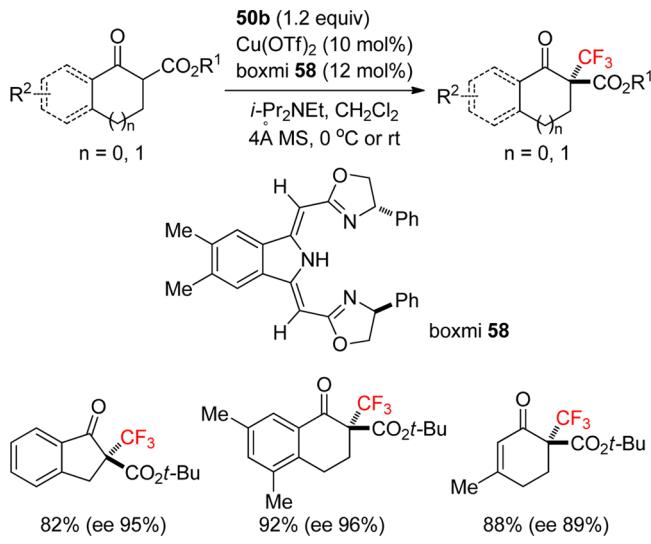


ionic pathway involving the nucleophilic attack on trifluoromethyl by isocyanides is possible due to the lack of any obvious radical initiator, the radical pathway has not been ruled out considering that isocyanides are well-known radical acceptors.<sup>88</sup>

**3.1.4.2. Transition Metal-Assisted Reactions.** In recent years, with the assistance of a transition metal, the synthetic potential of the sulfonium salts has been largely expanded, thus many aromatic and aliphatic trifluoromethylations that are otherwise difficult to tackle have been achieved.

**3.1.4.2.1. Trifluoromethylation of  $\beta$ -Ketoesters.** The racemic  $\alpha$ -trifluoromethylation of  $\beta$ -ketoesters has been studied extensively; however, examples for the enantioselective introduction of a  $\text{CF}_3$  are rare.<sup>89</sup> It is only very recently that a highly enantioselective  $\alpha$ -trifluoromethylation of  $\beta$ -ketoesters was achieved by Gade and co-workers, using catalytic quantities of  $\text{Cu}(\text{OTf})_2$  and a chiral pincer ligand, boxmi **58** (Scheme 27).<sup>90</sup> The reaction with sulfonium salt **50b** is not only

Scheme 27

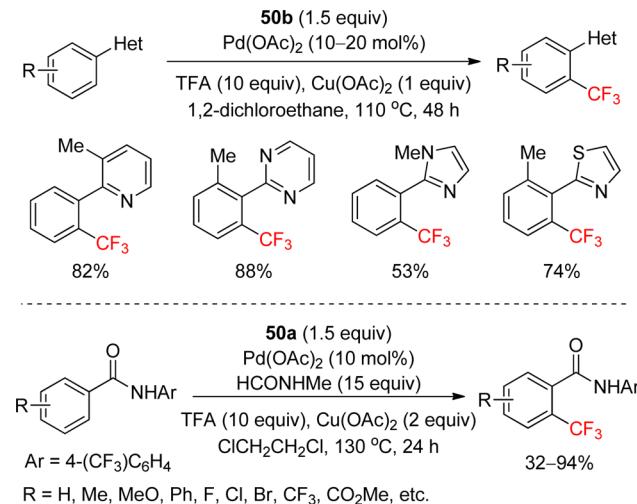


applicable for 5-membered cyclic  $\beta$ -ketoesters, but also works well for the 6-membered ones, which are trifluoromethylated with a lower enantioselectivity when the hypervalent iodine(III) reagent is used.

**3.1.4.2.2. Aromatic Trifluoromethylation.** In 2010, a contribution from Yu and co-workers described a  $\text{Pd}(\text{OAc})_2$ -catalyzed *ortho*-trifluoromethylation of arenes such as 2-phenylpyridines with sulfonium salt **50b** through C–H

functionalization,<sup>91</sup> which is the first report on the application of trifluoromethylsulfonium salts in transition metal-assisted reactions (Scheme 28). The use of trifluoroacetic acid (TFA) is

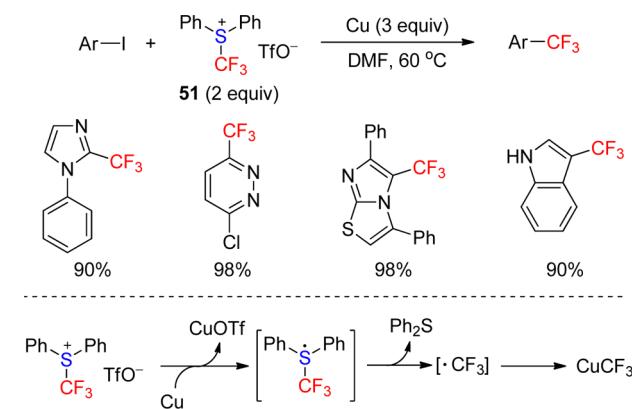
Scheme 28



critical for the success of this C–H trifluoromethylation, and  $\text{Cu}(\text{OAc})_2$  can enhance the catalytic turnover by eliminating the inhibition effect of a sulfur-containing side product. Following this work, the Pd(II)-catalyzed trifluoromethylation of benzamides with sulfonium salt **50a** has been achieved with *ortho*-selectivity at the less hindered site (Scheme 28).<sup>92</sup> Compared to the previous reaction, an additional enabling ligand, such as *N*-methylformamide, is needed to promote the reaction. Mechanistic investigation showed that both the copper salt and the ligand are crucial for the formation of the C– $\text{CF}_3$  bond. Additionally, the Pd(II)-catalyzed *ortho*-trifluoromethylation of acetanilides<sup>93a</sup> and benzylamines<sup>93b</sup> with sulfonium salt **50b** has also been reported.

In 2011, Xiao and co-workers reported an effective trifluoromethylation of heteroaryl iodides with trifluoromethyl-diphenylsulfonium salt **51** through a reductive coupling reaction mediated by  $\text{Cu}(0)$  to give trifluoromethylated heteroarenes in high yields (Scheme 29).<sup>80a</sup> The protocol is also very efficient for simple iodobenzene derivatives. As for the mechanism, a  $\text{CuCF}_3$  species that is generated via the reduction of **51** by  $\text{Cu}(0)$  in SET pathway is suggested to be the actual trifluoromethylation reagent.<sup>80a</sup> The feasibility of generating a

Scheme 29

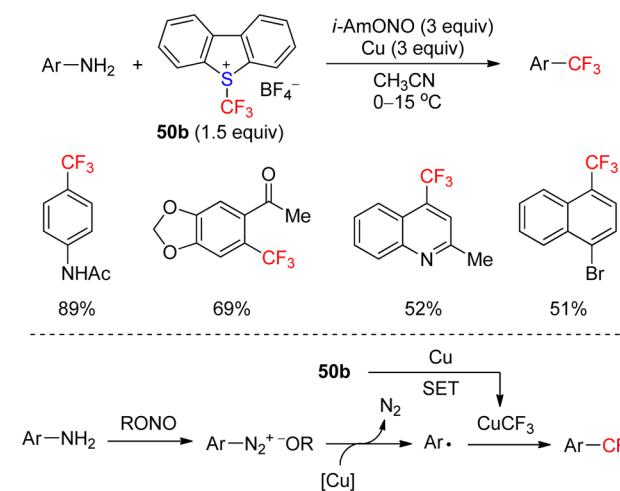


$\text{CF}_3$  radical is supported by the fact that when styrenes and **51** are reacted in the presence of a SET reagent, such as  $\text{HOCH}_2\text{SO}_2\text{Na}$ , the  $\beta$ -trifluoromethyl ketones are given in modest yields (21–39%).<sup>94</sup>

The combination of **51**/Cu(0) exhibits higher reactivity than several common trifluoromethylcopper sources, including Cu(I)/ $\text{TMSCF}_3$  and the well-defined  $\text{CuCF}_3$  complexes,<sup>76,80a,e</sup> and has been used in the reactions with benzyl bromides, propargyl acetates, even  $\alpha,\beta$ -unsaturated carbonyl compounds, to give the corresponding trifluoroethyl arenes,<sup>76a</sup> trifluoromethyl alkenes,<sup>80e</sup> and  $\beta$ -trifluoromethyl ketones.<sup>76b</sup>

The combination of Umemoto reagent/Cu(0) is also capable of generating trifluoromethylcopper species.<sup>95</sup> A typical example of the application of this system is deaminotrifluoromethylation of (hetero)aryl amines with sulfonium salt **50b**, a transformation coupled the copper-promoted Sandmeyer reaction with the copper-promoted trifluoromethylation to convert a primary amino group to a  $\text{CF}_3$  group (Scheme 30).<sup>95b</sup>

Scheme 30



The Ar-CF<sub>3</sub> bond is suggested to be formed by the reaction between CF<sub>3</sub>Cu and an aryl radical generated from the aryldiazonium ion (produced *in situ* from the aryl amine and alkyl nitrite).<sup>95b</sup>

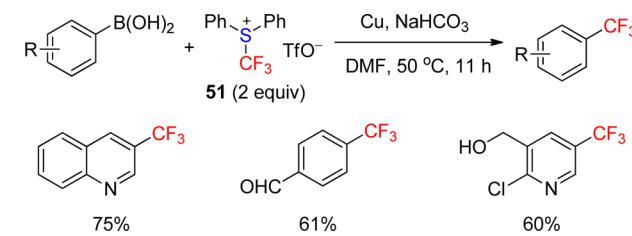
As an alternative approach, trifluoromethylated (hetero)arenes have been obtained by trifluoromethylation of aromatic boronic acids with the sulfonium salts, an overall redox neutral process that can be promoted by either a Cu(I) salt or Cu(0) metal.<sup>80b,96</sup> The CuOAc-catalyzed trifluoromethylation with **50a** needs stoichiometric quantities of 2,4,6-trimethylpyridine (2 equiv) as the ligand;<sup>96</sup> whereas the Cu(0)-promoted trifluoromethylation with **51** proceeds smoothly in the absence of a ligand (Scheme 31).<sup>80b</sup> Besides, the Cu(I)-catalyzed C–H trifluoromethylation of terminal alkynes with **50a** or **51** under similar conditions can afford trifluoromethyl alkynes.<sup>80d,97</sup>

#### 3.1.4.2.3. Trifluoromethylation of Alkenes and Alkynes.

The functionalization of alkenes can provide a broad spectrum of commodity chemicals. In recent years, much attention has been paid on the derivation of alkenes to structure-diverse aliphatic trifluoromethylated compounds with various CF<sub>3</sub> sources. In this context, the Umemoto reagents **50** have been used for the transformation of alkenes via substitution or addition reactions under metal catalysis.

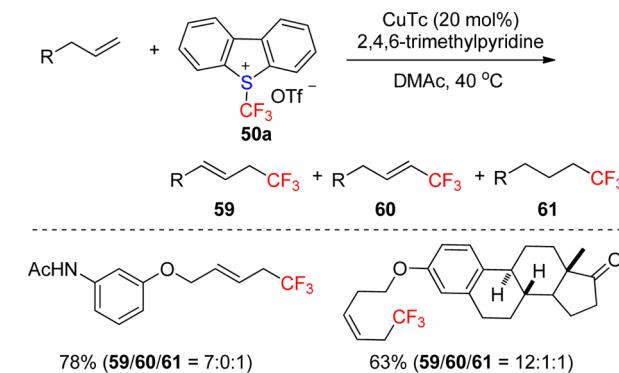
In 2011, Fu, Liu and co-workers conducted a Cu-catalyzed trifluoromethylation of electron-neutral terminal alkenes with

Scheme 31



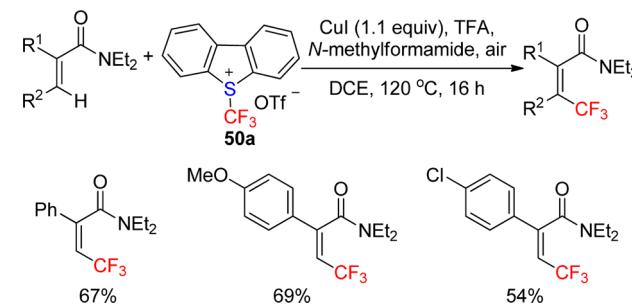
**50a** through allylic C–H activation (Scheme 32). In this reaction, monosubstituted terminal alkenes are transformed to

Scheme 32



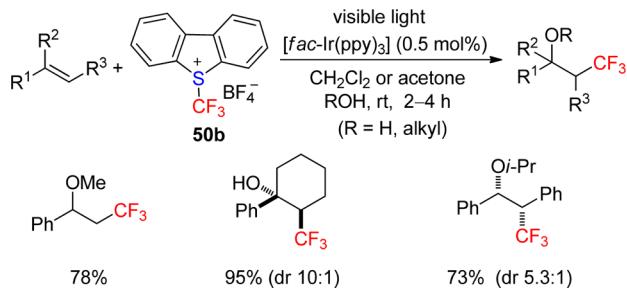
linear allylic trifluoromethylation product in modest to good yields (32–78%).<sup>98</sup> Although this reaction was suggested to proceed via a Cu(III)–CF<sub>3</sub> intermediate by the authors, the possibility of a SET pathway involving the CF<sub>3</sub> radical addition to alkenes could not be ruled out.<sup>99a</sup> Additionally, the Cu-assisted protocol is also applicable to the styrene systems.<sup>100</sup> For example, the treatment of  $\beta$ -aryl *N,N*-diethylacrylamides with **50a** using stoichiometric quantities of CuI in the presence of trifluoroacetic acid could afford the olefinic C–H trifluoromethylation products as single *Z* isomers in moderate yields (34–69%) (Scheme 33).<sup>100b</sup>

Scheme 33



The sulfonium salts can also produce CF<sub>3</sub> radical via visible light photoredox catalysis. In 2012, Yasu, Koike and Akita reported a difunctionalization of styrene derivatives and electron-rich alkenes with **50b** in the presence of an oxygen nucleophile, which proceeds with an Ir(III) complex *fac*-Ir(ppy)<sub>3</sub> (ppy = 2-phenylpyridine) as catalyst under visible light irradiation, giving the oxytrifluoromethylation products in high yields (51–98%) (Scheme 34).<sup>99a</sup> A convincing radical mechanism has been proposed for this transformation: a CF<sub>3</sub>

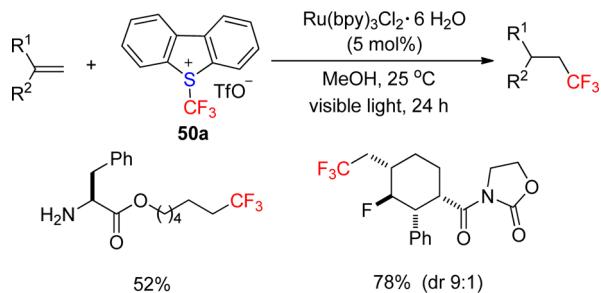
Scheme 34



radical generated from the reduction of **50b** by the excited Ir(III) complex first adds to alkene to give an alkyl radical intermediate, then the alkyl radical intermediate is oxidized to a carbocation by the Ir(IV) complex; eventually, the oxygen nucleophiles attack on the carbocation to give the oxytrifluoromethylation products.<sup>99a</sup> It is worthwhile noting that the sulfonium salt **50b** is more efficient than the hypervalent iodine(III) reagents for the selective reaction, which is consistent with its higher irreversible reduction potential than those of the later.<sup>99a</sup> By using this photoredox catalysis protocol, other transformations such as the intermolecular aminotri fluoromethylation<sup>101</sup> and trifluoromethylative lactonization<sup>102</sup> of styrene derivatives have also been achieved with **50b** as reagent.

Interestingly, when the electron-neutral terminal alkenes were treated with a sulfonium salt such as **50a** in MeOH as solvent, it is the hydrotrifluoromethylation products rather than the oxytrifluoromethylation products that were obtained due to the ready termination of the alkyl radical intermediate by MeOH, which serves as the hydrogen donor (Scheme 35).<sup>103</sup> Besides, the terminal alkynes with an alkyl substituent can undergo the similar reaction.<sup>103</sup>

Scheme 35

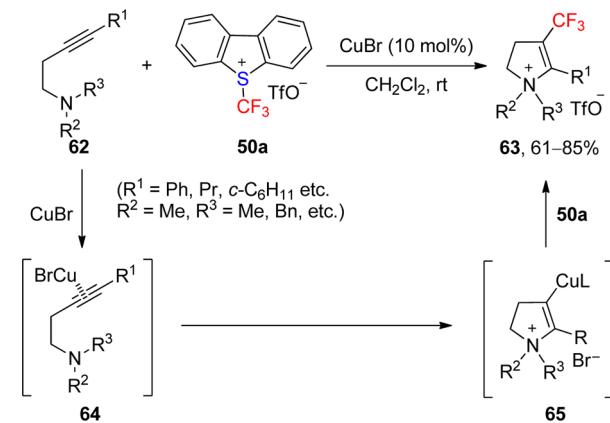


Very recently, the *S*-trifluoromethylsulfonium salt has been used for the synthesis of 4-trifluoromethyl-2,3-dihydropyrroliums **63** through CuBr-catalyzed domino cyclizations of homopropargyl amines **62** (Scheme 36). A plausible mechanism is the trifluoromethylation of the intermediate **65** by the sulfonium salt.<sup>104</sup>

### 3.1.5. Sulfinate Salts as Perfluoroalkylation Reagents.

Compared to perfluorinated carboxylic acids, whose oxidative decarboxylation is usually difficult,<sup>105</sup> the perfluoroalkanesulfinate salts ( $\text{R}_f\text{SO}_2\text{M}$ ) readily undergo oxidative desulfination to release perfluoroalkyl radicals due to the electron-richness of the sulfur atom. Therefore, perfluoroalkanesulfinate salts, which are commonly used as intermediates for the synthesis of sulfonyl halides and sulfonic acids,<sup>106</sup> have become an important class of bench-stable, user-friendly, and cost-effective

Scheme 36

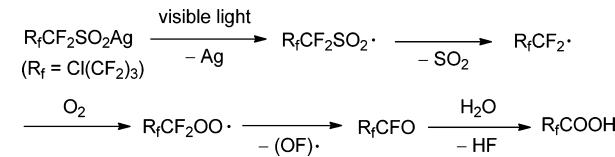


radical perfluoroalkylation reagents. Moreover, because of the water solubility of perfluoroalkanesulfinate salts, many reactions with them can be conducted in aqueous systems under very mild oxidative conditions with high functional group tolerance.

Perfluoroalkanesulfinate salts can be obtained in several ways. The early method for the preparation of perfluoroalkanesulfinate salts involves the reduction of perfluoroalkanesulfonyl fluorides or chlorides ( $\text{R}_f\text{SO}_2\text{F}$  or  $\text{R}_f\text{SO}_2\text{Cl}$ ) in the presence of reagents such as hydrazine,<sup>107</sup> sodium iodide,<sup>108</sup> zinc powder,<sup>109</sup> and sodium borohydride,<sup>110</sup> or the sulfination of perfluoroalkyl metals derived from perfluoroalkyl halides ( $\text{R}_f\text{X}$ , where X = Br or I) with sulfur dioxide.<sup>111</sup> In early 1980s, Huang and co-workers discovered a more convenient protocol to prepare perfluorinated sulfinate salts, that is, direct sulfinato-dehalogenation of  $\text{R}_f\text{X}$ , where X = Br or I, in the presence of a “ $\text{SO}_2$ ” source such as  $\text{Na}_2\text{S}_2\text{O}_4$ <sup>112</sup> and the application of this protocol has been extended to  $\text{R}_f\text{Cl}$  after a modification of the reaction conditions.<sup>113</sup> As for trifluoromethanesulfinate salts, in addition to the above-mentioned methods, other methods such as transformation of trifluoromethyl sulfones<sup>114</sup> and trifluoroacetates<sup>115</sup> are also available. In addition, the transition metal salts such as  $(\text{R}_f\text{SO}_2)_2\text{Cu}$  and  $\text{R}_f\text{SO}_2\text{Ag}$ , which have been used for the in situ generation of sulfonyl iodides (see Section 3.1.6), can be prepared by a metathesis between the corresponding sodium salts and nitrates in an aqueous solution.<sup>116</sup>

**3.1.5.1. Perfluoroalkylation ( $\text{R}_f = \text{C}_n\text{F}_{2n+1}$ ,  $n > 1$ ).** The transfer of a perfluoroalkyl ( $\text{R}_f$ ) with perfluorinated sulfinate salts relies on a desulfination process. In 1989, Huang and co-workers first proposed the direct generation of perfluoroalkyl radical from perfluoroalkanesulfinate salts through single-electron oxidation (Scheme 37), as was evidenced by the fact

Scheme 37

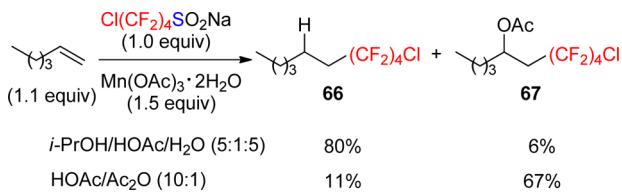


that silver perfluoroalkanesulfinate decomposed readily upon exposure to light in air to give perfluorinated carboxylic acids, Ag and  $\text{SO}_2$ .<sup>117</sup> The free radical type of reactivity was verified by treating sodium perfluoroalkanesulfinate either with mild oxidants such as cerium ammonium nitrate (CAN), or with electrolysis on a platinum anode, to afford a mixture of

perfluorinated carboxylic acids, perfluoroalkyl homocoupling products ( $R_f-R_f$ ), and 1-*H*-perfluoroalkanes ( $R_fH$ ) in varying ratios.<sup>117</sup> Furthermore, the perfluoroalkyl radical generated from UV-light irradiated aerobic oxidation of sodium perfluoroalkanesulfinate can be trapped by *t*-BuNO and detected by electron spin resonance (ESR) spectroscopy.<sup>118</sup> In this context, Huang and co-workers have developed perfluoroalkanesulfinate salts to be useful perfluoroalkylation reagents for the transformation of alkenes and (hetero)aromatic compounds under the action of various oxidants.<sup>119–125</sup>

**3.1.5.1.1. Perfluoroalkylation of Alkenes.** In alkene addition reactions, depending on the conditions used, either the hydroperfluoroalkylation or perfluoroalkylation-functionalization products can be formed as the major products.<sup>119</sup> For example, in the reaction of 1-hexene with sodium perfluoroalkanesulfinate  $Cl(CF_2)_4SO_2Na$  in the presence of  $Mn(OAc)_3 \cdot 2H_2O$  as oxidant at 80 °C, perfluoroalkylated alkane **66** was given as the major product with the addition of a good hydrogen atom source such as *i*-PrOH, whereas the oxy-perfluoroalkylation product **67** is formed predominantly in HOAc/Ac<sub>2</sub>O as solvent (Scheme 38).<sup>119b</sup> The further

Scheme 38

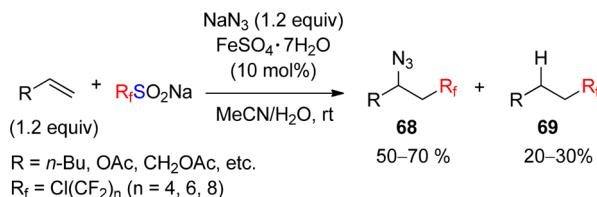


functionalization was proposed to arise from the capture of the carbocation, which is generated from the oxidation of  $\beta$ -perfluoroalkylated alkyl radical.<sup>119b</sup> In the presence of a chloride salt such as LiCl, the chloro-fluoroalkylated product is given in good yield. Other single-electron oxidizing agents, such as  $Ce(SO_4)_2$ ,  $HgSO_4$ , and  $Co_2O_3$ , can also be used to perform the reaction.<sup>119b</sup>

The perfluoroalkylation with  $R_fSO_2Na$  can proceed catalytically. Huang and Lu in 1992 achieved an iron-catalyzed perfluoroalkyl-azidation by performing the reaction of alkenes,  $R_fSO_2Na$  and sodium azide, with  $H_2O_2$  as the oxidant in the presence of  $FeSO_4 \cdot 7H_2O$  (10 mol %), in aqueous acetonitrile solution at room temperature (Scheme 39). However, the substrate scope is limited to electron neutral and rich alkenes; other alkenes such as styrene and methyl acrylate cannot take part in the reaction.<sup>120</sup>

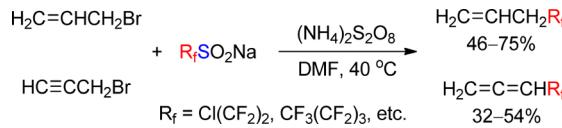
When allyl and propargyl halides are used instead of the simple alkenes, a radical addition–elimination reaction readily takes place; thus, treatment of allyl and propargyl halides with  $R_fSO_2Na$  in the presence of  $(NH_4)_2S_2O_8$  in DMF as solvent at 40 °C, gives allylic and allenic perfluoroalkylation products, respectively (Scheme 40). In contrast, the reactions of allyl

Scheme 39



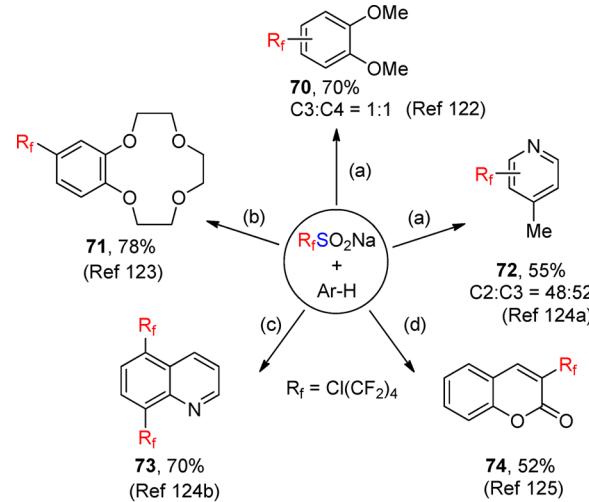
acetate and allyltrimethylsilane only gives the hydroperfluoroalkylation products.<sup>121</sup>

Scheme 40



**3.1.5.1.2. (Hetero)aromatic Perfluoroalkylation.** Under reaction conditions similar to that for the transformation of alkenes, the perfluoroalkylation of (hetero)arenes have been achieved through C–H substitution reactions (Scheme 41). The first

Scheme 41



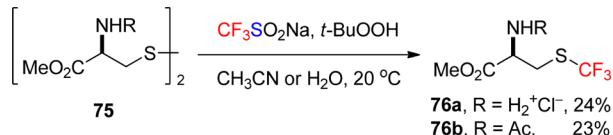
Conditions: (a)  $Mn(OAc)_3$ , MeCN/H<sub>2</sub>O/HOAc, 80 °C; (b)  $CeSO_4$ , MeCN/H<sub>2</sub>O/HOAc, 80 °C; (c)  $Mn(OAc)_3$ , MeCN/HOAc/Ac<sub>2</sub>O, 80 °C; (d)  $Mn(OAc)_3$ , MeCN/H<sub>2</sub>O/HOAc, 80 °C.

reported oxidative perfluoroalkylation of aromatic compounds is conducted with electron-rich arenes, such as 1,2-dimethoxybenzene, which gives a mixture of regioisomers, such as **70**, in moderate to good yields.<sup>122</sup> In the following investigation, it was found that the steric hindrance of the substituent can influence the regioselectivity, as is exemplified in the perfluoroalkylation of benzo-12-crown-4, which gives 4-substituted arene **71** as the only product.<sup>123</sup> This methodology has also been extended to the perfluoroalkylation of heteroarenes such as pyridines and quinolines.<sup>124</sup> In the reaction of quinoline, the electrophilic perfluoroalkyl radical preferentially attacks the relatively electron-rich benzene-ring, and its perfluoroalkylation with excess  $R_fSO_2Na$  affords the 5,8-disubstituted quinoline **73** as the product.<sup>124b</sup> On the contrary, in the case of coumarine, which is also a benzofused  $\alpha,\beta$ -unsaturated system, the perfluoroalkylation preferentially takes place on the alkene moiety to give 3-perfluoroalkyl-coumarine **74**, as the product.<sup>125</sup>

**3.1.5.2. Trifluoromethylation.** Although trifluoromethanesulfinate salts have similar reactivity to other perfluoroalkanesulfinate salts, their synthetic application in trifluoromethylation had never been demonstrated in Huang's pioneering work. In 1991, Langlois and co-workers first used sodium trifluoromethanesulfinate ( $CF_3SO_2Na$ ) to generate trifluoromethyl radical under oxidation conditions.<sup>126</sup> Thus, trifluoromethyl sulfides

were obtained from the reaction between disulfides and  $\text{CF}_3\text{SO}_2\text{Na}$  in the presence of an oxidizing agent such as *tert*-butyl hydroperoxide (TBHP), CAN, and  $\text{K}_2\text{S}_2\text{O}_8$ . Using TBHP as the optimal oxidant, S-trifluoromethylated amino acid esters **76**, has been obtained by reacting dithio-amino acid esters **75** with  $\text{CF}_3\text{SO}_2\text{Na}$  in acetonitrile or water as solvent (Scheme 42).<sup>127</sup> However, in the following 20 years since its first

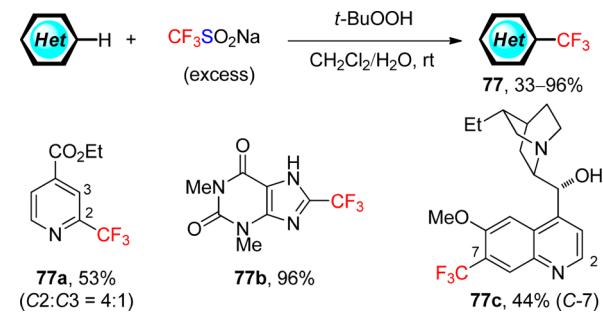
Scheme 42



discovery, only few examples on trifluoromethylation with  $\text{CF}_3\text{SO}_2\text{Na}$  appeared in literature, mostly with poor selectivity.<sup>128a–e</sup> Since 2011, the renaissance in free radical trifluoromethylation has emerged and much attention has been attracted to the use of  $\text{CF}_3\text{SO}_2\text{Na}$  as a trifluoromethyl radical source,<sup>129</sup> and this compound has become to be known as Langlois reagent.<sup>128f</sup>

**3.1.5.2.1. (Hetero)aromatic Trifluoromethylation.** Langlois and co-workers demonstrated that when electron-rich arenes and  $\text{CF}_3\text{SO}_2\text{Na}$  are subject to the oxidation conditions with TBHP in the presence of catalytic quantities of  $\text{Cu}(\text{OTf})_2$ , an aromatic hydrogen substitution gives trifluoromethylated arenes with poor regioselectivity. For instance, the reaction of *N*-phenylacetamide led to the *o*-, *m*-, and *p*-trifluoromethylated products in a 4:1:2 ratio.<sup>128a</sup> In 2011, Baran and co-workers disclosed a very practical C–H trifluoromethylation of *N*-heterocyclic compounds, which is applicable to a variety of heteroaromatic systems and exhibits high functional group tolerance, albeit in many cases with low to moderate regioselectivity (Scheme 43).<sup>129</sup> The reaction is noble metal-free and can be applied

Scheme 43



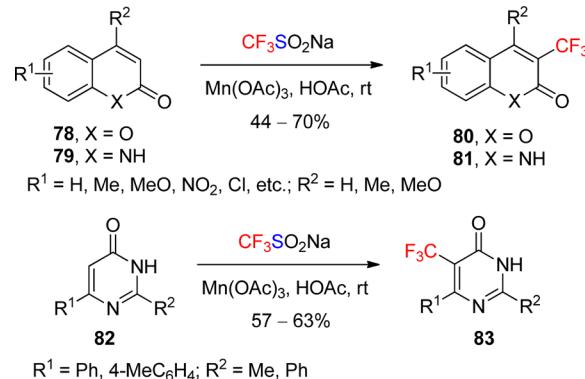
directly to the unprotected molecules. For instance, dihydroquinine, a cinchona alkaloid, reacts with  $\text{CF}_3\text{SO}_2\text{Na}$  in the presence of TBHP in  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  as solvent at room temperature, to give trifluoromethylation product **77c**, with regioselectivity toward the less steric-hindered *o*-position of methoxy group, also demonstrating the electrophilic property of  $\text{CF}_3$  radical.<sup>129</sup> The zinc salt  $(\text{CF}_3\text{SO}_2)_2\text{Zn}$ , with a highly active counteraction, can also be used for this transformation.<sup>130</sup>

Very recently, Fennewald and Lipshutz improved this reaction by using a recyclable, organic solvent-free medium consisting of the surfactant TPGS-750-M (2 wt %) and water.<sup>131</sup> A combination of  $\text{CF}_3\text{SO}_2\text{Na}$  and TBHP can be used

to effect trifluoromethylation of several heterocyclic arrays, including heteroaromatics at room temperature.

In addition to TBHP, other oxidants, manganese(III) salts<sup>132</sup> and hypervalent iodine reagents,<sup>133</sup> have also been explored for C–H trifluoromethylation of (hetero)aromatics.  $\text{Mn}(\text{OAc})_3$ -mediated direct trifluoromethylation of coumarins **78** with  $\text{CF}_3\text{SO}_2\text{Na}$ , which is conducted similar to the previously reported perfluoroalkylation of coumarins,<sup>125</sup> affords 3-trifluoromethyl coumarins **80** in moderate to good yields.<sup>132</sup> This oxidant is also applicable for the trifluoromethylation of quinolinones **79** and pyrimidinones **82** (Scheme 44). Although

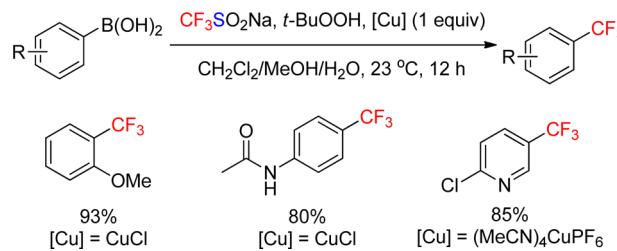
Scheme 44



trifluoromethylation of electron rich aromatics with the combination of  $\text{CF}_3\text{SO}_2\text{Na}/\text{PIFA}$  (phenyliodine bis(trifluoroacetate)) is of poor *o/m/p* selectivity, the reaction can proceed within a very short period of time (5 min).<sup>133</sup>

As a complementary to the above-mentioned C–H trifluoromethylation of (hetero)arenes, the copper-assisted trifluoromethylation of (hetero)aryl boronic acids or trifluoroborates can regiospecifically introduce a  $\text{CF}_3$  into the aromatic rings.<sup>134</sup> A representative contribution from Sanford is shown in Scheme 45. Using TBHP as the oxidant, the reaction of

Scheme 45



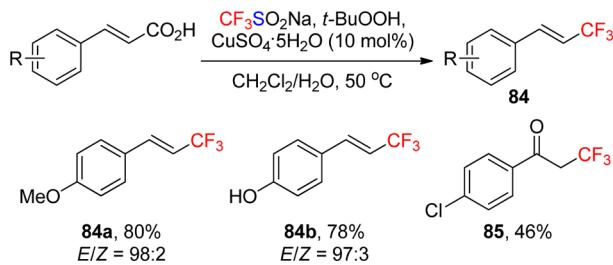
(hetero)aryl boronic acids and  $\text{CF}_3\text{SO}_2\text{Na}$  proceeds smoothly in the presence of stoichiometric quantities of a Cu(I) salt at room temperature, affording the trifluoromethylation products in high yields.<sup>134a</sup> The reaction can also be performed with catalytic amount of a Cu(II) salt, such as  $\text{Cu}(\text{OAc})_2$ ; however, the yields are somewhat lower than the stoichiometric method.<sup>134b</sup> Additionally, trifluoromethylated alkenes<sup>134b–d</sup> and alkynes<sup>135</sup> have been accessed from the corresponding boronic acids or trifluoroborates under similar conditions.

**3.1.5.2.2. Trifluoromethylation of Alkenes and Alkynes.** Similar to other perfluorinated sulfinate salts,  $\text{CF}_3\text{SO}_2\text{Na}$  is capable, under mild oxidative conditions, of converting alkenes to structurally diverse aliphatic trifluoromethylation com-

pounds, a process most probably dictated by the initial  $\text{CF}_3$  radical addition to  $\text{C}=\text{C}$  double bond. According to the structures of alkenes and the conditions used, mechanistically, the  $\beta$ -trifluoromethyl alkyl radical intermediate can undergo either  $\beta$ -elimination or further functionalization. Notably, using  $\text{CF}_3\text{SO}_2\text{Na}$  as the radical source, the trifluoromethylation of electron-deficient alkenes, which is disfavored in atom transfer radical addition reactions, can be achieved by a reasonable design of the tandem process, such as oxidative  $\beta$ -elimination,<sup>136,137</sup> radical termination,<sup>138–141</sup> and radical cyclization<sup>142,143</sup> to drive the reaction.

$\alpha,\beta$ -Unsaturated carboxylic acids, which are frequently used in transition metal-catalyzed decarboxylative cross-coupling reactions, can also undergo trifluoromethylation to afford trifluoromethylated alkenes, which is first demonstrated with a hypervalent iodine reagent, 1-(trifluoromethyl)-1,2-benziodoxol-3(1H)-one, as the limiting reactant.<sup>144</sup> By using the much more stable  $\text{CF}_3\text{SO}_2\text{Na}$  as an alternative trifluoromethyl source, several oxidative decarboxylative trifluoromethylations in the presence of copper or iron have been achieved (Scheme 46).<sup>136</sup>

Scheme 46

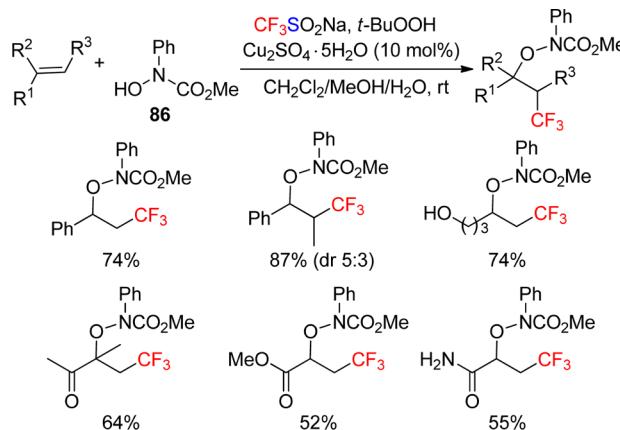


However, when only copper salt, such as  $\text{CuSO}_4$ , is used as the catalyst, the TBHP-promoted trifluoromethylation of electron-deficient aryl substituted acids, such as (*E*)-3-(4-chlorophenyl)-acrylic acid, gives  $\beta$ -trifluoromethyl ketones, such as **85**, instead of the desired trifluoromethyl alkenes.<sup>136a</sup> A modification of the reaction conditions by using  $\text{Ag}_2\text{CO}_3$  as an additive not only suppresses the formation of ketones, but also expands the substrate scope; both  $\beta$ -mono- and disubstituted acids are converted to the desired alkenes with high *E*-selectivity.<sup>136b</sup> Considering that  $\text{K}_2\text{S}_2\text{O}_8/\text{FeCl}_3$  oxidation system also works for this transformation,<sup>136c</sup> the decarboxylation is more likely to proceed through the single-electron oxidation of the benzylic radical that arises from the addition of a  $\text{CF}_3$  radical to the carboxylic acids.<sup>136a</sup>

A typical example for the radical termination reaction is a recently reported Cu-catalyzed oxy-trifluoromethyl addition to alkenes, which is conducted with  $\text{CF}_3\text{SO}_2\text{Na}$  and hydroxamic acids **86** under the oxidation of TBHP (Scheme 47).<sup>138</sup> In the reaction, both  $\text{CF}_3$  and amidoxy radicals are generated via oxidation of their precursors with  $\text{CuSO}_4$  as the catalyst, and react with alkenes through  $\text{CF}_3$  radical addition to  $\text{C}=\text{C}$  followed by trapping of the newly formed radical with amidoxy radical. Importantly, not only unactivated alkenes such as styrenes and aliphatic alkenes, but also activated alkenes such as  $\alpha,\beta$ -unsaturated esters, ketones, and amides can undergo this oxytrifluoromethylation with high functional group tolerance.<sup>138</sup>

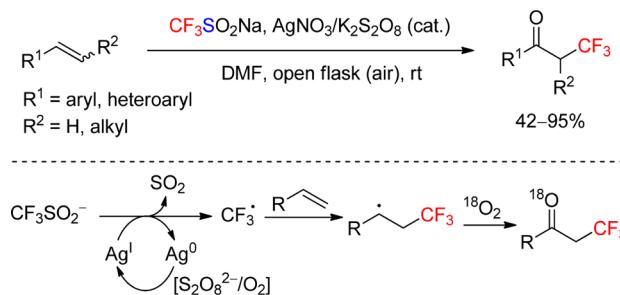
A similar type of example is the Ag-catalyzed oxidative trifluoromethylation of unactivated aromatic alkenes with  $\text{K}_2\text{S}_2\text{O}_8$  as the cocatalyst and air as the oxidant to afford  $\beta$ -

Scheme 47



trifluoromethyl ketones in moderate to excellent yields (42–95%) (Scheme 48).<sup>140</sup> However, the reaction of aliphatic

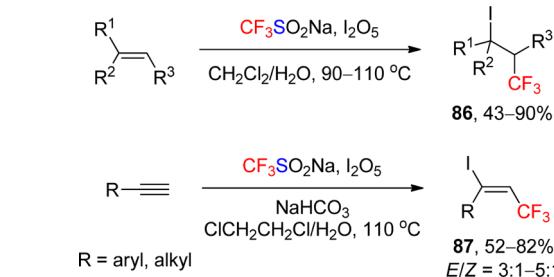
Scheme 48



alkenes is complicated and usually gives an inseparable mixture. An  $^{18}\text{O}$ -labeling experiment confirmed that the oxygen atom of the ketone comes from both air and  $\text{K}_2\text{S}_2\text{O}_8$ .<sup>140</sup>

Very recently, Liu and co-workers have developed a scalable, selective, and operationally easy iodotrifluoromethylation of a wide range of alkenes and alkynes by using the combination of  $\text{CF}_3\text{SO}_2\text{Na}/\text{I}_2\text{O}_5$  as an alternative for the gaseous trifluoriodomethane ( $\text{CF}_3\text{I}$ ) (Scheme 49).<sup>141</sup> This strategy can be used for the convenient preparation of a series of  $\text{CF}_3$ -containing building blocks such as  $\beta$ - $\text{CF}_3$  alkyl iodides **86** and  $\beta$ - $\text{CF}_3$  alkenyl iodides **87**.

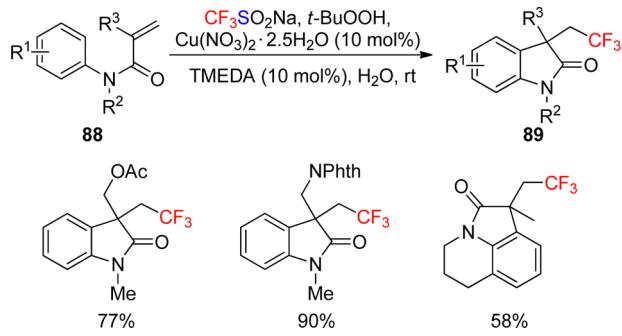
Scheme 49



Oxindoles are important scaffolds used in medicinal and biological chemistry because of their unique bioactivities. Recently, many methods have been developed for the synthesis of trifluoromethylated oxindoles **89** by the reaction of *N*-arylacrylamides **88** with various trifluoromethyl sources, among which,  $\text{CF}_3\text{SO}_2\text{Na}$  is one of the most economical reagents.<sup>142</sup>

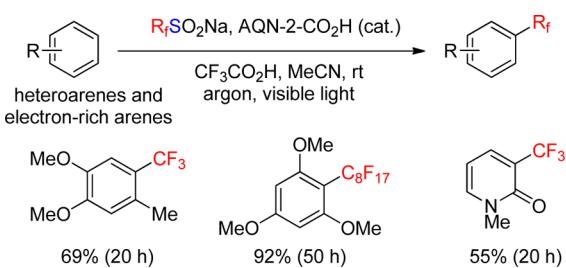
The trifluoromethylation with  $\text{CF}_3\text{SO}_2\text{Na}$  proceeds through the addition of a  $\text{CF}_3$  radical to the alkene followed by radical cyclization. To achieve the reaction, both metal-catalyzed<sup>142a,b</sup> and metal-free<sup>142c,e</sup> oxidative conditions have been developed to generate a  $\text{CF}_3$  radical from  $\text{CF}_3\text{SO}_2\text{Na}$ . Of note is that the Cu-catalyzed reaction can be performed in water at room temperature, and the aqueous medium can be easily recycled and reused without additional Cu-catalyst (Scheme 50).<sup>142a</sup>

Scheme 50



**3.1.5.3. Photoredox Catalysis.** In the reactions with perfluorinated sulfinate salts described thus far, the generation of the perfluoroalkyl radical needs stoichiometric quantities of additional oxidants to accept electrons from the sulfinate. Exceptionally, two recent contributions have described an additional oxidant free method to realize the perfluoroalkyl transfer, which relies on the single electron oxidation of the sulfinate by organic photoredox catalysts under the irradiation of visible light.<sup>145</sup> Itoh and co-workers reported the C–H perfluoroalkylation of arenes and heteroarenes using anthraquinone-2-carboxylic acid (AQN-2-CO<sub>2</sub>H) as catalyst, in which SO<sub>2</sub> is proposed to be the oxidant to regenerate the catalyst, and the perfluoroalkyl radical as the hydrogen abstractor to aromatize the perfluoroalkyl-arene adduct (Scheme 51).<sup>145a</sup>

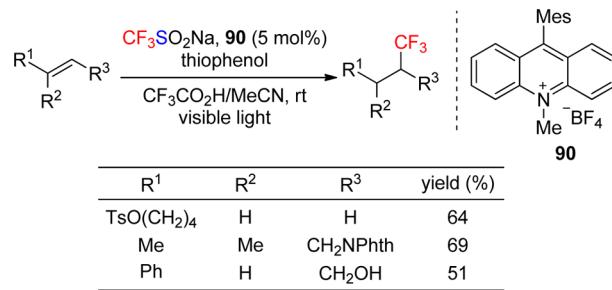
Scheme 51



Nicewicz and co-workers reported the hydrotrifluoromethylation of styrenes and unactivated alkenes with *N*-methyl-9-mesityl acridinium tetrafluoroborate (**90**) as the catalyst, which proceeds smoothly in the presence of a hydrogen donor to afford the products in moderate yields (29–69%) with high regioselectivity (Scheme 52).<sup>145b</sup> In this reaction, the radical generated from the hydrogen source, such as thiophenols, is suggested to be the oxidant to regenerate the acridinium cation.

**3.1.6. Sulfonyl Halides as Perfluoroalkylation Reagents.** Compared to the perfluoroalkanesulfinate salt, which needs an additional oxidant to generate the perfluoroalkyl radicals, the perfluoroalkanesulfonyl halides  $\text{R}_f\text{SO}_2\text{X}$ , where X = Cl, Br, I, produce the perfluoroalkyl radicals with loss of SO<sub>2</sub>

Scheme 52



under redox neutral conditions. The stronger electron-withdrawing ability of perfluoroalkanesulfonyl group than a simple perfluoroalkyl group significantly improves the electropositivity of the halide atom in  $\text{R}_f\text{SO}_2\text{X}$  than that in the corresponding  $\text{R}_f\text{X}$ ; therefore,  $\text{R}_f\text{SO}_2\text{X}$  can be used as a superior perfluoroalkyl halide.<sup>146</sup> On one hand, in radical chain reactions,  $\text{R}_f\text{SO}_2\text{X}$  can take part in a much faster chain transfer process than  $\text{R}_f\text{X}$ , thus allowing alkenes and alkynes that are difficult to react with  $\text{R}_f\text{X}$  to smoothly undergo haloperfluoroalkylation. On the other hand, in single-electron-transfer process,  $\text{R}_f\text{SO}_2\text{X}$  are more powerful electron acceptors than  $\text{R}_f\text{X}$ , which permits transition metal-promoted perfluoroalkylation to be carried out under mild conditions. The reactivity of the three sulfonyl halides increases in the following order: Cl < Br < I.<sup>147</sup> Perfluoroalkanesulfonyl chlorides, bromides, and iodides have been used for the perfluoroalkylation of unsaturated systems such as alkenes and aromatics.

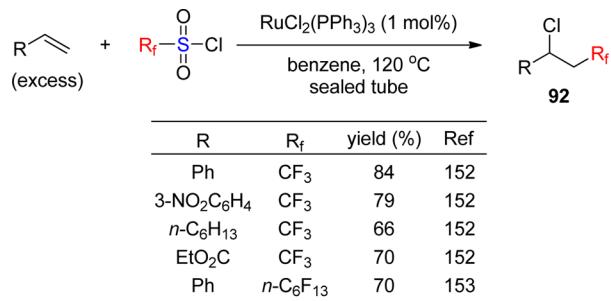
A general method to prepare perfluoroalkanesulfonyl chlorides and bromides is the halogenation of the corresponding sulfinate salts in aqueous solution with Cl<sub>2</sub> or Br<sub>2</sub>.<sup>106,148</sup> Perfluoroalkanesulfonyl chlorides can also be prepared by chlorination of the sulfonic acids or sulfonate salts with phosphorus pentachloride.<sup>149</sup> Perfluoroalkanesulfonyl iodides, which are less stable than other sulfonyl halides due to the ready extrusion of SO<sub>2</sub>,<sup>112a,150</sup> has been prepared in situ by iodination of the corresponding copper(II) sulfinate salts with KI or silver(I) sulfinate salts with I<sub>2</sub>.<sup>116</sup>

**3.1.6.1. Perfluoroalkylation of Alkenes.** The earliest application of perfluoroalkanesulfonyl halides (including trifluoromethanesulfonyl chloride) in perfluoroalkylation is probably the radical addition of  $\text{R}_f\text{SO}_2\text{Cl}$  to aliphatic alkenes under the initiation of peroxides or UV light to afford the net  $\text{R}_f\text{Cl}$  adducts, which has appeared in several patent documents in 1960s.<sup>26,151</sup>

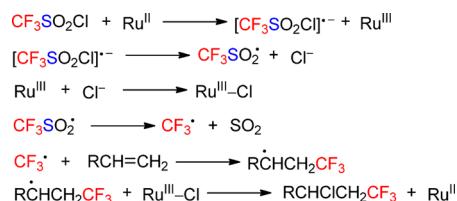
In 1989, Kamigata and co-workers introduced  $(\text{Ph}_3\text{P})_3\text{RuCl}_2$  as an effective catalyst to conduct the similar reaction.<sup>152</sup> The reaction with perfluoroalkanesulfonyl chlorides, such as  $\text{CF}_3\text{SO}_2\text{Cl}$  (**91**), is compatible with both electron-neutral and -deficient alkenes, producing chloro-perfluoroalkylation products **92** in moderate to good yields (Scheme 53).<sup>152,153</sup> However, it was found that a temperature as high as 120 °C is required to achieve a complete perfluoroalkylation; at a lower temperature, the perfluoroalkanesulfonylation occurs as a side reaction.<sup>154</sup> This Ru(II)-catalyzed reaction is proposed to proceed via a single-electron transfer process, as is shown in Scheme 54.<sup>152</sup>

Very recently, a new approach has been applied to realize such a transformation, which relies on a combination of the transition metal catalysis and photoredox strategy.<sup>103,155</sup> The reaction of  $\text{CF}_3\text{SO}_2\text{Cl}$  (**91**) with aliphatic alkenes in the

Scheme 53

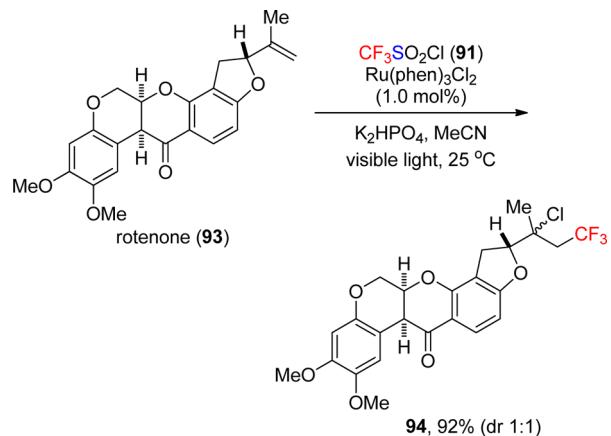


Scheme 54



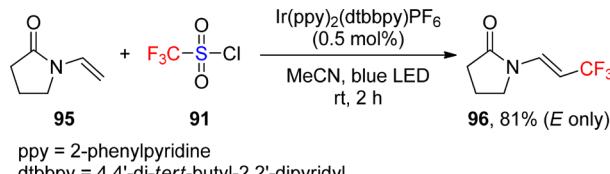
presence of a catalytic quantity of  $\text{Ru}(\text{phen})_3\text{Cl}_2$  (phen = phenanthroline), upon the irradiation of visible light at ambient temperature, gives the chloro-trifluoromethylation product in high yields (54–99%) (Scheme 55). For example, the chloro-trifluoromethylation of rotenone (93), which has been used as an effective pesticide, afforded 94 in 92% yield, albeit with 1:1 diastereoselectivity.<sup>155</sup>

Scheme 55



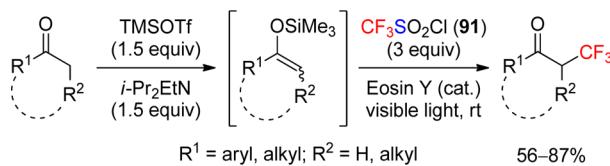
In the cases of electron-rich alkenes, following the trifluoromethyl radical addition, a facile  $\beta$ -elimination readily takes place to give the chlorine-free products.<sup>156</sup> The reaction of  $\text{CF}_3\text{SO}_2\text{Cl}$  (91) with enamides, such as 95, under the catalysis of an Ir(III) complex upon irradiation of visible light, gives the C–H trifluoromethylation products, such as 96, a possible mechanism being the single-electron oxidation of the trifluoromethylated  $\alpha$ -amidoalkyl radical to  $N$ -acyliminium cation followed by deprotonation (Scheme 56).<sup>156c</sup> The reaction of enol acetates with  $\text{CF}_3\text{SO}_2\text{Cl}$  under similar conditions affords trifluoromethyl ketones in good yields.<sup>156d</sup> Very recently,  $\beta$ -trifluoromethyl ketones have been prepared from the enolizable ketones and  $\text{CF}_3\text{SO}_2\text{Cl}$  (91) by means of a continuous flow, 2-step procedure, which relies on trifluor-

Scheme 56



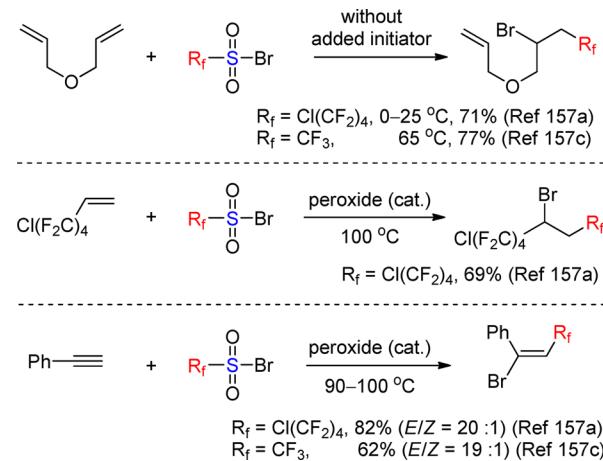
omethylation of the silyl enol ether intermediates using Eosin-Y as the organic photoredox catalyst (Scheme 57).<sup>156e</sup>

Scheme 57



Compared to perfluoroalkanesulfonyl chlorides, perfluoroalkanesulfonyl bromides<sup>157</sup> and iodides<sup>116</sup> are more reactive toward alkenes. Huang and co-workers showed that perfluoroalkanesulfonyl bromides react with alkenes and alkynes to give the bromo-perfluoroalkylation adducts (Scheme 58).<sup>157</sup> Inter-

Scheme 58

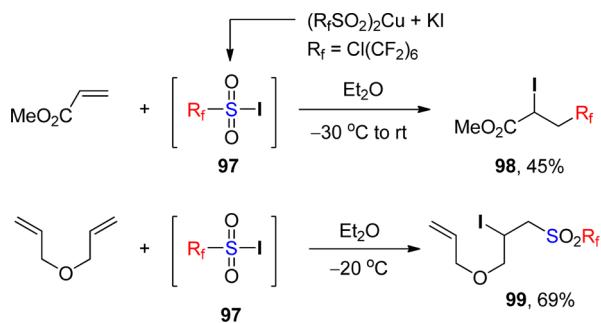


estingly, the reaction of  $\text{R}_f\text{SO}_2\text{Br}$  with electron-rich alkenes proceeds smoothly in the absence of a peroxide initiator, and it is not suppressed by a small amount of radical inhibitor such as hydroquinone, as well as electron scavenger such as 1,4-dinitrobenzene. In the case of diallyl ether, which usually gives a cyclization product in a typical radical addition reaction, its reaction with  $\text{R}_f\text{SO}_2\text{Br}$  only produces the linear monoadduct,<sup>157a</sup> suggesting that the chain transfer between the intermediated  $\beta$ -perfluoroalkylated alkyl radical and  $\text{R}_f\text{SO}_2\text{Br}$  is much faster than that of the cyclization process due to the facile cleavage of S–Br bond.<sup>157c</sup> However, the reaction of  $\text{R}_f\text{SO}_2\text{Br}$  with electron-deficient alkenes and alkynes requires added peroxide to initiate the reaction.<sup>157a,c</sup>

Perfluoroalkanesulfonyl iodides ( $\text{R}_f\text{SO}_2\text{I}$ ) are only of intermediate stability and can be *in situ* generated from  $(\text{R}_f\text{SO}_2)_2\text{Cu}$  or  $\text{R}_f\text{SO}_2\text{Ag}$  at –20 to –30 °C, and react with alkynes and some relatively electron-deficient alkenes such as methyl acrylate to give the iodo-perfluoroalkylation products,

such as **98** (Scheme 59).<sup>116</sup> The reaction of electron-rich alkenes such as diallyl ether, however, affords the monoaddition products **99** without extrusion of  $\text{SO}_2$ .<sup>116</sup>

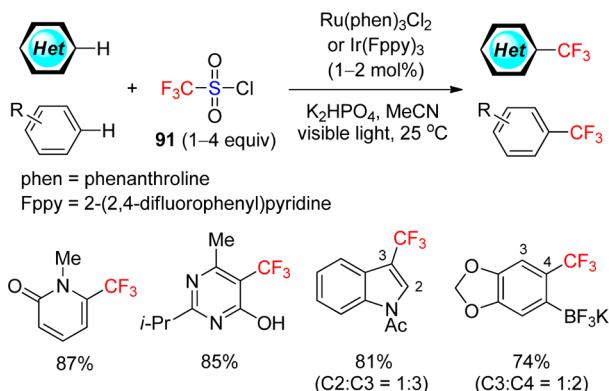
Scheme 59



**3.1.6.2. Aromatic Perfluoroalkylation.** Perfluoroalkanesulfonyl chlorides have also been used for C–H perfluoroalkylation of aromatic systems. The early applications focus on light-initiated<sup>148</sup> or Ru(II)-catalyzed<sup>158</sup> perfluoroalkylation of simple arenes, *N*-substituted pyrroles, and thiophenes at high temperatures (such as 120 °C) by using excess amounts of substrates (2 to 5 equiv), usually leading to moderate yields with limited functional group tolerance.

In 2011, a contribution from MacMillan's group described an efficient and general photoredox strategy for trifluoromethylation of (hetero)aromatic compounds with a Ru(II) or Ir(III) complex as photosensitizer at ambient temperature, which is achieved by taking advantage of the good electron-accepting ability of  $\text{CF}_3\text{SO}_2\text{Cl}$  ( $E_{1/2}^{\text{red}} = -0.18$  V vs SCE) than  $\text{CF}_3\text{I}$  ( $E_{1/2}^{\text{red}} = -1.52$  V vs SCE) (Scheme 60).<sup>146c</sup> This photoredox

Scheme 60



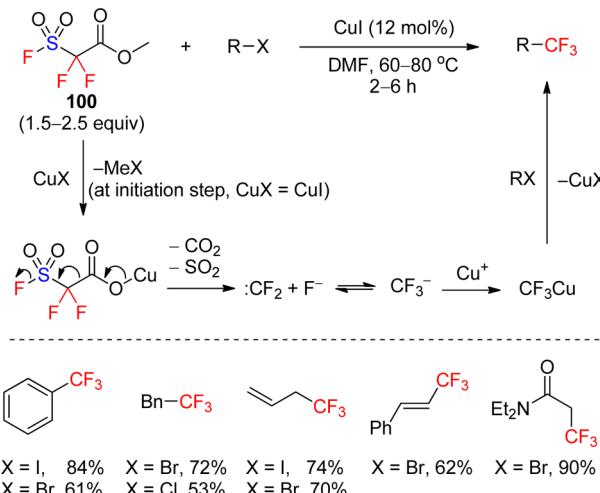
strategy enables the selective incorporation of trifluoromethyl group into a broad range of simple benzene derivatives and (hetero)arene rings, such as unprotected pyrroles and indoles, furans, thiophenes, thiazoles, pyridines, pyrazines, and pyrimidines at the relatively electron-rich site with tolerance of potential reactive functional groups such as trifluoroborate and alcoholic hydroxyl.

**3.1.7. Tetrafluoroethane  $\beta$ -Sultone Derivatives as Difluorocarbene Sources for Transition Metal-Mediated Trifluoromethylation.** As a classical transformation, trifluoromethylation of organohalides is one of the most reliable methods to obtain trifluoromethylated compounds.<sup>12t</sup> Among various trifluoromethyl sources, methyl fluorosulfonyldifluor-

acetate (also called as Chen reagent, **100**) derived from tetrafluoroethane  $\beta$ -sultone (an important intermediate in the manufacture of perfluorinated sulfonic acid ion exchange resins) is an inexpensive, stable, and mild reagent for trifluoromethylation of (hetero)aryl, alkenyl, allyl, even alkyl halides with good functional groups tolerance.<sup>159</sup>

In 1989, Chen and Wu first disclosed the use of **100** as reagent for the trifluoromethylation of a wide range of organohalides, with procedures being carried out in the presence of a catalytic amount of CuI (12 mol %) in DMF as solvent at moderately high temperatures (60–80 °C) (Scheme 61).<sup>159</sup> Note that this is also the first example of a

Scheme 61

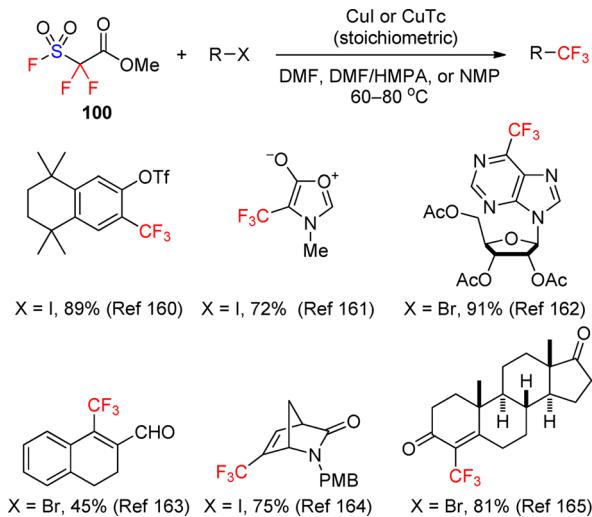


copper-catalyzed aromatic trifluoromethylation. The reaction proceeds most probably with the participation of a  $\text{CuCF}_3$  species as the key intermediate, which is formed through the copper-promoted decomposition of **84** to fluoride and difluorocarbene followed by their recombination. A modification of the reaction conditions by using stoichiometric amounts of CuI has led to the successful preparation of many important intermediates and target molecules from the corresponding bromides or iodides, with some examples being shown in Scheme 62.<sup>160–165</sup>

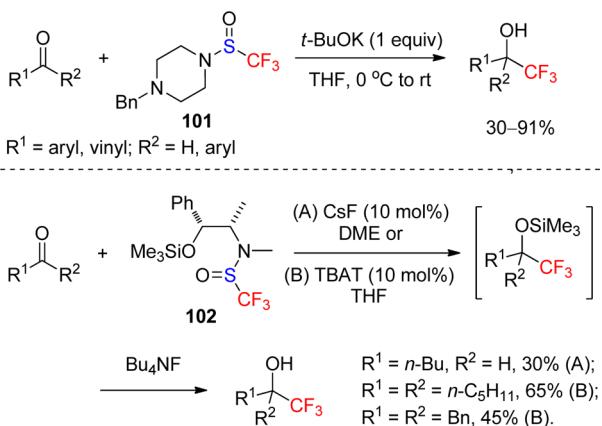
For more information on the trifluoromethylation with various tetrafluoroethane  $\beta$ -sultone derivatives bearing a  $\text{FSO}_2\text{CF}_2$  moiety, such as  $\text{FSO}_2\text{CF}_2\text{I}$ ,  $\text{FSO}_2(\text{CF}_2)_2\text{O}(\text{CF}_2)_2\text{I}$  and  $\text{FSO}_2(\text{CF}_2)_2\text{OCF}_2\text{CO}_2\text{R}$ , one is suggested to refer to a recent comprehensive review.<sup>12k</sup>

**3.1.8. Other Sulfur-Based Perfluoroalkylation Reagents.** Trifluoromethanesulfonic acid esters and trifluoromethanesulfonamides have also been used as trifluoromethyl anion sources. In early 2003, Billard and Langlois and co-workers demonstrated an alkoxide-induced trifluoromethylation of electrophiles such as aldehydes, ketones and disulfides, using secondary trifluoromethanesulfonamides and alkyl trifluoromethanesulfonates, which can be easily prepared from trifluoromethanesulfinate salts.<sup>166</sup> The reaction with benzophenone and benzaldehyde in the presence of *t*-BuOK showed that trifluoromethanesulfonamides are more efficient than the trifluoromethanesulfonates, with the *N*-benzylpiperazine derivative **101** giving the optimal results. The scope of carbonyl compounds, however, is limited to nonenolizable aldehydes and ketones due to the use of strong base *t*-BuOK (Scheme 63).

Scheme 62



Scheme 63

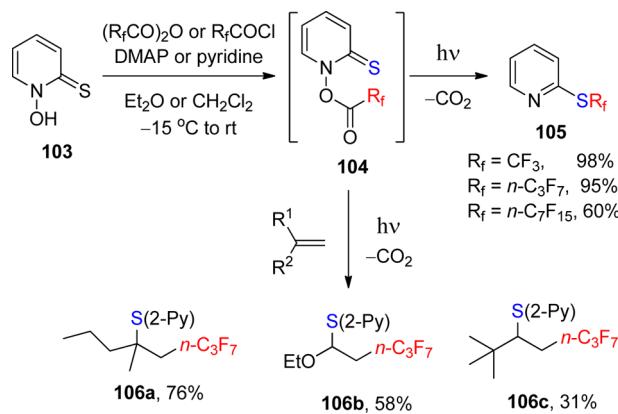


When trifluoromethanesulfonamide **102** is used as the reagent,<sup>166</sup> both nonenolizable and enolizable carbonyl compounds can be trifluoromethylated under the initiation of catalytic quantities of cesium fluoride or tetrabutylammonium triphenyldifluorosilicate (TBAT) to give  $\alpha$ -trifluoromethyl alcohols in moderate to good yields (30–90%) (Scheme 63).

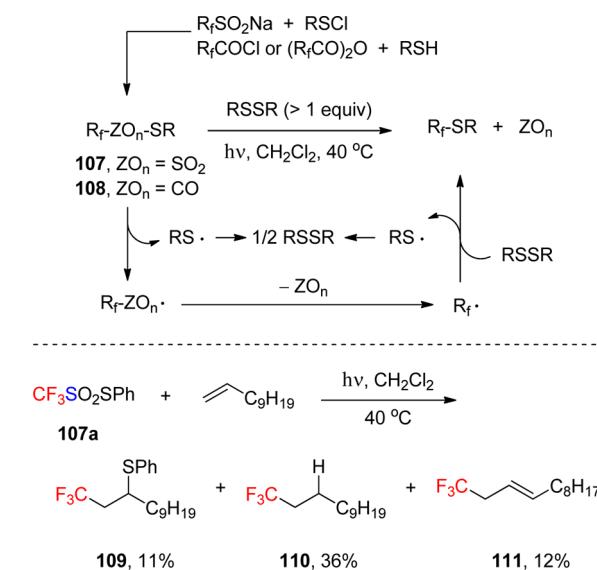
In 1983, Barton and co-workers developed a mild and efficient method for producing alkyl radicals from primary, secondary and tertiary aliphatic and alicyclic carboxylic acids via their thiohydroxamate esters (Barton esters).<sup>167</sup> This decarboxylation methodology has been extended to the transformation of perfluorinated acids (Scheme 64).<sup>168</sup> Irradiating the Barton esters **104** in situ generated from perfluorinated acid anhydrides or chlorides and 1-hydroxypyridine-2(1*H*)-thione (**103**) affords the perfluoroalkyl 2-pyridyl sulfides **105** in high yields. The perfluoroalkyl radicals can also be trapped by electron-rich alkenes to give the thioperfluoroalkylation products **106**; however, perfluoroalkyl sulfides **105** are usually formed as the major side products due to the highly electrophilic nature of the perfluoroalkyl radicals.

In 1999, Langlois and co-workers showed that in the presence of stoichiometric amounts of disulfides, thioesters of perfluoroalkanesulfonic acids and perfluorinated carboxylic acids,  $R_fSO_2SR$  (**107**) and  $R_fCOSR$  (**108**), can undergo formal photolytic desulfonylation and decarbonylation, respectively, via a radical mechanism (Scheme 65).<sup>128d</sup> The perfluoroalkyl

Scheme 64



Scheme 65



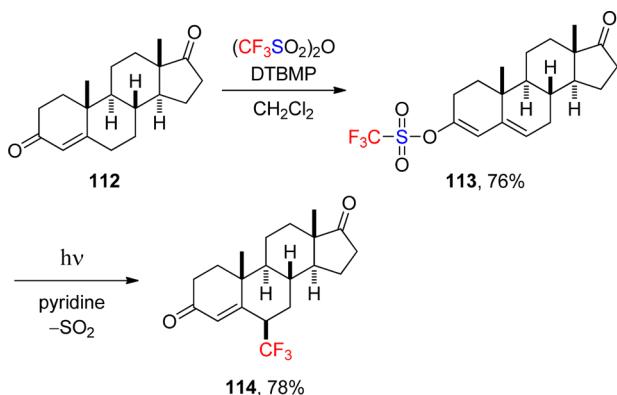
radical generated from **107** and **108** can also be trapped by alkenes to afford thioperfluoroalkylation and/or hydroperfluoroalkylation products; however, in some cases, the allylic perfluoroalkylation products arising from disproportionation of the radical addition intermediate are formed as by-products.<sup>169</sup> For instance, the reaction of phenyl trifluoromethanethiosulfonate (**107a**) and undec-1-ene in 1:1 molar ratio gives a mixture of **109**, **110**, and **111** in 11%, 36%, and 12% yields, respectively (Scheme 65).

Triflic acid anhydride ( $Tf_2O$ ) is also a possible but not often used trifluoromethylation reagent.<sup>170,171</sup> In 1987, Elliott and co-workers disclosed that the steroidal dienol triflate prepared from the corresponding enone via treatment with triflic acid anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) can undergo rearrangement to give  $6\beta$ -trifluoromethyl enone.<sup>171a</sup> Thus, photolysis of **113** in pyridine solution using a medium pressure mercury lamp leads to **114** in 78% yield (Scheme 66). The reaction probably proceeds through the generation of a  $CF_3$  radical via homolytic cleavage of the S–O bond followed by a fragmentation of the  $CF_3SO_2$  radical via loss of sulfur dioxide.

### 3.2. For Difluoromethylation

The difluoromethyl group can be used as a bioisostere of a carbinol moiety and as a more lipophilic hydrogen bond

### Scheme 66



donor.<sup>172</sup> However, in sharp contrast to the trifluoromethylation, the available reagents for direct difluoromethylation are largely limited to electrophilic reactions, not to mention the lack of general applicability.<sup>13d</sup> The direct nucleophilic difluoromethylation reagents represented by (difluoromethyl)-silanes<sup>173</sup> and (difluoromethyl)stannanes<sup>174</sup> also suffer from limitations such as harsh reaction conditions and narrow substrate scope. The installation of a removable functional group on the difluoromethylene, not only facilitates the generation of the specific reactive species for fluoroalkylation, but also provides opportunities to achieve synthetic diversity. Among all the available removable functional group-assisted nucleophilic difluoromethylations,<sup>13d,175</sup> difluoromethylations with  $\alpha$ -difluorinated sulfides, sulfoxides, sulfones, and sulfoximines constitute a major strategy for the selective introduction of a CF<sub>2</sub>H group due to the versatile chemistry of organic sulfur compounds;<sup>19</sup> not only nucleophilic difluoromethylation, but also radical and electrophilic difluoromethylation have been realized with these sulfur-based reagents.<sup>13h</sup> Moreover, many direct difluoromethylation reactions, that is, the direct transfers of a CF<sub>2</sub>H group into organic molecules, also rely on the sulfur-based reagents, such as sulfonium salts, sulfoximines, sulfinate salts, and tetrafluoroethane  $\beta$ -sultone derivatives. Although several reviews dealing with special topics including selective fluoroalkylation,<sup>13g</sup> synthetic application of difluorocarbene,<sup>13c</sup> C-difluoromethylation,<sup>13d</sup> as well as difluoro(phenylsulfonyl)methylation,<sup>13h</sup> have covered a part of this chemistry, this section aims to provide a full review on difluoromethylation with all the available sulfur-based reagents, with an emphasis on the most recent development.

### 3.2.1. Sulfides and Xanthates as Difluoromethylation

**Reagents.** Since an arylthio group can be readily substituted by a hydrogen atom via radical desulfenylation or oxidation—desulfonylation, the difluoro(arylthio)methylation can serve as an effective approach to introduce a difluoromethyl group.

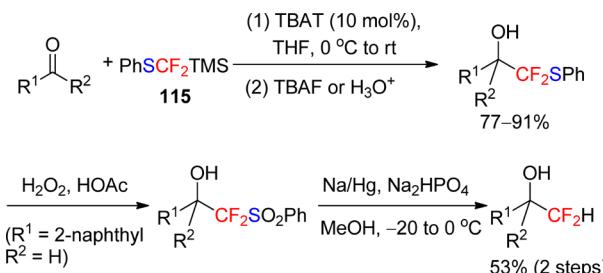
### *3.2.1.1. Nucleophilic Difluoro(phenylthio)methylation.*

One method for introducing a PhSCF<sub>2</sub> group is the nucleophilic difluoro(phenylthio)methylation with [difluoro(phenylthio)methyl]trimethylsilane (PhSCF<sub>2</sub>TMS, 115) or difluoromethyl phenyl sulfide (PhSCF<sub>2</sub>H, 116).

In 2003, Prakash, Hu and Olah described the preparation of PhSCF<sub>2</sub>TMS (**115**) from bromodifluoromethyl phenyl sulfide (PhSCF<sub>2</sub>Br, **117**), magnesium, and trimethylsilyl chloride (TMSCl) in DMF as solvent via a Barbier coupling process.<sup>64</sup> In 2005, the authors demonstrated the nucleophilic difluoro-(phenylthio)methylation of simple carbonyl compounds with **115** under the initiation of a catalytic amount of tetrabutyl-

lammonium triphenyldifluorosilicate (TBAT), which proceeds in a similar manner as the nucleophilic trifluoromethylation with  $\text{TMSCF}_3$  (Scheme 67).<sup>176</sup> This new methodology

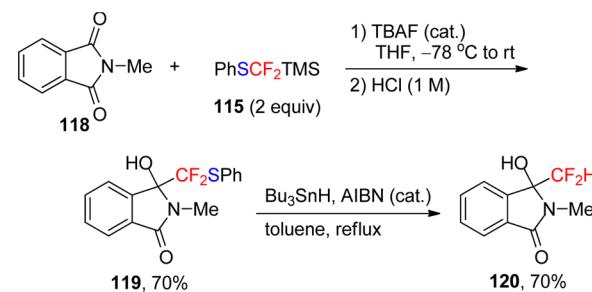
**Scheme 67**



efficiently transfers PhSCF<sub>2</sub> group into both enolizable and nonenolizable aldehydes as well as ketones to give  $\alpha$ -difluoro(phenylthio)methylated alcohols in good to excellent yields (77–91%). Although radical desulfenylation is an effective method to remove the phenylthio group, an alternative method, the oxidation-desulfonylation, was used by the authors to transform the PhSCF<sub>2</sub>-containing alcohols into  $\alpha$ -difluoromethyl alcohols in moderate yields, which avoids the use of toxic tributyltin hydride (Bu<sub>3</sub>SnH).<sup>176</sup> Moreover, the silylated carbinol intermediates obtained by reacting 115 and aromatic aldehydes can be transformed to difluoromethyl ketones via oxidation to sulfoxides followed by flash vacuum pyrolytic elimination.<sup>177</sup>

In addition to simple aldehydes and ketones, mult carbonyl compounds such as  $\alpha$ - and  $\gamma$ -ketoesters,<sup>178</sup> cyclic imides,<sup>179</sup> and succinic anhydrides<sup>180</sup> can be selectively difluoro(phenylthio)-methylated with reagent 115 in high yields under the action of catalytic amounts of a fluoride salt. The further desulfonylation with  $\text{Bu}_3\text{SnH}$  in the presence of stoichiometric amounts of 2,2'-azo bis(isobutyronitrile) (AIBN) affords the corresponding  $\alpha$ -difluoromethyl alcohols. For instance, using this protocol, difluoromethylpyrrolidinone 120 was synthesized in moderate overall yield (49%) from 2-methylisoindoline-1,3-dione 118 (Scheme 68).<sup>179</sup>

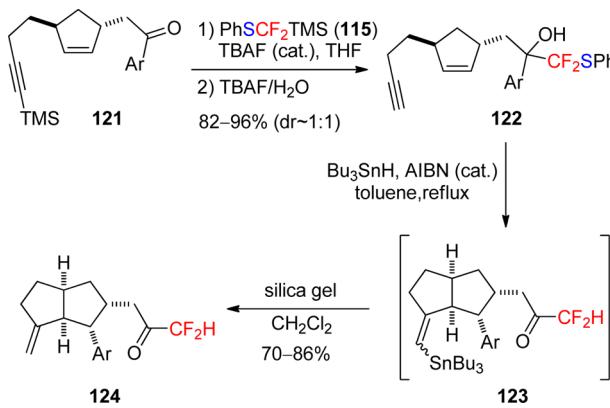
**Scheme 68**



However, the competitive radical cyclization to form 5- or 6-membered *gem*-difluorinated rings (see Section 3.3.2) usually limits the application of this radical desulfenylation method in unmasking CF<sub>2</sub>H from difluoro(phenylthio)methyl compounds containing an alkene moiety.<sup>179–184</sup> As an exception, the treatment of ene-yne-containing  $\alpha$ -difluoro(phenylthio)methyl- $\alpha$ -aryl alcohols **122** with Bu<sub>3</sub>SnH/AIBN affords the difluoromethyl ketones **124** as a single stereoisomer (Scheme 69).<sup>185</sup> The reaction proceeds through a tandem process that involves

tributyltin radical addition to alkyne/5-exo cyclization/*ipso*-1,4-aryl migration/phenylthio group elimination.

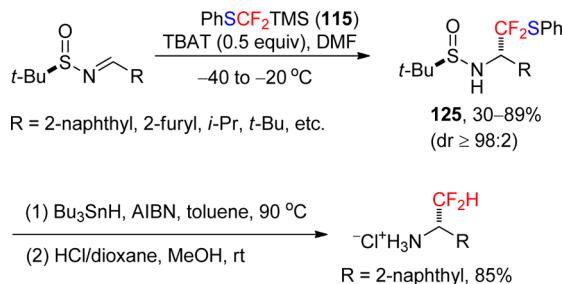
Scheme 69



The substrate scope for nucleophilic difluoro(phenylthio)methylation with  $\text{PhSCF}_2\text{TMS}$  (**115**) is not limited to carbonyl compounds; other electrophiles such as imines,<sup>186–188</sup> enamines (electrophile as their iminium tautomer),<sup>188</sup> alkyl halides,<sup>189</sup> even DAST<sup>50</sup> and  $\text{SO}_2$ <sup>190</sup> can also be difluoro(phenylthio)methylated.

The reaction between activated aldimines such as (*R*)-(*N*-*tert*-butylsulfinyl)imines and  $\text{PhSCF}_2\text{TMS}$  (**115**) in the presence of substoichiometric quantities of a Lewis basic initiator, such as tetrabutylammonium triphenyldifluorosilicate (TBAT), affords the corresponding products **125** in good yields with high diastereoselectivity ( $\text{dr} \geq 98:2$ ) (Scheme 70).<sup>186</sup> Nevertheless, *N*-alkylated imines and *N,N*-dialkylated

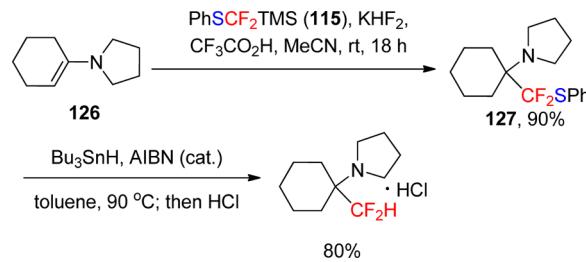
Scheme 70



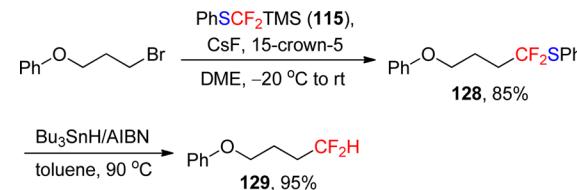
enamines, which are unreactive toward fluoroalkylsilane reagents under conventional Lewis basic conditions, have to be activated by a Brønsted acid or an *N*-alkylation reagent, to form the iminium salts for further reactions.<sup>12v</sup> For example, enamine **126** is difluoro(phenylthio)methylated by **115** under the action of the combination of  $\text{KHF}_2$  and  $\text{CF}_3\text{CO}_2\text{H}$  to give the tertiary amine **127** in good yield (Scheme 71).<sup>188</sup> Using the  $\text{Bu}_3\text{SnH}/\text{AIBN}$ -mediated desulfenylation method,  $\alpha$ -difluoromethyl amines can be prepared from the precursors such as **125** and **127**.

The nucleophilic difluoromethylation of alkyl halides with  $\text{PhSCF}_2\text{TMS}$  (**115**) can be achieved through fluoride-mediated substitution followed by desulfenylation (Scheme 72).<sup>189a</sup> The substitution reaction proceeds smoothly with primary alkyl bromides and iodides as the limiting reactant and cesium fluoride as the fluoride source, in the presence of 15-crown-5 as a critical additive.

Scheme 71



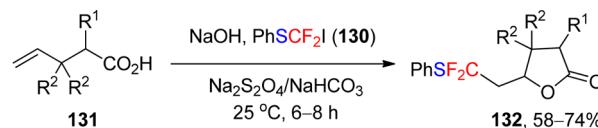
Scheme 72



As an alternative reagent for nucleophilic difluoro(phenylthio)methylation, difluoromethyl phenyl sulfide ( $\text{PhSCF}_2\text{H}$ , **116**), which is readily available from the reaction between sodium thiophenate and a difluorocarbene reagent,<sup>13c</sup> has been used for the transformation of carbonyl compounds and activated imines under the action of a base such as KOH, *t*-BuOK, and phosphazene base.<sup>191</sup> However, this protocol is not compatible with readily enolizable aldehydes due to the use of stoichiometric quantities of strong bases.

**3.2.1.2. Radical Difluoro(phenylthio)methylation.** An alternative method for incorporation of a  $\text{PhSCF}_2$  group is the radical difluoro(phenylthio)methylation with halodifluoromethyl phenyl sulfide  $\text{PhSCF}_2\text{X}$ , where X = Br (**117**, for its addition to alkenes, see Scheme 119)<sup>192</sup> or I (**130**). Bromodifluoromethyl phenyl sulfide (**117**) can be prepared by treatment of sodium thiophenate and dibromodifluoromethane in an aprotic solvent,<sup>193</sup> whereas the more reactive  $\text{PhSCF}_2\text{I}$  (**130**) is available through the substitution reaction of **117** with sodium iodide.<sup>194</sup> In the presence of sodium dithionite ( $\text{Na}_2\text{S}_2\text{O}_4$ ) as radical initiator, compound **130** not only can undergo ATRA reaction with simple alkenes,<sup>194</sup> but also can react with functionalized alkenes,<sup>195</sup> such as pent-4-enoic acids **131**, to afford cyclization products, such as  $\gamma$ -butyrolactones **132**, in moderate to good yields (Scheme 73).

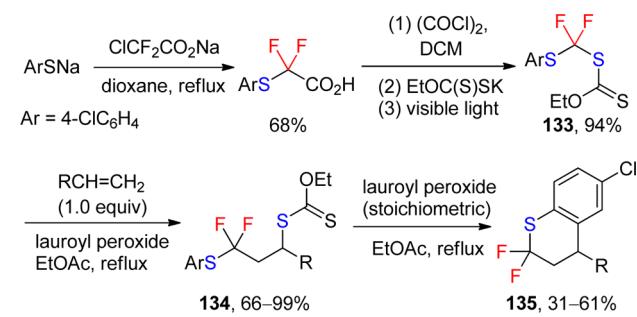
Scheme 73



$\text{R}^1 = \text{H}, \text{Me}, \text{Bn}, \text{Ph}, 4\text{-MeOC}_6\text{H}_4\text{CONH}; \text{R}^2 = \text{H}, \text{Me}$

In early 2014, Salomon and Zard synthesized a novel *O*-ethyl-*S*-(4-chlorophenylthio)difluoromethyl xanthate (**133**) and used it in the radical difluoro(arylthio)methylation of alkenes (Scheme 74).<sup>196</sup> Under the common conditions used for radical addition of xanthates to alkenes, difluorinated xanthate **133** adds across a series of terminal alkenes regiospecifically to afford the adducts **134** in high yields (66–99%), with good tolerance of functionalities such as epoxide, carbohydrate, urea,

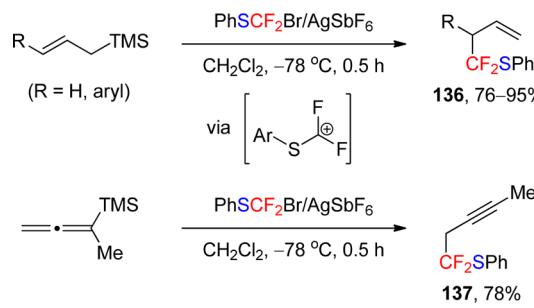
Scheme 74



and pyrazole. The xanthyl group in the adducts **134** can be removed by using triethylammonium salt of hypophosphorous acid or tris(trimethylsilyl)silane as the reducing agent.<sup>196</sup> Moreover, the adducts **134** can undergo dianthylative intramolecular cyclization in the presence of stoichiometric quantities of lauroyl peroxide to give difluorothiochromanes **135** in moderate yields (31–61%).<sup>196</sup>

**3.2.1.3. Electrophilic Difluoro(phenylthio)methylation.** Electrophilic difluoro(phenylthio)methylation with difluoro(phenylthio)methyl cation is also available, although the synthetic utility of the fluorinated cations is very limited due to the harsh conditions required for their generation, usually leading to nonfluorinated products.<sup>197</sup> Very recently, Reutrakul and co-workers reported that the reaction of allylsilanes and allenylsilanes with  $\text{PhSCF}_2\text{Br}$  (**117**) in the presence of silver hexafluoroantimonate ( $\text{AgSbF}_6$ ) as bromide abstractor at  $-78^\circ\text{C}$ , affords the allylic and propargylic difluoro(phenylthio)methylation products, **136** and **137**, respectively, in high yields (Scheme 75).<sup>198</sup> The structural assignment and observation of the difluoro(arylthio)methyl cation were supported by NMR and theoretical calculations.

Scheme 75



### 3.2.2. Sulfones as Difluoromethylation Reagents.

Compared to difluoro(phenylthio)methylation, difluoro(phenylsulfonyl)methylation is a more powerful method to achieve difluoromethylation not only because the unmasking of  $\text{CF}_2\text{H}$  from  $\alpha$ -difluorinated sulfones can proceed much more easily under the action of a metal reductant, but also because the phenylsulfonyl group is a more effective activation group to facilitate the introduction of the difluorinated moiety in nucleophilic, radical, and electrophilic manners. Among several hydrodesulfonylation systems used to unmask  $\text{CF}_2\text{H}$ ,<sup>199</sup> the  $\text{Na(Hg)}$ <sup>199c</sup> and the  $\text{Mg/HOAc/NaOAc}$ <sup>199e</sup> system usually work equally well to give the difluoromethyl compound in high yields. Moreover, the “chemical chameleon”<sup>200</sup> character of the phenylsulfonyl group enables the transformation of the difluoro(phenylsulfonyl)methyl group into other highly useful

fluorinated functionalities such as difluoromethylene ( $-\text{CF}_2-$ ), and difluoromethylidene ( $=\text{CF}_2$ ) groups (see sections 3.3.3 and 3.4.3). In this context, selective difluoro(phenylsulfonyl)methylations have been systematically studied by Prakash, Olah, Hu and their co-workers since 2003, and a review on this topic was published by one of us in 2009.<sup>13h</sup> In this section, we briefly introduce the major progress before 2009, and pay more attention to the more recent development of this chemistry.

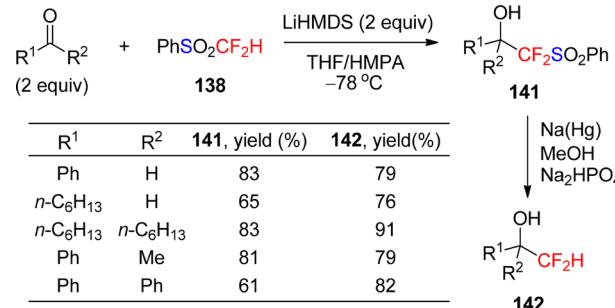
#### 3.2.2.1. Nucleophilic Difluoro(phenylsulfonyl)methylation.

Nucleophilic difluoro(phenylsulfonyl)methylation is a major approach to introduce  $\text{PhSO}_2\text{CF}_2$  into a molecule, which has been investigated with several reagents including difluoromethyl phenyl sulfone ( $\text{PhSO}_2\text{CF}_2\text{H}$ , **138**),<sup>199a–d,201</sup> [difluoro(phenylsulfonyl)methyl]trimethylsilane ( $\text{PhSO}_2\text{CF}_2\text{TMS}$ , **139**),<sup>199e</sup> and bromodifluoromethyl phenyl sulfone ( $\text{PhSO}_2\text{CF}_2\text{Br}$ , **140**).<sup>202</sup>

**3.2.2.1.1. Using  $\text{PhSO}_2\text{CF}_2\text{H}$  Reagent.** Difluoromethyl phenyl sulfone ( $\text{PhSO}_2\text{CF}_2\text{H}$ , **138**) is currently the most frequently used nucleophilic difluoro(phenylsulfonyl)methylation reagent, which was first prepared by Hine and Porter in 1960 via oxidation of the corresponding sulfide **116** with  $\text{H}_2\text{O}_2/\text{HOAc}$ ,<sup>203</sup> a procedure still being used today. In 1972, Edwards and co-workers claimed in a patent that  $\text{PhSO}_2\text{CF}_2^-$  anion (derived from compound **138** and *t*-BuOK in diglyme/Et<sub>2</sub>O at  $-78^\circ\text{C}$ ) was able to undergo 1,4-addition to a cyclic  $\alpha,\beta$ -unsaturated ketone.<sup>204</sup> In early 1989, Stahly reported the difluoromethylation of aldehydes with **138**, which was achieved via the nucleophilic addition of **138** to aldehydes in a two phase system (50% aqueous  $\text{NaOH}/\text{CH}_2\text{Cl}_2/\text{Aliquat 336}$ ) at room temperature followed by desulfonylation with sodium metal.<sup>199a</sup> However, this protocol is only applicable for aromatic aldehydes and sterically hindered aliphatic aldehydes such as isobutyraldehyde.

Subsequently, a modified procedure was developed by using lithium hexamethyldisilazide (LiHMDS) as the base and hexamethylphosphoric triamide (HMPA) as an additive at a low temperature such as  $-78^\circ\text{C}$  to achieve the carbonyl addition, which works well for various ketones and non-enolizable aldehydes, affording the difluoro(phenylsulfonyl)methyl carbinols in good to excellent yields (Scheme 76).<sup>205</sup> As for enolizable aldehydes such as heptanal, only moderate yields are obtained albeit using two equiv of aldehydes.<sup>205b</sup>

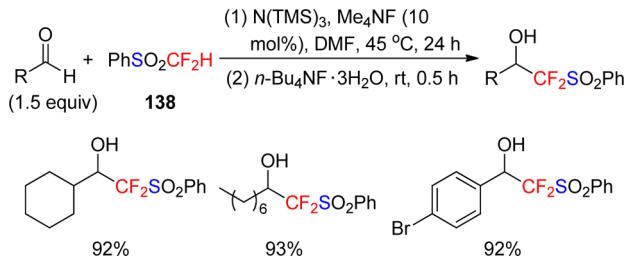
Scheme 76



Very recently, a new base system, the combination of stoichiometric quantities of  $\text{N}(\text{TMS})_3$  and substoichiometric quantities of  $\text{Me}_4\text{NF}$ , has been used to realize the efficient difluoro(phenylsulfonyl)methylation of aromatic and aliphatic aldehydes with **138** (Scheme 77).<sup>206</sup> The bis(trimethylsilyl)amide anion ( $(\text{TMS})_2\text{N}^-$ ) *in situ* generated from  $(\text{TMS})_3\text{N}$  is

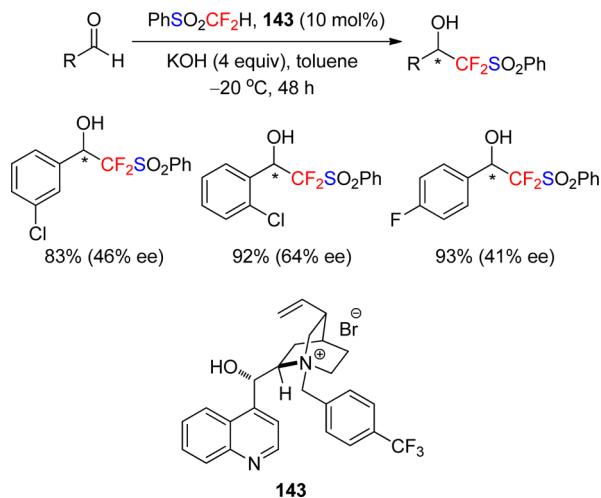
always in low concentration, thus circumventing the enolization of aliphatic aldehydes.

Scheme 77



In addition, the enantioselective nucleophilic difluoromethylation of aromatic aldehydes is also viable with  $\text{PhSO}_2\text{CF}_2\text{H}$  (138) (Scheme 78). By using solid KOH as a base and chiral

Scheme 78



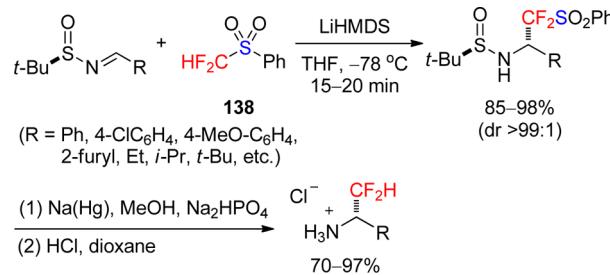
quaternary ammonium salt 143 as a catalyst, an ee up to 64% has been obtained.<sup>207</sup> This reaction represents the first example of an enantioselective difluoromethylation reaction.

Using the combination of  $\text{PhSO}_2\text{CF}_2\text{H}$  (138)/base, many other electrophiles including activated imines,<sup>208</sup> alkyl halides,<sup>199c</sup> cyclic sulfates and sulfamidates,<sup>209</sup> esters<sup>210</sup> and heteroatom electrophiles such as disulfides<sup>201</sup> and halogens<sup>199c,211</sup> have been difluoro(phenylsulfonyl)methylated for further transformation.

Enantiomerically pure *N*-(*tert*-butylsulfinyl)imines can be used for the synthesis of a variety of structurally diverse chiral amines due to their excellent reactivity toward 1,2-addition with many different types of nucleophiles.<sup>212</sup> Thus, the highly diastereoselective addition of  $\text{PhSO}_2\text{CF}_2\text{H}$  (138) to *N*-(*tert*-butylsulfinyl)imines under the action of a sterically hindered base is one of the most effective protocols to synthesize enantioenriched  $\alpha$ -difluoromethyl amines (Scheme 79).<sup>208a–c</sup> The substrate scope is broad; not only various chiral aldimines, but also chiral ketimines, which could not react with other difluoromethylating agents such as  $\text{TMSCF}_2\text{H}$ ,<sup>173a</sup>  $\text{PhSCF}_2\text{TMS}$  (115),<sup>186</sup> and  $\text{PhSCF}_2\text{H}$  (116),<sup>191a</sup> work well in this difluoromethylation reaction.

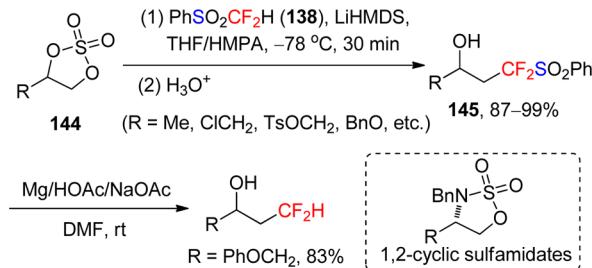
The nucleophilic substitution reaction with 138 is of high demand to the steric environment of the substrates and the nucleofugality of the leaving groups. Thus, difluoro-

Scheme 79



(phenylsulfonyl)methylation of primary alkyl iodides gives 1,1-difluoroalkanes after reductive desulfonylation.<sup>199c</sup> Although epoxides are less reactive toward  $\text{PhSO}_2\text{CF}_2\text{H}$  anion, their surrogates 1,2-cyclic sulfates 144 can be difluoromethylated to afford  $\beta$ -difluoromethyl alcohols via nucleophilic difluoro(phenylsulfonyl)methylation/desulfonylation (Scheme 80).<sup>209</sup> Similarly, 1,2-cyclic sulfamidates can be converted to  $\beta$ -difluoromethyl amines.<sup>209</sup>

Scheme 80

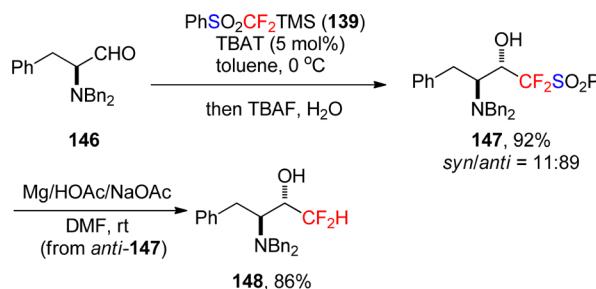


**3.2.2.1.2. Using  $\text{PhSO}_2\text{CF}_2\text{TMS}$  Reagent.** [Difluoro(phenylsulfonyl)methyl]trimethylsilane ( $\text{PhSO}_2\text{CF}_2\text{TMS}$ , 139) can be used as an alternative nucleophilic difluoro(phenylsulfonyl)methylation reagent to  $\text{PhSO}_2\text{CF}_2\text{H}$  (138). Compound 139 was first prepared in 2003 via *m*-chloroperoxybenzoic acid-mediated oxidation of  $\text{PhSCF}_2\text{TMS}$  (115) in 51% yield.<sup>64</sup> In 2005, a practical synthesis of 139 was developed via the reaction of  $\text{PhSO}_2\text{CF}_2\text{Br}$  (140), BuLi and  $\text{TMSCl}$  in  $\text{THF}$  at  $-78^\circ\text{C}$ .<sup>199e,213</sup> Similar to the reaction with  $\text{TMSCF}_3$ , the transfer of  $\text{PhSO}_2\text{CF}_2$  with reagent 139 proceeds smoothly under the action of a nucleophilic initiator such as tetrabutylammonium triphenyldifluorosilicate (TBAT), KF,  $\text{KHF}_2$ , and  $\text{K}_2\text{CO}_3$ .

Compound 139 was initially used in difluoro(phenylsulfonyl)methylation of carbonyl compounds under the action of catalytic amounts of initiator to preclude the need of stoichiometric quantities of a strong Brønsted base, which could lead to the enolization of aliphatic aldehydes such as heptanal, thus lowering the yield.<sup>199e</sup> By using this reagent, diastereoselective difluoromethylation of  $\alpha$ -amino aldehydes, such as 146, affords the amino alcohol product 147 in 92% yields with a syn/anti ratio of 11:89 (Scheme 81).<sup>213</sup> However, the combination of  $\text{PhSO}_2\text{CF}_2\text{H}/\text{LiHMDS}$  gives only a moderate yield.<sup>213</sup>

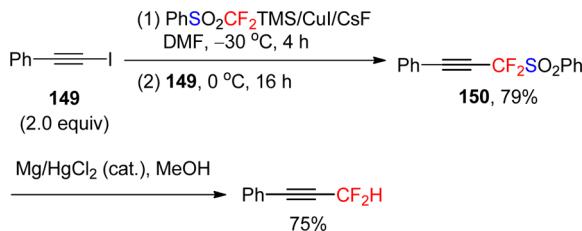
Recently, the advantageous use of  $\text{PhSO}_2\text{CF}_2\text{TMS}$  (139) over reagent 138 has been demonstrated in the difluoro(phenylsulfonyl)methylation of nonactivated imines,<sup>188</sup> enamines,<sup>188</sup> *N,N*-acetals,<sup>214</sup> as well as alkyl, propargyl and alkynyl halides.<sup>189,215</sup> Difluoro(phenylsulfonyl)methylation of propargyl chlorides and alkynyl halides can be achieved with reagent

Scheme 81



**139** under the promotion of CuI, giving PhSO<sub>2</sub>CF<sub>2</sub>-substituted allenes and alkynes, respectively. For example, reaction of alkynyl iodide **149** with the “PhSO<sub>2</sub>CF<sub>2</sub>Cu” reagent pregenerated from **139**, CuI and CsF gives the cross-coupling product **150** in 79% yield. Reductive desulfonylation affords the difluoromethyl compound in overall moderate yield (Scheme 82).<sup>215a</sup>

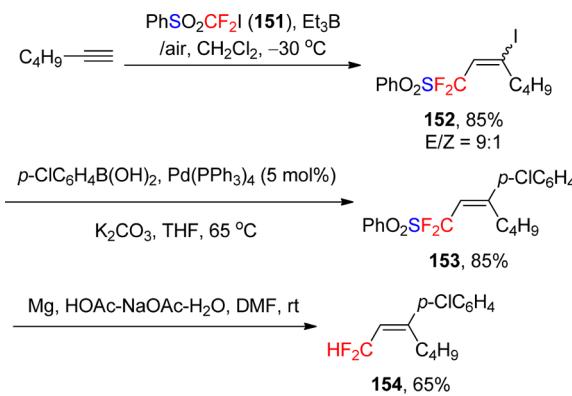
Scheme 82



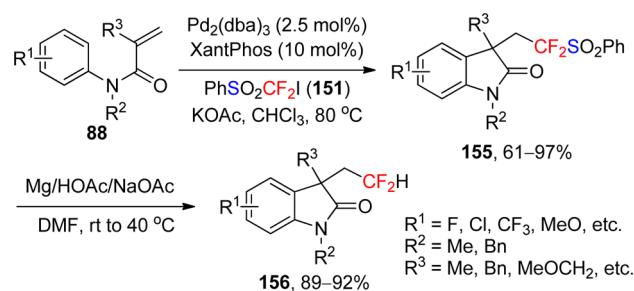
**3.2.2.2. Radical Difluoro(phenylsulfonyl)methylation.** Iododifluoromethyl phenyl sulfone (PhSO<sub>2</sub>CF<sub>2</sub>I, **151**), as the surrogate of HCF<sub>2</sub>I, was first prepared by Prakash and Hu via iodination of PhSO<sub>2</sub>CF<sub>2</sub>H with elemental iodine in the presence of *t*-BuOK in DMF.<sup>199c</sup> In 2007, Hu and co-workers reported the first free radical difluoro(phenylsulfonyl)methylation of alkenes with **151**.<sup>216</sup> By using the Et<sub>3</sub>B/air-initiation system, a variety of structurally diverse terminal alkenes are transformed to products with good tolerance of functionalities such as carbonyl, ester, carboxylic acid, ether, and hydroxyl groups. Similarly, the atom transfer radical addition (ATRA) of **151** across terminal alkynes, such as hex-1-yne, affords the corresponding iodo-difluoro(phenylsulfonyl)methylation products, such as **152**, with moderate to good E/Z stereoselectivity (Scheme 83).<sup>217</sup> The obtained PhSO<sub>2</sub>CF<sub>2</sub>-substituted iodoalkenes, such as **152**, can further undergo coupling reactions to prepare CF<sub>2</sub>H-substituted alkenes, such as **154**.<sup>217</sup>

Very recently, PhSO<sub>2</sub>CF<sub>2</sub>I has been used in transition metal-catalyzed difluoromethylation reactions by Wang and co-workers.<sup>218,219</sup> A Pd(0)-catalyzed intramolecular aryldifluoromethylation of activated alkenes, *N*-arylacrylamides **88**, with PhSO<sub>2</sub>CF<sub>2</sub>I provides an efficient method to construct a variety of difluoromethylated oxindoles **156** (Scheme 84).<sup>218a</sup> Note that the phosphine ligand can significantly influence the reaction, with XantPhos attaining the highest catalytic reactivity. Mechanistic investigations indicate that a PhSO<sub>2</sub>CF<sub>2</sub> radical, which is generated via one-electron reduction by Pd(0), initiates the tandem sequence through an addition to the alkene. The same radical reaction has also been achieved with an iron catalyst.<sup>218b</sup> Thus, treatment of **88** and PhSO<sub>2</sub>CF<sub>2</sub>I

Scheme 83



Scheme 84



(**151**) with H<sub>2</sub>O<sub>2</sub> and catalytic ferrocene (FeCp<sub>2</sub>) in DMSO/THF as solvent at 60 °C affords **155** in 48–93% yields.

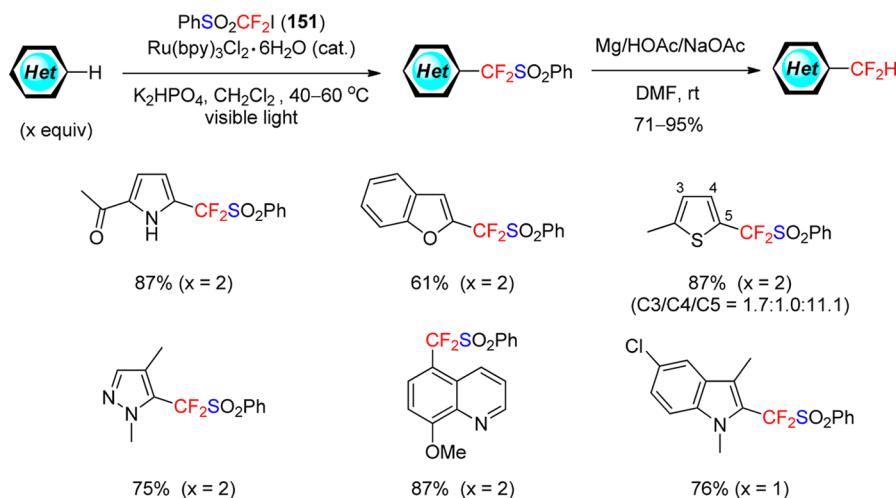
By using a visible light photoredox catalyst such as Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O, the C–H difluoromethylation of several electron-rich heteroarene arrays including N-, O-, and S-containing heteroarenes with PhSO<sub>2</sub>CF<sub>2</sub>I under mild reaction conditions has been achieved (Scheme 85),<sup>219</sup> with site selectivity toward the relatively electron-rich (hetero)aromatic rings, which is in contrast to the oxidative heteroaromatic C–H difluoromethylation with (HCF<sub>2</sub>SO<sub>2</sub>)<sub>2</sub>Zn (see Scheme 96).<sup>220</sup> This difference can be explained by the higher electrophilicity of the PhSO<sub>2</sub>CF<sub>2</sub> radical than the HCF<sub>2</sub> radical.

As a complementary to the radical difluoro(phenylsulfonyl)methylation with PhSO<sub>2</sub>CF<sub>2</sub>I, the bromodifluoromethyl phenyl sulfone (PhSO<sub>2</sub>CF<sub>2</sub>Br, **140**), which was first reported by Burton and Wiemers<sup>221</sup> in 1981 and has been used as an important source of PhSO<sub>2</sub>CF<sub>2</sub> anion for nucleophilic reaction,<sup>199e</sup> can be used in C–H functionalization of styrenes (Scheme 86), vinyl ethers, and heteroaromatics through palladium-mediated reactions to give the corresponding products in moderate to good yields.<sup>222</sup> Although a radical inhibitor did not suppress the reaction significantly, the possibility of a single-electron-transfer (SET) pathway could not be ruled out.

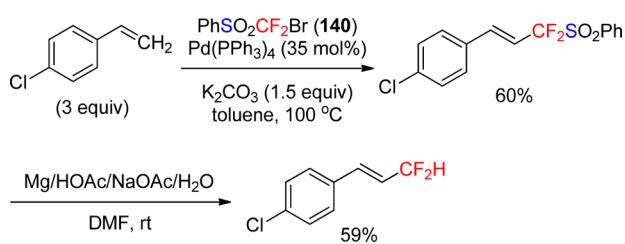
**3.2.2.3. Electrophilic Difluoro(phenylsulfonyl)methylation.** Inspired by the electrophilic trifluoromethylation with hypervalent iodine(III)-CF<sub>3</sub> reagents<sup>223</sup> and S-trifluoromethyl sulfonium reagents,<sup>82</sup> the electrophilic difluoro(phenylsulfonyl)methylation has been developed in a similar manner.

In 2008, Hu and co-workers first prepared the hypervalent iodine(III)-CF<sub>2</sub>SO<sub>2</sub>Ph reagent **158** by reacting precursor **157** with PhSO<sub>2</sub>CF<sub>2</sub>TMS under the action of catalytic quantities of tetrabutylammonium triphenyldifluorosilicate (TBAT) (Scheme 87).<sup>224</sup> Reagent **158** can efficiently transfer a

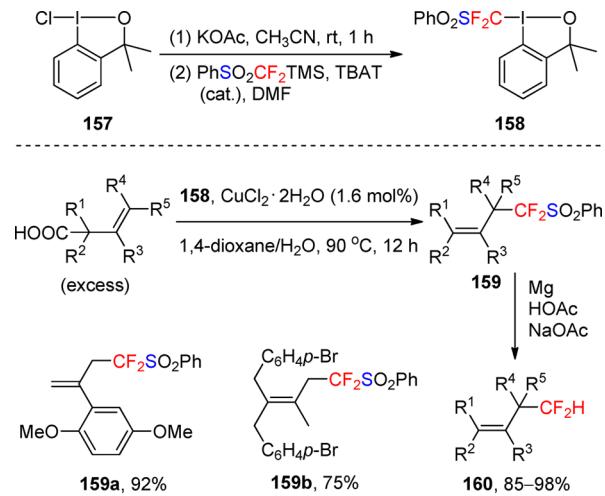
Scheme 85



Scheme 86



Scheme 87

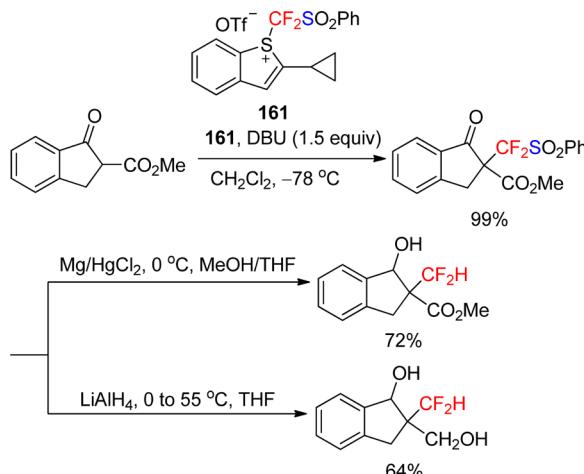


PhSO2CF2 group to a diverse range of sulfur-nucleophiles,<sup>224</sup> and it also reacts with unsaturated carboxylic acids under the catalysis of a Cu(II) salt, to afford the decarboxylative difluoro(phenylsulfonyl)methylation products.<sup>144,225</sup> The reaction of  $\alpha,\beta$ -unsaturated acids with reagent **158** under the catalysis of CuF2 affords the vinylic difluoro(phenylsulfonyl)methylation products,<sup>144</sup> whereas the reaction of  $\beta,\gamma$ -unsaturated carboxylic acids with reagent **158** is an efficient allylic difluoromethylation method (Scheme 87), furnishing the  $\gamma$ -attack products **159** exclusively. However, reagent **158** failed to transfer a PhSO2CF2 group to carbon acids.<sup>224</sup>

Electrophilic difluoro(phenylsulfonyl)methylation of  $sp^3$ -carbon nucleophiles can be achieved by using a sulfonium salt. Very recently, Shibata and co-workers developed S-

difluoro(phenylsulfonyl)methyl sulfonium salts such as **161**,<sup>226</sup> which are obtained in a similar manner as the *S*-trifluoromethyl sulfonium salts **53**.<sup>82</sup> The sulfonium salts such as **161** were found to be efficient electrophilic fluoroalkylating agents for introducing a PhSO2CF2 group to  $sp^3$ -hybridized carbon acids such as  $\beta$ -ketoesters (Scheme 88). The PhSO2CF2 group in the  $\beta$ -ketoesters can be readily unmasked to reveal CF2H, with the reduction of the ketone functional group to alcohol.

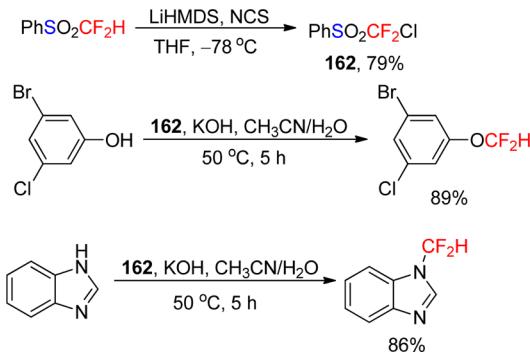
Scheme 88



**3.2.2.4. Direct Difluoromethylation.** The direct difluoromethylation with a sulfone reagent is rare. Hine and Porter in 1960 had shown that difluoromethyl sulfone can serve as a difluorocarbene source;<sup>203</sup> however, its reaction with sodium methoxide and sodium thiophenolate provides the corresponding difluoromethyl (thio)ethers in low yields. In 2007, Hu and co-workers<sup>227</sup> disclosed that the chlorination of PhSO2CF2H leads to a novel nonozone-depleting-substance-based difluorocarbene reagent **162**, which can difluoromethylate O- and N-nucleophiles under aqueous basic conditions through nucleophilic activation of the C–S bond by hydroxide ion (Scheme 89).

The Barbier-type reaction between PhSO2CF2H (**138**) and chlorosilanes, such as TMSCl, under the action of magnesium

Scheme 89



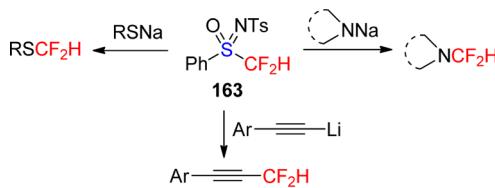
provided difluoromethylsilanes, such as  $\text{TMSCF}_2\text{H}$ , in moderate to good yields (51–76%).<sup>64</sup>  $\text{TMSCF}_2\text{H}$  has been used in the difluoromethylation of carbonyl compounds and aryl iodides.<sup>173</sup>

### 3.2.3. Sulfoximines as Difluoromethylation Reagents.

*S*-Difluoromethyl sulfoximines are more robust electrophilic difluoromethylating agents (compared with difluoromethyl sulfones) because the replacement of one of the sulfonyl oxygens by a nitrogen allows ready modulation of the reactivity. Thus, neutral *S*-difluoromethyl sulfoximines with either an electron-withdrawing group<sup>228</sup> or an electron-donating group<sup>229</sup> on the nitrogen and *N,N*-dimethyl-*S*-difluoromethyl sulfoximinium salts<sup>230</sup> have been developed for electrophilic and nucleophilic difluoromethylations that are difficult to achieve by using difluoromethyl sulfone reagents. Generally, *S*-difluoromethyl sulfoximines can be synthesized either via oxidative imination of difluoromethyl sulfoxides<sup>228,230</sup> or via electrophilic fluorination of *S*-methylsulfoximines.<sup>229</sup> Recent reviews<sup>73</sup> on fluorinated sulfoximines have described the preparation and some reactions of *S*-difluoromethyl sulfoximines. This subsection aims at demonstrating the advantages of sulfoximine reagents over sulfone reagents, with a focus on the most recent development.

**3.2.3.1. Direct Difluoromethylation.** In 2008, Hu and co-workers disclosed the preparation of the first *S*-difluoromethyl sulfoximine **163**, and applied it in the difluoromethylation of *S*-, *N*-, and *C*-nucleophiles (Scheme 90).<sup>228</sup> Deuterium labeling

Scheme 90



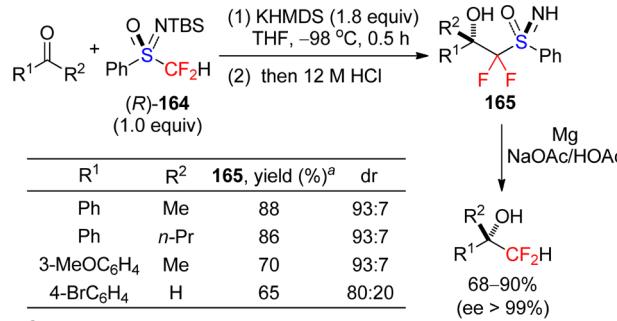
experiments suggested that difluorocarbene is involved in this reaction. In a related work, Prakash and co-workers<sup>230</sup> prepared *N,N*-dimethyl-*S*-phenyl-*S*-difluoromethylsulfoximinium tetrafluoroborate, which was found to be a highly reactive difluoromethylation reagent toward a wide range of *N*-, *P*-, *S*-, and *O*-nucleophiles. It is impressive that even alcohols can be difluoromethylated, and the reaction of deuterated methanol  $\text{CD}_3\text{OD}$  gives  $\text{CD}_3\text{OCF}_2\text{H}$  as the sole product, thus ruling out the participation of a difluorocarbene.<sup>230</sup>

### 3.2.3.2. Nucleophilic Difluoro(sulfonimidoyl)methylation.

In 2012, Hu and co-workers disclosed that the reactivity of *S*-

difluoromethyl sulfoximine can be switched from electrophilic to nucleophilic by a modification of the substituent on nitrogen atom.<sup>229</sup> Thus, the *N*-*tert*-butyldimethylsilylated sulfoximine **164** has been used as a nucleophilic difluoromethylation reagent under the action of a base (Scheme 91). By taking

Scheme 91

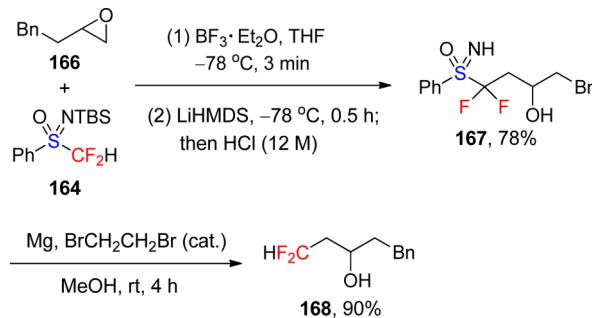


<sup>a</sup> Yield of the major isomer.

advantage of the sulfur chirality of sulfoximines, the diastereoselective addition of enantiopure sulfoximine (*R*)-**164** to aromatic aldehydes and ketones followed by reductive desulfonimidoylation constitutes a protocol for enantioselective nucleophilic difluoromethylation of prochiral carbonyl compounds. This method is useful for the synthesis of enantioenriched difluoromethyl alcohols, especially the tertiary alcohols.<sup>229</sup>

*N*-*tert*-Butyldimethylsilyl-*S*-phenylsulfonimidoyl group is also superior to phenylsulfonyl group in stabilizing a difluorinated carbanion.<sup>231</sup> Very recently, Hu and co-workers reported an efficient ring-opening nucleophilic difluoromethylation of epoxides by using racemic **164** as the reagent (Scheme 92).<sup>231a</sup> The reaction is carried out by adding a base, such as

Scheme 92

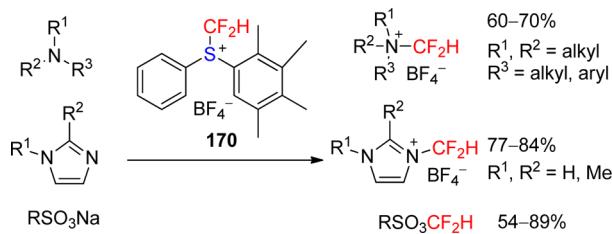


LiHMDS, to a THF solution of **164**, epoxides such as **166** and  $\text{BF}_3\cdot\text{Et}_2\text{O}$  at  $-78^\circ\text{C}$ , giving the  $\beta$ -difluoro(sulfonimidoyl)-methylated alcohols such as **167** in good yields. Note that the pretreatment of **164** and epoxides with  $\text{BF}_3\cdot\text{Et}_2\text{O}$  is crucial for the success of this reaction, which otherwise is difficult to achieve. The substrate scope of epoxides was shown to be broad; substituted oxiranes, 4-membered oxetanes, and 5-membered tetrahydrofuran can all undergo this reaction. In contrast, the difluoro(phenylsulfonyl)methylation of epoxides, such as 2-methyloxirane, with  $\text{PhSO}_2\text{CF}_2\text{H}$  (**138**) using the same procedure afforded the ring-opening products in much lower yields, which is attributed to the lower thermal stability of the  $\text{PhSO}_2\text{CF}_2$  anion.<sup>231a</sup>

**3.2.4. Sulfonium Salts as Difluoromethylation Reagents.** As described in section 3.1.4, *S*-trifluoromethylsulfonium salts are well-known to be powerful electrophilic trifluoromethylating agents, which are successfully used for the trifluoromethylation of a wide range of substrates differing in reactivity. However, the application of their difluorinated analogs in electrophilic difluoromethylation is quite limited. In addition to the aforementioned *S*-difluoro(phenylsulfonyl)-methyl sulfonium salts **161** (see Scheme 88), several *S*-difluoromethyl and *S*-bromodifluoromethyl sulfonium salts have also been developed.

In 2007, Prakash and co-workers<sup>232</sup> synthesized the first stable sulfonium salt that contains a partially fluorinated alkyl group, that is, *S*-difluoromethylsulfonium tetrafluoroborate **170**, via the reaction of PhSO<sub>2</sub>CF<sub>3</sub> (169), 1,2,3,4-tetramethylbenzene and triflic anhydride followed by anion exchange with NaBF<sub>4</sub>. The sulfonium salt **170** was shown to be an efficient reagent for the introduction of an electrophilic difluoromethyl group into the heteroatoms of sulfonic acids, carboxylic acids, tertiary amines, imidazole derivatives, and phosphines (Scheme 93).<sup>232a</sup> However, reagent **170** failed to transfer a CF<sub>2</sub>H group

Scheme 93

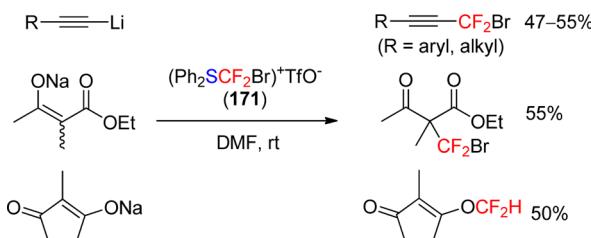


to phenols, carbon nucleophiles, and primary and secondary amines, probably due to the lability of the CF<sub>2</sub>H group of **170** in the presence of these basic nucleophiles.

Very recently, a similar difluoromethylsulfonium salt with tetra[3,5-bis(trifluoromethyl)phenyl]borate as the counter-anion has been used as a difluorocarbene source for the prepreparation of [<sup>18</sup>F]trifluoromethylcopper reagent, which is especially suitable for the efficient and clean [<sup>18</sup>F]-trifluoromethylation of (hetero)arylboronic acids at ambient temperatures.<sup>233</sup>

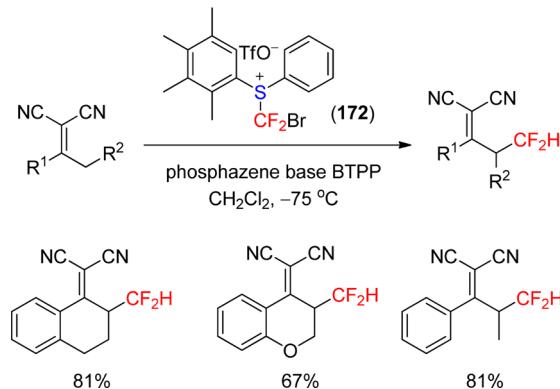
In 2010, Xiao and co-workers synthesized *S*-bromodifluoromethyl sulfonium salt **171** through the one-pot reaction of BrCF<sub>2</sub>SO<sub>2</sub>Na, triflic anhydride, and benzene.<sup>234</sup> They found that **171** can serve both as C-bromodifluoromethylation reagent toward terminal alkynes and acyclic  $\beta$ -ketoesters and O-difluoromethylating agent toward cyclic 1,3-diones such as 2-methylcyclopentane-1,3-dione (Scheme 94).<sup>234</sup> Shibata and co-workers improved the difluoromethylation of cyclic 1,3-diones<sup>235</sup> by using sulfonium salt **172**,<sup>236</sup> and extended the

Scheme 94



scope of sp<sup>3</sup>-carbon acids to dicyanoalkylidenes and  $\beta$ -keto esters (Scheme 95).<sup>237</sup> In these difluoromethylation reactions,

Scheme 95

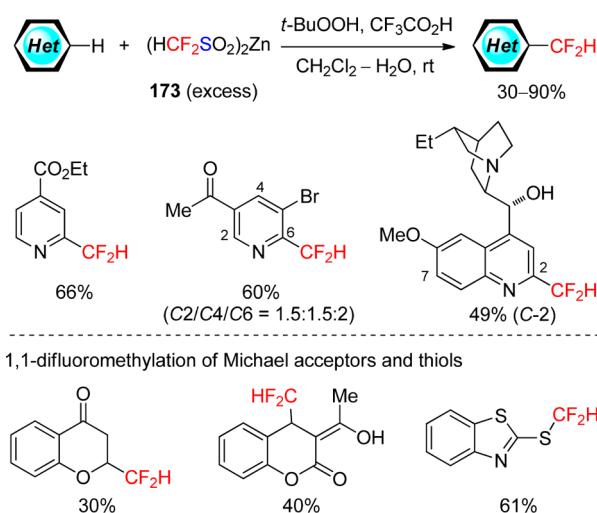


the substrates also serve to activate the sulfonium salt such as **172** to generate difluorocarbene. The reaction between dicyanoalkylidenes and **172** gives allylic difluoromethylation compounds in good yields whereas the reaction of  $\beta$ -keto esters gives a mixture of C- and O-difluoromethylation products.<sup>237</sup>

**3.2.5. Sulfinate Salts as Difluoromethylation Reagents.** In analogy to aforementioned trifluoromethylation with trifluoromethanesulfinate salts (see Section 3.1.5), the difluoromethylation can be achieved by using difluoromethanesulfinate salts.

In 2012, Baran and co-workers first prepared zinc difluoromethanesulfinate (**173**) by reduction of difluoromethanesulfonyl chloride with zinc metal<sup>238</sup> and used it in the innate C–H difluoromethylation of organic substrates including heteroarenes,  $\alpha,\beta$ -unsaturated enones and aromatic thiols under the action of *tert*-butyl hydroperoxide (Scheme 96).<sup>220</sup>

Scheme 96



In most cases, heteroaromatics with multiple potential reaction sites exhibit high levels of regioselectivity, commonly producing only one observable regioisomer with C–H difluoromethylation occurring at electron-deficient positions, indicating the nucleophilic character of a difluoromethyl radical, which is distinct from the highly electrophilic character of a trifluoromethyl radical. For example, difluoromethylation of dihy-

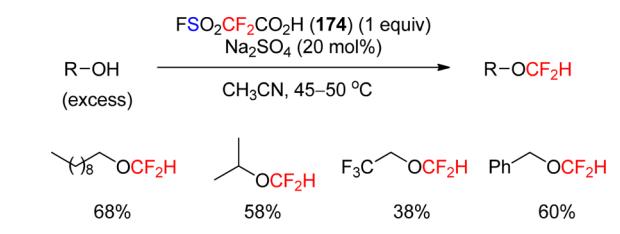
droquinine takes place at C-2 site, whereas trifluoromethylation occurs at C-7 site (see Scheme 43).<sup>220</sup>

The zinc salt **173** has also been used in iron-catalyzed decarboxylative difluoromethylation of  $\alpha,\beta$ -unsaturated carboxylic acids with *tert*-butyl hydroperoxide as oxidant.<sup>136a</sup> Various electron-rich aryl-substituted acrylic acids undergo the reaction to afford difluoromethyl-substituted (*E*)-alkenes in moderate yields (35–68%) with high stereocontrol. However, electron-deficient aryl-substituted acrylic acids gave very low yields of the desired products under these conditions. Very recently, the synthesis of difluoromethylated oxindoles **156** (for structures, see Scheme 84) by the reaction of *N*-arylacrylamides **88** with zinc salt **173** has been published.<sup>239</sup>

**3.2.6. Tetrafluoroethane  $\beta$ -Sultone Derivatives as Difluorocarbene Sources for Heteroatom Difluoromethylation.** The tetrafluoroethane  $\beta$ -sultone derivatives fluorosulfonyldifluoroacetic acid ( $\text{FSO}_2\text{CF}_2\text{CO}_2\text{H}$ , **174**)<sup>240</sup> and trimethylsilyl (fluorosulfonyl)difluoroacetate (TFDA,  $\text{FSO}_2\text{CF}_2\text{CO}_2\text{TMS}$ , **175**)<sup>241</sup> developed by Chen, Dolbier and co-workers are commercially available difluorocarbene source of complex heteroatom difluoromethylation. The release of difluorocarbene from **174** and **175** proceeds in a similar manner as the aforementioned  $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}$  (**100**),<sup>159</sup> that is, via decomposition of (fluorosulfonyl)difluoroacetate anion. Details on difluoromethylation with **174** and **175** have been covered in recent reviews;<sup>12k,13c</sup> therefore, only a brief summary of the application of these reagents is presented here.

Some significant application of **174** includes both *O*-difluoromethylation of aliphatic alcohols (a class of challenging substrates in *O*-fluoroalkylations) under the catalysis of  $\text{Na}_2\text{SO}_4$  (Scheme 97)<sup>242</sup> and *N*-difluoromethylation of heteroaromatic

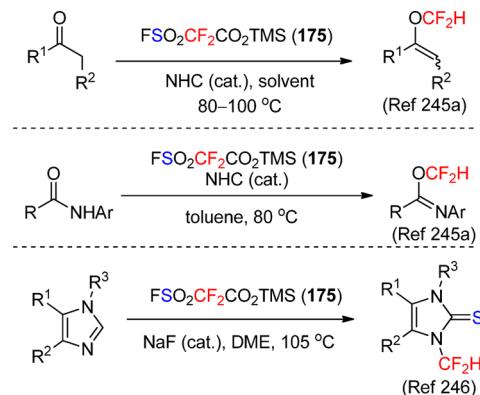
Scheme 97



compounds such as pyridines, imidazoles and triazoles in the presence of a base.<sup>243</sup> Reagent **174** is also applicable for *O*-difluoromethylation of carboxylates, sulfonates and phosphates, *S*-difluoromethylation of dithiocarbamates and sulfonates.<sup>240</sup> However, it is not effective for *O*-difluoromethylation of phenols and *S*-difluoromethylation of thiols.<sup>240,242</sup>

TFDA (**175**), which was originally developed for difluorocyclopropanation of alkenes (see Section 3.3.6),<sup>241,244</sup> has found application in *O*-difluoromethylation of unactivated ketones<sup>245</sup> and secondary amides<sup>245a</sup> to afford enol difluoromethyl ethers and difluoromethyl carboximides, respectively (Scheme 98). In these reactions, either sodium fluoride or an *N*-heterocyclic carbene (NHC) can be used as the catalyst, with the latter being more effective.<sup>245a</sup> In addition, TFDA has also been used for *N*-difluoromethylation of *N*-alkylated imidazoles (Scheme 98) under the catalysis of sodium fluoride, accompanied by the incorporation of a thione sulfur into the products.<sup>246</sup>

Scheme 98



### 3.3. For Difluoromethylation and Other Difluoroalkylation

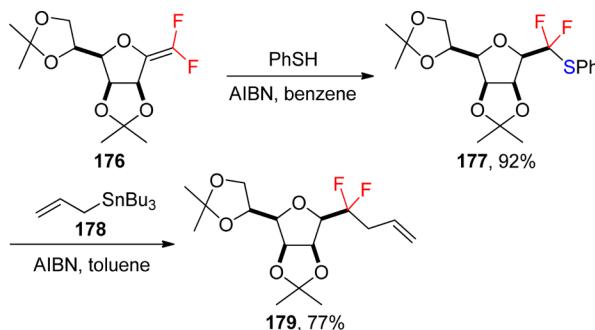
The  $\text{sp}^3$ -hybridized difluoromethylene functionality is known to be isosteric and isopolar to an ethereal oxygen, and it has been used to replace the metabolically labile oxygen atom in functionalities such as ether, phosphonate and sulfate in medicinal chemistry research.<sup>6,247</sup> On the other hand, difluorination of a methylene group can alter the conformation and reactivity of a molecule, and thus provides the opportunity to develop new scaffolds that are useful in biology and material sciences.<sup>7,247b</sup> The sulfur-containing compounds play an important role in introducing the  $\text{CF}_2$  moiety into a molecule. This chemistry can be achieved by the use of sulfides, sulfoxides, sulfones, and tetrafluoroethane  $\beta$ -sultone derivatives either as a difluoromethylene or an  $\alpha,\alpha$ -difluoroalkyl equivalent. To emphasize the unique role of sulfur in these reactions, the monofluoroalkylation and monodifluoromethylation are discussed separately.

#### 3.3.1. Sulfides and Xanthates as Difluoroalkylation Reagents.

$\alpha,\alpha$ -Difluorinated sulfides can be prepared via phenylthiolation of 1,1-difluoroalkenes, difluorination of sulfides, or the aforementioned difluoro(arylthio)methylation. Owing to the easy availability of an array of  $\alpha$ -difluorinated sulfides, difluoroalkylation of alkenes with these compounds is an important method to introduce a difluoroalkyl into an organic compound.

The sulfide-based difluoroalkylation mainly relies on the radical pathway. The homolytic cleavage of a C–S bond of a difluoroalkyl sulfide for radical fluoroalkylation was first demonstrated by Motherwell and co-workers<sup>248</sup> in 1989 during their research on the synthesis of difluoromethylene-linked C-glycosides and disaccharides (Scheme 99). The  $\alpha$ -difluoroalkyl

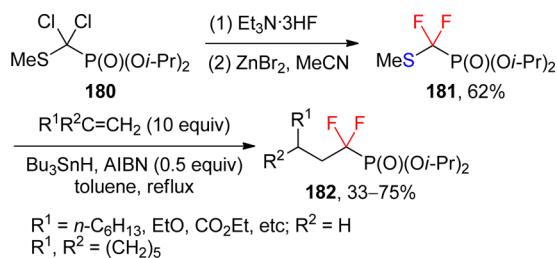
Scheme 99



radical precursors, such as **177**, were obtained through AIBN-initiated stereoselective radical addition of thiophenol to *gem*-difluoroolefins, such as **176**; then the difluorinated sulfides, such as **176**, were subject to the radical addition–elimination reaction with allylstannanes, such as **178**, under the initiation of AIBN in toluene, to afford the allylic difluoroalkylation products, such as **179**, in low to good yields (36–77%).

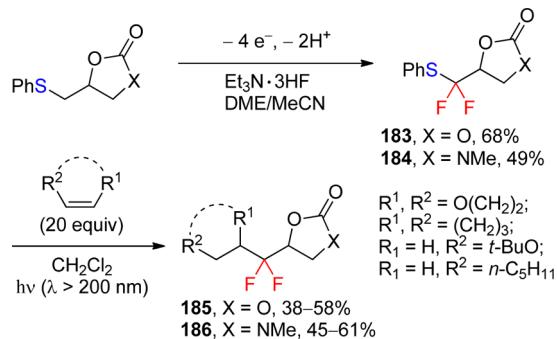
In 2001, Lequeux and Piettre and co-workers<sup>249</sup> developed a novel (phosphoryl)difluoromethylation reagent **181**, which can be prepared in a nonozone-depleting-substance-based method by treatment of the dichlorinated compound **180** with triethylamine trihydrofluoride in the presence of zinc bromide. The  $\text{Bu}_3\text{SnH}$ /AIBN mediated radical reaction between **181** and alkenes affords the (phosphoryl)difluoromethylation products **182** in moderate yields (Scheme 100).

Scheme 100



Similar intermolecular radical difluoroalkylation has been used by Fuchigami and co-workers<sup>250</sup> to synthesize difluoromethylene-substituted compounds from electrochemically prepared  $\alpha$ -difluorinated thioethers, such as **183** and **184**, under photochemical conditions (Scheme 101). In these reactions, the hydrogen atom source seems to be the alkene substrate.

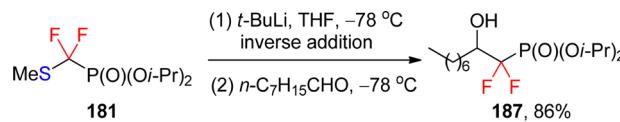
Scheme 101



It is worthwhile noting that, the C–S bond of a difluoroalkyl sulfide can also be heterolytically cleaved through a sulfur–lithium exchange reaction. Lequeux and co-workers<sup>251</sup> have shown that the aforementioned compound **181** can be used as a freon-free source of (phosphoryl)difluoromethyl anion under the action of *tert*-butyllithium, which is useful to synthesize structurally diverse  $\alpha$ -difluorinated phosphonate.<sup>252</sup> For example, its reaction with octanal affords product **187** in 86% yield (Scheme 102).<sup>251</sup> Previously, the synthesis of difluorinated phosphonates mainly relies on the freon-derived reagents such as  $\text{HCF}_2\text{P}(\text{O})(\text{OEt})_2$  and  $\text{BrCF}_2\text{P}(\text{O})(\text{OEt})_2$ .<sup>253</sup>

The radical chlorodifluoromethylation is rare due to the lack of a practical precursor.<sup>254</sup> In their continuous efforts to

Scheme 102



develop radical fluoroalkylation reactions with xanthates, Salomon and Zard very recently described the preparation of *O*-octadecyl-*S*-chlorodifluoromethyl xanthate (**188**) from chlorodifluoroacetic acid and its use as a convenient source of chlorodifluoromethyl radicals (Scheme 103).<sup>255</sup> A sequential addition-reductive desulfenylation reaction with **188** transforms a series of simple alkenes to chlorodifluoromethylated alkanes **189** in good yields with tolerance of functions such as carbamates and free alcohols. The radical addition–elimination on 2-fluoropyridyl derivatives of allylic alcohols, such as **190**, with **188** affords the allylic chlorodifluoromethylation products, such as **191**, in good yields.

### 3.3.2. Sulfides as Difluoromethylation Reagents.

Intermolecular radical difluoroalkylations with sulfides are usually of low efficiency, and thus large excess of alkenes are needed to capture the difluoroalkyl radical. As described in section 3.2.1, the nucleophilic difluoro(phenylthio)methylation is a facile method to introduce a  $\text{PhSCF}_2$  into various substrates, thus providing the opportunity to put the alkene and the difluorinated sulfide in one molecule, which can significantly improve the conversion of alkenes.

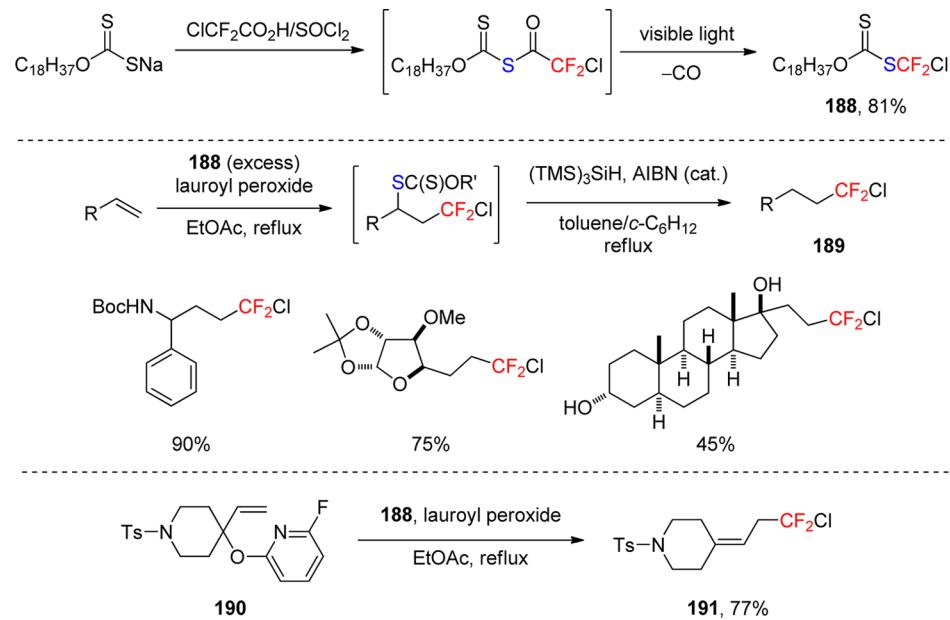
In early 2007, Hu and Li reported an intramolecular difluoroalkylation by using  $\text{PhSCF}_2\text{TMS}$  (**115**) as a difluoromethylene radical anion equivalent.<sup>186</sup> The allylation of difluoro(phenylthio)methylated sulfinylamides **125** that are obtained via the reaction of *N*-(*tert*-butylsulfinyl)imines and  $\text{PhSCF}_2\text{TMS}$  (**115**) (see Scheme 70), followed by treatment with  $\text{Bu}_3\text{SnH}$  in the presence of a small amount of AIBN, furnishes the 5-exo cyclization products **160** in moderate yields with high *trans* diastereoselectivity (dr up to 11:1) (Scheme 104).

Pohmakotr and co-workers have extended this difluoromethylation methodology to the transformation of carbonyl compounds.<sup>179–184</sup> Difluoro(phenylthio)methylation of *N*-alkenylated cyclic imides **194** followed by radical cyclization afforded *gem*-difluoromethylenated 1-azabicyclic compounds **196** with *trans*-stereoselectivity (Scheme 105).<sup>179</sup> These compounds can be further transformed to various *gem*-difluoromethylenated pyrrolizidinones and indolizidinones, such as **197**. In addition, homoallyl and pent-4-enyl ketones can also undergo this difluoro(phenylthio)methylation/cyclization process to give *gem*-difluoromethylenated cyclopentanols and cyclohexanols.<sup>181,183,184</sup> Note that the difluoro(phenylthio)methyl group can tolerate many reaction conditions such as olefin cross metathesis, which is useful for further derivation of the difluoro(phenylthio)methyl compounds.<sup>181,184</sup>

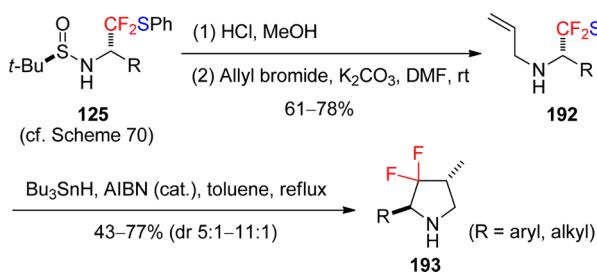
### 3.3.3. Sulfones as Difluoromethylation Reagents.

**3.3.3.1. Phenyl Sulfones.** Resembling trifluoromethylation with  $\text{PhSO}_2\text{CF}_3$  (**39**), the difluoro(phenylsulfonyl)methyl compounds, which are readily available via difluoro(phenylsulfonyl)methylation reactions (see Section 3.2.2), can undergo further desulfonylation reaction to afford difluoroalkyl compounds. Therefore, the aforementioned various difluoro(phenylsulfonyl)methylating agents also serve as difluoromethylene synthons.

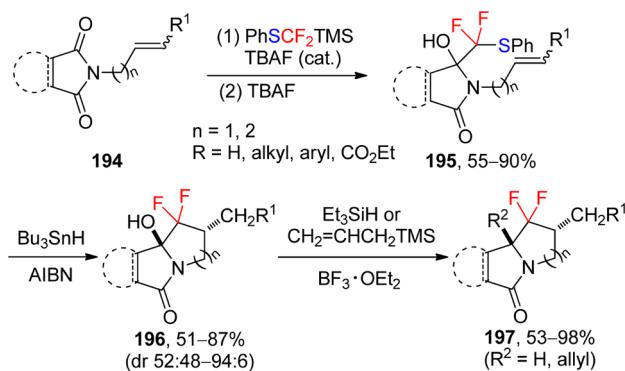
Scheme 103



Scheme 104

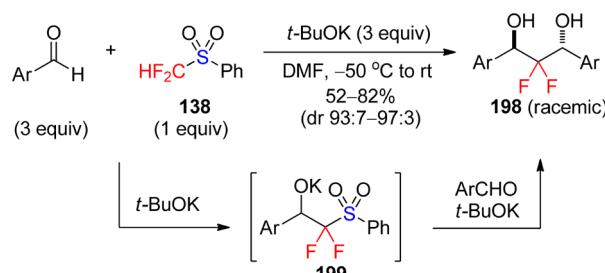


Scheme 105



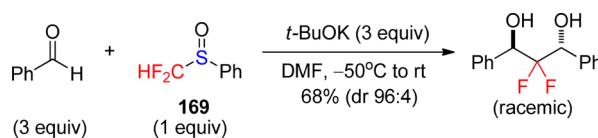
As described previously, the reaction between **138** and carbonyl compounds in the presence of a base gives  $\alpha$ -difluoro(phenylsulfonyl)methyl alcohols (see Section 3.2.2.1). However, by use of an alkoxide such as *t*-BuOK as the base, sulfone **138** can react with two molecules of aryl aldehydes to give 2,2-difluorinated *anti*-1,3-diols **198** with high diastereoselectivity (anti/syn up to 97:3) (Scheme 106).<sup>256</sup> The reaction is proposed to proceed through the further reaction of alcoholates **199** with a second molecule of aldehydes under the action of the alkoxide. Similarly, sulfone **138** readily reacts with PhSSPh (2 equiv) in the presence of *t*-BuOK (4 equiv) to give PhSCF<sub>2</sub>SPh in high yield.<sup>256</sup> In analogy to PhSO<sub>2</sub>CF<sub>2</sub>H, the

Scheme 106



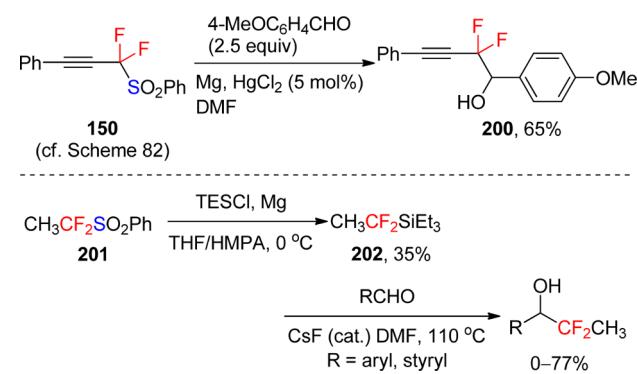
sulfoxide **169** can also work as the difluoromethylene equivalent to couple two molecules of aryl aldehydes (Scheme 107).<sup>257</sup>

Scheme 107



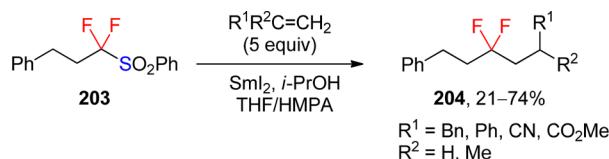
The difluoro(phenylsulfonyl)methyl compounds can also undergo reductive coupling reaction with an electrophile (Scheme 108).<sup>215a,258</sup> Compound **150**, which is prepared from PhSO<sub>2</sub>CF<sub>2</sub>TMS and phenylacetylene iodide or bromide (see Scheme 82), has been used as a nucleophilic fluoroalkylating agent to react with 4-methoxybenzaldehyde in the presence of Mg/HgCl<sub>2</sub> (cat.), affording the addition product **200** in 65% yield.<sup>215a</sup> Compound **201**, which is prepared from PhSO<sub>2</sub>CF<sub>2</sub>H and methyl iodide, has been used to prepare 1,1-difluoroethylsilanes, such as **202**, as 1,1-difluoroethylating reagents.<sup>173a,258</sup>

Scheme 108



*α,α*-Difluorinated sulfones are also 1,1-difluoroalkyl radical precursors, though they are less commonly used in fluoroalkylation reactions. Reutrakul and Pohmakotr and co-workers<sup>192</sup> showed that the reaction of 1,1-difluoro-3-phenylpropyl phenyl sulfone (**203**) with alkenes (5 equiv) in the presence of SmI<sub>2</sub> and *i*-PrOH gave *gem*-difluoroalkanes **204** in 21–74% yields (Scheme 109).

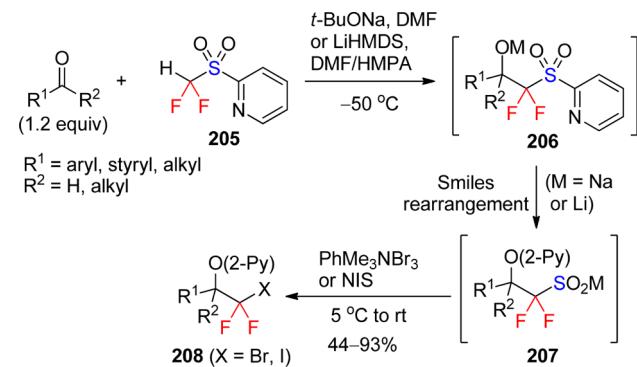
Scheme 109



**3.3.3.2. Heteraryl Sulfones.** Difluoromethyl 2-pyridyl sulfone (**205**) is a difluoroolefinating agent toward carbonyl compounds (see section 3.4.3). The key intermediate in the olefination, a difluorinated sulfinate salt **206**, although not stable enough to be isolated, could be captured with CH<sub>3</sub>I to afford the corresponding methyl sulfones.<sup>259</sup> On the other hand, the halogenation of the in situ-generated sulfinate salt **206** gives the halodifluoromethylated compounds **208**.<sup>260</sup> Thus, a wide range of aldehydes and ketones could be transformed to the formal nucleophilic bromo- and iododifluoromethylation products in moderate to good yields by a combination of Julia–Kocienski reaction with **205** and desulfinatohalogenation reaction of difluorinated sulfonates (Scheme 110).

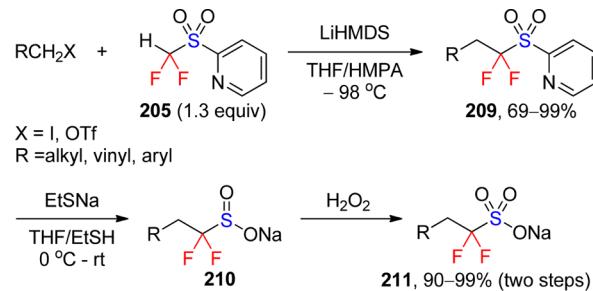
**3.3.4. Sulfones as Difluoroalkylation Reagents.** Difluoromethyl 2-pyridyl sulfone (**205**), which was initially developed for *gem*-difluoroolefination of carbonyl compounds

Scheme 110



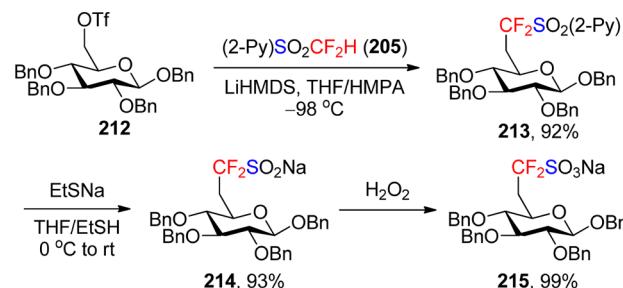
(see section 3.4.3), can also be used to prepare stable *α*-difluorinated sulfinate salts (Scheme 111).<sup>261</sup> The nucleophilic

Scheme 111



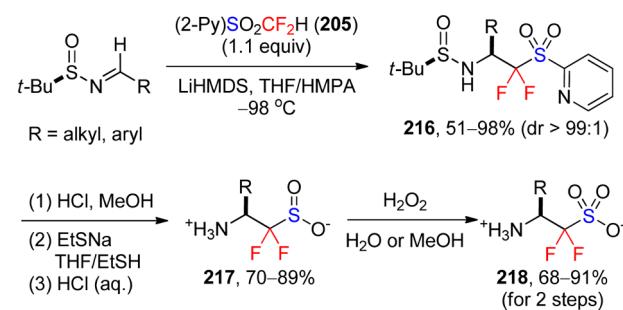
difluoro[(2-pyridyl)sulfonyl]methylation of primary alkyl halides or triflates and benzyl bromides under the action of a base, such as LiHMDS, in THF as solvent with HMPA as an additive at -98 °C leads to the substituted products **209** in good yields. Subsequently, the difluorinated sulfinate salts **210** are readily released from sulfones **209** via an intermolecular, aromatic substitution by using a less basic nucleophile, such as sodium ethanethiolate. The so-obtained difluorinated sulfonate salts can be oxidized to difluorinated sulfonate salts **211**, which are difficult to prepare via direct nucleophilic difluoro(sulfonato)-methylation with difluoromethanesulfonic acid esters. This methodology is also applicable for modification of functionalized molecules such as carbohydrates (Scheme 112).<sup>261</sup>

Scheme 112



Similarly, the novel *α,α*-difluoro-β-amino sulfinic and sulfonic acids, **217** and **218**, which are potentially useful building blocks to construct difluorinated peptidosulfonamides, are obtained via nucleophilic difluoro(2-pyridylsulfonyl)methylation of *N*-*tert*-butanesulfinyl imines followed by depyridylation (Scheme 113).<sup>262</sup>

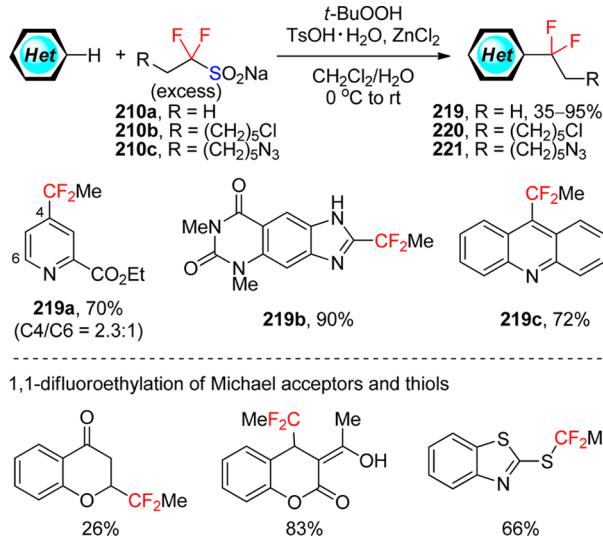
Scheme 113



### 3.3.5. Sulfinate Salts as Difluoroalkylation Reagents.

In analogy to perfluoroalkylation and difluoromethylation with sulfinate salts, 1,1-difluoroalkanesulfinate salts, which can be readily prepared from difluoromethyl 2-pyridyl sulfone and an alkyl iodide (see Scheme 111),<sup>261</sup> are useful 1,1-difluoroalkylation reagents. In 2013, Baran and co-workers demonstrated a 1,1-difluoroethylation by using sodium 1,1-difluoroethanesulfinate **210a** as the reagent, following a procedure similar to the aforementioned heteroaromatic difluoromethylation reactions (see Scheme 96), although using *p*-toluenesulfonic acid instead of trifluoroacetic acid with the addition of zinc chloride (Scheme 114).<sup>263</sup> Note that this 1,1-difluoroethylation

**Scheme 114**



possesses similar substrate scope, functionality tolerance, and site selectivity to that of difluoromethylation with zinc difluoromethanesulfinate (**173**). Moreover, other 1,1-difluoroalkylsulfinate salts such as **210b** and **210c** can also undergo the C–H functionalization to give the corresponding difluoroalkylation products, and sulfinate **210c** has been used in native chemical tagging of natural products and pharmaceuticals.<sup>264</sup>

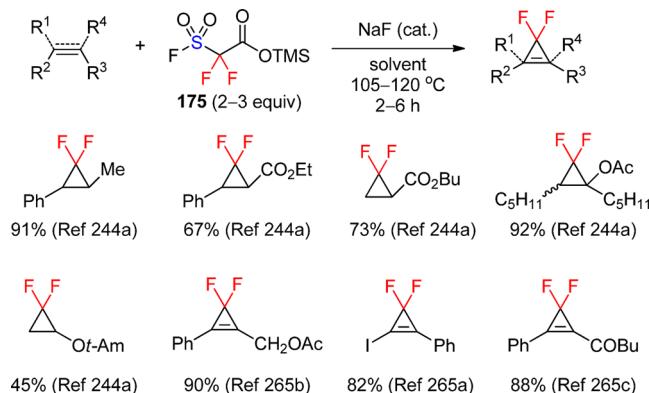
### 3.3.6. Tetrafluoroethane $\beta$ -Sultone Derivatives as Difluorocarbene Sources for Difluorocyclization.

Among various tetrafluoroethane  $\beta$ -sultone derivatives, trimethylsilyl (fluorosulfonyl)difluoroacetate (TFDA, FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>TMS, **175**) and methyl fluorosulfonyldifluoroacetate (MDFA, **100**) are two important difluorocarbene sources for difluorocyclopropanation of alkenes and difluorocyclopropagation of alkynes.<sup>13c</sup> Together with difluoromethylation with tetrafluoroethane  $\beta$ -sultone derivatives, the difluorocyclization mentioned here has been covered in recent reviews.<sup>12k,13c</sup>

The use of TFDA (**175**) for the synthesis of *gem*-difluorocyclopropanes was developed by Chen, Dolblier and co-workers in 2000.<sup>241</sup> TFDA generates difluorocarbene in a fluoride-catalyzed chain process with the release of CO<sub>2</sub> and SO<sub>2</sub>; thus, difluorocyclopropanation<sup>244</sup> and difluorocyclopropagation<sup>265</sup> with TFDA can be conducted under mild conditions with broad substrate scope and high efficiency (Scheme 115).

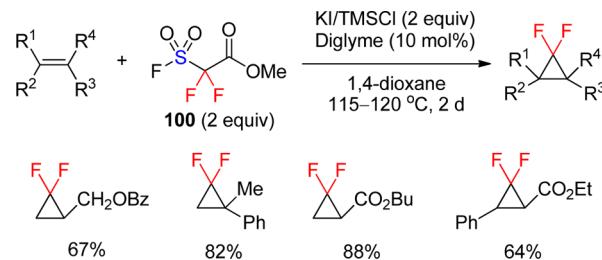
As described in section 3.1.7, methyl fluorosulfonyldifluoroacetate (MDFA, **100**) was first used as a difluorocarbene reagent for copper-mediated trifluoromethylation.<sup>159</sup> Due to the factors such as low cost, high safety, and ease of reaction,

**Scheme 115**



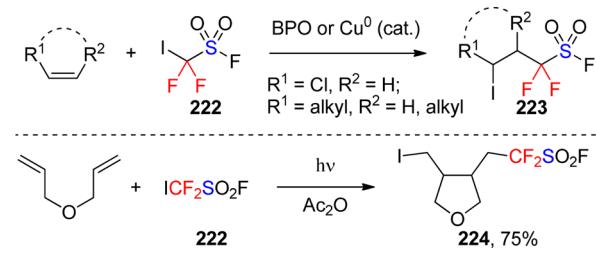
very recently, MDFA has also been used as a substitute of TFDA to synthesize *gem*-difluorocyclopropanes (Scheme 116).<sup>266</sup>

**Scheme 116**



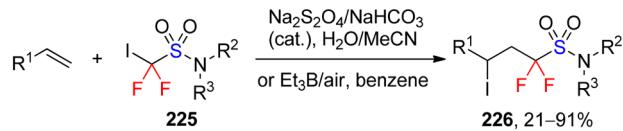
**3.3.7. Tetrafluoroethane  $\beta$ -Sultone Derivatives as Difluorocarbene Sources for Difluorocyclization.** Tetrafluoroethane  $\beta$ -sultone derivatives can also be used as fluoroalkylating agents to transfer a functionalized methyl group. Some early investigations showed that (iododifluoromethyl)sulfonyl fluoride (FSO<sub>2</sub>CF<sub>2</sub>I, **222**) can react with alkenes via an ATRA reaction to afford the difluoro(fluorosulfonyl)methylation products **223** and **224** (Scheme 117).<sup>267</sup> Recently, iododifluoromethanesulfonamides **225** and mixed amide-sulfonamides such as **227** have been developed as fluoroalkylating agents to introduce a difluoromethylene sulfonamide (Scheme 118).<sup>268</sup> The difluoromethylene sulfonamide anion in situ generated from diamide **227** and *t*-BuOK reacts with aldehydes to afford  $\beta$ -hydroxy sulfonamides **228** in good yields. Moreover, diamide **227** can work similarly to PhSO<sub>2</sub>CF<sub>2</sub>H (**138**), reacting with two molecules of aromatic aldehydes to give difluoromethylenated 1,3-alcohols **198** in moderate yields (18–64%).<sup>268</sup>

**Scheme 117**

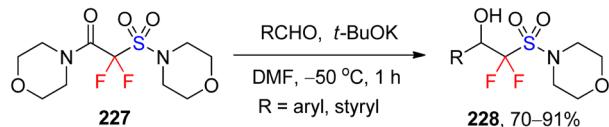


fonamides **225** and mixed amide-sulfonamides such as **227** have been developed as fluoroalkylating agents to introduce a difluoromethylene sulfonamide (Scheme 118).<sup>268</sup> The difluoromethylene sulfonamide anion in situ generated from diamide **227** and *t*-BuOK reacts with aldehydes to afford  $\beta$ -hydroxy sulfonamides **228** in good yields. Moreover, diamide **227** can work similarly to PhSO<sub>2</sub>CF<sub>2</sub>H (**138**), reacting with two molecules of aromatic aldehydes to give difluoromethylenated 1,3-alcohols **198** in moderate yields (18–64%).<sup>268</sup>

Scheme 118



R<sup>1</sup> = alkyl, CH<sub>2</sub>OH, CH<sub>2</sub>NH<sub>2</sub>, TMS, etc.  
R<sup>2</sup>R<sup>3</sup>N = 1-piperidinyl, morpholino



### 3.4. For Difluoroolefination

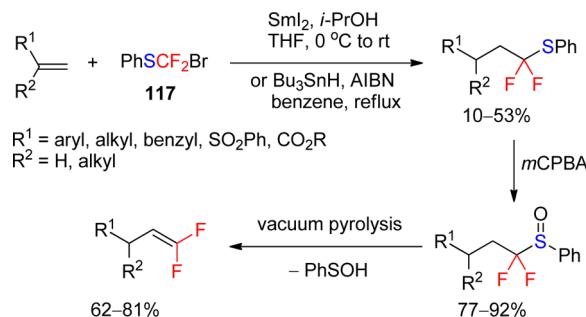
The *gem*-difluorovinyl functionality (C=CF<sub>2</sub>) is known to act as a bioisostere for the carbonyl group, which has been used in the design of mechanism-based enzyme inhibitors.<sup>269,270</sup> Among various methods for the synthesis of 1,1-difluoroalkenes, the selective difluoromethylidenation can modify a target molecule without significant alternation of its scaffold. However, the traditional difluoromethylidenation method, Wittig olefination, suffers from restrictions in terms of substrate scope and environment-benignity of the reagents used.<sup>270</sup> The sulfur-based transformation is a powerful method to introduce a difluoromethylidene group into substrates not limited to but including carbonyl compounds. This section aims to provide an introduction on *gem*-difluoroolefination with various sulfur-based fluoroalkylation reagents, with emphasis on recent achievements on the use of heteroaryl sulfone, sulfoxime, and TFDA reagents. Parts of the material discussed here have also included in a review<sup>271</sup> published in early 2012.

#### 3.4.1. Sulfides and Xanthates as Difluoroolefination Reagents

**Reagents.** As described in section 3.2.1, various difluoro(phenylthio)methyl compounds can be prepared by using PhSCF<sub>2</sub>TMS (115), PhSCF<sub>2</sub>H (116), PhSCF<sub>2</sub>Br (117), and PhSCF<sub>2</sub>I (130) as the fluoroalkylation reagents. Some of the so-obtained difluoro(phenylthio)methyl compounds have been used to prepare *gem*-difluoroalkenes through oxidation to sulfoxides followed by thermal elimination (Schemes 119 and 120).<sup>192,272</sup> Therefore, the aforementioned difluoro(phenylthio)methylation reagents can be considered as the difluoromethylidene synthons.

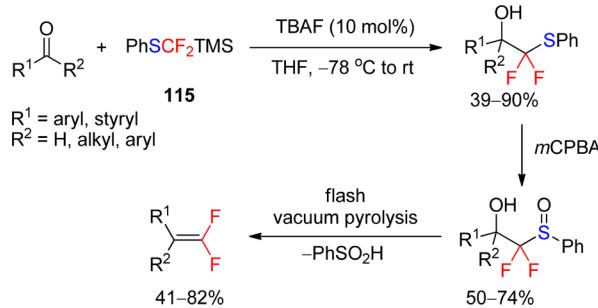
The chlorodifluoromethyl compounds obtained from the reaction of alkene with *O*-octadecyl-*S*-chlorodifluoromethyl xanthate (188) (see section 3.3.1) can be further transformed to *gem*-difluoroalkenes and -dienes in the presence of an organic base (Scheme 121).<sup>255</sup> Particularly, in the case of *N*-allyl anilines, the indolines, such as 229, resulting from the

Scheme 119

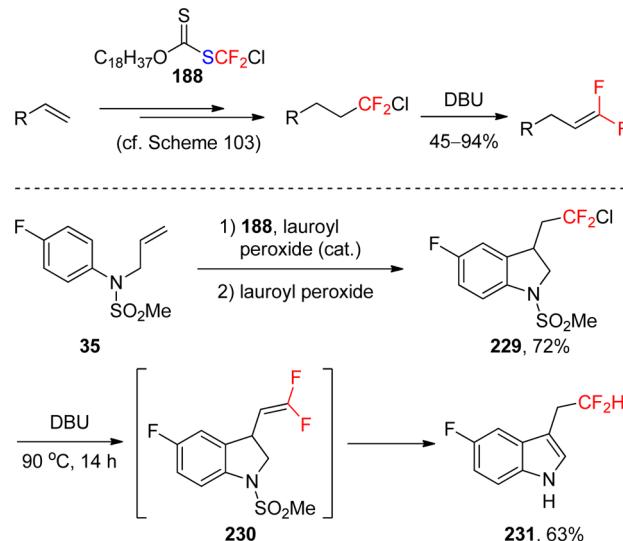


R<sup>1</sup> = aryl, alkyl, benzyl, SO<sub>2</sub>Ph, CO<sub>2</sub>R  
R<sup>2</sup> = H, alkyl

Scheme 120



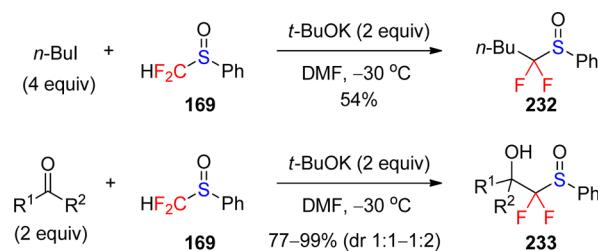
Scheme 121



further cyclization of the adducts, can be eventually converted to the difluoromethylindoles, such as 231, via isomerization of the *gem*-difluoroalkene intermediates.

**3.4.2. Sulfoxides as Difluoroolefination Reagents.** As described in Section 3.4.1, difluorinated sulfoxides can be transformed to *gem*-difluoroalkenes via elimination reaction. Thus, the difluoro(arylsulfinyl)methylation with difluoromethyl sulfoxides, although less used in sulfur-assisted fluoroalkylation, is also a viable access to olefins. Racemic difluoromethyl phenyl sulfoxide (169) can be prepared by simple oxidation of PhSCF<sub>2</sub>H (116) with *m*-chloroperbenzoic acid (*m*CPBA).<sup>257</sup> It has been reported that primary alkyl iodide, such as *n*-butyl iodide, reacts with 169 in the presence of *t*-BuOK, to give the substitution product, such as 1,1-difluoropentyl phenyl sulfoxide (232), in moderate yield (Scheme 122).<sup>199c</sup> Nucleophilic difluoro(phenylsulfinyl)methylation of both enolizable and nonenolizable aldehydes and ketones has also been

Scheme 122



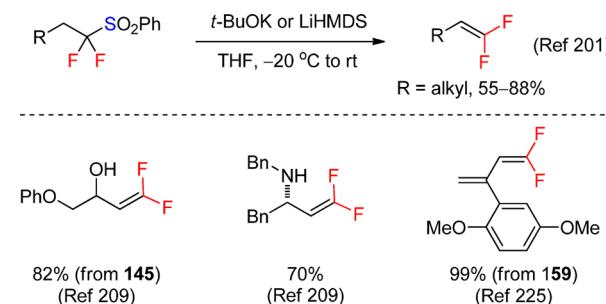
achieved by using **169** as the limiting reagent (Scheme 122).<sup>257</sup> Although the chemical yields of the reactions are good to excellent, the observed diastereoselectivity is poor (1:1–1:2).

### 3.4.3. Sulfones as Difluoroolefination Reagents.

**3.4.3.1. Base-Induced Dehydrosulfonylation.** As described in Section 3.2.2, structurally diverse difluoro(phenylsulfonyl)-methyl compounds can be accessed through difluoro(phenylsulfonyl)methylation reactions. Base-induced dehydrosulfonylation constitutes the most common pathway to synthesize *gem*-difluoroalkenes from difluoro(phenylsulfonyl)-methyl compounds.<sup>199a,201</sup>

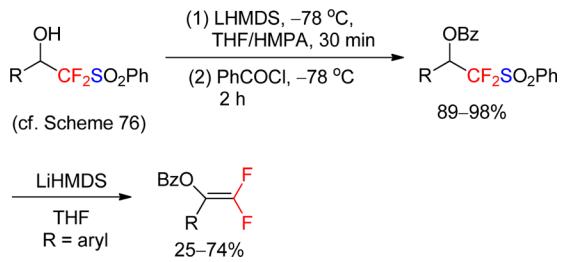
In 2004, Prakash, Hu and co-workers<sup>201</sup> reported a facile synthesis of *gem*-difluoroalkenes via difluoro(phenylsulfonyl)-methylation followed by dehydrosulfonylation. Thus, treatment of  $\text{PhSO}_2\text{CF}_2$  compounds, which are obtained from the reaction between primary alkyl iodides or bromides and  $\text{PhSO}_2\text{CF}_2\text{H}$  (138), with *t*-BuOK in THF solution affords 1,1-difluoroalkenes in good yields (Scheme 123). Using this

### Scheme 123



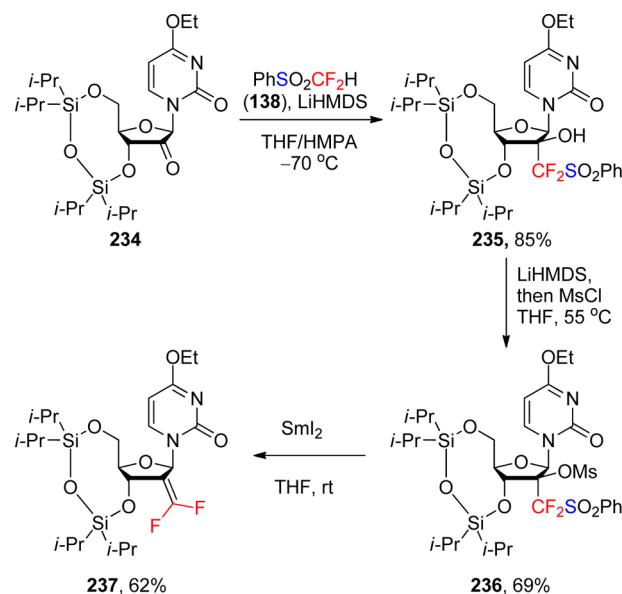
base-induced  $\beta$ -elimination reaction, *gem*-difluorinated allyl alcohols and amines,<sup>209</sup> 1,3-dienes,<sup>225</sup> as well as enol esters (Scheme 124)<sup>273</sup> have been prepared from the corresponding difluoro(phenylsulfonyl)methyl compounds.

**Scheme 124**



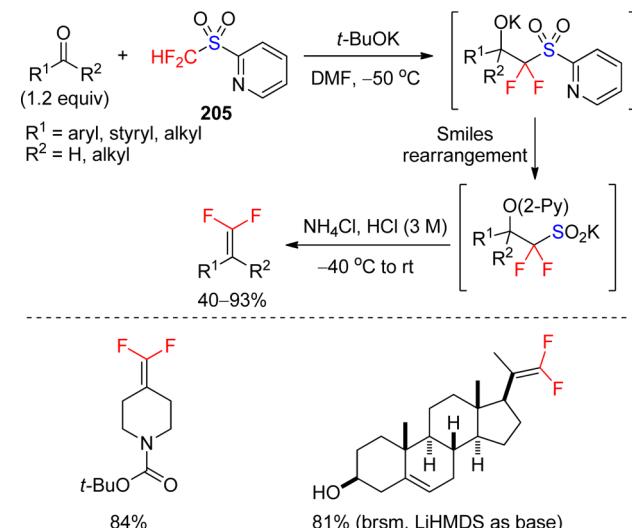
**3.4.3.2. Julia-Lythgoe Reaction.** In 1992, Sabol and McCarthy<sup>205a</sup> reported the first example of *gem*-difluoroolefination of carbonyls with  $\text{PhSO}_2\text{CF}_2\text{H}$ , employing a modified Julia olefin synthesis with  $\text{SmI}_2$  as the electron transfer reagent (Scheme 125). This 3-step synthesis of 1,1-difluoroalkene 237 provides a new route to highly functionalized and sensitive difluoroolefins that are difficult to prepare using other deoxygenative *gem*-difluoroolefination methods,<sup>205a</sup> such as Horner-Wittig reaction with difluoromethylidiphenylphosphine oxide<sup>274</sup> and Wittig reactions with the combination of  $\text{CF}_2\text{Br}_2/\text{P}(\text{NMe}_2)_3$ .<sup>275</sup> In addition to  $\text{SmI}_2$ ,  $\text{Na}/\text{Hg}$  can also be used as the electron transfer reagent to achieve this *gem*-difluoroolefination.<sup>202</sup>

### Scheme 125



**3.4.3.3. Julia-Kocienski Reaction.** In 2010, Hu and co-workers<sup>259</sup> reported the first Julia-Kocienski-type *gem*-difluoroolefination reaction with a previously unknown compound, that is, difluoromethyl 2-pyridyl sulfone (2-PySO<sub>2</sub>CF<sub>2</sub>H, **205**), which provides a one-pot synthesis of 1,1-difluoroalkenes from carbonyl compounds (Scheme 126). Reagent **205** is a bench-

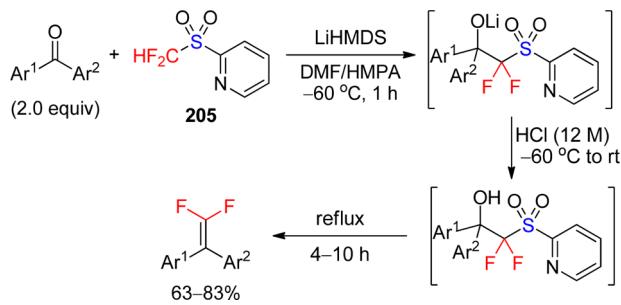
**Scheme 126**



stable crystalline solid that can be readily prepared by oxidation of the corresponding sulfide. Note that although 2-pyridyl sulfones are less commonly used in Julia-Kocienski olefination reactions,<sup>276</sup> reagent **205** shows unexpectedly better reactivity in *gem*-difluoroolefination reaction than other difluoromethyl heteroaryl sulfones such as difluoromethyl 1,3-benzothiazol-2-yl (BT) sulfone, difluoromethyl 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone, and difluoromethyl 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) sulfone.<sup>259</sup> A variety of aldehydes and ketones were difluoroolefinated by reaction with **205** in the presence of a base, such as *t*-BuOK, followed by treatment with an acid to afford the 1,1-difluoroalkenes in good yields.

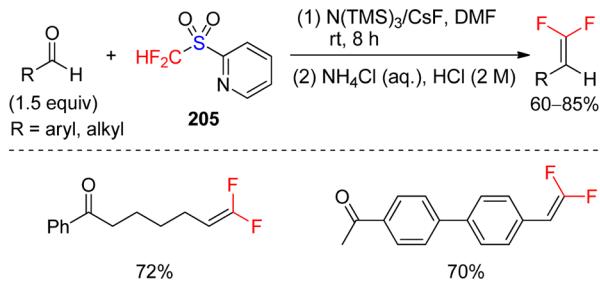
However, the alcoholate intermediates of the reaction of diaryl ketones with **205** readily undergo a retro-aldol type reaction at the temperatures that are required for Smiles rearrangement, thus the olefination products were given in very low yields.<sup>270</sup> To improve the *gem*-difluoroolefination, the quenching of the alcoholate intermediate with an acid at a low temperature, such as  $-60^{\circ}\text{C}$  followed by acid-promoted elimination reaction could afford 2,2-diaryl-1,1-difluoroalkenes in good yields (Scheme 127).<sup>270</sup>

Scheme 127



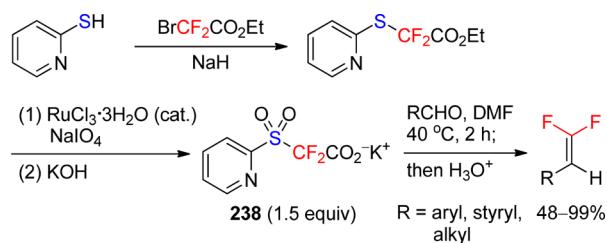
The *gem*-difluoroolefination of aliphatic aldehydes with **205** can be achieved through the use of *in situ* generated amide base (from CsF and tris(trimethylsilyl)amine), which diminishes the undesired enolization of aliphatic aldehydes and provides a synthetically powerful method for selective *gem*-difluoroolefination of mult carbonyl compounds (Scheme 128).<sup>270</sup>

Scheme 128



Following the *gem*-difluoroolefination with reagent **205**,<sup>259</sup> Xiao and co-workers<sup>277</sup> very recently developed a decarboxylative Julia–Kocienski reaction by using potassium 2-pyridinyl sulfonyl-difluoroacetate (**238**) as the base-free olefination reagent (Scheme 129). To promote the decarboxylation process, the reaction is conducted in a polar solvent DMF at  $40^{\circ}\text{C}$ . The current protocol, however, is only amenable with aldehydes.

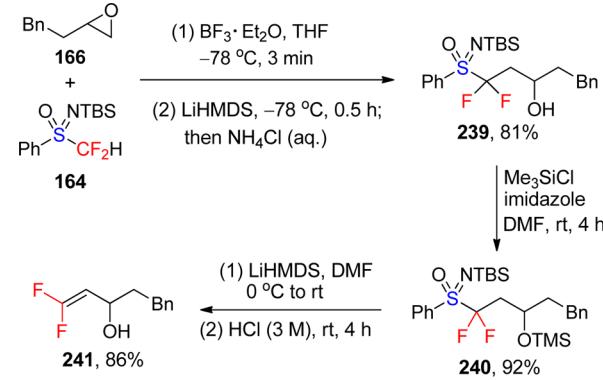
Scheme 129



### 3.4.4. Sulfoximines as Difluoroolefination Reagents.

Sulfoximines can also undergo  $\beta$ -elimination reaction; thus, dehydrosulfonimidoylation of  $\alpha$ -difluorinated sulfoximines with a base is also viable for 1,1-difluoroalkenes (Scheme 130).<sup>231</sup>

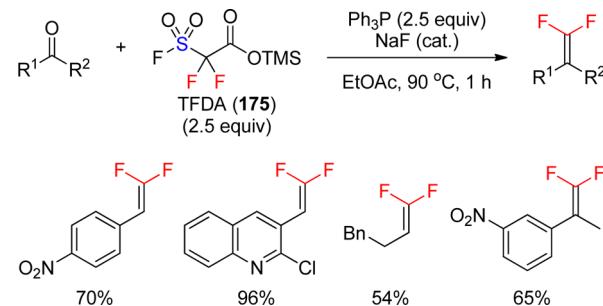
Scheme 130



### 3.4.5. Tetrafluoroethane $\beta$ -Sultone Derivatives as Difluoroolefination Reagents

In 2013, Xiao and co-workers reported that, under the catalysis of fluoride salts, such as NaF, TFDA (**175**)<sup>241</sup> could react with PPh<sub>3</sub> to generate highly reactive difluoromethylene ylide CF<sub>2</sub>=PPh<sub>3</sub> for Wittig-type *gem*-difluoroolefination.<sup>278</sup> The reaction is applicable to aromatic, heteroaromatic, and aliphatic aldehydes and activated ketones (Scheme 131).<sup>278</sup> Note that the CF<sub>2</sub>=PPh<sub>3</sub> generated

Scheme 131



from TFDA is able to difluoroolefinate electron-deficient aldehydes such as 4-nitrobenzaldehyde, which had been reported to give a low yield of the difluoroolefination product using other Wittig-type olefination reagents, such as FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>Me (**100**)/PPh<sub>3</sub>/KI<sup>279</sup> and ClCF<sub>2</sub>CO<sub>2</sub>Na/PPh<sub>3</sub>.<sup>280</sup>

### 3.5. For Monofluoromethylation

Similar to the difluoromethyl group, the monofluoromethyl group (CH<sub>2</sub>F) is also important in isostere-based drug design.<sup>281</sup> Although there are numerous methods available for the synthesis of monofluoromethyl compounds via fluorination reactions, the direct introduction of a CH<sub>2</sub>F group is not trivial. Direct monofluoromethylations are limited to electrophilic and radical reactions with the following reagents: fluoromethanol, halofluoromethanes (CH<sub>2</sub>FX, where X = Cl, Br, and I), monofluoromethyl sulfonates (CH<sub>2</sub>FOSO<sub>2</sub>R, where R = CF<sub>3</sub>, Me, and tolyl), S-fluoromethyl sulfonium salts, S-fluoromethyl sulfoximines, and fluoromethanesulfinate salts.<sup>13d,g</sup> As for direct nucleophilic monofluoromethylations, it has been known that reactions with fluoromethyl lithium (FCH<sub>2</sub>Li) and fluoromethyl

Grignard reagent ( $\text{FCH}_2\text{MgX}$ ) are challenging due to their rather low thermal stability.<sup>282</sup> Consequently, the nucleophilic monofluoromethylations have resorted to monofluoromethyl anion equivalents that are stabilized by one or two removable functional groups. Among various functional groups, the sulfonyl groups have been frequently used not only because of their ready removability from the monofluorinated carbon to unmask the  $\text{CH}_2\text{F}$  group at the final stage of the transformation, but also because of the ready availability of various monofluorinated sulfone reagents. The sulfonimidoyl group recently also has been applied due to their excellent stereocontrol ability. In addition, as is seen from the above listed direct monofluoromethylation reagents, the sulfur-based reagents also account for a large number. In these senses, the sulfur plays a more important role in monofluoromethylations than difluoromethylations, since the former rely more largely on sulfur-based reagents. This section provides a full review on the development of monofluoromethylations under the framework of sulfur-based reagents, including sulfones, sulfoximines, sulfonium salts, and sulfinate salts, with subdivisions according to the role of sulfur, if applicable. A recent review on di- and monofluoromethylations covers part of this topic.<sup>13d</sup>

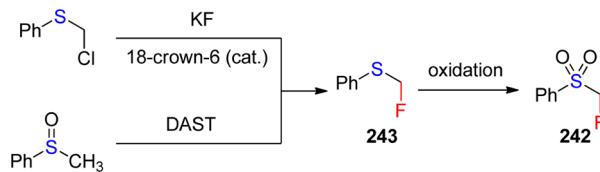
### 3.5.1. Sulfones as Monofluoromethylation Reagents.

Both phenyl sulfones and electron-deficient heteroaryl sulfones can be used to introduce a fluoromethyl group; the phenylsulfonyl group on a monofluorinated carbon can be removed under the reduction of a metal reductant, such as sodium amalgam  $\text{Na}(\text{Hg})$  and  $\text{Mg}^{13g}$  and the heteroarylsulfonyl group such as (2-pyridyl)sulfonyl can be easily removed under the radical conditions of  $\text{Bu}_3\text{SnH}/\text{AIBN}$ .<sup>283</sup> Compared to difluoromethylation with sulfones, monofluoromethylation with sulfones can be realized via fluoro(sulfonyl)methylation and fluoro[bis(sulfonyl)]methylation since only one substituent on the  $\text{sp}^3$ -carbon is predetermined by fluorine.

**3.5.1.1. Nucleophilic Fluoro(sulfonyl)methylation.** Nucleophilic fluoro(sulfonyl)methylation is an important method to introduce a fluoromethyl group into a molecule, which has been realized by using both phenyl and 2-pyridyl sulfones.

**3.5.1.1.1. Using Fluoromethyl Phenyl Sulfone.** Fluoromethyl phenyl sulfone ( $\text{PhSO}_2\text{CH}_2\text{F}$ , **242**) was first prepared by Yagupol'skii and Aleksandrov in 1968 via hydrolysis of perfluoroprop-1-en-1-yl phenyl sulfone or ethyl 2-fluoro-2-(phenylsulfonyl)acetate.<sup>284</sup> As a widely used fluoroalkylation reagent, **242** is usually synthesized through the oxidation of fluoromethyl phenyl sulfide ( $\text{PhSCH}_2\text{F}$ , **243**), in which the fluorine atom is from readily available nucleophilic fluorination reagents such as KF and DAST (Scheme 132).<sup>285</sup> The

Scheme 132



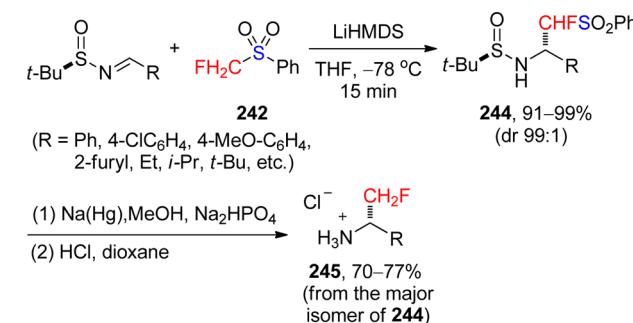
intermediate  $\text{PhSCH}_2\text{F}$  (**243**) is also the precursor to prepare other fluoroalkylation reagents, such as fluoromethyl sulfoxide, S-fluoromethyl sulfoximines, and S-fluoromethyl sulfonium salts.

In 1985, Peet, McCarthy, and co-workers first used fluoro(phenylsulfonyl)methylolithium (prepared by lithiation of

compound **242** with  $\text{BuLi}$  at  $-78^\circ\text{C}$ ) as a nucleophilic fluoro(phenylsulfonyl)methylation reagent toward aldehydes and ketones for the synthesis of terminal monofluoroalkenes via a nucleophilic addition–dehydration–reductive desulfonylation sequence (see Section 3.7.2.1).<sup>286</sup> Although the fluoro(phenylsulfonyl)methylated carbinols were prepared at that time, no attempt was made to convert it into  $\alpha$ -fluoromethyl alcohols. In 2001, Shimizu et al. serendipitously obtained  $\alpha$ -fluoromethyl alcohols as the side products during their efforts on the introduction of a 19-fluoromethylene group to a (SE)-19-nor-10-oxo-vitamin D derivative by reduction of the corresponding fluoro(phenylsulfonyl)methylated carbinols with  $\text{Na}(\text{Hg})$ , which is the first time to introduce a monofluoromethyl group via fluoro(phenylsulfonyl)methylation with  $\text{PhSO}_2\text{CH}_2\text{F}$  (**242**).<sup>287</sup>

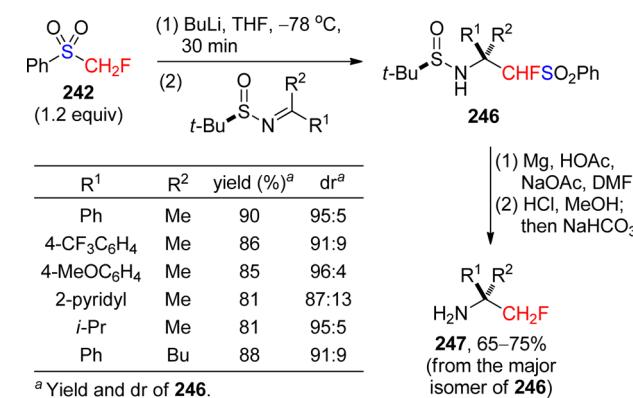
However, the synthetic potential of compound  $\text{PhSO}_2\text{CH}_2\text{F}$  (**242**) as a useful monofluoromethylation reagent was not fully recognized until 2006, when a diastereoselective synthesis of  $\alpha$ -fluoromethyl amines was achieved by Hu and co-workers via nucleophilic fluoro(phenylsulfonyl)methylation of *N*-(*tert*-butylsulfinyl)aldimines with compound **242** (Scheme 133).<sup>288</sup>

Scheme 133



Subsequently, this synthetic methodology was extended to both the  $\alpha$ -amino aldimines<sup>208b</sup> and the ketimines (Scheme 134).<sup>289</sup>

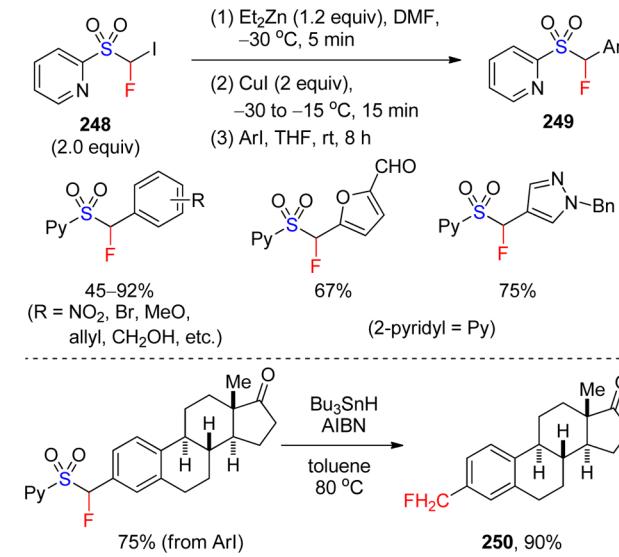
Scheme 134



For sterically less hindered aldimines, nucleophilic fluoro(phenylsulfonyl)methylation with the *in situ* generated  $\text{PhSO}_2\text{CHF}^-$  anion readily takes place to afford the addition products in good yields whereas the nucleophilic addition to sterically more hindered ketimines requires the pregenerated  $\text{PhSO}_2\text{CHF}^-$  anion to avoid the competitive azo-enolization of the ketimines.

**3.5.1.2. Using Fluoroiodomethyl 2-Pyridyl Sulfone.** To realize the monofluoromethylation of aryl halides, Hu and co-workers in 2012 developed fluoroiodomethyl 2-pyridyl sulfone (**248**) as an efficient monofluoromethylation reagent (Scheme 135).<sup>290</sup>

Scheme 135

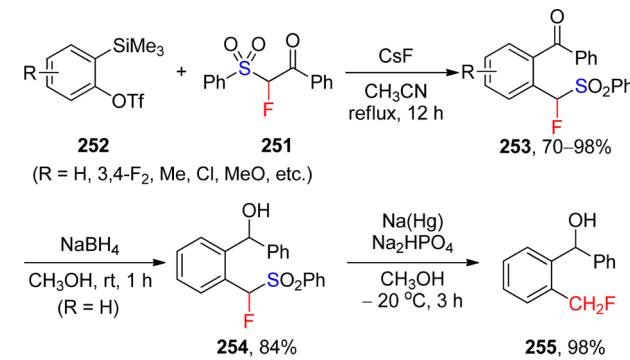


Compound **248** can be prepared by diiodination of fluoromethyl 2-pyridyl sulfone followed by selective deiodination.<sup>290</sup> It was found that in the reaction of aryl iodides, compound **248** displays much higher reactivity than other fluoroiodomethyl sulfones including a phenyl sulfone. Thus, the cross-coupling reaction of aryl iodides with **248** under the action of stoichiometric quantities of  $\text{CuI}$  and  $\text{Et}_2\text{Zn}$  in DMF as solvent affords the coupling products in moderate to good yields (45–90%). In this reaction, [fluoro(2-pyridylsulfonyl)methyl]copper, which is pregenerated by zinc-iodide exchange between **248** and  $\text{Et}_2\text{Zn}$  followed by transmetalation with  $\text{CuI}$ , is the reactive species toward aryl iodides. The reaction can also proceed catalytically with 30 mol % of  $\text{CuI}$ ; however, the yields are somewhat lower than the stoichiometric reaction. The application of this protocol in monofluoromethylation has been demonstrated with the synthesis of biologically active 3-fluoromethyl-3-deoxylestrone (**250**), which is obtained in 68% overall yield from the corresponding iodide through the coupling reaction with reagent **248** and subsequent desulfonylation with  $\text{Bu}_3\text{SnH}/\text{AIBN}$ .

**3.5.1.3. Using  $\alpha$ -Functionalized Monofluoromethyl Sulfones.** Compared to fluoromethyl sulfones, such as  $\text{PhSO}_2\text{CH}_2\text{F}$  (**242**), the introduction of a second electron-withdrawing group not only stabilizes the formed  $\alpha$ -fluorocarbanion, but also increases the nucleophilicity of the fluorinated carbanion by its softening ability, thus allowing reactions that are difficult to achieve with fluoromethyl sulfones, to occur effectively under mild conditions.<sup>13f,291</sup> In this context, the fluoromethyl sulfone derivatives, that is,  $\alpha$ -fluoro- $\beta$ -ketosulfones and 2-fluoro-2-(arylsulfonyl)acetates have been used as fluoro(sulfonyl)methylation reagents, due to the lability of the C–C(O) bonds in fluorine-containing densely functionalized compounds. Fluorobis(phenylsulfonyl)methane, as a widely used monofluoromethylation reagent, is described separately in section 3.5.1.2.

During their investigation on hard/soft nature of fluorinated carbanions, Hu and co-workers in 2008 described an aromatic monofluoromethylation by using the anion of  $\alpha$ -fluoro- $\beta$ -ketosulfone **251** as soft nucleophiles (Scheme 136). An

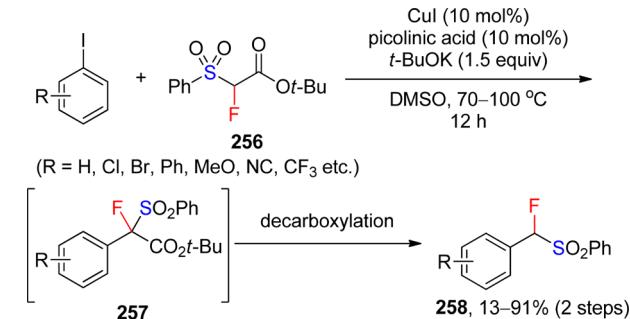
Scheme 136



intramolecular tandem reaction between **251** and aryne precursors **252** in the presence of cesium fluoride affords the fluoro(phenylsulfonyl)methyl-benzoylation products **253** in high yields (70–98%), albeit with low site selectivity in the cases of unsymmetrical arynes. The reduction of compounds **253** with  $\text{NaBH}_4$  followed by reductive desulfonylation with  $\text{Na(Hg)}$  furnishes the aromatic monofluoromethylation products, such as **255**, in good yields.

Alternatively, copper(I)-catalyzed coupling reaction between aryl or heteroaryl iodides and *tert*-butyl 2-fluoro-2-(phenylsulfonyl)acetate (**256**) can also introduce a fluoro(phenylsulfonyl)methyl group into an aromatic system (Scheme 137), which have been claimed by Inoue and Araki

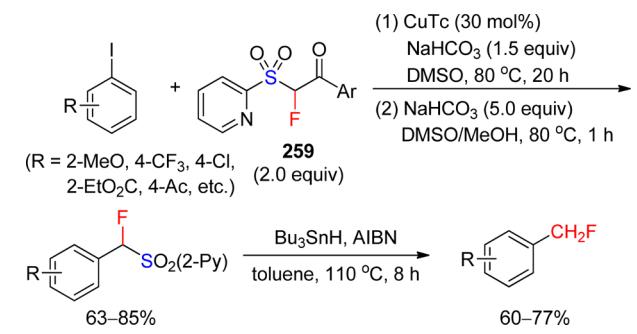
Scheme 137



in a patent.<sup>292</sup> The reaction is conducted using  $t\text{-BuOK}$  as base with catalytic quantities of  $\text{CuI}$  in the presence of picolinic acid as ligand in  $\text{DMSO}$  as solvent at  $70$  to  $100^\circ\text{C}$ . After hydrolysis-decarboxylation of **257**, fluoro(phenylsulfonyl)methylated arenes **258** are obtained as the major products in 13–91% yields.

However, the similar copper-catalyzed debenzoylative fluoroo(phenylsulfonyl)methylation of aryl iodides with  $\alpha$ -fluoro- $\beta$ -ketosulfone **251** was found to be very sluggish.<sup>293</sup> Using the 2-pyridyl sulfone reagent **259** instead, Hu and co-workers in 2013 developed a copper-catalyzed debenzoylative fluoro(2-pyridylsulfonyl)methylation of aryl iodides for the synthesis of fluoromethylated arenes (Scheme 138).<sup>293</sup> The debenzoylation reaction, which takes place after the coupling reaction between aryl iodides and **259**, can be achieved by using additional  $\text{NaHCO}_3$  as the base.

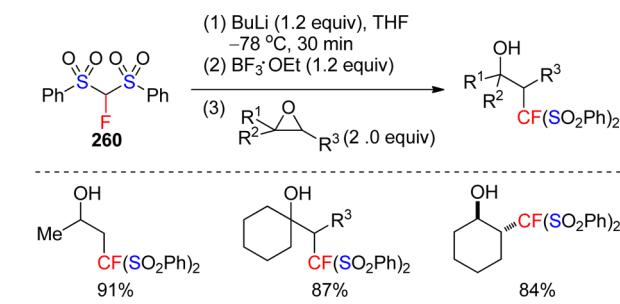
Scheme 138



**3.5.1.2. Nucleophilic Fluorobis(sulfonyl)methylation.** Fluorobis(phenylsulfonyl)methane (FBSM, **260**) can be prepared either by fluorination of  $(\text{PhSO}_2)_2\text{CH}_2$ <sup>291,294</sup> and  $\text{PhSO}_2\text{CH}_2\text{SPh}$ <sup>295</sup> or by phenylsulfonylation of  $\text{PhSO}_2\text{CH}_2\text{F}$  (**242**)<sup>296</sup> with the latter being a more practical route due to the easy separation process. FBSM can be deprotonated under much milder basic conditions than those required for the deprotonation of  $\text{PhSO}_2\text{CH}_2\text{F}$ , and its anion with a tetrabutylammonium counterion has been characterized with X-ray crystallography.<sup>297</sup> Compared to  $\text{PhSO}_2\text{CHF}^-$  anion, the combined stabilization and softening effects of the additional phenylsulfonyl group make  $(\text{PhSO}_2)_2\text{CHF}^-$  anion a superior nucleophile in many cases, especially in enantioselective synthesis.

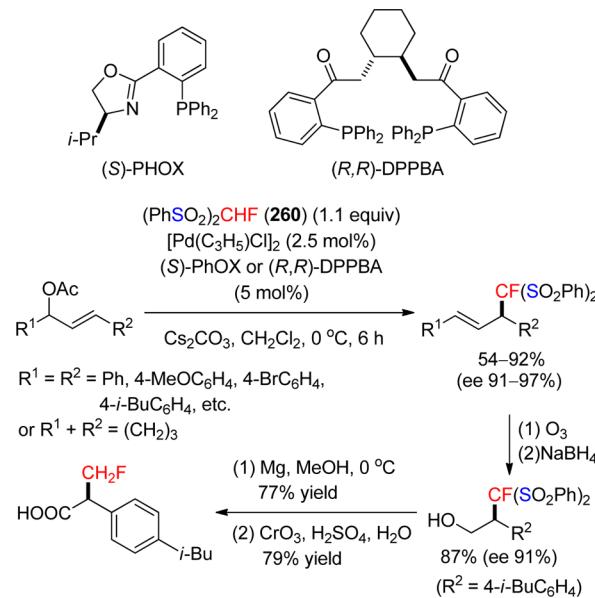
In 2006, Hu's group<sup>291</sup> and Shibata's group<sup>294</sup> independently developed FBSM (**260**) as a monofluoromethylation reagent, which can be used for the construction of a C– $\text{CH}_2\text{F}$  bond after reductive desulfonylation. Hu and co-workers used FBSM for nucleophilic ring-opening of epoxides and aziridines to eliminate the negative fluorine effect that is encountered by using  $\text{PhSO}_2\text{CH}_2\text{F}$  (Scheme 139), whereas Shibata and co-workers used FBSM in palladium catalyzed asymmetric allylic monofluoromethylation of 1,3-disubstituted allyl acetates (Scheme 140).

Scheme 139

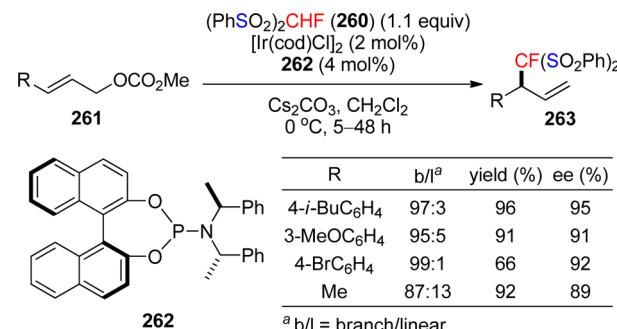


**3.5.1.2.1. Other Allylation Reactions.** The allylic monofluoromethylation has also been studied by using other substrates including allyl carbonates,<sup>298</sup> alkynes (via allyl acetates),<sup>299</sup> and substituted 2-bromo-1,3-dienes<sup>300</sup> under various catalysis conditions. The iridium-catalyzed asymmetric reaction of monosubstituted allyl carbonates **261** with FBSM (**260**) in the presence of a chiral phosphoramidite ligand, such as **262**, can give the branched products **263** predominantly with high enantioselectivities (Scheme 141).<sup>298a</sup> In cases of Morita–Baylis–Hillman (MBH) carbonates **264**, the organocatalyzed reaction with FBSM using a bis(cinchona alkaloid), hydroquinidine (anthraquinone-1,4-diyl) diether ((DHQD)<sub>2</sub>AQN),

Scheme 140

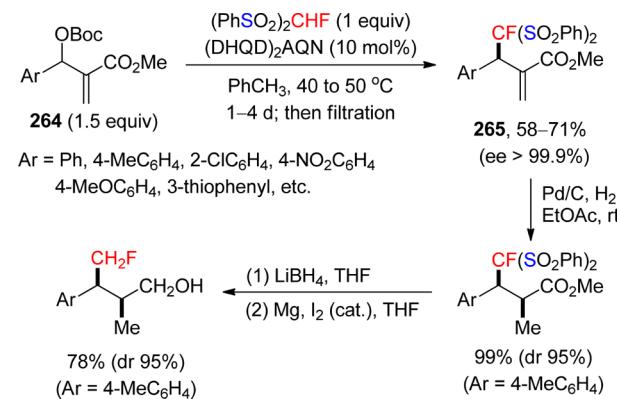


Scheme 141



provides allylic fluorobis(phenylsulfonyl)methylation products **265** in good yields with excellent enantioselectivities (Scheme 142).<sup>298d</sup>

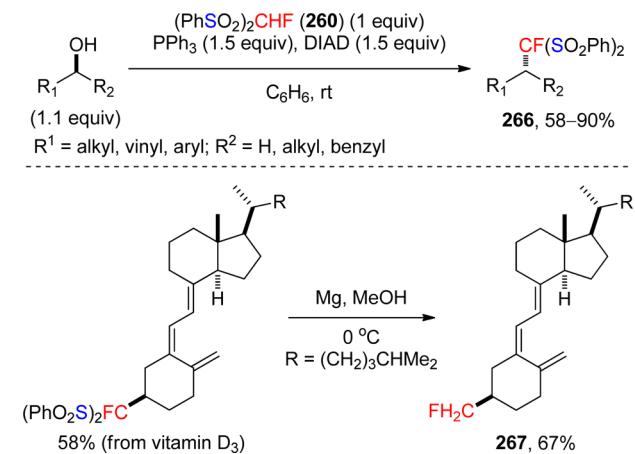
Scheme 142



**3.5.1.2.2. Mitsunobu Reaction.** Prakash and co-workers have used FBSM (**260**) in allylic monofluoromethylation.<sup>301</sup> In 2007, they reported an enantioselective nucleophilic substitution reaction between chiral secondary alcohols and FBSM under Mitsunobu reaction conditions, which gives the fluorobis(phenylsulfonyl)methyl products (**266**) with full

inversion of the configuration (Scheme 143).<sup>301a</sup> Compared to the substitution reaction with alkyl halides,<sup>301b</sup> which is less

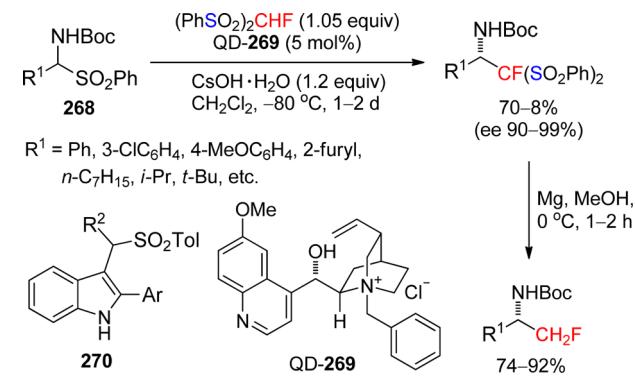
Scheme 143



efficient for secondary halides, this Mitsunobu reaction is amenable to a broad scope of substrates including primary, secondary, allylic, benzylic, and alicyclic alcohols. By using this methodology, the monofluoromethylated vitamin D<sub>3</sub> analogue 267 was stereoselectively synthesized in 39% overall yield from vitamin D<sub>3</sub>.

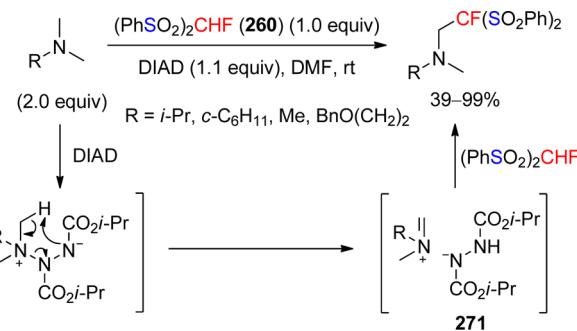
**3.5.1.2.3. Mannich Reaction and Related Transformation.** The synthesis of  $\alpha$ -fluoromethyl amides and amines under Mannich-type conditions is also viable by using FBSM as the reagent. In 2007, a contribution from Shibata and co-workers described the first enantioselective monofluoromethylation of *in situ* generated imines from  $\alpha$ -amido sulfones 268 with FBSM as the monofluoromethyl equivalent in the presence of *N*-benzylquinidinium chloride (QD-269) as the phase transfer catalyst (Scheme 144).<sup>302</sup> This methodology has been extended

Scheme 144



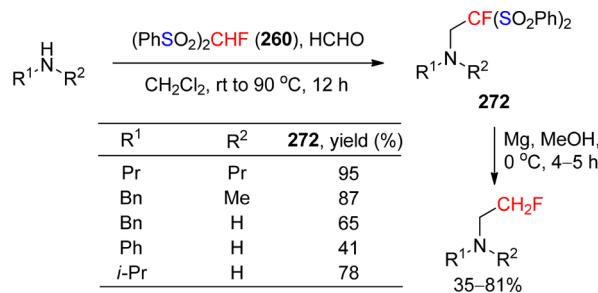
to monofluoromethylation of arylsulfonyl C2-arylindoles 270 via *in situ* generated vinylogous imino intermediates by using the benzylcinchoninium salt bearing a sterically demanding benzyl substituent as the catalyst.<sup>303</sup> In 2013, Hu and co-workers reported a diisopropyl azodicarboxylate (DIAD)-mediated monofluorobis(phenylsulfonyl)methylation of the  $\alpha$ -C–H bonds of aliphatic tertiary amines (Scheme 145),<sup>304</sup> in which the C–C bond formation also involves a Mannich-type reaction, proceeding through the addition of FBSM (260) to the iminium ion 271 *in situ* generated from the oxidation of tertiary amines by DIAD. Additionally, Prakash, Mathew and

Scheme 145



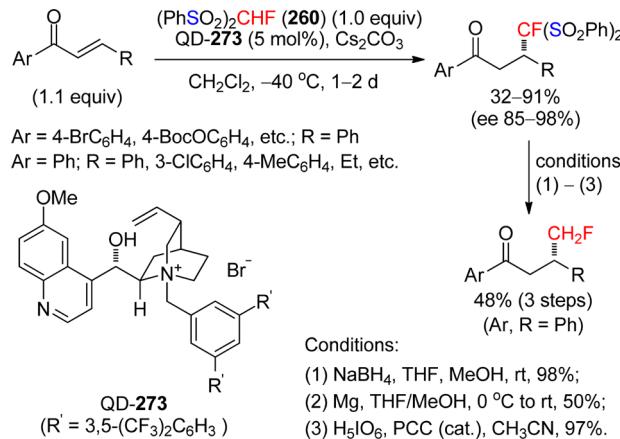
co-workers in 2013 developed a three component Mannich reaction of formaldehyde, amine, and FBSM (260) for the facile synthesis of  $\beta$ -fluoro- $\beta$ -di(phenylsulfonyl)ethylamines (Scheme 146).<sup>305</sup> This protocol is feasible for introducing a 2-fluoroethyl group into the nitrogen of primary and secondary amines.

Scheme 146



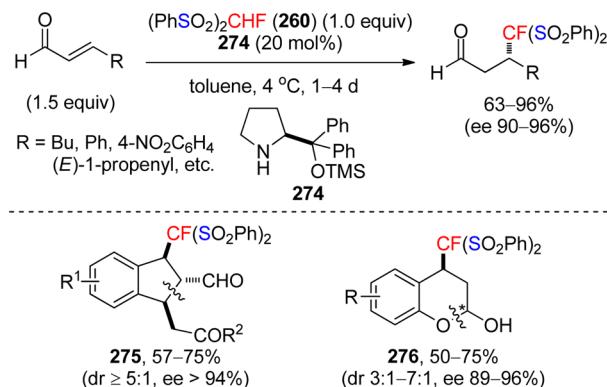
**3.5.1.2.4. Michael Addition and Related Transformation.** FBSM (260) easily undergoes conjugate addition reaction to Michael acceptors due to the delocalization of the negative charge of the  $\alpha$ -fluoro carbanion by two phenylsulfonyl groups.<sup>291b,306</sup> In 2008, Shibata and co-workers reported the first enantioselective conjugate addition of FBSM to  $\alpha,\beta$ -unsaturated carbonyl compounds by using aryl vinyl ketones as the Michael acceptors and  $Cs_2CO_3$  as the base under the catalysis of a sterically hindered quinidinium salt, QD-273 (Scheme 147).<sup>302</sup> As a complementary to Shibata's protocol, Kim and co-workers reported a catalytic enantioselective conjugate addition reaction

Scheme 147



of FBSM to alkyl vinyl ketones by using *epi*-9-amino-9-deoxyquinine as the chiral bifunctional organocatalyst under neutral conditions, which provides  $\beta$ -fluorobis(phenylsulfonyl)-methyl ketones in good yields (85–93%) with up to 93% ee.<sup>307</sup> In 2009, three groups led by Moyano and Rios, Córdova, and Wang almost simultaneously reported the enantioselective conjugate addition of FBSM (260) to  $\alpha,\beta$ -enals by using the TMS (274) and TBS ethers of diarylprolinols as the catalysts (Scheme 148).<sup>308</sup> Very recently, this methodology has been

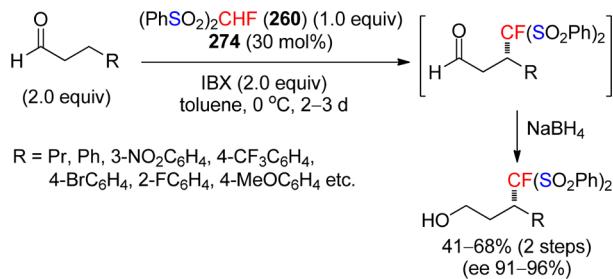
Scheme 148



extended to the enantioselective synthesis of fluoromethylated indanes 275 and chromanols 276 by means of a double Michael reaction or Michael-hemiacetal formation via the addition of FBSM (260) to enals.<sup>309</sup>

Relating to the synthesis of  $\beta$ -fluorobis(phenylsulfonyl)-methyl aldehydes, Wang and co-workers in 2011 described an enantioselective  $\beta$ -C–H functionalization of saturated aldehydes with FBSM (260) by using 2-iodoxybenzoic acid (IBX) as the oxidant under the catalysis of diarylprolinol derivative 274 (Scheme 149),<sup>310</sup> which proceeds through the dehydro-

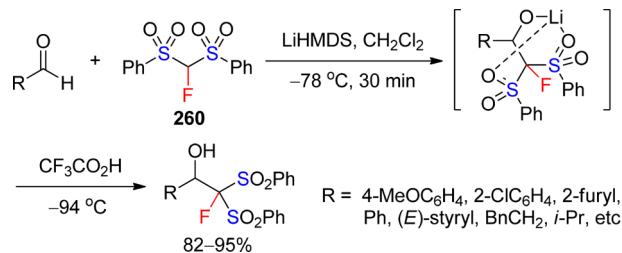
Scheme 149



genative oxidation of enamines of the saturated aldehydes to the iminium ions of  $\alpha,\beta$ -enals, thus obviating the need for preactivated substrates, that is,  $\alpha,\beta$ -enals.

**3.5.1.2.5. Carbonyl Addition.** Hu and co-workers in 2011 found that the nucleophilic addition reaction between FBSM (260) and the carbonyl group of aldehydes including the  $\alpha,\beta$ -enals can be successfully accomplished at low temperatures by using LiHMDS as the base (Scheme 150).<sup>311</sup> Comparative experiments with NaHMDS and KHMDS indicate that the strong Li–O coordination at a low temperature plays an important role in the stabilization of the alcoholates. Interestingly, under the same reaction conditions,  $(\text{PhSO}_2)_2\text{CHX}$ , where X = H or Cl, cannot react with an aldehyde, suggesting that the fluorine

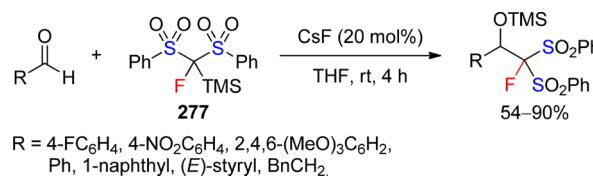
Scheme 150



substitution is also important for the success of the addition reaction.

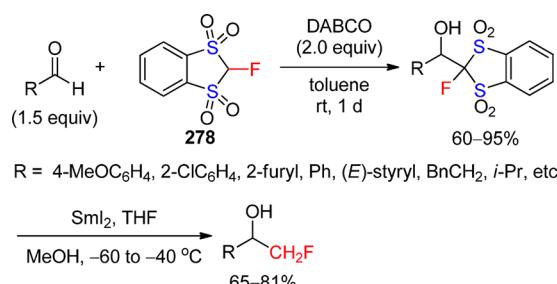
However, under mild conditions, FBSM (260) fails to undergo base-promoted nucleophilic addition to aldehydes,<sup>312</sup> probably due to the high stability of  $(\text{PhSO}_2)_2\text{CF}^-$  caused by the two separated phenylsulfonyl groups, which can lead to a faster retro-type reaction of the alcoholate intermediates under thermodynamically controlled conditions. By using [fluorobis(phenylsulfonyl)methyl]trimethylsilane (277) as the fluoroalkylation reagent, Prakash and co-workers achieved the nucleophilic fluorobis(phenylsulfonyl)methylation of aldehydes at room temperature via in situ capture of the alcoholate intermediates by silyl cation (Scheme 151).<sup>313</sup> Alternatively,

Scheme 151



Shibata and co-workers realized the fluorobis(sulfonyl)-methylated of aldehydes at room temperature by using the fluorobis(sulfonyl)methane with a constrained structure, that is, 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (278), as the pronucleophile (Scheme 152).<sup>312</sup> Very recently, an asymmetric

Scheme 152

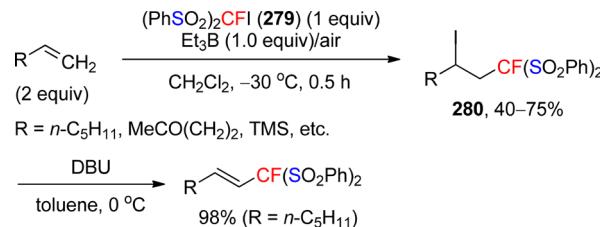


monofluoromethylation of aldehydes with 278 was achieved under the catalysis of a bifunctional thiourea with  $\text{Ti}(\text{O}i\text{-Pr})_4$  as an additive, affording the fluorobis(sulfonyl)methylated alcohols in good yields (73–91%) with varying enantioselectivity (32–96% ee) depending on the structures of the aldehydes.<sup>314</sup>

**3.5.1.3. Free Radical Fluorobis(sulfonyl)methylation.** Fluoroiodobis(phenylsulfonyl)methane (279) can be prepared in quantitative yield by iodination of FBSM (260) with diiodine. Prakash and co-workers in 2008 described a free radical fluorobis(phenylsulfonyl)methylation of various terminal alkenes with 279 by using  $\text{Et}_3\text{B}/\text{air}$  as the initiation system

(Scheme 153).<sup>315</sup> The adducts **280** can be transformed to the *E* isomers of fluorobis(phenylsulfonyl)methylated alkenes via

Scheme 153

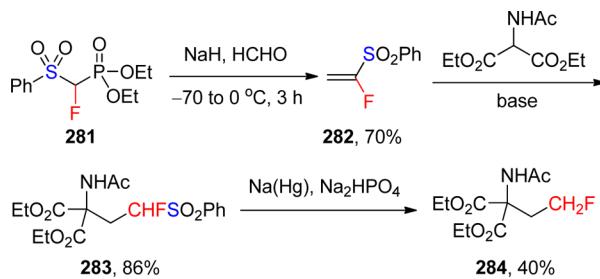


dehydriodination with DBU as the base. However, the further conversion of these fluorobis(phenylsulfonyl)methyl compounds to monofluoromethyl compounds is not reported.

**3.5.1.4. Fluoro(sulfonyl)olefination-Directed Transformations.** Fluoromethylation can also be achieved through nucleophilic *gem*-fluorosulfonylolefination followed by further transformation; however, tedious synthetic routes are required.

In an early contribution, Koizumi and co-workers in 1987 described a *gem*-fluoro(sulfonyl)olefination-nucleophilic conjugate addition sequence for the synthesis of  $\beta$ -fluoromethyl amino acid derivative (Scheme 154).<sup>316</sup> The olefination of

Scheme 154

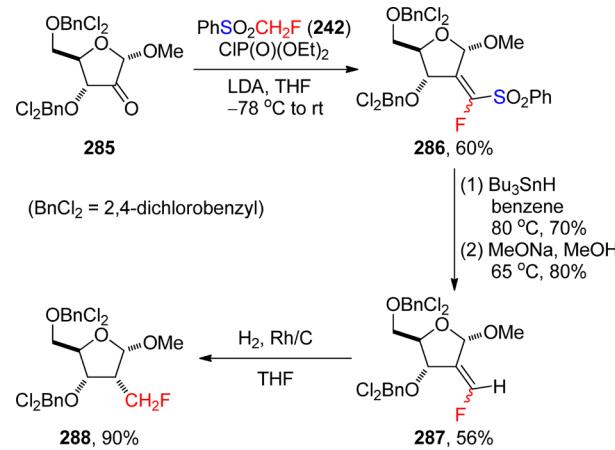


formaldehyde with **281** affords 1-fluoro-1-(phenylsulfonyl)-ethene (**282**), which undergoes conjugate addition reaction with diethyl 2-acetamidomalonate to give the fluoro-(phenylsulfonyl)methyl compound **283** in 86% yield. After reductive desulfonylation of **283** with Na(Hg), monofluoromethylated product **284** was obtained in 40% yield.

In addition, Schmit in 1994 applied a monofluoroolefination-hydrogenation procedure to synthesize 2'-deoxy-2'- $\alpha$ -monofluoromethyl nucleosides, since it is difficult to introduce a fluorine atom to a 2'-hydroxymethylated thymidine or sugar with a deoxygenative fluorination reagent.<sup>317</sup> By using McCarthy's monofluoroolefination protocol (see Section 3.7.2.1), the starting material 2'-ketone derivative **285** is transformed into a mixture of *E* and *Z* fluoroolefins **287** in 34% overall yield, which is subject to a catalytic hydrogenation to furnish the key intermediate for nucleosides, 2'-deoxy-2'- $\alpha$ -monofluoromethyl ribose derivative **288**, as a single stereoisomer in 90% yield (Scheme 155).

**3.5.2. Sulfoximines as Monofluoromethylation Reagents.** Similar to *S*-difluoromethyl sulfoximines, *S*-mono-fluoromethyl sulfoximines are versatile monofluoromethylation reagents, which are suitable for both electrophilic monofluoromethylation of an array of heteroatom nucleophiles and enantioselective nucleophilic monofluoromethylation of carbon electrophiles, such as carbonyl compounds. The racemic fluoromethyl sulfoximines used as monofluoromethylation

Scheme 155

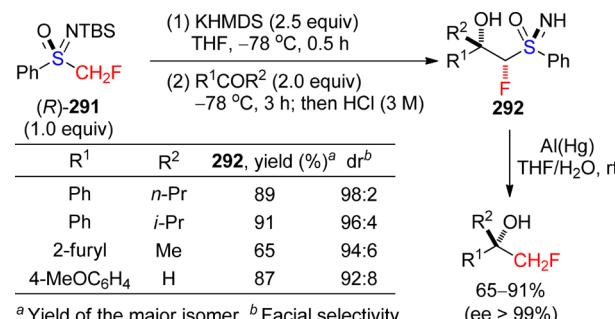


reagents have been prepared in two ways: one is the oxidative imination of monofluoromethyl sulfoxides, such as PhSO<sub>2</sub>CH<sub>2</sub>F (**289**), followed by *N*-functionalization,<sup>318</sup> the other is the oxidative imination of monofluoromethyl sulfides, such as PhSCH<sub>2</sub>F (**243**), followed by oxidation.<sup>72a</sup> The enantiopure monofluoromethyl sulfoximines have been prepared by electrophilic fluorination of their nonfluorinated counterparts.<sup>319</sup> A recent review on fluorinated sulfoximines has covered this topic;<sup>73b</sup> this subsection only provides an introduction of their synthetic application to demonstrate the unique reactivities of sulfoximine reagents.

**3.5.2.1. Nucleophilic Fluoro(sulfonimidoyl)methylation.** Following Johnson's sulfoxime olefination methodology, Finch and co-workers in 1988 developed a nucleophilic monofluoro(sulfonimidoyl)methylation reaction to synthesize terminal monofluoroalkenes by using *N*-methyl-*S*-monofluoromethyl-*S*-phenylsulfoximine (**290**) as the reagent (see Scheme 194).<sup>318a</sup> They found that  $\alpha$ -monofluoromethyl alcohols are formed as the major products when Na(Hg) is used instead of Al(Hg); however, they did not make a further investigation on monofluoromethylation.

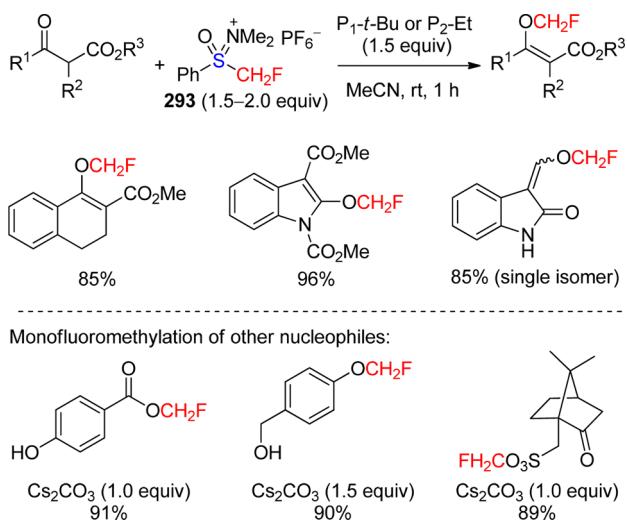
In 2014, Hu and co-workers extended the chiral *N*-*tert*-butyldimethylsilyl sulfoximine-based stereoselective nucleophilic fluoroalkylation strategy from difluoromethylation to monofluoromethylation, and realized the synthesis of optically pure  $\alpha$ -monofluoromethyl tertiary alcohols through a nucleophilic fluoroalkylation approach by using enantiopure *S*-fluoromethyl sulfoximine (*R*)-**291** as the reagent (Scheme 156).<sup>319c</sup> The complete control of the stereoselectivity at the fluorinated carbon stereogenic center of **292** is attributed to a dynamic kinetic resolution of the chiral  $\alpha$ -fluoro carbanion.

Scheme 156



**3.5.2.2. Direct Monofluoromethylation.** As an extension of their previously developed trifluoromethylation with *S*-trifluoromethyl sulfoximinium salt **47** (see Scheme 21), Shibata and co-workers in 2011 reported a preparation and application of the monofluoromethylated analogue **293** (Scheme 157).<sup>318b</sup>

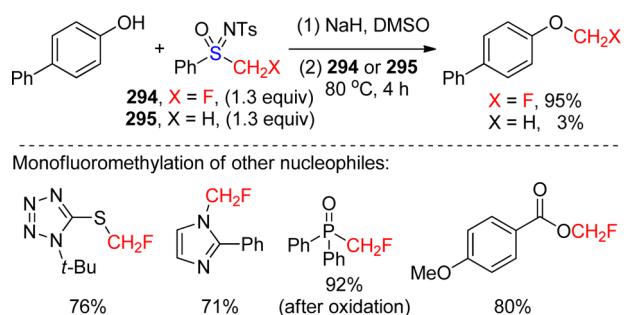
Scheme 157



Compound **293** exhibits inherent oxygen preference in enolate monofluoromethylation, which is fundamentally different from the exclusive C-selectivity in enolate trifluoromethylation with **47**. Other oxygen nucleophiles including phenolates, carboxylates, sulfonates, and some fluorinated alcoholates also undergo *O*-alkylation to give monofluoromethyl compounds in high yields, with chemoselectivity toward the less basic oxygen. Of note is that *O*-alkylation with reagent **293** provides a unique method for the synthesis of monofluoromethyl enol ethers from enolates.

In their continuing efforts to explore the versatile reactivity of sulfoxime-based fluoroalkylation reagents, Hu and co-workers in 2014 disclosed that the electron-neutral *N*-tosyl sulfoxime **294**, which was previously used as a monofluoromethylene synthon in the monofluorocyclopropanation of  $\alpha,\beta$ -unsaturated Weinreb amides (see Scheme 170), is also a good reagent for monofluoromethylation of phenols, thiols, aromatic N-heterocycles, phosphines, and carboxylic acids (Scheme 158).<sup>72a</sup> On the basis of the fact that the  $\alpha$ -fluorine substitution can accelerate the alkylation process, preliminary mechanistic study suggested that the fluoromethylation with **294** is more likely to proceed through a radical mechanism involving an SET

Scheme 158

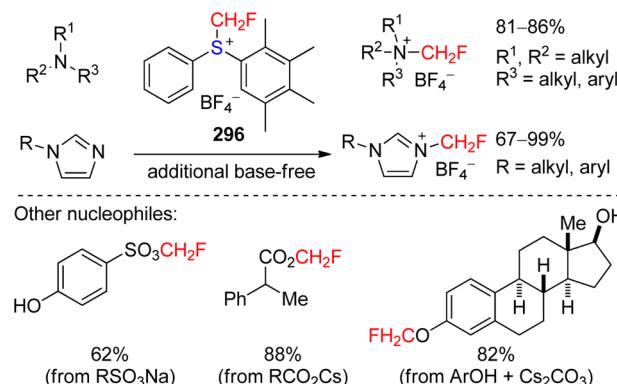


process, which is instructive for understanding the mechanism of other electrophilic monofluoromethylation reactions.

### 3.5.3. Sulfonium Salts as Monofluoromethylation Reagents.

Encouraged by their success in direct electrophilic difluoromethylation with *S*-difluoromethyl diarylsulfonium salt **170** (see Scheme 93), Prakash and Olah and co-workers in 2008 reported a direct electrophilic monofluoromethylation by using the novel *S*-monofluoromethylsulfonium salt **296**, which is prepared similarly to **170**, but more stable than **170** (Scheme 159).<sup>320</sup> Compound **296** is effective for the introduction of an

Scheme 159



electrophilic monofluoromethyl group into not only neutral heteroatom nucleophiles including tertiary amines, both *N*-substituted and -unsubstituted imidazoles, as well as triphenylphosphine, but also anionic heteroatom nucleophiles such as sulfonates, carboxylates, phenolates, some fluorinated alcoholates, and thiophenolates. However, the alcoholates of conventional alcohols, such as 1,3,5-trimethylbenzyl alcohol, cannot undergo *O*-monofluoromethylation, since they can destroy **296** through a deprotonation reaction. Compound **296** is also less efficient for C-monofluoromethylation. Nevertheless, very recently, compound **296** has been used to synthesize fluoromethylated carnitine biosynthesis intermediates, that is, fluorinated derivatives of  $\gamma$ -butyrobetaine and trimethyllysine.<sup>321</sup>

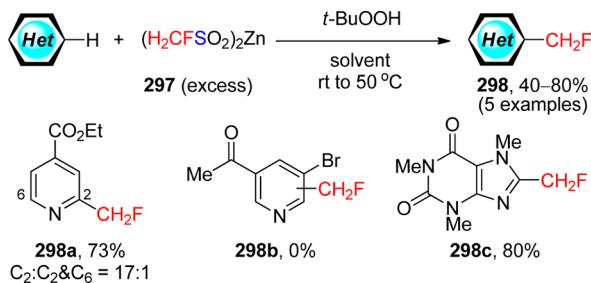
### 3.5.4. Sulfinate Salts as Monofluoromethylation Reagents.

As a part of a zinc bis(alkanesulfinate) salt toolkit for innate C–H functionalizations of aromatic heterocycles, zinc monofluoromethanesulfinate (**297**) was developed by Baran and co-workers in 2012 via reduction of fluoromethanesulfonyl chloride with zinc metal.<sup>130a</sup> Compared to its difluorinated analogue, reagent **297** behaves more like a nonfluorinated alkane sulfinate, and reacts well only with some heteroaromatics such as 2-methylquinoxaline, 1-(1-methyl-1*H*-pyrrol-3-yl)ethanone, ethyl isonicotinate, and caffeine (Scheme 160).<sup>130a</sup>

### 3.6. For Monofluoromethylation and Other Monofluoroalkylation

In addition to monofluoromethylations, the sulfur-based reagents have also been used in some other monofluoroalkylations. This section makes a summary of the synthesis of other monofluorinated compounds via constructing a monofluorinated  $sp^3$ -hybridized carbon center with monofluorinated sulfides, sulfoxides, sulfones, and sulfoximines as the reagents. In these reactions, the reagents can serve as either a monofluoroalkyl equivalent or a monofluoromethylene equivalent. To differentiate the role of sulfur in these reactions, the

Scheme 160

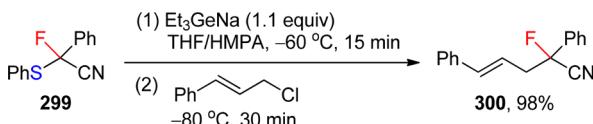


monofluoroalkylation and monofluoromethylation are listed separately.

**3.6.1. Sulfides and Xanthates as Monofluoroalkylation Reagents.** Monofluorinated sulfides and xanthates have been used in monofluoroalkylation reactions to synthesize  $\alpha$ -functionalized- $\alpha$ -monofluorinated compounds. In these reactions, the sulfur atom serves as the reactive site to generate the monofluoroalkyl anion or radical species.

By using of their Et<sub>3</sub>GeNa-activation strategy (see section 3.1.1), Yokoyama and co-workers in 1999 developed an efficient synthesis of fluorinated homoallylic and homoprop-2-ynyl cyanides by using 2-fluoro-2-phenylthio-2-phenyl-acetonitrile (**299**) as the pronucleophile (Scheme 161).<sup>322</sup>

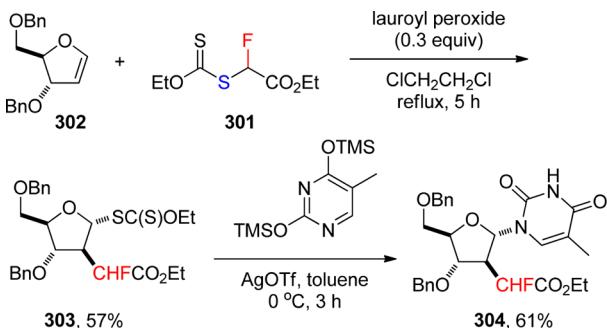
Scheme 161



For example, the nucleophilic activation of the C–S bond in **299** with Et<sub>3</sub>GeNa followed by the addition of cinnamyl chloride affords the allylation product **300** in 98% yield. This synthetic methodology has been extended to the fluoromethylation of other electrophiles, such as alkyl bromides, carbamoyl chlorides, and  $\alpha,\beta$ -unsaturated ketones, to give products containing a monofluorinated quaternary carbon center.<sup>323</sup>

Inspired by Zard's radical trifluoromethylation with trifluoromethylated xanthates (see section 3.1.1), Lequeux and co-workers prepared the monofluorinated xanthate **301** through the reaction of ethyl bromofluoroacetate and potassium O-ethyl carbonodithioate and used compound **301** as an efficient fluoroacetate group transfer reagent (Scheme 162).<sup>324</sup> The reaction of **301** with 2,3-dihydrofuran derivatives such as **302**, provides the anomeric xanthate intermediates, such as **303**,

Scheme 162



which can be displaced by a nucleophile to afford the 3-monofluoroalkylated tetrahydrofuran derivatives, such as **304** (Scheme 162).

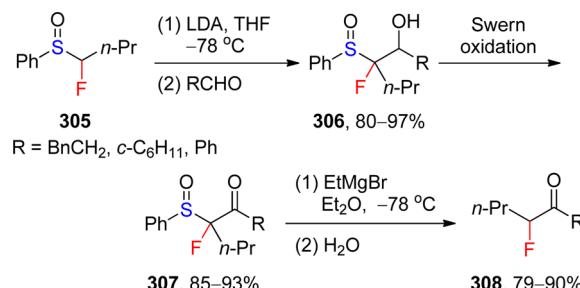
### 3.6.2. Sulfoxides as Monofluoroalkylation Reagents.

Monofluoromethyl aryl sulfoxides, such as monofluoromethyl phenyl sulfoxides (PhSOCH<sub>2</sub>F, **289**), can be prepared by the oxidation of monofluoromethyl aryl sulfides, such as PhSCH<sub>2</sub>F (**243**). The 1-fluoroalkyl sulfoxides can be prepared either through nucleophilic monofluoro(sulfinyl)methylation of alkyl halides with a monofluoromethyl sulfoxide<sup>325</sup> or oxidation of 1-fluoroalkyl sulfides that are obtained from the fluorination of alkyl sulfoxides with DAST.<sup>326</sup>

Sulfoxides can undergo ligand-exchange reaction with alkyl metal species to give new sulfoxides and new alkyl or aryl metal species.<sup>327</sup> In the case of alkyl aryl sulfoxides bearing a monofluoroalkyl group, the sulfur-alkyl bonds are cleaved predominantly to give monofluoroalkyl metal species.

In an early contribution, Yamakawa and co-workers in 1991 described an efficient synthesis of  $\alpha$ -fluoroketones **308** from 1-fluorobutyl phenyl sulfoxide (**305**) and aldehydes through an addition-oxidation-desulfinylation sequence (Scheme 163).<sup>328</sup>

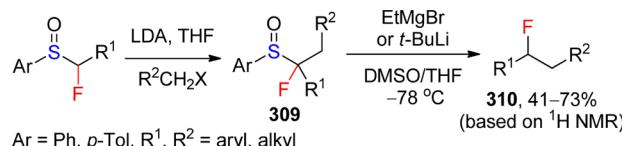
Scheme 163



The desulfinylation of the  $\beta$ -ketosulfoxide **307** with EtMgBr in Et<sub>2</sub>O as solvent at  $-78\text{ }^{\circ}\text{C}$  gives the 2-fluoroenolate intermediates, which are quenched with water to afford products **308** in high overall yields.

In 1996, Satoh and Takano showed that monofluorosulfoxides **309** derived from monofluoroalkyl aryl sulfoxides and alkyl halides can be desulfinylated with EtMgBr or t-BuLi in the presence of a proton source such as DMSO to give secondary alkyl fluorides **310** in moderate yields (Scheme 164).<sup>329</sup>

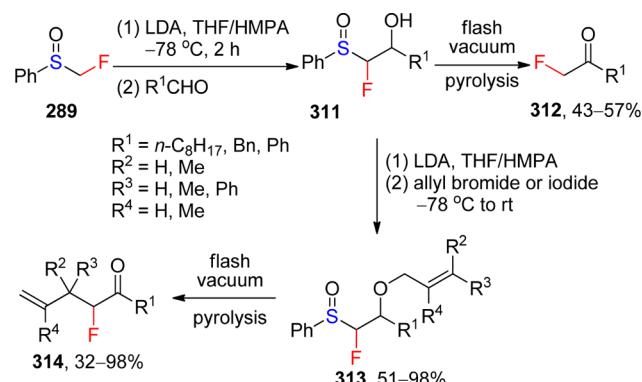
Scheme 164



**3.6.3. Sulfoxides as Monofluoromethylation Reagents.** In 1983, Reutrakul and Rukachaisirikul reported the generation and synthetic application of monofluoro-(phenylsulfinyl)methyl lithium (derived from PhSOCH<sub>2</sub>F) and found that this monofluorinated sulfinyl carbanion “seems to be stable at  $0\text{ }^{\circ}\text{C}$  for at least 1 h”.<sup>325,330</sup> They showed that  $\alpha$ -fluoro(phenylsulfinyl)methyl alcohols **311** that are obtained from the addition of monofluoro(phenylsulfinyl)methyl lithium to aldehydes can undergo flash vacuum pyrolytic elimination of sulfinic acid to afford monofluoromethyl ketones **312** in low to

moderate overall yields (Scheme 165).<sup>325,331</sup> Moreover, pyrolysis of the allyl ethers of alcohols **311** leads to 1-

Scheme 165

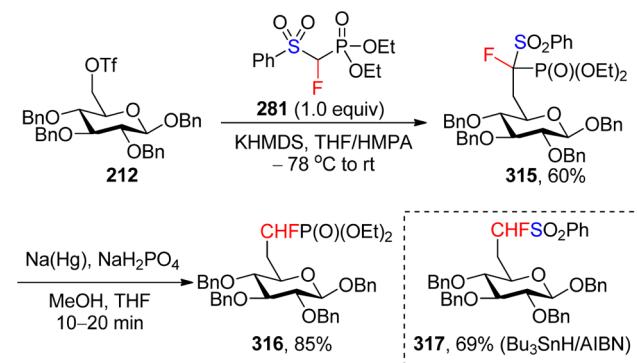


fluorohomoallyl ketones **314**, which are formed through sulfenic acid elimination followed by the Claisen rearrangement.<sup>322</sup>

**3.6.4. Sulfones as Monofluoroalkylation Reagents.** As previously mentioned, introducing an additional electron-withdrawing functional group into PhSO<sub>2</sub>CH<sub>2</sub>F (**242**) can stabilize the formed  $\alpha$ -fluoro carbanion and facilitate the nucleophilic fluoro(phenylsulfonyl)methylation reactions. On the other hand, the phenylsulfonyl group also stabilizes  $\alpha$ -functionalized monofluoromethyl anions, thus improving their reactivity.

$\alpha$ -Monofluorinated phosphonates are of great importance in the design of phosphate mimics; however, their direct synthesis through nucleophilic substitution reactions with fluoro-(phosphoryl)methyl anions is difficult to handle.<sup>333</sup> The use of phenylsulfonyl stabilized fluoro(phosphoryl)methyl anion as the nucleophile can circumvent this problem. In a much earlier contribution, Koizumi and co-workers in 1987 described the alkylation of [fluoro(phenylsulfonyl)methyl]phosphonate **281** with primary alkyl halides.<sup>316</sup> The subsequent treatment of the alkylation products with Na(Hg) in the presence of Na<sub>2</sub>HPO<sub>4</sub>, however, failed to give the desulfonylation products. Berkowitz and co-workers in 2001 revisited the reaction by using primary alkyl triflates and iodides as the electrophiles and found that **281** is an expedient reagent for synthesizing CHF-phosphonates (Scheme 166).<sup>334</sup> For example, the glucopyranosyl triflate **212** reacts smoothly with the potassium salt of **281** to give a moderate yield (60%) of  $\alpha$ -sulfonylated phosphonate **315**, which is cleanly desulfonylated with Na(Hg) in the presence of

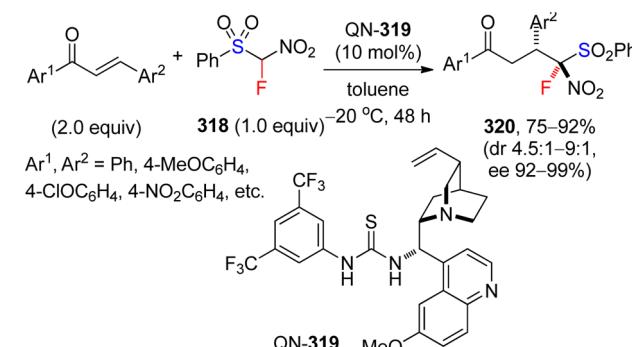
Scheme 166



NaH<sub>2</sub>PO<sub>4</sub> as a pH buffer in THF/MeOH to furnish the CHF-phosphonate **316** in good yield (85%). Note that the use of NaH<sub>2</sub>PO<sub>4</sub> is critical for this highly selective desulfonylation, since the P–C bond of a densely functionalized compound such as **315** is instable toward base-catalyzed solvolysis.<sup>316,335</sup> Interestingly, when the phenylsulfonylated phosphonate **315** is subjected to the radical reaction with Bu<sub>3</sub>SnH/AIBN, the unexpected dephosphorylation takes place to give the fluoro-(phenylsulfonyl)methyl compound **317** in 69% yield, which is in contrast with the reactions of  $\alpha$ -fluoro- $\alpha$ -heteroaryl- $\alpha$ -(phosphoryl)methyl compounds under the same conditions.<sup>283a</sup>

In addition to the aforementioned asymmetric monofluoromethylation with FBSM (**260**), the use of monofluorinated sulfones of the general formula PhSO<sub>2</sub>CH<sub>2</sub>F, where R are electron-withdrawing functional groups rather than a sulfonyl group, in asymmetric synthesis has emerged to construct fluorine-substituted chiral quaternary carbon centers. In early 2009, a contribution from Prakash and Olah and co-workers reported the first enantioselective  $\alpha$ -functionalized- $\alpha$ -fluoro-(phenylsulfonyl)methylation by using  $\alpha$ -fluoro- $\alpha$ -nitro-(phenylsulfonyl)methane (FNSM, **318**)<sup>301a,306</sup> as the fluoroalkylation reagent.<sup>336</sup> The reaction between chalcones and FNSM (**318**) under the catalysis of the chiral amine-thiourea bifunctional catalyst QN-319 provides the 1,4-addition products **320** stereoselectively in high yields (Scheme 167).

Scheme 167

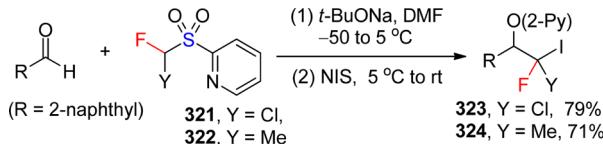


Mechanistic investigation suggests that the high stereoselectivity on the fluorinated carbon center originates from the C–C bond forming process rather than the deprotonation process. Inspired by this achievement, FNSM (**318**) and some  $\alpha$ -fluoro- $\beta$ -ketosulfones have been used in asymmetric fluoroalkylation of  $\alpha,\beta$ -enals,  $\beta$ -nitrostyrenes, imines, and even alkynyl hypervalent iodines compounds.<sup>337</sup> However, in all cases of the reaction with FNSM (**318**), no further transformation of the  $\alpha$ -fluoro- $\alpha$ -nitro- $\alpha$ -sulfonylmethyl group was conducted probably due to the difficulty in removing either a sulfonyl or a nitro group in these densely functionalized compounds.<sup>338</sup>

**3.6.5. Sulfones as Monofluoromethylation Reagents.** Monofluorinated sulfones can also be used as the sp<sup>3</sup>-hybridized monofluoromethylene equivalent (-CHF-). In the  $\alpha$ -fluoro- $\alpha$ -(phosphoryl)methylation with reagent **281** (see Scheme 166), PhSO<sub>2</sub>CH<sub>2</sub>F (**242**) can be considered as the monofluoromethylene source, since reagent **281** is readily prepared by phosphorylation of PhSO<sub>2</sub>CH<sub>2</sub>F.<sup>339</sup> In addition, in a contribution on difluorohalomethylation with difluoromethyl 2-pyridyl sulfone via in situ halogenation of Julia–Kocienski

intermediates (see Scheme 110), Hu and co-workers showed that monofluorinated 2-pyridyl sulfones **321** and **322** can be used for monofluorohaloalkylation of aldehydes to afford the monofluoromethylenated products **323** and **324**. (Scheme 168)<sup>260</sup>

### Scheme 168

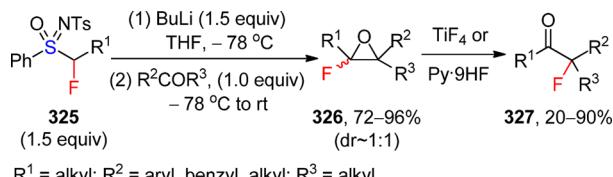


### 3.6.6. Sulfoximines as Monofluoromethylenation

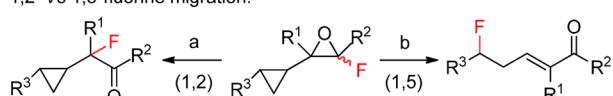
**Reagents.** Compared to the *N*-(*tert*-butyldimethylsilyl)-sulfonimidoyl group, the more electron-deficient *N*-(tosyl)-sulfonimidoyl group is a better leaving group, and metatalated *S*-monofluoroalkyl-*S*-phenyl-*N*-tosyl sulfoximine displays the typical reactivity of a carbenoid. Several monofluorinated *S*-phenyl-*N*-tosyl sulfoximines have been used as monofluoromethylation reagents through the nucleophilic addition followed by 1,3-elimination reaction.

In 2010, Hu and co-workers reported an efficient synthesis of monofluorinated epoxides through the base-promoted reaction between S-(1-fluoroalkyl)-N-tosyl sulfoximines **325** and carbonyl compounds (Scheme 169).<sup>340</sup> By using BuLi as the base

### Scheme 169



### 1,3- vs 1,5-fluorine migration:



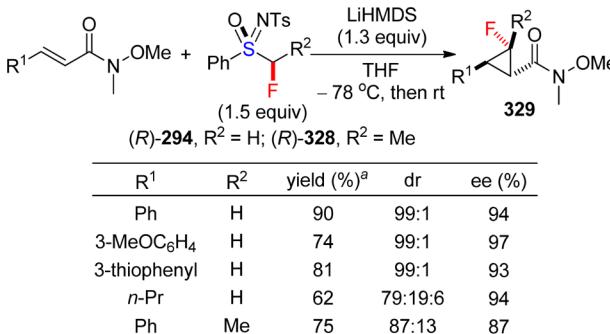
Conditions: (a)  $\text{K}_2\text{CO}_3$ , MeCN, 60 °C; (b)  $\text{PhCO}_2\text{H}$  (cat.),  $\text{CH}_2\text{Cl}_2$ , rt.

and THF as the solvent, the addition of the lithiated sulfoximines **325** to ketones followed by *O*-cyclization furnishes the tetra-substituted  $\alpha$ -fluoroepoxides **326** in high yields (72–96%, based on  $^{19}\text{F}$  NMR), albeit with nearly 1:1 diastereoselectivity. However, the reaction of aldehydes gives a complex mixture probably due to the instability of the trisubstituted  $\alpha$ -fluoroepoxides under such conditions. Although most of the prepared epoxides are not stable enough to be isolated, the crude epoxides can be readily transformed into  $\alpha$ -fluoroketones **327** via a formal 1,2-fluorine migration promoted by an additional fluoride. By using this synthetic methodology to epoxides, Hu and co-workers very recently realized rearrangements of cyclopropyl-substituted fluoroepoxides via 1,2- and 1,5-fluorine migration in the absence of additional fluoride (Scheme 169).<sup>341</sup>

However, the reaction of  $\alpha,\beta$ -unsaturated carbonyl compounds with monofluorinated *N*-tosylsulfoximines proceeds diastereoselectively. By using enantiopure fluorosulfoximines as the chiral reagents, Hu and co-workers in 2012 reported the first enantio- and diastereoselective monofluorocyclopropanation.

tion of  $\alpha,\beta$ -unsaturated carbonyl compounds (Scheme 170).<sup>319b</sup> The reaction between  $\alpha,\beta$ -unsaturated Weinreb

### Scheme 170



<sup>a</sup> Yields are of the major isomers.

amides and the anion of (*R*)-*N*-tosyl-*S*-fluoromethyl-*S*-phenyl-sulfoximine ((*R*)-294) affords cyclopropanes that contain fluorinated tertiary stereogenic carbon centers in high yields with excellent stereoselectivities. Enantiopure *S*-(1-fluoroalkyl)-*N*-tosylsulfoximines, such as (*R*)-328, also undergo the reaction to provide products in good yields however, stereoselectivities are lower to some extent.

### 3.7. For Monofluoroolefination

As an extension of the monofluoroalkylation (including monofluoromethylation) reactions, this section aims to describe the synthesis of monofluoroolefins with sulfur based mono-fluoroalkylation reagents. These olefination reactions involve a monofluoroalkylation and subsequent formation of the fluorinated C=C double bond via elimination in various forms. A review by Paquin and co-workers on the synthesis of monofluoroalkenes has covered most of the publications on this topic before October 2010.<sup>13i</sup> However, in recent years, some progress has been made in the synthesis of mono-fluoroalkenes with sulfur-based reagents. For completeness of this review, this section gives a historical retrospection of sulfur-based monofluoroolefination before October 2010 and summarizes the development in this field thereafter. This section is divided according to the type of sulfur reagents used (sulfoxides, sulfones, sulfoximines) and subdivided according to the role of sulfur in the olefination reaction (auxiliary group or reactive site), and further classified in terms of the reaction type. Parts of the material treated here have also been discussed in other reviews.<sup>13j-l,342</sup>

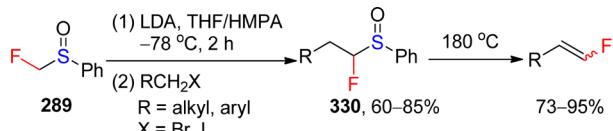
### 3.7.1. Sulfoxides as Monofluoroolefination Reagents.

Monofluorinated sulfoxides have found application in the synthesis of monofluoroalkenes, although commonly thermal elimination is required. Compared to the conventional fluorination methods to obtain monofluorinated sulfoxides (the monofluoroolefins precursors), the monofluoro(sulfinyl)-alkylation with  $\alpha$ -fluorosulfoxides  $\text{ArSOCHF}_R$  (where R is hydrogen, alkyl, or an electron-withdrawing functional group), represents a straightforward and convenient protocol.

In a 1983 report on synthetic application of PhSOCH<sub>2</sub>F (289), Reutrakul and Rukachaisirikul described the first monofluoro(sulfinyl)methylation of primary alkyl halides by using 289 as the fluoroalkylation reagent (see section 3.6.3).<sup>325</sup> They found that the pyrolysis of the 1-fluoroalkyl phenyl sulfoxides in a sealed tube at 180 °C gives disubstituted terminal monofluoroalkenes as a mixture of isomers in good to

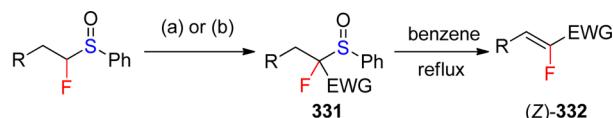
excellent yields (62–95%) (Scheme 171).<sup>331</sup> The further functionalization of **330** can be used to synthesize function-

### Scheme 171



alized monofluoroalkenes.<sup>343</sup> For instance, Yamakawa and co-workers in 1994 reported that the pyrolysis of  $\alpha$ -fluoro- $\alpha$ -sulfinyl esters and aldehydes, which are obtained by reaction of 1-fluoroalkyl phenyl sulfoxides with alkyl chloroformates and alkyl formates, respectively, gives the (Z)- $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl compounds 332 in moderate to good overall yields (Scheme 172).<sup>343a</sup> In this context, 1-fluoroalkyl phenyl sulfoxides are monofluorovinyl equivalent.

### Scheme 172

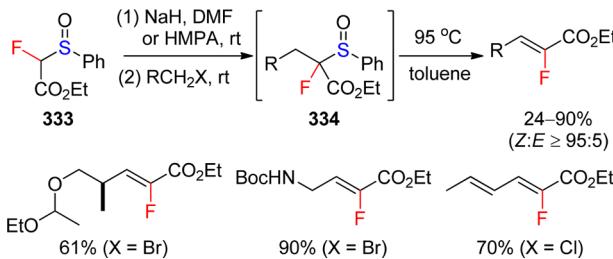


Conditions: (a) (1) LTMP, THF, -100 °C; (2) ClCO<sub>2</sub>Et  
 (b) (1) LDA, THF, -60 °C; (2) HCO<sub>2</sub>Me

R	EWG	331, yield (%)	332, yield (%)
Ph	CO <sub>2</sub> Et	76	78
<i>n</i> -C <sub>9</sub> H <sub>19</sub>	CO <sub>2</sub> Et	62	97
Ph	CHO	82	93
<i>n</i> -C <sub>9</sub> H <sub>19</sub>	CHO	95	75

In 1991, by using the fluoroalkylation strategy, Allmendinger developed a one-pot synthesis of  $\alpha$ -fluoroalkenoates by the reaction of primary/secondary alkyl halides (Scheme 173) and

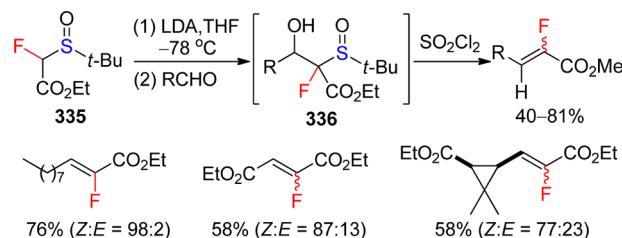
### Scheme 173



activated terminal alkenes with phenylsulfinyl fluoroacetates 333 followed by thermal elimination.<sup>344</sup> The reaction with primary halides affords trisubstituted products in moderate to good yields (24–90%) with high stereoselectivity ( $Z/E \geq 95:5$ ) being attributed to the steric repulsion of the R substituent and the ester group in the transition state.

The reaction of carbonyl compounds with  $\alpha$ -fluorosulfoxides is also a feasible monofluoroolefination method.<sup>345</sup> Lequeux and co-workers in 2002 described the preparation of  $\alpha$ -fluoroalkenoates via reaction of aldehydes with *tert*-butylsulfinyl fluoroacetates 335. The reaction proceeds through the addition of lithiated 2-(*tert*-butylsulfinyl)-2-fluoroacetate to the aldehydes followed by a formal *tert*-butylsulfinic acid elimination in the presence of  $\text{SO}_2\text{Cl}_2$  (Scheme 174),<sup>345c</sup> giving  $\alpha$ -

### Scheme 174



fluoroalkenoates in 40–81% yields with good to moderate (*Z*)-selectivity. However, this protocol is not applicable to monoolefination of aromatic aldehydes due to the ready retro-addition reaction of the corresponding alcoholates.

### 3.7.2. Sulfones as Monofluoroolefination Reagents.

Compared to difluoroolefination with sulfone reagents, the monofluoroolefination with sulfone reagents is more versatile, since another substituent is possible on the fluorinated carbon of the formed olefins. Thus, various monofluorinated alkenes have been synthesized from both aryl and heteroaryl sulfones either via monofluoro(sulfonyl)olefination or direct monofluoroolefination reactions. In the olefination process, the sulfonyl group serves either as a removable auxiliary group or a reactive site to form the C=C double bond.

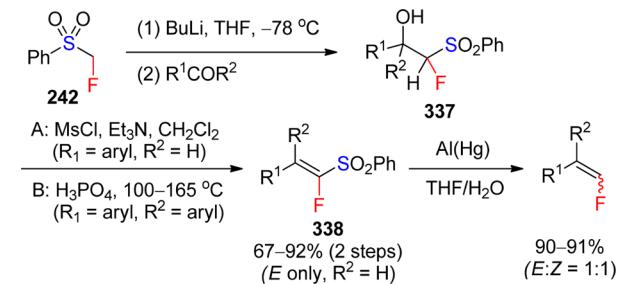
### 3.7.2.1. Fluoro(sulfonyl)olefination.

$\alpha$ -fluorovinyl sulfones can be substituted by a hydrogen; thus, terminal monofluoroolefination has been achieved via monofluoro(sulfonyl)olefination by using either monosulfone or bis-sulfone reagents. Moreover, the  $\alpha$ -fluorovinyl sulfones obtained in such a way can be used for the stereoselective synthesis of internal monofluoroalkenes.

3.7.2.1.1. Aldol-Type Condensation. As mentioned in Section

3.5.1.1, Peet and McCarthy and co-workers in 1985 first developed the nucleophilic addition of  $\text{PhSO}_2\text{CH}_2\text{F}$  (242) to carbonyl compounds and used the  $\alpha$ -fluoro(phenylsulfonyl)-methyl alcohols 337 in the synthesis of terminal monofluoroolefins through a formal water elimination reaction followed by reductive desulfonylation (Scheme 175).<sup>286</sup> However, this

Scheme 175



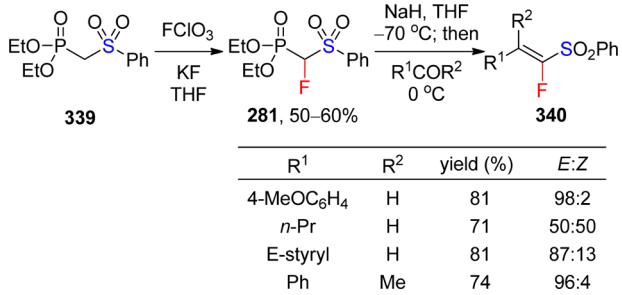
protocol is only applicable for converting aromatic aldehydes to terminal monofluoroolefins, since other carbonyl compounds such as acetophenone bearing  $\alpha$ -hydrogens cannot afford  $\alpha$ -fluorovinyl sulfones due to the elimination from the non-fluorinated carbon side of the alcoholates. Moreover, the reductive desulfonylation with Al(Hg) is nonstereoselective, affording a 1:1 mixture of *E* and *Z* isomers.

### 3.7.2.1.2. Horner–Wadsworth–Emmons (HWE) Olefination.

In 1987, Koizumi and co-workers first prepared diethyl [fluoro(phenylsulfonyl)methyl]phosphonate (**281**) through electrophilic fluorination of its nonfluorinated counterpart

339 and used it for the convenient synthesis  $\alpha$ -fluorovinyl phenyl sulfones via Horner–Wadsworth–Emmons reaction (Scheme 176).<sup>316</sup> By using NaH as the base, not only various

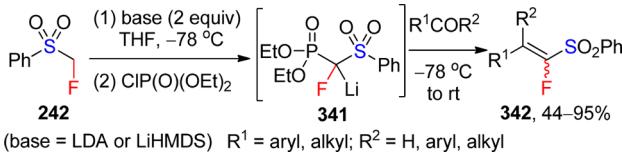
Scheme 176



aldehydes, but also various ketones readily undergo the olefination reaction with 281 to afford the corresponding products 340 in high yields (64–95%) with excellent stereoselectivities in most cases. This olefination methodology has been extended to the synthesis of  $\alpha$ -fluorovinyl heteroaryl sulfones by using the monofluorinated phosphonate that contains a pyridylsulfonyl, pyrimidylsulfonyl, or (1,3-benzothiazol-2-yl)sulfonyl group at the  $\alpha$ -position.<sup>283c,346</sup>

In 1990, McCarthy and co-workers modified Koizumi's fluoro(phenylsulfonyl)olefination procedure by using the lithiated [fluoro(phenylsulfonyl)methyl]phosphonate 341 pre-generated from the readily available PhSO<sub>2</sub>CH<sub>2</sub>F (242) (Scheme 177).<sup>347</sup> Thus, treatment of PhSO<sub>2</sub>CH<sub>2</sub>F (242) and

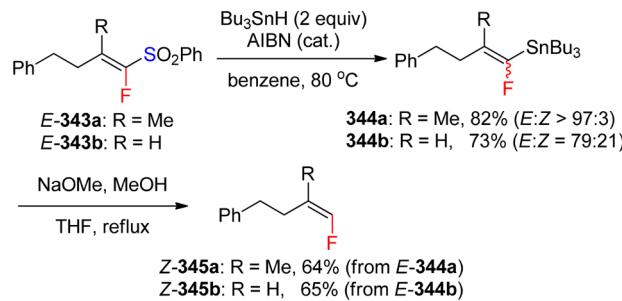
Scheme 177



diethyl chlorophosphate with 2 equiv of a base followed by the addition of the carbonyl compounds, affords various  $\alpha$ -fluorovinyl sulfones 342 in moderate to excellent yields with low to moderate stereoselectivity. The relatively lower stereoselectivity than that of the reaction shown in Scheme 176 (vide supra) probably arises from the counterion effect.

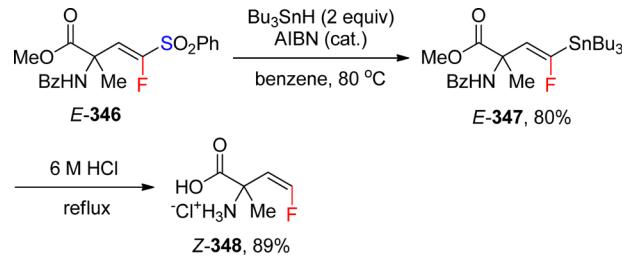
During their research on the synthesis of 2'-deoxy-2'-fluoromethylene nucleosides, McCarthy and co-workers developed a mild desulfonylation method, that is, stannyldesulfonylation followed by destannylation, which affords both the *E* and the *Z* stereoisomers of the terminal monofluoroolefins and avoids the separation of isomers in the final step of the synthesis (Scheme 178).<sup>348</sup> The stannylation of 2,2-disubstituted fluorovinyl sulfones, such as 343a, with 2 equiv of Bu<sub>3</sub>SnH in the presence of catalytic quantities of AIBN affords the  $\alpha$ -fluorovinyl stannanes, such as 344a, with retention of the configuration, whereas the reaction of 2-monosubstituted fluorovinyl sulfones, such as 343b, leads to a mixture of *E* and *Z* isomers. The subsequent destannylation of various  $\alpha$ -fluorovinyl stannanes proceeds smoothly under mild basic conditions, providing the corresponding terminal monofluoroolefins with retention of the configuration (Schemes 178). Note that Berkowitz and co-workers in 2004 observed that the stannyldesulfonylation of the *E* isomers of sterically demanding

Scheme 178



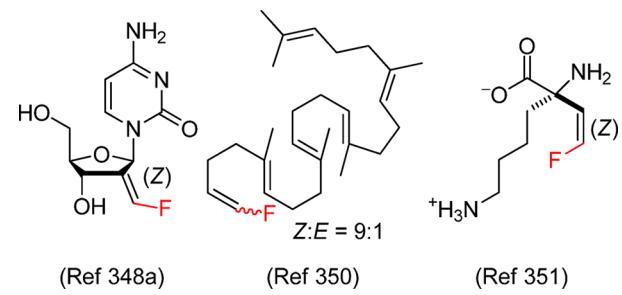
2-monosubstituted fluorovinyl sulfones, such as 346, also proceeds with retention of the configuration (Scheme 179).<sup>349</sup>

Scheme 179



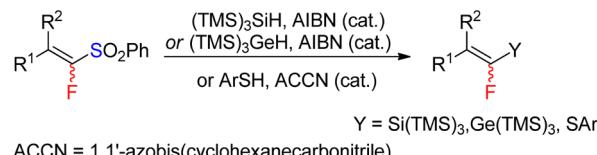
The combination of HWE fluoro(phenylsulfonyl)olefination and Bu<sub>3</sub>SnH mediated desulfonylation constitutes an efficient method to stereoselectively prepare terminal monofluoroolefins, although multistep operation is required. This methodology has been used for the synthesis of enzyme inhibitors, with some examples being shown in Scheme 180.<sup>348a,350,351</sup>

Scheme 180



In addition, Wnuk and co-workers showed that the  $\alpha$ -fluorovinyl sulfones can also undergo radical silyl-, germyl-, and sulfonyl desulfonylations, to afford  $\alpha$ -fluorovinyl silanes, germanes, and sulfides, respectively (Scheme 181).<sup>346,352</sup> The  $\alpha$ -fluorovinyl silanes and germanes, as well as the aforementioned stannanes have been used as building blocks in transition metal-

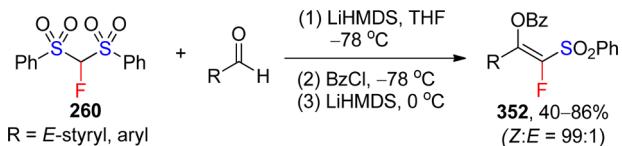
Scheme 181



catalyzed coupling reactions to stereoselectively synthesize tri- and tetra-substituted monofluoroalkenes.<sup>346,353</sup>

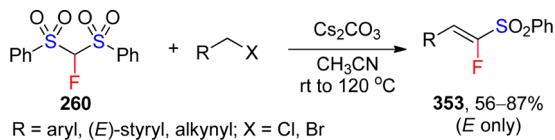
**3.7.2.1.3. Other Fluoro(sulfonyl)olefination Reactions.** In recent years, new monofluoroolefination methods for the synthesis of  $\alpha$ -fluorovinyl sulfones by using  $\text{PhSO}_2\text{CHF}$ , where R is phenylsulfonyl (**260**), benzo[*d*]thiazol-2-ylsulfonyl (**349**), [1-(*tert*-butyl)-1*H*-tetrazol-5-yl]sulfonyl (**350**), and *tert*-butyldimethylsilyl (**351**) groups, have been developed. These methods rely on the transformation of carbonyl compounds via addition-deprotonation elimination (Scheme 182),<sup>311,354</sup> Julia-

Scheme 182



Kocienski olefination,<sup>355</sup> and Peterson olefination<sup>356</sup> or transformation of alkyl halides via substitution-deprotonation elimination (Scheme 183).<sup>301b</sup> However, most of these

Scheme 183



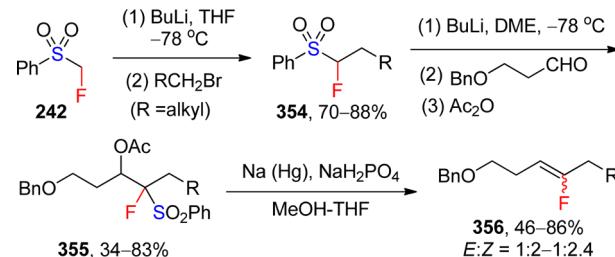
methods are limited to the synthesis of 2-monosubstituted  $\alpha$ -fluorovinyl sulfones, except in the case of the reaction of aldehydes with FBSM (**260**), which affords 2,2-disubstituted  $\alpha$ -fluorovinyl sulfone **352**, precisely, a monofluoroenolate.<sup>354</sup>

**3.7.2.2. Direct Monofluoroolefination.** In these reactions, the desired monofluoroalkene functionality is constructed directly and no further transformation is needed.

**3.7.2.2.1. Julia-Lythgoe Reaction.** The Julia-Lythgoe reaction is a classical olefination method, which mainly relies on the transformation of phenyl sulfones; however, it is scarcely used in monofluoroolefinations. As mentioned in Section 3.5.1.1, Shimizu and co-workers in 1992 reported the preparation of (10*Z*)- and (10*E*)-19-fluoro-1*α*,25-dihydroxyvitamin D3, a Z/E mixture of terminal monofluoroalkenes, via direct reduction of the corresponding  $\alpha$ -fluoro(phenylsulfonyl)methyl alcohols with Na(Hg), which is probably the first example of Julia-Lythgoe type monofluoroolefination.<sup>287</sup> In 2006, Usuki and co-workers reported the synthesis of monofluoroalkenes with 1-fluoroalkyl phenyl sulfones as the monofluoroolefination reagents, which is performed using a typical Julia-Lythgoe procedure.<sup>357</sup> The trisubstituted internal monofluoroalkenes are prepared from aldehydes in moderate overall yields with moderate Z-selectivities (Scheme 184).

**3.7.2.2.2. Julia-Kocienski Reaction.** The Julia-Kocienski reaction is an important method to convert the carbonyl compounds into alkenes in one step,<sup>276</sup> which has found many applications in the synthesis of both internal and terminal monofluoroalkenes.<sup>358,359–376</sup> Mechanically, these reactions commences with the nucleophilic addition of the  $\alpha$ -monofluorinated sulfone anion to a carbonyl compound followed by a Smiles rearrangement, and concludes with the formation of a fluorinated C=C double bond, which links the nonfluorinated and monofluorinated motifs together in one

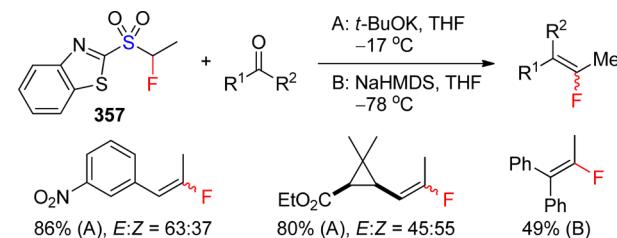
Scheme 184



molecule. Two key issues in direct monofluoroolefination are the incorporation of a fluorine atom into the  $\alpha$ -position of heteroaromatic or electron-deficient aromatic sulfones and the control of the stereoselectivity of the olefination reaction. The latter issue is also the common concern in the synthesis of nonfluorinated alkenes via Julia-Kocienski olefination, which is usually complicated by both the structures of the reactants and the reaction conditions used, and is thus often difficult to predict.<sup>276b</sup> In respect to the first issue of the monofluoroolefination, generally, two methods are available to prepare the monofluorinated sulfone reagents: one is fluorination of heteroaryl or electron-deficient aryl sulfides or sulfones followed by further elaboration;<sup>358,367–375</sup> the other is the oxidation of monofluorinated sulfides derived from haloformomethyl compounds such as ethyl bromofluoroacetate and chlorofluoromethane followed by further transformation.<sup>355b,359–367,376</sup>

In a seminal contribution, Lequeux and Pazenok and co-workers in 2003 described the first synthesis of monofluoroalkenes from aldehydes and ketones by using 2-(1-fluoroethyl)sulfonyl-1,3-benzothiazole (**357**) as the monofluoroolefination reagent (Scheme 185), in which the fluorine atom

Scheme 185



is introduced via halogen exchange reaction.<sup>358</sup> This contribution is an important application of the Julia-Kocienski reaction and opens a new avenue to the synthesis of monofluorinated alkenes.

Since 2006, two groups led by Lequeux and Zajc have made major contribution in Julia-Kocienski monofluoroolefination with 1,3-benzothiazol-2-yl (BT) sulfones; the Lequeux group aims at developing olefination reagents via nucleophilic methods,<sup>359–365</sup> whereas the Zajc group focus on the preparation of the reagents using electrophilic fluorination protocol.<sup>367–374</sup> By using various  $\alpha$ -fluoro BT sulfones as the olefination reagents, an array of functionalized monofluoroolefins, including stilbene- and styrene-like fluoroolefins,<sup>367</sup>  $\alpha$ -fluoroacrylates,<sup>359,360,369</sup>  $\alpha$ -fluoroacrylonitriles,<sup>368</sup>  $\alpha$ -fluorovinyl Weinreb amides<sup>370</sup> and ketones,<sup>370</sup> 2-fluoro-1,3-enynes,<sup>372</sup>  $\alpha$ -fluorovinyl triazoles,<sup>371</sup> and 2-fluoroallyl amines,<sup>362,363,366</sup> have been prepared (Scheme 186). Although all these reagents exhibit high reactivity toward both aromatic and aliphatic

Scheme 186

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	conditions	yields	E/Z	Ref
aryl, heteroaryl	2-naphthyl, (E)-styryl, 2-thienyl, Fc, n-C <sub>7</sub> H <sub>15</sub>	H	LiHMDS, THF, 0 °C	86–99%	0:100–82:18	368
aryl, heteroaryl			LiHMDS, THF, 0 °C	62–91%	78:22–95:5	368
CO <sub>2</sub> t-Bu	2-naphthyl, (E)-styryl, 2-thienyl, n-C <sub>7</sub> H <sub>15</sub> , etc.	H	DBU, CH <sub>2</sub> Cl <sub>2</sub> , rt	70–99%	57:43–88:12	369
CO <sub>2</sub> Et	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , 3-MeOC <sub>6</sub> H <sub>4</sub> , 2-thienyl, c-C <sub>6</sub> H <sub>11</sub> , etc.	H	DBU, MgBr <sub>2</sub> , THF, 20 °C	27–90%	6:94–49:51	359
CO <sub>2</sub> Et			DBU, THF, rt	40–70%	n. r. <sup>a</sup>	360
C≡N	2-naphthyl, 3-MeOC <sub>6</sub> H <sub>4</sub> , n-C <sub>7</sub> H <sub>15</sub> , 3-pentyl, etc.	H	DBU, CH <sub>2</sub> Cl <sub>2</sub> , -78 °C	77–97%	8:92–27:73	367
CONMe(OMe)	2-naphthyl, 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , 2-thienyl, n-C <sub>7</sub> H <sub>15</sub>	H	DBU, DMPU, rt	69–93%	67:33–86:14	370
CONMe(OMe)	2-naphthyl, 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , 2-thienyl, n-C <sub>7</sub> H <sub>15</sub> , etc.	H	NaH, THF, rt	71–99%	2:98–0:100	370
CONMe(OMe)			Cs <sub>2</sub> CO <sub>3</sub> , DMF, rt	59%	n. a. <sup>b</sup>	370
COR (R = Ph, n-Pr)	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , 4-MeOC <sub>6</sub> H <sub>4</sub> , 2-thienyl, BnCH <sub>2</sub> , etc.	H	DBU, THF, 0 °C or reflux	61–90%	0:100	370
C≡C-TMS	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , 4-MeOC <sub>6</sub> H <sub>4</sub> , 2-thienyl, BnCH <sub>2</sub> , etc.	H	LiHMDS, THF, -78 °C	59–97% <sup>c</sup>	70:30–95:5	372
C≡C-TMS	Ph	Me	LiHMDS, THF, -78 °C	88% <sup>c</sup>	100:0	372
	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , 4-MeOC <sub>6</sub> H <sub>4</sub> , BnCH <sub>2</sub> , 3-pentyl, etc.	H	LiHMDS, DMF, DMPU, -78 °C	47–90%	38:62–7:93	371
			LiHMDS, DMF, DMPU, -78 °C	87%	n. a. <sup>b</sup>	371
	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , 4-MeOC <sub>6</sub> H <sub>4</sub> , 3-pyridyl, n-C <sub>6</sub> H <sub>13</sub> , etc.	H	NaHMDS, THF, -78 to -20 °C	52–88%	4:96–41:59	362
			LiHMDS, BF <sub>3</sub> ·OEt <sub>2</sub> , THF, -78 °C	61%	20:80	366

<sup>a</sup> n. r. = not reported. <sup>b</sup> n. a. = not applicable. <sup>c</sup> Yields of the desilylation products.

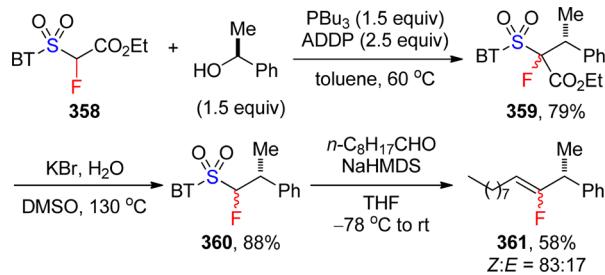
aldehydes, most of them have limited application in monofluoroolefination of ketones, probably due to the steric hindrance in the carbonyl addition step. The olefination reactions usually give moderate stereoselectivities, with the exception in the synthesis of  $\alpha$ -fluorovinyl Weinreb amides and ketones.<sup>370</sup> In many cases, the dominance of E- or Z-isomer could be controlled by altering the reaction conditions. Moreover, Zajc and co-workers demonstrated that, compared to their nonfluorinated analogues, the  $\alpha$ -fluorosulfone reagents are more reactive in olefination reactions.<sup>355a,369,372</sup>

Enantioselective synthesis of fluoroalkenes containing a chiral allylic center is a challenge. Very recently, Linclau and Lequeux and co-workers demonstrated the application of the BT sulfone based monofluoroolefination strategy in the synthesis of enantiopure fluoroalkenes that contain a chiral center next to the fluorinated carbon ( $\alpha_{(F)}$ ) (Scheme 187).<sup>365</sup> As mentioned

at the beginning of this part, the key to achieve this synthetic target is preparation of the fluorinated sulfone reagents. Thus, taking a nucleophilic monofluoro(sulfonyl)methylation approach, a modified Mitsunobu reaction between the readily available BT-sulfonylated fluoroacetate **358** and enantiopure secondary alcohols, such as (S)-1-phenylethanol, followed by a Krapcho decarboxylation under the promotion of the less basic KBr, gives the required homochiral monofluorinated sulfone reagents, such as **360**. The condensation between **360** and aldehydes with NaHMDS as the base furnishes the  $\alpha_{(F)}$ -branched fluoroalkenes with E-selectivity for aromatic aldehydes and Z-selectivity for aliphatic aldehydes. For example, the reaction of **360** with nonanal affords **361** in 58% yield with a Z/E ratio up to 83:17.

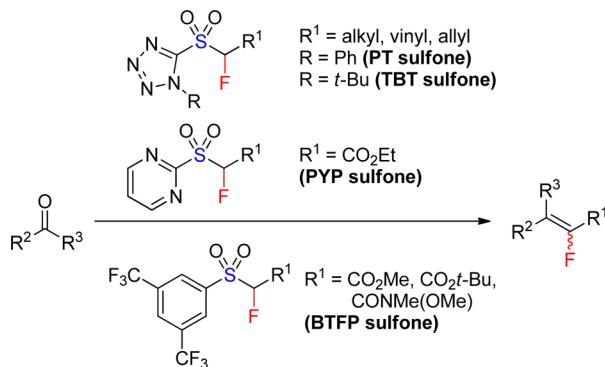
In addition to BT sulfones, the application of other Julia–Kocienski olefination reagents such as 3,5-bis(trifluoromethyl)-

Scheme 187



phenyl (BTFP),<sup>375,376</sup> 1-phenyl-1*H*-tetrazol-5-yl (PT),<sup>374</sup> 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT),<sup>355b</sup> and 2-pyrimidinyl (PYP) sulfones,<sup>377</sup> in monofluoroolefination has also been investigated (Scheme 188). Alonso and Nájera and co-workers in 2008

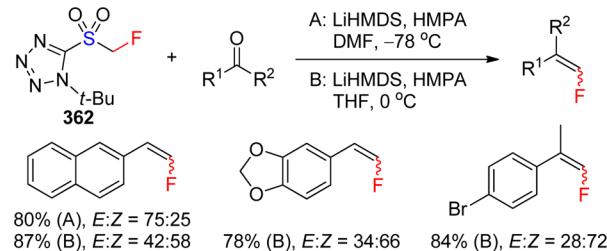
Scheme 188



reported that  $\alpha$ -fluoroacetates containing a BTFP-sulfonyl group at the  $\alpha$ -position can undergo olefination reaction with aromatic aldehydes to afford  $\alpha$ -fluoroacrylates with high *Z*-selectivity, and the corresponding Weinreb amides can react with both aromatic and aliphatic aldehydes to give  $\alpha$ -fluorovinyl Weinreb amides with high *Z*-selectivity.<sup>375</sup> Zajc and co-workers in 2009 showed that 1-fluoroalkyl PT sulfones, which are more easily accessible through electrophilic fluorination, can be used as fluoroalkylation reagents.<sup>374</sup> Generally speaking, these BTFP, PT, and TBT sulfones reagents exhibit similar stereocontrol ability to that of the BT sulfone reagents. Very recently, Lequeux and co-workers showed that PYP sulfones are superior to BT sulfones in the synthesis of 2-fluoroalkenoates from aldehydes.<sup>377</sup> Thus, the use of ethyl fluoro(2-pyrimidinylsulfonyl)acetate for the olefination of both aromatic and aliphatic aldehydes yields the *Z*-isomers in very high stereoselectivity (*Z/E* > 95:5).

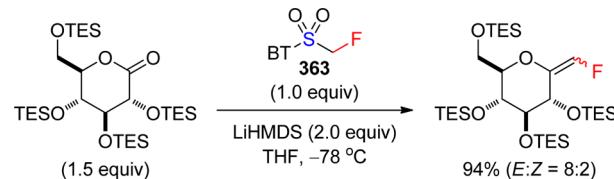
Finally, the Julia–Kocienski olefination is also effective for the synthesis of terminal monofluoroolefins.<sup>355b,375,376</sup> Hu and co-workers in 2010 reported that monofluoromethyl TBT sulfone is an efficient monofluoromethylidenation reagent, which reacts with both aldehydes and ketones to provide the corresponding monofluorinated alkenes in good yields with moderate *E/Z* selectivity (Scheme 189).<sup>355b</sup> Similar to other monofluoroolefination reactions, the stereochemical outcome can be tuned toward either *E*- or *Z*-selectivity by selection of proper reaction parameters. Monofluoromethyl BTFP sulfone has also been developed for the same purpose; interestingly, cesium fluoride can be used as a base to promote its reaction with nonenolizable aldehydes and ketones.<sup>376</sup> In 2013, Gueyraud and co-workers reported the monofluoroolefination

Scheme 189



of functionalized lactones derived from carbohydrates by using monofluoromethyl BT sulfone (363), which affords fluorinated enol ethers in moderate to excellent yields (43–94%) with moderate stereocontrol (Scheme 190).<sup>366</sup> This is probably the first report on the direct monofluoroolefination of an ester carbonyl group.

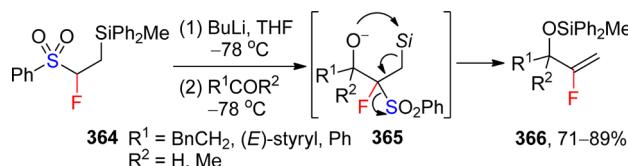
Scheme 190



**3.7.2.3. Monofluorovinylation.** In addition to the previously described transformation of  $\alpha$ -fluorovinyl sulfones (see section 3.7.2.1), monofluorovinylation can be as well achieved via reactions with  $\alpha$ -fluoro- $\beta$ -silylsulfones and  $\alpha$ -fluoro- $\beta$ -ketosulfones.

In 1994, Tokoroyama and co-workers reported a monofluorovinylation of aldehydes and ketones using 2-(diphenylmethylsilyl)-1-fluoro-1-(phenylsulfonyl)ethane (364) as the reagent (Scheme 191).<sup>378</sup> The carbanion generated from

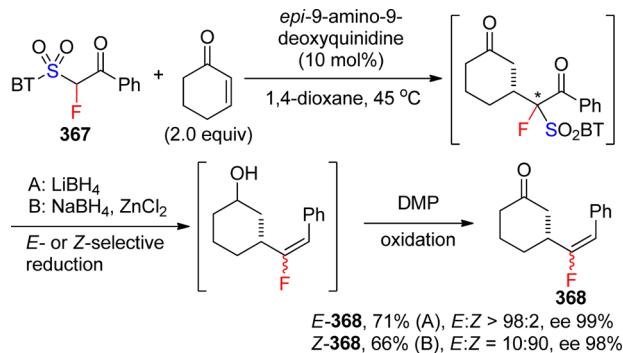
Scheme 191



sulfone 364 adds to the carbonyl compounds affording the  $\beta$ -silylalcoholate intermediates 365, which undergo 1,4-silyl migration followed by  $\beta$ -elimination of phenylsulfinate to give good yields (71–89%) of  $\alpha$ -fluorovinyl compounds 366.

In 2011, Jøgenson and co-workers disclosed a catalytic enantioselective nucleophilic fluorovinylation by using  $\alpha$ -fluoro- $\beta$ -keto-(BT-sulfones), such as 367, as the  $\alpha$ -fluorovinyl anion equivalents under the catalysis of a chiral primary amine (Scheme 192).<sup>379</sup> The transformation proceeds via asymmetric addition of 367 to a prochiral electrophile, such as 2-cyclohexenone, followed by diastereoselective reduction to achieve a stereoselective Julia–Kocienski-like olefination. Notably, the configuration of the monofluorovinyl group can be controlled by selection of the reductant.  $\alpha,\beta$ -Unsaturated cyclic and acyclic ketones undergo the  $\alpha$ -fluorovinylation to produce both *E*- and *Z*-isomers of the monofluorovinylated products, such as 368, in high yields (41–86%) with excellent

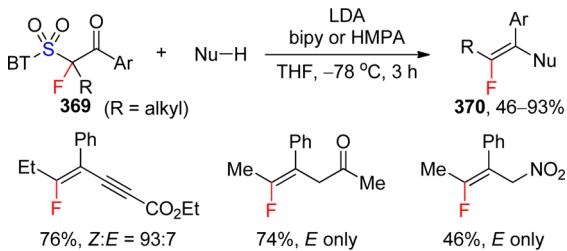
Scheme 192



enantioselectivities (up to 99% ee). In addition, by employing a chiral ammonium salt derived from quinine as the catalyst, this synthetic methodology has been extended to the asymmetric monofluorovinylation of activated imines with high E/Z selectivities; however, the enantioselectivities are only moderate (63–84% ee) at present.

Finally, as an exception to the monofluoroalkylation-dictated monofluoroolefination discussed in this section, an interesting nucleophilic addition of carbon nucleophiles to  $\alpha$ -fluoro- $\beta$ -keto-heteroarylsulfones is shown in Scheme 193, which is

Scheme 193

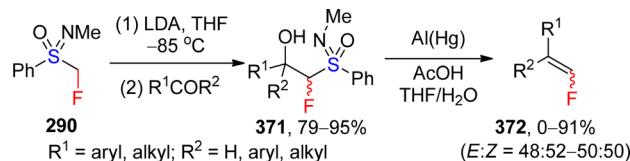


related to the stereoselective synthesis of tetra-substituted monofluoroolefins.<sup>380</sup> In the presence of a metal ion chelating additive such as 2,2'-bipyridine (bipy) and HMPA, not only various alkyl lithium reagents, but also carbanions derived from ketones, esters, amides, as well as nitromethane undergo the formal  $\beta$ -fluorovinylation to give the corresponding monofluoroalkenes 370 in moderate to excellent yields with very high stereoselectivities. In this reaction,  $\alpha$ -fluoro- $\beta$ -keto-heteroarylsulfones 369 serve as  $\beta$ -fluorovinyl cation equivalents.<sup>380</sup>

**3.7.3. Sulfoximines as Monofluoroolefination Reagents.** The N-alkylated and N-silylated monofluorosulfoximes have been applied for monofluoroolefination, and they possess similar reactivity to that of phenyl sulfones. As mentioned in section 3.5.2.1, Finch and co-workers in 1988 developed *N*-methyl-*S*-monofluoromethyl-*S*-phenylsulfoxime (290) as the monofluoroolefination reagent by reduction of its carbonyl adduct with aluminum amalgam; however, this olefination usually gives a 1:1 mixture of E- and Z-isomers (Scheme 194).<sup>318a</sup>

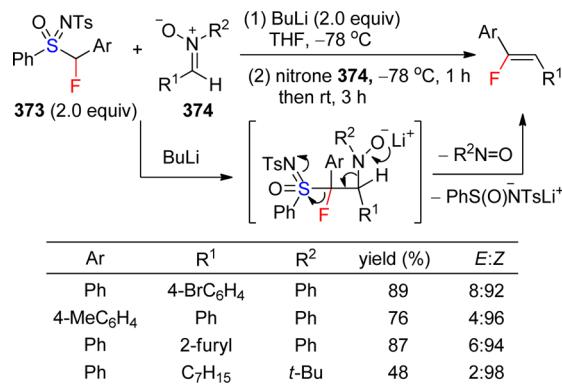
It is known that *N*-tosylsulfonimidoyl is a good leaving group, and the anions of *N*-tosylsulfoximes usually react with carbonyl compounds (aldehydes and ketones), imines, and  $\alpha,\beta$ -unsaturated compounds in an addition-1,3-elimination manner to give epoxides, aziridines, and cyclopropanes, respectively.<sup>381</sup> However, their reaction with nitrones is not the case. In 2009, Hu and co-workers reported an unprecedented olefination

Scheme 194



reaction between *N*-tosylsulfoximes and nitrones, which proceeds through an addition-1,2-elimination pathway (Scheme 195).<sup>382</sup> By using  $\alpha$ -fluorinated *N*-tosyl-*S*-benzylsulfoximes

Scheme 195



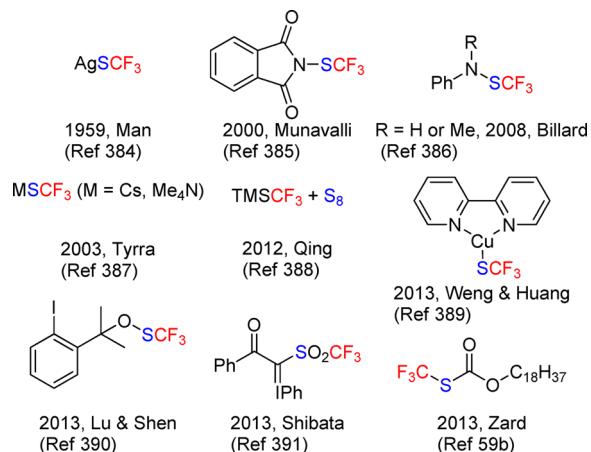
373 as the olefination reagents,  $\beta$ -substituted- $\alpha$ -fluorostyrenes are prepared in good yields with very high Z-selectivities. According to the proposed mechanism, the excellent stereocontrol probably results from the stereoselective addition reaction. Although nonfluorinated *N*-tosylsulfoximes can also undergo this olefination reaction with similar stereoselectivity, the products are given in low yields, indicating that fluorinated *N*-tosylsulfoximes are more reactive toward nitrones for this olefination reaction.

#### 4. TRIFLUOROMETHYLTHIOLATION AND PENTAFLUOROSULFANYLATION

As a supplementary to this review, this section gives an outline of trifluoromethylthiolation and pentafluorosulfanylation.

The trifluoromethylthio ( $\text{CF}_3\text{S}$ ) group has fascinated researchers for decades due to its remarkably higher lipophilicity than a trifluoromethyl group.<sup>6,383</sup> However, it is only in the last five years that many aromatic and aliphatic trifluoromethylthiolation methods have been developed by using either known or newly developed reagents.<sup>52b,59b,384–393</sup> A list of easily available and user-friendly reagents that have been used for this purpose is given in Figure 2; for further information on their synthetic applications, the readers may refer to several recent comprehensive reviews on trifluoromethylthiolation.<sup>52b,392,393</sup>

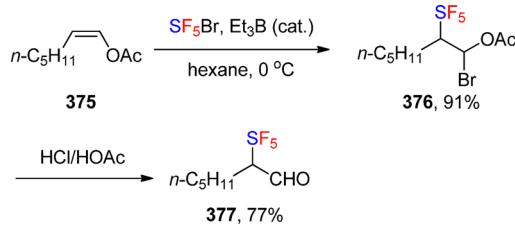
The strong electron-withdrawing pentafluorosulfanyl group is usually considered as a “super-trifluoromethyl group”;<sup>4</sup> it is not only of high chemical and metabolic stability, but also possesses significantly higher lipophilicity than a trifluoromethyl group.<sup>394</sup> However, methods for the synthesis of aliphatic pentafluorosulfanyl compounds are rare.<sup>395</sup> The radical reactions of  $\text{SF}_5\text{Cl}$  and  $\text{SF}_5\text{Br}$  with alkenes or alkynes have been used to obtain various  $\text{SF}_5$ -containing building blocks that are useful for the synthesis of aliphatic and some aromatic pentafluorosulfanylated compounds.<sup>396</sup> For example, reaction



**Figure 2.** Typical trifluoromethylthiolation reagents.

of enol acetate **375** with  $\text{SF}_5\text{Br}$  under the initiation of triethylborane gives an excellent yield of the addition product **376**, which can be converted to the  $\alpha$ - $\text{SF}_5$  substituted aldehyde **377** through hydrolysis (Scheme 196).<sup>396g</sup> Note that the direct aromatic pentafluorosulfanylation is still unknown due to the lack of proper reagents or methods.<sup>397</sup>

### Scheme 196



## 5. CONCLUSIONS AND PERSPECTIVES

Fluorine is no doubt one of the most fabulous and magical chemical elements in our universe. Organofluorine compounds and materials have found wide applications ranging from refrigerants, medicines, agrochemicals, surfactants, to the coatings of our textiles and buildings, and the past decade has witnessed a renaissance of fluorine-related science and technology. Since Nature has a lack of efficient mechanisms to make carbon–fluorine bonds, all the organofluorine compounds that we are using today have to be man-made. Fluorine exists as inorganic fluorides (such as  $\text{CaF}_2$ ) in Nature, which has to be converted to  $\text{HF}$  (and sometimes further to  $\text{F}_2$ ) before an efficient C–F bond formation could be accomplished. Owing to the high toxicity and/or explosive nature of  $\text{HF}$  and  $\text{F}_2$ , chemists have been seeking other milder and safer alternatives for selective fluorination and fluoroalkylation. In this context, the continuous development of sulfur-based reagents over the years represents an excellent example of these efforts.

Sulfur and fluorine truly form a good “partnership” in modulating many different types of fluorination and fluoroalkylation reactions through various sulfur/fluorine-containing inorganic and organic compounds/reagents. The rich chemistry of sulfur compounds, along with the intrinsic differences (in bond strengths) of S–F, S–O, S–C, and C–C bonds, enable these sulfur-based reagents to exhibit

remarkable fluorination and fluoroalkylation powers with a wide range of substrates. In retrospect, the historical development of deoxygenative fluorination reagents along the path from  $\text{SF}_4$ , DAST, Deoxo-Fluor to XtalFluors and Fluolead, clearly demonstrates the excellent modulating ability of sulfur-containing groups for efficient and safe fluorination reagents. On the other hand, fluorinated organosulfur compounds, such as sulfones, sulfoximines, sulfinate salts, sulfoxides, sulfilimines, sulfides, among others, often exhibit unique (sometimes even unexpected) chemical reactivities that are different from their nonfluorinated counterparts. Many of these fluorinated organosulfur compounds have become nucleophilic, electrophilic, radical tri-, di-, monofluoromethylating agents, as well as di- and monofluoromethylenating agents. In the years to come, it is anticipated that the transition metal-mediated fluorination and fluoroalkylation reactions with these sulfur-based reagents (as shown in Figure 1) and other new ones will continue to advance at a rapid pace. New asymmetric fluorination and fluoroalkylation reactions with sulfur-based reagents will be another research focus in the field. There is no doubt that sulfur-based fluorination and fluoroalkylation reagents will continue to find wide applications in synthesizing new fluorine-containing pharmaceuticals, agrochemicals, and advanced materials. Fluorine is sometimes called “the element at the end of the Universe”,<sup>398</sup> but now it seems evident that sulfur is able to modulate fluorine and bring it to the center stage of modern chemistry.

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### Author Contributions

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

### Notes

The authors declare no competing financial interest.

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## ACKNOWLEDGMENTS

We thank the National Basic Research Program of China (2012CB215500 and 2012CB821600), the National Natural Science Foundation of China (21372246, 21202189), Shanghai QMX program (13QH1402400), MSD China R&D Postdoc Fellowship (to M.H.), and Chinese Academy of Sciences for financial support.

## ABBREVIATIONS

Ac	= acetyl
ACCN	= 1,1'-azobis(cyclohexanecarbonitrile)
ADDP	= 1,1'-(azodicarbonyl)dipiperidine
AIBN	= 2,2'-azo bis(isobutyronitrile)
Am	= amyl
Ar	= aryl
ATRA	= atom transfer radical addition
Bn	= benzyl
BnCl <sub>2</sub>	= 2,4-dichlorobenzyl
Boc	= <i>tert</i> -butoxycarbonyl
BPO	= benzoyl peroxide
BT	= 1,3-benzothiazol-2-yl
BTFP	= 3,5-bis(trifluoromethyl)phenyl
BTPP	= <i>tert</i> -butylimino-tri(pyrrolidino)phosphorane
Bu	= butyl
Bz	= benzoyl
CAN	= cerium ammonium nitrate
Cbz	= benzyloxycarbonyl
DABCO	= 1,4-diazabicyclo[2.2.2]octane
DAST	= <i>N,N</i> -diethylaminosulfur trifluoride
DBU	= 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	= 1,2-dichloroethane
Deoxo-Fluor	= bis(2-methoxyethyl)aminosulfur trifluoride
DIAD	= diisopropyl azodicarboxylate
DMA	= <i>N,N</i> -dimethylacetamide
DMAc	= <i>N,N</i> -dimethylacetamide
DMAP	= 4-dimethylaminopyridine
DME	= 1,2-dimethoxyethane
DMF	= dimethylformamide
DMSO	= dimethyl sulfoxide
DTBMP	= 2,6-di- <i>tert</i> -butyl-4-methylpyridine
EDG	= electron donating group
ESR	= electron spin resonance
Et	= ethyl
EWG	= electron withdrawing group
FBSM	= fluorobis(phenylsulfonyl)methane
Fluolead	= 4- <i>tert</i> -butyl-2,6-dimethylphenylsulfur trifluoride
FNSM	= $\alpha$ -fluoro- $\alpha$ -nitro-(phenylsulfonyl)methane
Het	= heteroaryl
HMPA	= hexamethylphosphoramide
IBX	= 2-iodylbenzoic acid
KHMDS	= potassium hexamethyldisilazide
LDA	= lithium diisopropylamide
LiHMDS	= lithium hexamethyldisilazide
LTMP	= lithium 2,2,6,6-tetramethylpiperidine
MDFA	= methyl fluorosulfonyldifluoroacetate
Me	= methyl
MOST	= morpholinosulfur trifluoride
Ms	= methanesulfonyl (or mesyl)
NaHMDS	= sodium hexamethyldisilazide
NCS	= <i>N</i> -chlorosuccinimide
NHC	= <i>N</i> -heterocyclic carbene
Nphth	= phthalimido
Nu	= nucleophile
P <sub>2</sub> -Et	= tetramethyl(tris(dimethylamino)-phosphoranylidene)phosphorictriimid-Et-imin
PBSF	= perfluorobutanesulfonyl fluoride
P <sub>1</sub> - <i>t</i> -Bu	= <i>tert</i> -butylimino-tris(dimethylamino)phosphorane
Ph	= phenyl
Pr	= propyl
PT	= 1-phenyl-1 <i>H</i> -tetrazol-5-yl

Py = pyridyl  
 PYP = 2-pyrimidinyl  
 R<sub>f</sub> = perfluoroalkyl or polyfluoroalkyl  
 SET = single-electron transfer  
 TASF = tris(dimethylamino)sulfonium difluorotrimethylsilylate  
 TBAF = tetrabutylammonium fluoride  
 TBAT = tetrabutylammonium triphenyldifluorosilicate  
 TBHP = *tert*-butyl hydroperoxide  
 TBS = *tert*-butyldimethylsilyl  
 TBT = 1-*tert*-butyl-1*H*-tetrazol-5-yl  
 Tc = thiophene-2-carbonyloxy  
 TES = triethylsilyl  
 Tf = trifluoromethanesulfonyl (or triflyl)  
 TFA = trifluoroacetic acid  
 TFAA = trifluoroacetic anhydride  
 TFDA = trimethylsilyl (fluorosulfonyl)difluoroacetate  
 THF = tetrahydrofuran  
 TMEDA = tetramethylethylenediamine  
 Tmob = 2,4,6-trimethoxybenzyl  
 TMS = trimethylsilyl  
 Ts = 4-toluenesulfonyl (or tosyl)  
 XtalFluor-E = (diethylamino)difluorosulfonium tetrafluoroborate  
 XtalFluor-M = difluoro(morpholino)sulfonium tetrafluoroborate

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