

# A Fruitful Decade of Organofluorine Chemistry: New Reagents and Reactions

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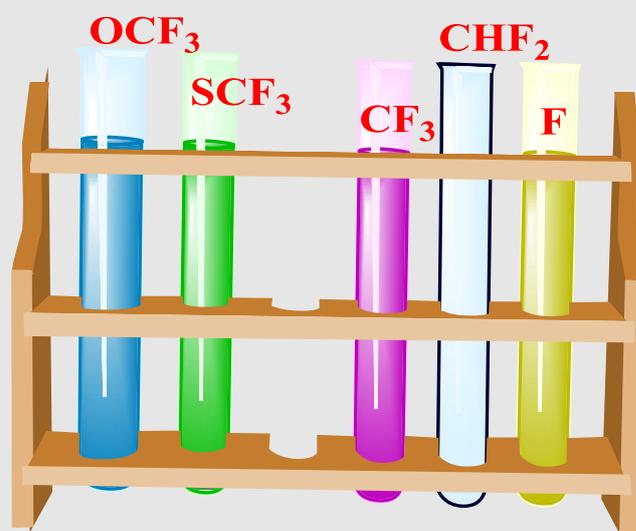
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The development of synthetic methods for the introduction of the fluorine atom and fluoroalkyl groups into organic molecules has gained increased attention. Synthetic organic chemists have recently jumped into the field of organofluorine chemistry and have thus made significant contributions. Furthermore, these newly developed methods are typically safer and more effective than the traditional methods. In this review, we will summarize the representative contributions of new reagents and reactions developed in the past decade.



**Keywords:** fluorination, fluoroalkylation, reagent, reaction, fluorine chemistry

## Introduction

The fluorine atom is very small, and fluorine is the most electronegative element in the periodic table. Consequently, with a short bond length and high bond dissociation energy, the C–F bond is one of the strongest covalent single bonds.<sup>1</sup> The incorporation of a fluorine atom into a

compound has a significant electronic consequence and can greatly change the physicochemical properties, such as metabolic stability, lipophilicity, and permeability. Owing to this unique property, fluorinated compounds have found widespread application in the preparation of pharmaceuticals, agrochemicals, and materials. It has been estimated that approximately 20% of pharmaceuticals

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and 50% of agrochemicals contain one or more fluorine atoms.<sup>2</sup> In addition, <sup>18</sup>F-labeled molecules are frequently used as imaging probes in positron emission tomography for diagnosis,<sup>3</sup> an important tool to track many diseases at an early stage of development.

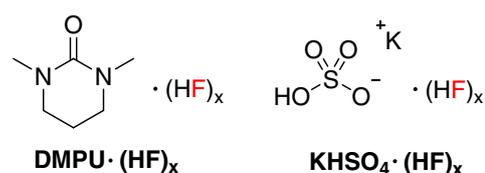
Although fluorine is abundant on Earth, it exists mainly in the form of inorganic calcium fluoride (CaF<sub>2</sub>), known as fluorite or flourspar. Due to the inert reactivity of CaF<sub>2</sub>, Nature has hardly evolved a biosynthesis of fluorinated compounds. Therefore, natural products containing at least one fluorine atom are virtually nonexistent, albeit with occasional occurrence.<sup>4</sup> And almost all organofluorine compounds used in academia and industry have been synthesized by chemists, thanks to the successful reaction of CaF<sub>2</sub> with a strong acid, which provides hydrofluoric acid (HF) as a viable fluorine source. Accordingly, many fluorination reagents have been developed, ranging from those corrosive reagents that were developed in early times to the recently developed bench-stable reagents. At the same time, synthetic methods based on nucleophilic, electrophilic, or radical strategies for selective fluorination and fluoroalkylation on many functionalities have also been disclosed. In particular, the advance of transition metal catalysis, photoredox catalysis, and electrochemical catalysis have driven the burgeoning development of fluorination reagents and reactions in the past decade. This review is organized into two parts: new reagents and new reactions. We will focus on the most recent and representative contributions of reagents and synthetic methods for fluorination, monofluoroalkylation, difluoroalkylation, trifluoromethylation, trifluoromethylthiolation, trifluoromethoxylation, defluorofunctionalization, and so on. We regret that many excellent works were not included because of space limitation.

## New Fluorinating and Fluoroalkylating Reagents

### Fluorinating reagents

#### Nucleophilic fluorinating reagents

The commonly used nucleophilic fluorinating reagents include metal fluoride salts (KF, CsF, and AgF), HF-based reagents (Et<sub>3</sub>N·3HF and pyridine·9HF),



**Figure 1** | New nucleophilic fluorinating reagents.

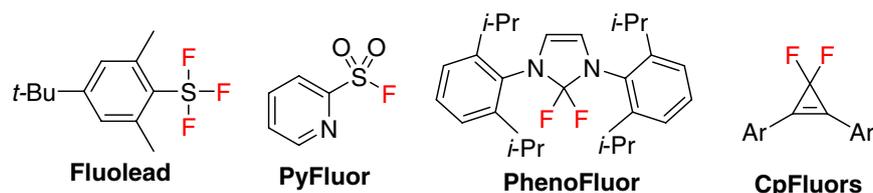
tetraalkylammonium fluorides, and fluorinated hypervalent silicates. Over the past decade, several types of new nucleophilic fluorinating reagents have been developed (Figure 1). Hammond et al. reported two novel HF-based reagents, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)·(HF)<sub>x</sub> and KHSO<sub>4</sub>·(HF)<sub>x</sub>.<sup>5,6</sup>

#### Deoxyfluorinating reagents

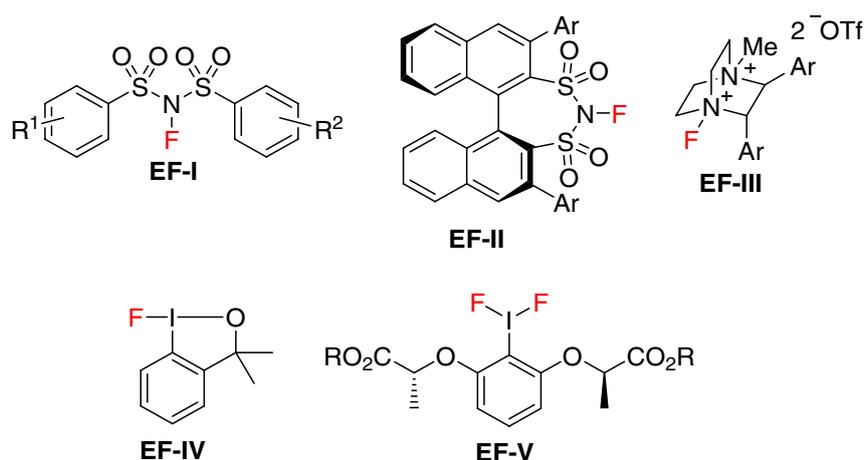
The deoxyfluorination reactions typically proceed through in situ activation of the hydroxyl group followed by nucleophilic substitution with a fluoride. Classic deoxyfluorinating reagents include SF<sub>4</sub> and its derivatives (e.g., diethylaminosulphur trifluoride (DAST), DeoxyFluor, and XtalFluor). In 2010, Umemoto et al. discovered 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead) as a deoxyfluorinating agent with high thermal stability and unusual resistance to aqueous hydrolysis (Figure 2).<sup>7</sup> 2-Pyridinesulfonyl fluoride (PyFluor) was developed by Doyle et al. as an inexpensive and thermally stable deoxyfluorinating reagent.<sup>8</sup> In 2011, Ritter et al. reported a new deoxyfluorinating reagent PhenoFluor.<sup>9</sup> In 2017, Hu et al. reported the use of 3,3-difluoro-1,2-diarylcyclopropenes (CpFluors) as a class of novel deoxyfluorinating reagents with an all-carbon scaffold.<sup>10</sup>

#### Electrophilic fluorinating reagents

The appearance of commercially available and easy-to-handle electrophilic fluorinating reagents including *N*-fluorobenzenesulfonimide (NFSI), Selectfluor, *N*-fluoropyridinium salts (NFPY), and ArIF<sub>2</sub> has brought a breakthrough in synthetic fluorine chemistry. Over the past decade, a series of new electrophilic fluorinating reagents have been developed (Figure 3). Shibata et al. and Yang et al. independently reported the



**Figure 2** | New deoxyfluorinating reagents.



**Figure 3** | New electrophilic fluorinating reagents.

synthesis of substituted *N*-fluorobenzenesulfonimide (NFSI) derivatives (**EF-I**).<sup>11,12</sup> The chiral analogs of NFSI (**EF-II**) based on the C<sub>2</sub>-symmetric chiral binaphthyl bis (sulfonimide) topology as a privileged motif were initially reported by Cahard et al.<sup>13</sup> Gouverneur et al. prepared a new class of chiral electrophilic fluorinating reagents **EF-III**, based on the dicationic structural core of Selectfluor.<sup>14</sup> In 2013, Stuart et al. reported an air- and moisture-stable cyclic hypervalent iodine-based electrophilic fluorinating reagents **EF-IV**.<sup>15</sup> Nevado et al. synthesized chiral iodine (III) reagents **EF-V**.<sup>16</sup>

reported trifluoromethyl-substituted sulfonium ylide as the electrophilic trifluoromethylating reagents (**ETF-I**) (Figure 4).<sup>17</sup> In 2017, Umemoto et al. reported powerful, thermally stable, one-pot-preparable and recyclable second-generation Umemoto's reagents (**Umemoto reagents II**).<sup>18</sup> In 2021, Ritter et al. described the Umemoto type reagent trifluoromethyl thianthrenium triflate (TT-CF<sub>3</sub><sup>+</sup>OTf<sup>-</sup>, **ETF-III**). TT-CF<sub>3</sub><sup>+</sup>OTf<sup>-</sup> that could serve not only as a competent electrophilic or a radical trifluoromethylating reagent but also as a nucleophilic trifluoromethylating reagent.<sup>19</sup>

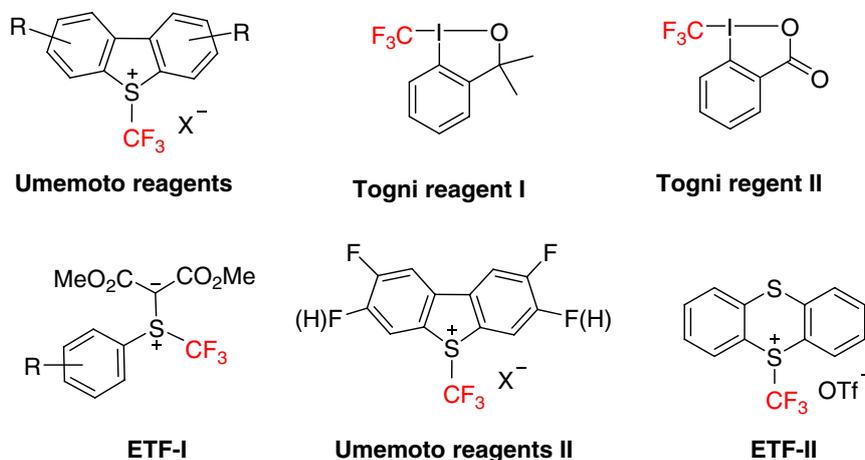
## Trifluoromethylating reagents

### Electrophilic trifluoromethylating reagents

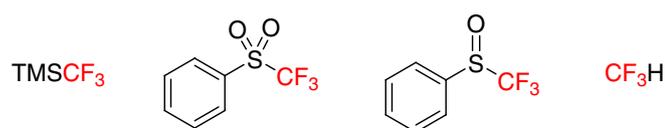
(Trifluoromethyl)dibenzothiophenium salts (**Umemoto reagents**) and 1-trifluoromethyl-3,3-dimethyl-1,2-benziodoxole or 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (**Togni reagents I and II**) are widely used as the electrophilic trifluoromethylating reagents. In 2015, Shen et al.

### Nucleophilic trifluoromethylating reagents

The most studied nucleophilic trifluoromethylating reagent was TMSCF<sub>3</sub> (Figure 5), the so-called Ruppert-Prakash reagent. PhSO<sub>2</sub>CF<sub>3</sub> and PhSOCF<sub>3</sub> can also serve as nucleophilic trifluoromethylating reagents in the presence of an alkoxide. Fluoroform (CF<sub>3</sub>H) can also serve as a nucleophilic trifluoromethylating reagent. In



**Figure 4** | Electrophilic trifluoromethylating reagents.



**Figure 5** | Nucleophilic trifluoromethylating reagents.

2011, Grushin et al. reported the reaction of  $\text{CF}_3\text{H}$  with  $\text{CuCl}/\text{KO}^t\text{Bu}$  in dimethylformamide (DMF) to give stable  $\text{CuCF}_3$  after treatment with  $\text{Et}_3\text{N}\cdot 3\text{HF}$  or  $\text{Py}\cdot n\text{HF}$ .<sup>20</sup>

### Radical trifluoromethylating reagents

Even though electrophilic trifluoromethylating reagents can serve as a trifluoromethyl radical precursor under certain conditions, several types of radical trifluoromethylating reagents have been developed (Figure 6). The gaseous nature of trifluoroiodomethane makes it difficult to be used efficiently. Ritter et al. found that 1:1 adduct of  $\text{CF}_3\text{I}$  and tetramethylguanidine (TMG) forms a stable liquid  $\text{TMG}\cdot\text{CF}_3\text{I}$ , which acted as a radical trifluoromethyl reagent.<sup>21</sup> Derivative of triflic acid or trifluoroacetic acid can also serve as trifluoromethyl radical precursor. One of the most studied radical trifluoromethyl reagents is  $\text{CF}_3\text{SO}_2\text{Na}$  (Langlois' reagent). Trifluoromethanesulfonyl chloride ( $\text{CF}_3\text{SO}_2\text{Cl}$ ) can also be used as a radical trifluoromethyl reagent<sup>22</sup> while trifluoromethane anhydride ( $\text{CF}_3\text{SO}_2)_2\text{O}$ ) has also been reported to be used as trifluoromethyl radical precursor by merging photoredox catalysis and pyridine activation.<sup>23</sup> Baran et al. described that  $(\text{CF}_3\text{SO}_2)_2\text{Zn}$  was a more efficient radical

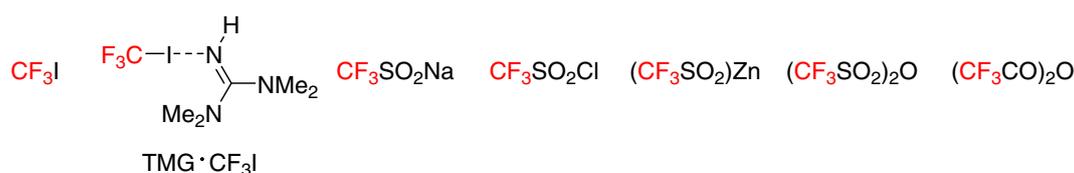
trifluoromethylating reagent.<sup>24</sup> Trifluoroacetic anhydride can serve as a trifluoromethyl radical reagent in the presence of pyridine *N*-oxide under irradiation of blue light in combination with a photoredox catalyst.<sup>25</sup>

### Difluoromethylating reagents

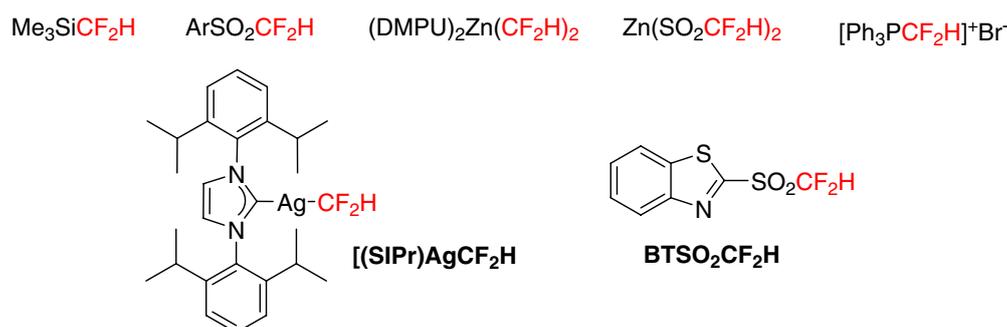
Among all nucleophilic difluoromethylating reagents,  $\text{Me}_3\text{SiCF}_2\text{H}$  (Figure 7) is currently the most used nucleophilic difluoromethylating source. Difluoromethyl aryl sulfone ( $\text{ArSO}_2\text{CF}_2\text{H}$ ) is a good alternative choice. In 2015, Shen et al. reported a thermally stable and well-defined NHC-ligated difluoromethylated silver complex  $[(\text{SIPr})\text{Ag}(\text{CF}_2\text{H})]$  which could be used in transition metal-mediated or -catalyzed difluoromethylating reactions.<sup>26</sup> An isolable and user-friendly zinc difluoromethyl reagent  $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$  was developed by Xu and Vicić.<sup>27</sup> In 2012, Baran et al. reported the invention of a novel radical reagent  $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$  that was an air-stable and free-flowing white powder.<sup>28</sup> Qing et al. disclosed that (difluoromethyl)triphenylphosphonium bromide ( $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ ) might be the most readily available and easily handled radical difluoromethylating reagent under visible-light photoredox conditions.<sup>29</sup> Hu et al. found that 2-[(difluoromethyl)sulfonyl]benzo[d]thiazole (**2-BT $\text{SO}_2\text{CF}_2\text{H}$** ) was used as the precursor of the difluoromethyl radical by visible-light photoredox catalysis.<sup>30</sup>

### Monofluoromethylating reagents

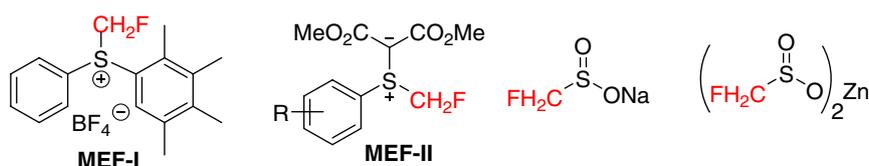
In 2008, Prakash et al. reported the first shelf-stable yet highly reactive electrophilic monofluoromethylating



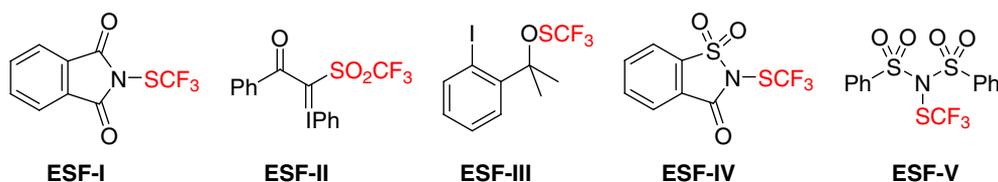
**Figure 6** | Radical trifluoromethylating reagents.



**Figure 7** | Difluoromethylating reagents.



**Figure 8** | Monofluoromethylating reagents.



**Figure 9** | Electrophilic trifluoromethylthiolating reagents.

reagent *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**MEF-I**) (Figure 8).<sup>31</sup> Shen et al. reported the electrophilic monofluoromethylating reagents based on sulfonium ylide skeleton (**MEF-II**).<sup>32</sup> In addition, two radical monofluoromethylating reagents  $\text{CH}_2\text{FSO}_2\text{Na}$  and  $(\text{CH}_2\text{FSO}_2)_2\text{Zn}$  have been reported by Hu et al.<sup>33</sup> and Baran et al.<sup>24</sup> respectively.

## Trifluoromethylthiolating reagents

### Electrophilic trifluoromethylthiolating reagents

Before 2010, the electrophilic trifluoromethylthiolating reagent *N*-(trifluoromethylthio)phthalimide (**ESF-I**, Munavalli reagent) was developed (Figure 9).<sup>34</sup> In early 2013, Shibata et al. reported a hypervalent iodonium ylide skeleton-based electrophilic trifluoromethylthiolating reagent (**ESF-II**).<sup>35</sup> In 2013, Shen et al. also reported a new electrophilic trifluoromethylthiolating reagent (**ESF-III**, Lu-Shen reagent).<sup>36</sup> Later *N*-trifluoromethylthiosaccharin (**ESF-IV**, Shen reagent)<sup>37</sup> showcased unparalleled high electrophilicity. Furthermore, *N*-trifluoromethylthio bis(phenylsulfonyl)imide (**ESF-V**, Shen reagent II) remarkably showed much higher electrophilicity.<sup>38</sup>

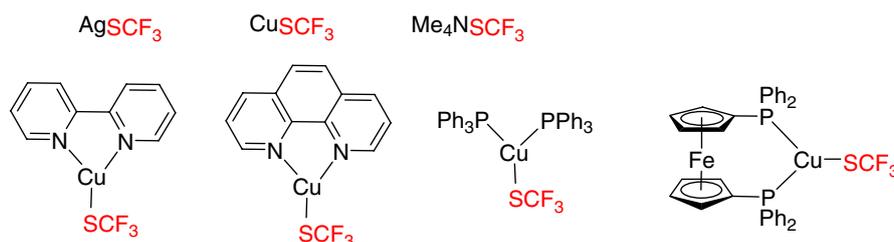
### Nucleophilic trifluoromethylthiolating reagents

$\text{AgSCF}_3$  and  $\text{CuSCF}_3$  as well as  $\text{Me}_4\text{NSCF}_3$  were widely used as the nucleophilic trifluoromethylthio sources (Figure 10). In 2012, Weng et al. reported the two stable nucleophilic trifluoromethylthiolating reagents (L) $\text{CuSCF}_3$  (L = 2,2-bipyridine (bpy) and 1,10-phenanthroline (phen)).<sup>39</sup> Likewise, in 2015, Vicic et al. also prepared two stable trifluoromethylthiolated copper(I) complexes  $(\text{Ph}_3\text{P})_2\text{CuSCF}_3$  and  $(\text{dppf})\text{CuSCF}_3$  as nucleophilic reagents.<sup>40</sup>

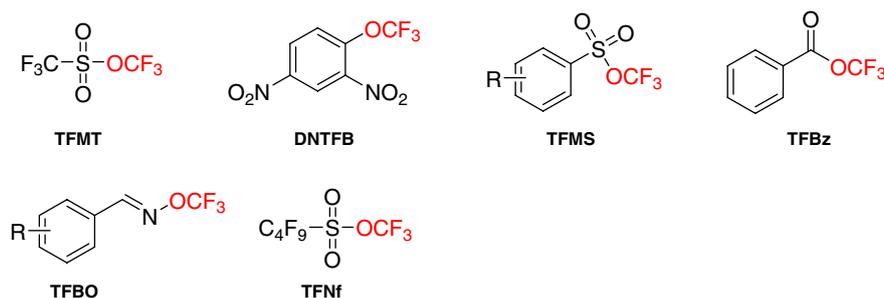
## Trifluoromethoxylating reagents

### Nucleophilic trifluoromethoxylating reagents

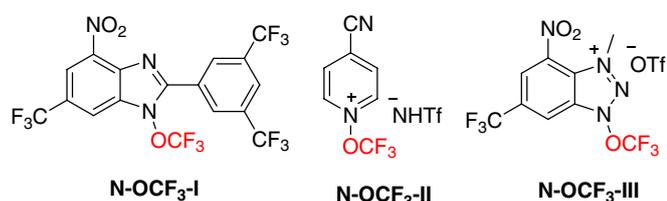
In 2007, Kolomeitsev et al. discovered that trifluoromethyl trifluoromethanesulfonate (**TFMT**, Figure 11) could generate  $\text{CF}_3\text{O}^-$  anion when treated with hard nucleophilic fluoride. In 2010, Langlois et al. found that 2,4-dinitro (trifluoromethoxy)benzene (**DNTFB**) could be used as a new precursor of trifluoromethoxide anion. Jiang and Tang discovered that trifluoromethyl sulfonates (**TFMS**) could be activated to release  $\text{CF}_3\text{O}^-$  in the presence of fluoride anions.<sup>41</sup> Hu et al. developed a new and practical



**Figure 10** | Nucleophilic trifluoromethylthiolating reagents.



**Figure 11** | Nucleophilic trifluoromethoxylating reagents.



**Figure 12** | Radical trifluoromethoxylating reagents.

trifluoromethoxylation reagent trifluoromethyl benzoate (**TFBz**).<sup>42</sup> In 2019, Tang et al. reported a new nucleophilic trifluoromethoxylating reagent (*E*)-*O*-trifluoromethylbenzaldoximes (**TFBO**).<sup>43</sup> Umemoto et al. discovered that trifluoromethyl nonafluorobutanesulfonate (**TFNF**) was a reactive trifluoromethoxylating reagent with a high boiling point.<sup>44</sup>

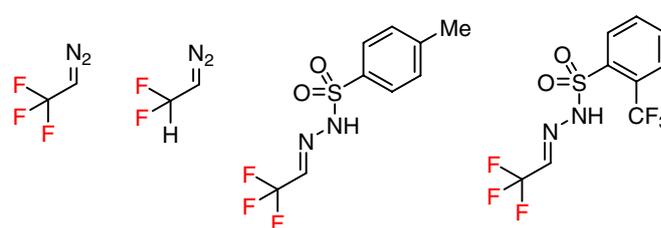
### Radical trifluoromethoxylating reagents

In 2018, Ngai et al. identified a benzimidazole bearing the  $N\text{-OCF}_3$  moiety as a novel radical trifluoromethoxylating reagent under irradiation of blue LED (**N-OCF<sub>3</sub>-I**, Figure 12).<sup>45</sup> Togni et al. also discovered that trifluoromethoxypyridinium salt (**N-OCF<sub>3</sub>-II**) was also a radical trifluoromethoxylating reagent under the irradiation of blue light.<sup>46</sup> Furthermore, Ngai et al. found that *N*-trifluoromethoxy triazolium salt (**N-OCF<sub>3</sub>-III**) favors the selective generation of a single  $\text{OCF}_3$  radical species after the single electron transfer (SET) reduction.<sup>47</sup>

### Fluorinated carbene (difluorocarbene) reagents

#### Fluoromethyl diazo and hydrazone reagents

Di- and trifluorodiazaoethane ( $\text{XCF}_2\text{CHN}_2$ ,  $\text{X} = \text{F}, \text{H}$ ) is an attractive precursor of  $\text{XCF}_2\text{CH}$ : carbene (Figure 13). In 2010, Morandi and Carreira disclosed the in situ generation of 2,2,2-Trifluorodiazaoethane ( $\text{CF}_3\text{CHN}_2$ ) in a mixture of water and organic solvents.<sup>48</sup> In 2012, Ma et al.



**Figure 13** | Fluoroalkyl diazo and hydrazone reagents.

developed a flow setup for the continuous gaseous  $\text{CF}_3\text{CHN}_2$  generation/transformation sequence.<sup>49</sup> Subsequently, Mykhailiuk<sup>50</sup> and Ma et al.<sup>51</sup> described the preparation of difluoromethyldiazo reagents. Zhang et al. took advantage of trifluoroacetaldehyde toluenesulfonylhydrazone for the in situ formation of  $\text{CF}_3\text{CHN}_2$ .<sup>52</sup> Bi et al. established trifluoroacetaldehyde *N*-trifluoromethylhydrazones as bench-stable crystalline precursor to  $\text{CF}_3\text{CHN}_2$ .<sup>53</sup>

#### Difluorocarbene reagents

Difluorocarbene can be generated from many available and stable precursors. The earlier studies in this area focused on the use of environmentally unfriendly or toxic reagents [such as  $\text{CHXF}_2$ ,  $\text{CX}_2\text{F}_2$  ( $\text{X} = \text{Cl}, \text{Br}$ ),  $\text{Me}_3\text{SnCF}_3$ , or  $\text{PhHgCF}_3$ ]. To overcome this problem, recent research has paid more attention to new surrogate molecules. Hu et al. has centered on the development of (halodifluoromethyl) trimethylsilanes and difluoromethyltri(*n*-butyl)ammonium chloride (Figure 14) for the generation of difluorocarbene.<sup>54–56</sup> Lin and Xiao demonstrated that the reaction of  $\text{BrCF}_2\text{CO}_2\text{K}$  and  $\text{Ph}_3\text{P}$  could smoothly afford the difluorocarbene precursor  $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$  ((triphenylphosphonio)difluoroacetate, PDFA).<sup>57</sup> Chen et al. found that difluoromethanesulfonyl fluoride ( $\text{HCF}_2\text{SO}_2\text{F}$ ) and difluoromethanesulfonic acid ( $\text{HCF}_2\text{SO}_3\text{H}$ ) could serve as difluorocarbene precursors. Subsequently, the corresponding fluorosulfonyldifluoroacetic acid ( $\text{FSO}_2\text{CF}_2\text{CO}_2\text{H}$ ) and its derivatives ( $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}$  and  $\text{FSO}_2\text{CF}_2\text{CO}_2\text{TMS}$ ) were directly used as difluorocarbene precursors.<sup>58</sup>

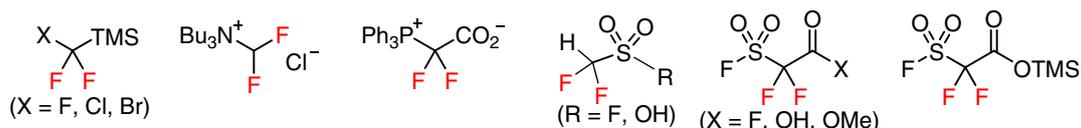


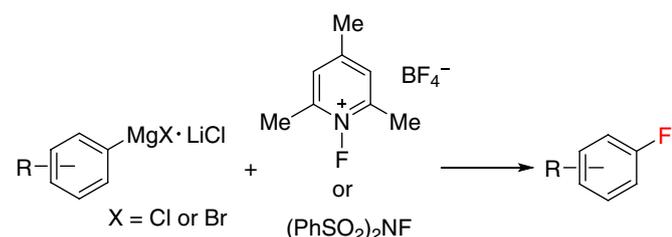
Figure 14 | Difluorocarbene reagents.

## New Fluorination and Fluoroalkylation Reactions

### Electrophilic fluorination and fluoroalkylation reactions

#### Fluorination

Aryl fluoride represents one of the most important structural motifs that is frequently found in many drug molecules. Classic methods for the preparation of aryl fluorides typically rely on the Balz-Schiemann reaction of aryl diazonium salts. An alternative and straightforward approach for the preparation of aryl fluorides is direct fluorination of aryl metal species with an



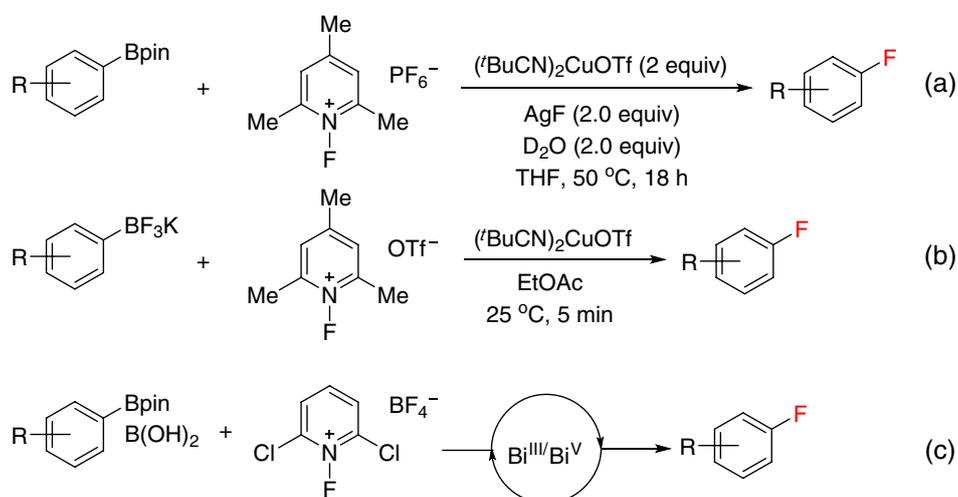
Scheme 1 | Aryl fluoride formation from Grignard reagents.

electrophilic reagent. In 2010, Knochel et al.<sup>59</sup> and Beller et al.<sup>60</sup> independently reported reactions of (hetero)aryl magnesium reagents with NFSI or *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (F-TMP-BF<sub>4</sub>) to give the corresponding (hetero)aryl fluorides in high yields (Scheme 1).

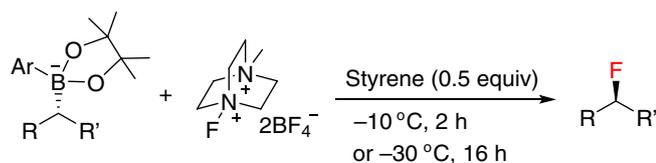
In 2013, Hartwig et al. described the first copper-mediated fluorination of arylboronate esters using F-TMP-BF<sub>4</sub> as the electrophilic fluorine source (Scheme 2a).<sup>61</sup> Shortly afterward, Ye and Sanford reported a similar process using *N*-fluoro-2,4,6-trimethylpyridinium triflate as the electrophilic fluorine source for direct fluorination of aryl trifluoroborates (Scheme 2b).<sup>62</sup> In 2020, Cornella et al. reported a bismuth-catalyzed direct fluorination of aryl boronic acids as well as aryl boronic esters using *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate as the electrophilic fluorine source (Scheme 2c).<sup>63</sup>

Aggarwal et al. reported that “ate”-type lithium aryl alkyl boronate complexes reacted efficiently with Selectfluor in the presence of styrene to give stereospecific alkyl fluorides with inversed configuration (Scheme 3).<sup>64</sup> It was proposed that the reaction proceeds via a polar S<sub>E</sub>2<sub>inv</sub> pathway, and the role of styrene is to act as a radical scavenger to prohibit the SET pathway.

An alternative approach to using an electrophilic fluorinating reagent is transition metal-catalyzed C-H fluorination. The first palladium-catalyzed directed arene *ortho* C-H bond fluorination was reported by



Scheme 2 | Aryl fluoride formation from aryl boronic acids and derivatives.



**Scheme 3** | Preparation of alkyl fluorides.

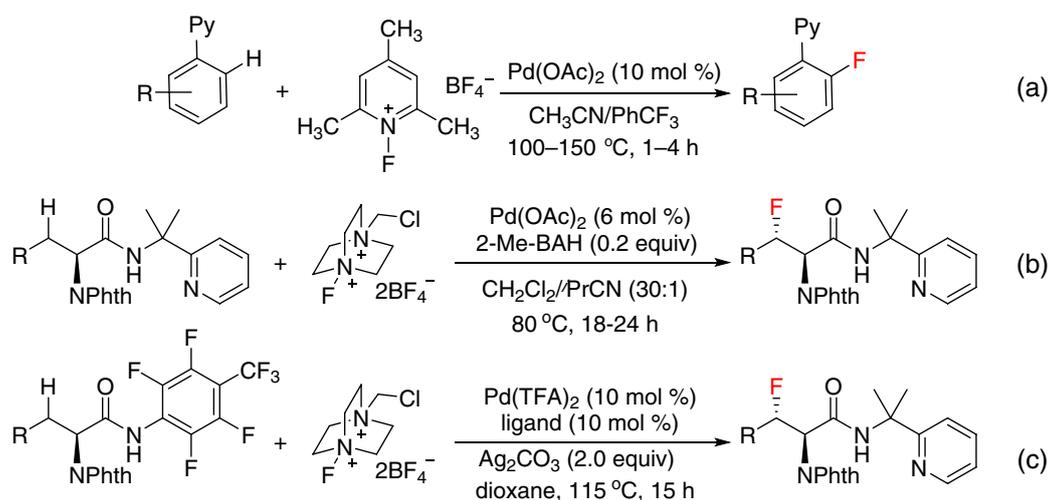
Sanford et al. in 2006 (Scheme 4a).<sup>65</sup> In 2015, Shi et al. (Scheme 4b)<sup>66</sup> and Yu et al. (Scheme 4c)<sup>67</sup> independently reported a Pd-catalyzed substrate-controlled methods for diastereoselective C(sp<sup>3</sup>)-H fluorination.

### Trifluoromethylation

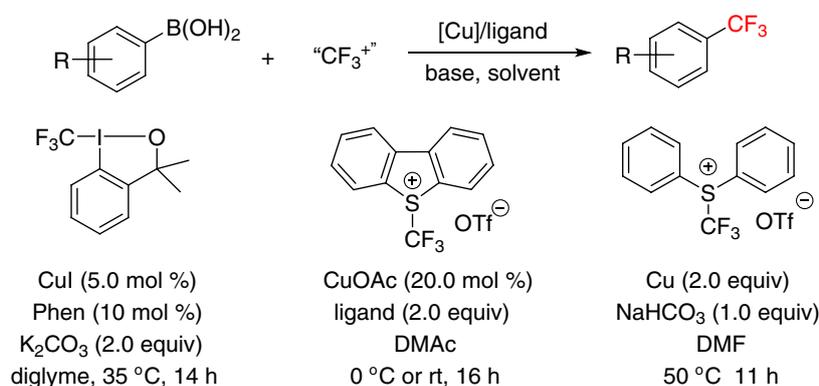
Trifluoromethylated (hetero)arenes are important structural motifs in drug molecules. Transition metal-catalyzed coupling of a nucleophilic aryl reagent with an

electrophilic trifluoromethylating reagent represents a general approach for the preparation of such compounds. In 2011, Shen, Liu and Xiao independently reported three copper-mediated trifluoromethylation of aryl boronic acids with an electrophilic trifluoromethylating reagent (Scheme 5).<sup>68</sup>

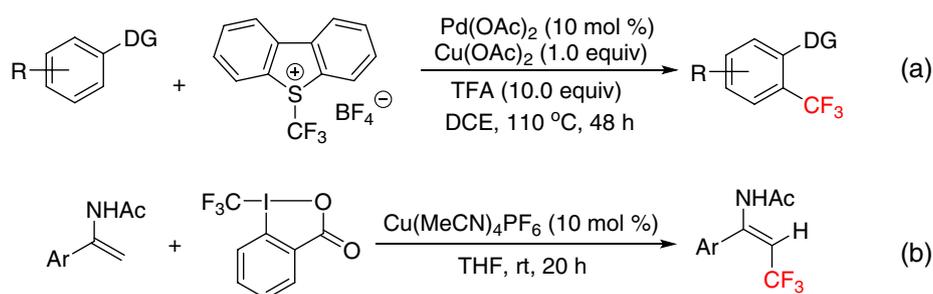
In 2010, Yu et al. reported the first Pd(OAc)<sub>2</sub>/Cu(OAc)<sub>2</sub> catalyzed *ortho*-C-H trifluoromethylation of arenes using pyridyl, pyrimidinyl, or thiazole as the directing group and (trifluoromethyl)dibenzothiophenium tetrafluoroborate salt as the electrophilic trifluoromethylating reagent (Scheme 6a).<sup>69</sup> Not only aromatic C-H bonds but olefinic C-H bonds can be trifluoromethylated by an electrophilic trifluoromethylating reagent. In 2012, Feng and Loh found initially that reactions of *N*-(1-phenylvinyl)acetamide with Togni's reagent II in the presence of 10 mol % Cu(MeCN)<sub>4</sub>PF<sub>6</sub> occurred smoothly to give the *trans*-trifluoromethylated alkenes in good yields (Scheme 6b).<sup>70</sup>



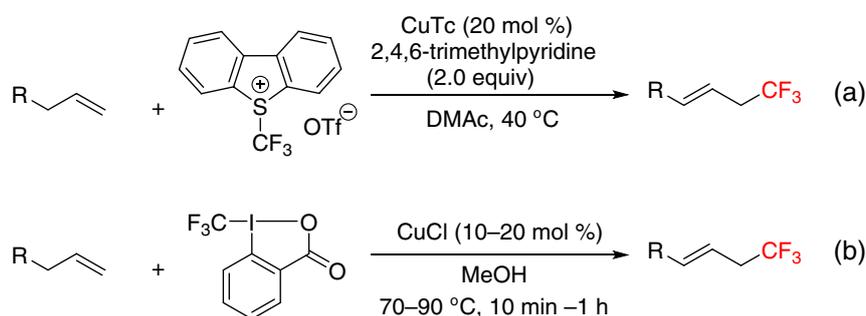
**Scheme 4** | Pd-catalyzed directed C-H fluorination.



**Scheme 5** | Copper-mediated trifluoromethylation of aryl boronic acids.



**Scheme 6** | *C-H trifluoromethylation.*

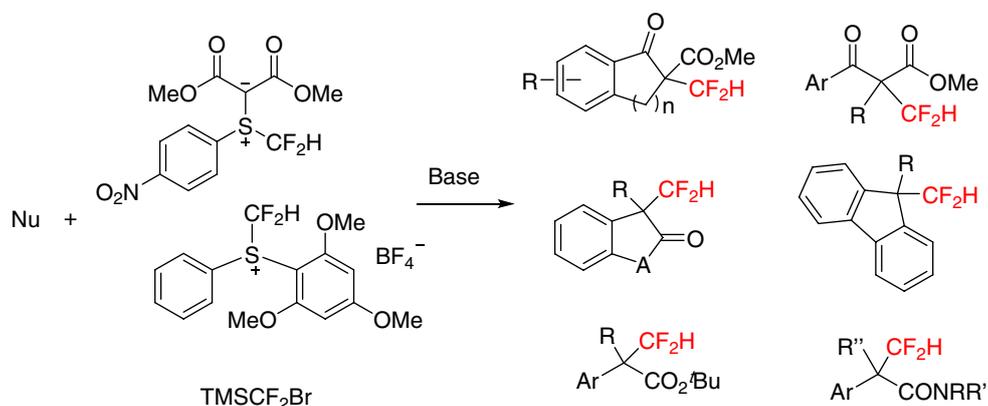


**Scheme 7** | *Cu-catalyzed allylic C-H trifluoromethylation.*

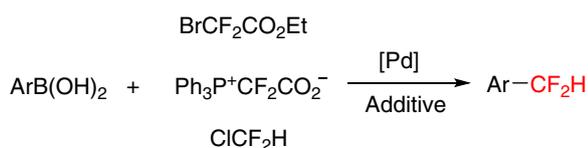
The allylic C-H bond also underwent C-H activation/trifluoromethylation, as the groups of Liu and Wang reported simultaneously in 2011. In Liu et al.'s protocol, terminal alkenes reacted with Umemoto's reagent to give the trifluoromethylated products in high yields (Scheme 7a).<sup>71</sup> Mechanistically, it was proposed that the reaction proceeds via a Heck-like four-membered-ring transition state. Likewise, Wang et al. reported the similar allylic trifluoromethylation with Togni' reagent in good to excellent yields (Scheme 7b).<sup>72</sup>

### Difluoromethylation

The direct introduction of the difluoromethyl group into organic molecules has been realized using the in situ-generated electrophilic difluorocarbene. The highly selective C-difluoromethylation of  $\beta$ -ketoesters was first reported in 2018 by Shen et al.<sup>73</sup> using an isolated shelf-stable difluoromethyl-substituted ylide as difluoromethylating source and using  $\text{Li}_2\text{CO}_3$  or  $\text{LiO}^t\text{Bu}$  as the base (Scheme 8). Mechanistic studies showed that the reaction occurred via a difluorocarbene intermediate,



**Scheme 8** | *C-selective difluoromethylation of soft carbon nucleophiles.*



**Scheme 9** | Pd-catalyzed difluoromethylation of aryl boronic acids.

and the lithium cation played an important role in alleviation of the nucleophilicity of the oxygen in the enolate. Likewise, in 2019, Liu et al. and Hu et al. reported that using *S*-(difluoromethyl)-*S*-phenyl-*S*-(2,4,6-trialkoxoxyphenyl) sulfonium salt<sup>74</sup> and  $\text{TMSCF}_2\text{Br}$ ,<sup>75</sup> respectively, as the difluorocarbene precursor could also achieve highly C-selective difluoromethylation of various soft carbon nucleophiles (Scheme 8).

Transition metal catalysis could also mediate the coupling of a nucleophile such as boronic acid with the in situ-generated difluorocarbene. Zhang et al. reported in 2016 that palladium-catalyzed coupling of aryl boronic acids with  $\text{BrCF}_2\text{CO}_2\text{Et}$ , a difluorocarbene precursor, reacted smoothly to give difluoromethylated arenes in good yields (Scheme 9).<sup>76</sup> Shortly thereafter, Xiao et al. reported a similar reaction, in which  $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$  (PDFA) was used as the difluorocarbene precursor.<sup>77</sup> In 2017, Zhang et al. improved such reaction by using  $\text{HCF}_2\text{Cl}$  as the difluorocarbene precursor.<sup>78</sup>

### Monofluoromethylation

The monofluoromethyl group is a hard electrophile, and the direct reaction of soft carbon nucleophiles with an electrophilic monofluoromethyl reagent often gives *o*-monofluoromethylated products. In 2017, Shen et al. discovered that a monofluoromethyl sulfonium ylide was able to react with soft carbon nucleophile malonates to give C-monofluoromethylated products in excellent yields (Scheme 10).<sup>32</sup> Likewise, Liu et al. found that *S*-(monofluoromethyl)-*S*-phenyl-*S*-(2,4,6-trimethoxyphenyl) sulfonium

salt is also a highly reactive electrophilic monofluoromethylating reagent which reacts with malonates, tetrahydroquinolinone carboxylate, and pyrrolidinone carboxylate to give C-monofluoromethylated products in excellent yields.<sup>79</sup>

### Trifluoromethylthiolation

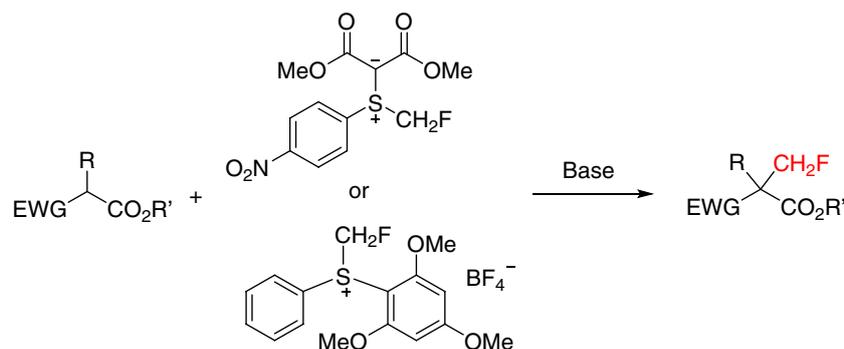
The first copper-catalyzed coupling of aryl boronic acids with an electrophilic trifluoromethylthiolating reagent was reported by Shen et al. in 2013 (Scheme 11).<sup>36</sup> In 2014, Rueping et al.<sup>80</sup> and Shen et al.<sup>81</sup> simultaneously reported a copper-catalyzed trifluoromethylthiolation of aryl boronic acids with *N*-trifluoromethylthiophthalimide (Manuvalli's reagent). In 2015, Billard et al. reported the copper-catalyzed trifluoromethylthiolation of aryl boronic acids with the second-generation Billard's reagent  $\text{TsN(Me)SCF}_3$ .<sup>82</sup>

The first transition metal-catalyzed directed C-H trifluoromethylthiolation was reported by Daugulis using  $\text{CF}_3\text{S-SCF}_3$  as the electrophilic trifluoromethylthiolating reagent (Scheme 12).<sup>83</sup> In 2015, Xu and Shen reported a palladium-catalyzed C-H trifluoromethylthiolation with *N*-trifluoromethylthiosuccinimide.<sup>84</sup> Similarly, Li and Yoshino/Matsunaga reported  $[\text{Cp}^*\text{RhCl}_2]_2$  and  $[\text{Cp}^*\text{Co}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2$  catalyzed directly C-H trifluoromethylthiolation, using Shen's *N*-trifluoromethylthiosaccharin and  $(\text{PhSO}_2)_2\text{NSCF}_3$  as the electrophilic trifluoromethylthiolating source respectively.<sup>85</sup>

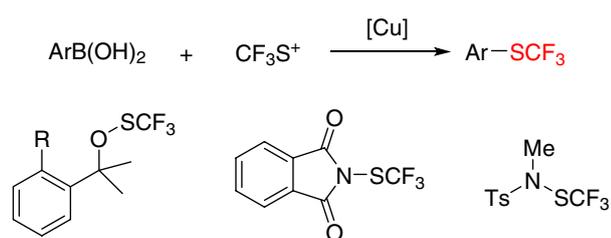
## Nucleophilic fluorination and fluoroalkylation reactions

### Fluorination

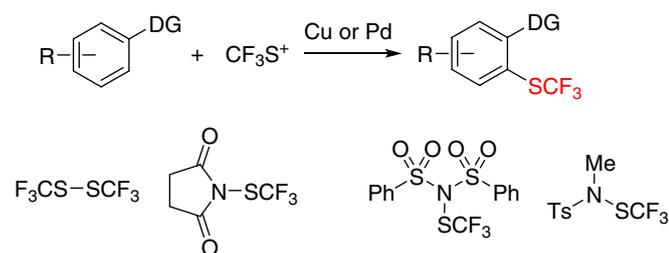
Daugulis et al. reported the first Cu-catalyzed directed C-H fluorination of arenes with  $\text{AgF}$  in combination with the terminal oxidant *N*-methylmorpholine *N*-oxide (Scheme 13a).<sup>86</sup> This C-H fluorination was proposed to possibly proceed through C-F reductive elimination from a high-oxidation-state  $\text{Cu}^{\text{III}}$  fluoride complex. Direct  $\text{sp}^3$  C-H fluorination is an efficient synthesis method



**Scheme 10** | C-selective monofluoromethylation of soft carbon nucleophiles.



**Scheme 11** | Cu-catalyzed trifluoromethylthiolation of aryl boronic acids.



**Scheme 12** | Transition metal-catalyzed C-H trifluoromethylthiolation.

for introducing fluorine atoms into alkanes. In 2012, Groves et al. reported manganese-catalyzed oxidative C-H bond fluorination using AgF (Scheme 13b).<sup>87</sup> This was the first catalytic method for selective and direct incorporation of fluoride ion into the unreactive  $\text{sp}^3$  C-H bond.

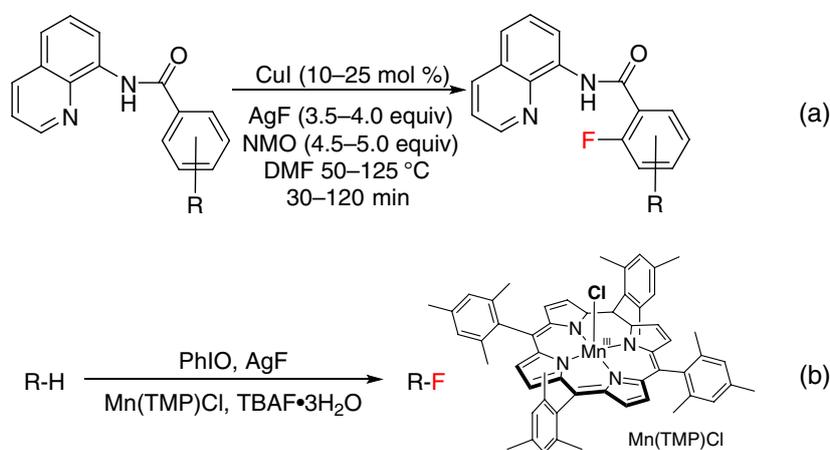
Deoxyfluorination of alcohols has found widespread applications due to the abundance and accessibility of alcohol-containing precursors. However, the traditional use of DAST for deoxyfluorination is limited by the functional group tolerance and formation of the elimination

side products. In 2015, Doyle et al. reported a low-cost and highly thermal stable deoxyfluorination reagent PyFluor for deoxyfluorination of alcohols (Scheme 14a).<sup>8</sup> Phenols are also an ideal starting material for fluorination reactions. In 2011, Ritter et al. developed a new deoxyfluorination reagent PhenoFluor for *ipso*-fluorination of phenols to deliver aryl fluorides in one-step (Scheme 14b).<sup>9</sup>

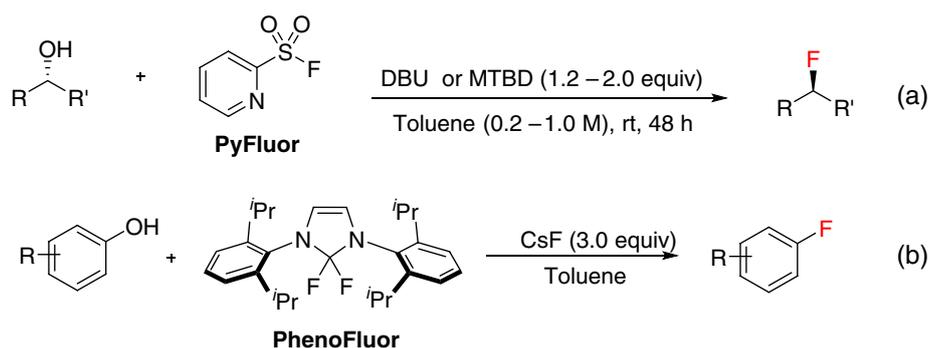
Aryl boron reagents are particularly attractive starting materials for C-F bond-forming reactions. In 2013, Sanford et al. reported a remarkably mild and general fluorination method by Cu-mediated fluorination of aryl-trifluoroborates with potassium fluoride (Scheme 15).<sup>88</sup> It was proposed that the Cu played a dual role in this transformation: first, it serves as a transition metal center to coordinate both the aryl and fluoride ligands; second, it serves as an oxidant to generate the key reactive Cu(III) intermediate.

Ritter et al. developed a photoinduced decarboxylative fluorination of benzoic acid derivatives with fluoride (Scheme 16a).<sup>89</sup> The author proposed that copper has two roles in this reaction: one is to reduce the barrier of photoinduced free radical decarboxylation, and the other is to capture aryl radicals to produce aryl radical intermediate. The emergence of electrochemistry provided a new way for organic synthesis. In 2020, Baran et al. reported an electrochemical method for the generation of carbocation from the readily available carboxylic acids, and the in situ-generated carbocation was captured by potassium fluoride to give the corresponding fluorinated products (Scheme 16b).<sup>90</sup>

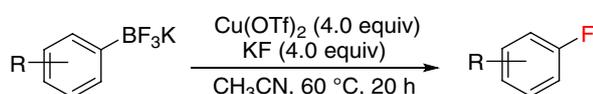
Pyridine/HF and triethylamine/HF have been explored extensively as nucleophilic fluorination reagents. Because of their strong alkalinity, they may interfere with many metal catalysts. In 2014, Xu et al. reported that DMPU/HF could be used in the gold-catalyzed high regioselective mono- and dihydrofluorination of alkynes (Scheme 17).<sup>5</sup>



**Scheme 13** | C-H fluorination.



**Scheme 14** | Deoxyfluorination of hydroxy group.



**Scheme 15** |  $\text{Cu(OTf)}_2$ -mediated fluorination of aryltrifluoroborates.

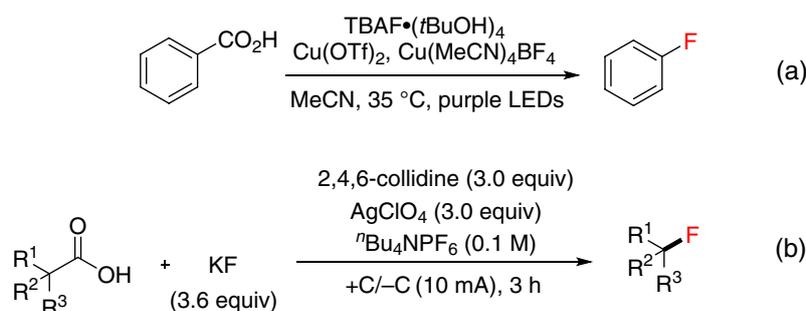
### Trifluoromethylation

The copper-mediated/catalyzed cross-coupling reaction of electrophiles with nucleophilic trifluoromethylating reagents has proven to be an efficient strategy for the construction of  $\text{C(sp}^2\text{)-CF}_3$  bonds.  $\text{TMSCF}_3$  is widely used as the nucleophilic trifluoromethyl source. The trifluoromethylation proceeded through the in situ-generated  $\text{CuCF}_3$  intermediate via transmetalation of the nucleophilic  $\text{CF}_3$  moiety to copper. Over the past decade, several well-defined trifluoromethylated copper(I) complexes have been prepared and evaluated in trifluoromethylation reactions. In 2011, Hartwig et al. developed an isolable and stable trifluoromethylcopper(I) reagent  $[(\text{phen})\text{CuCF}_3]$  for trifluoromethylations of aryl iodides and bromides in DMF at room temperature to  $110^\circ\text{C}$  (Scheme 18a).<sup>91</sup> Hartwig et al. also successfully achieved one-pot C-H

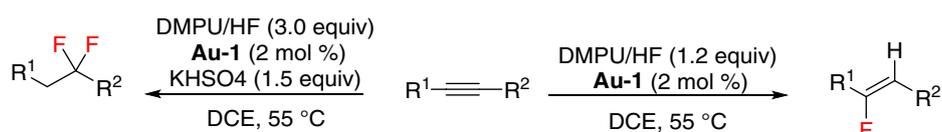
trifluoromethylation of arenes *via* the formation of an arylboronate ester in situ (Scheme 18b).<sup>92</sup> Arene was first converted to aryl boronate esters in the presence of Ir catalyst followed by copper-mediated oxidative trifluoromethylation with  $[(\text{phen})\text{CuCF}_3]$ .

It was suggested that  $[\text{Cu}(\text{CF}_3)_2]^-$  might act as the reservoir for the generation of active “ $\text{CuCF}_3$ ”. To verify the conjecture about whether and how the active “ $\text{CuCF}_3$ ” was produced from bistrifluoromethylated cuprate  $[\text{Cu}(\text{CF}_3)_2]^-$ , Liu and Shen prepared a stable bistrifluoromethylated cuprate  $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_3)_2]^-$  and tested its reactivity. It was found that the active “ $\text{CuCF}_3$ ” generated from  $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_3)_2]^-$  and  $\text{CuI}$  was highly reactive to allow the trifluoromethylation of activated heteroaryl bromides and chlorides (Scheme 19).<sup>93</sup>

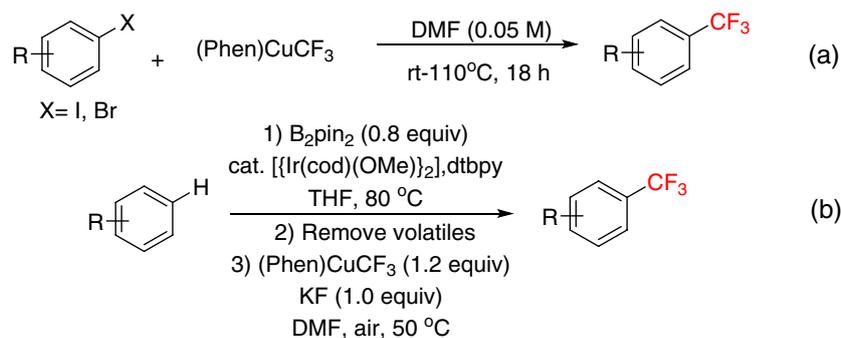
The  $\text{C(sp}^2\text{)-H}$  trifluoromethylation reaction has been extensively investigated for the installation of trifluoromethyl groups into arenes, heteroarenes, olefins, and aldehydes. However,  $\text{C(sp}^3\text{)-H}$  trifluoromethylation has rarely been reported, especially for those unactivated alkanes. In 2021, Hong et al. described a mild and efficient method for the direct  $\text{C(sp}^3\text{)-H}$  trifluoromethylation of the unactivated alkanes by using  $[\text{bpyCu}(\text{CF}_3)_3]$  as the initiator for the visible-light-promoted reaction, trifluoromethyl radical source for hydrogen atom transfer, and



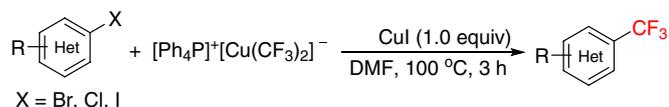
**Scheme 16** | Decarboxylative fluorination.



**Scheme 17** | Hydrofluorination of alkynes.



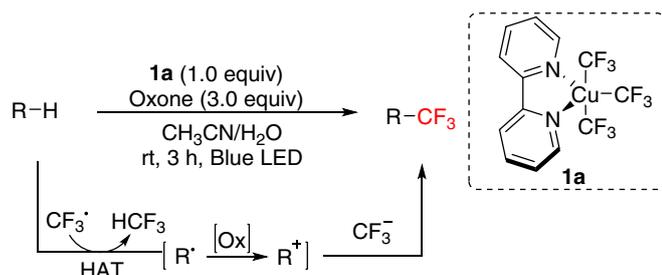
**Scheme 18** | Trifluoromethylation with *(phen)CuCF<sub>3</sub>*.



**Scheme 19** | Trifluoromethylation of activated heteroaryl halides.

trifluoromethyl anion source for trifluoromethylation (Scheme 20).<sup>94</sup>

In 2010, Chu and Qing proposed the concept of oxidative trifluoromethylation: the reaction of a nucleophilic substrate with a nucleophilic trifluoromethylating reagent in the presence of an oxidant.<sup>95</sup> The first oxidative trifluoromethylation was applied to alkynes using  $\text{TMSCF}_3$  as the nucleophilic trifluoromethyl source for the formation of

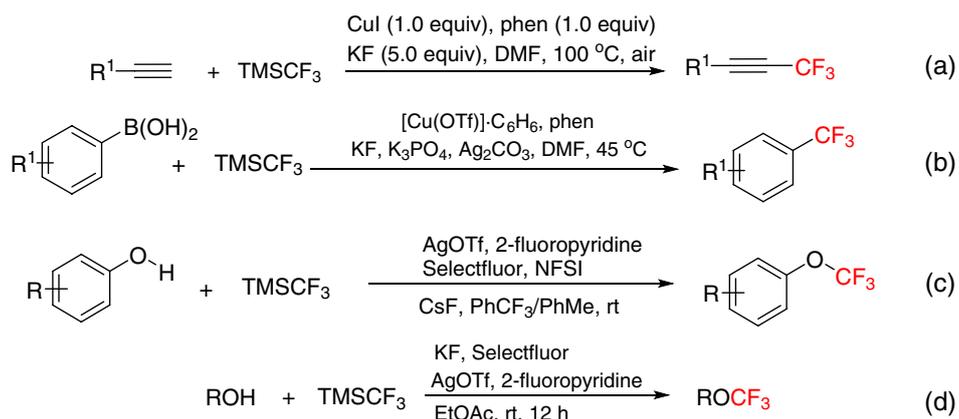


**Scheme 20** | Direct  $C(\text{sp}^3)\text{-H}$  trifluoromethylation of unactivated alkanes.

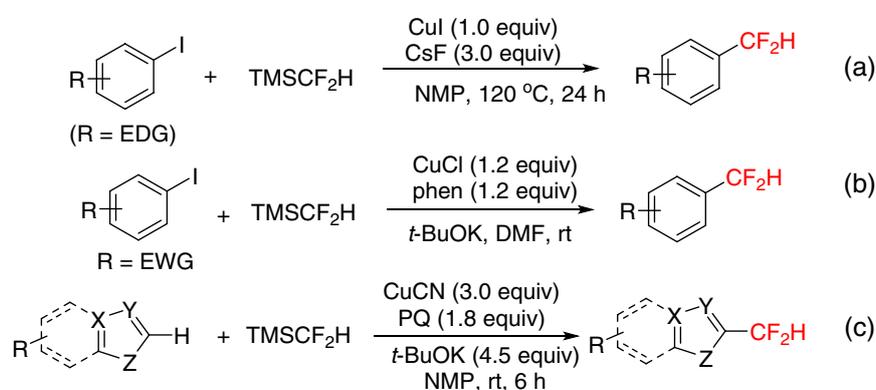
trifluoromethylated acetylenes (Scheme 21a).<sup>96</sup> Subsequently, the first copper-mediated oxidative trifluoromethylation of aryl boronic acids was developed (Scheme 21b).<sup>97</sup> An efficient method for the preparation of aryl(alkyl) trifluoromethyl ethers by  $\text{AgOTf}$ -mediated oxidative trifluoromethylation phenols(alcohols) with  $\text{TMSCF}_3$  using Selectfluor as the oxidant at room temperature was also developed (Schemes 21c and 21d).<sup>98,99</sup> Especially, trifluoromethylation of various primary, secondary, and tertiary alcohols and a series of structurally complex medicinal molecules with a hydroxy group proceeded efficiently under mild reaction conditions.

### Difluoromethylation

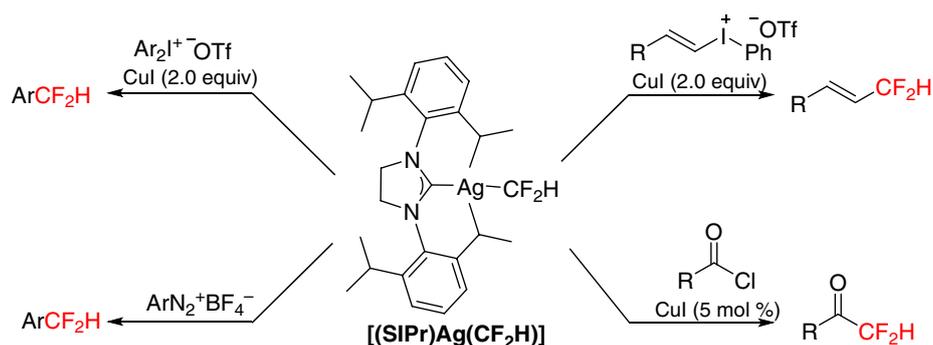
In 2012, Fier and Hartwig reported a copper-mediated difluoromethylation of aryl iodides with  $\text{TMSCF}_2\text{H}$  (Scheme 22a).<sup>100</sup> Nevertheless, the electron-deficient aryl iodides were not suitable for this transformation. Then in 2014, Qing et al. disclosed a copper-mediated direct difluoromethylation of electron-poor aryl iodides in the presence of phen that was an important complement to Hartwig's work (Scheme 22b).<sup>101</sup> In 2018, copper-mediated C–H oxidative difluoromethylation of heteroarenes using  $\text{TMSCF}_2\text{H}$  as the difluoromethyl source was developed by Qing et al. (Scheme 22c).<sup>102</sup> It is worth noting that the  $\text{CF}_2\text{H}$  group was regioselectively connected to the more acidic carbon of the heteroaromatic ring, implying that the deprotonation of the acidic C–H bond of heteroarenes in the presence of base was crucial to the oxidative difluoromethylation.



**Scheme 21** | Oxidative trifluoromethylation.



**Scheme 22** | Direct difluoromethylation with  $\text{TMSCF}_2\text{H}$ .

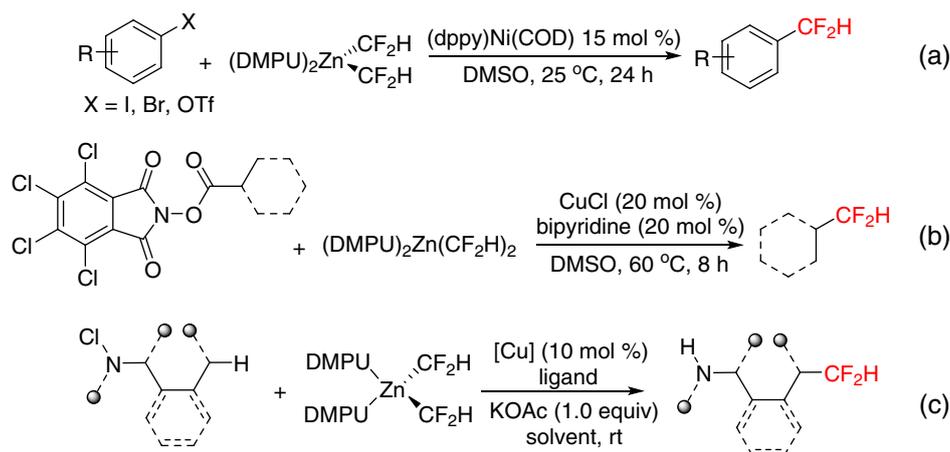


**Scheme 23** | Difluoromethylation with  $[(\text{SIPr})\text{Ag}(\text{CF}_2\text{H})]$ .

In 2015, Shen et al. successfully achieved the difluoromethylation of a variety of activated electrophiles including diaryliodonium salts, vinyl(aryl)iodonium salts, aryldiazonium salts, and acid chlorides using  $[(\text{SIPr})\text{Ag}(\text{CF}_2\text{H})]$  as the difluoromethyl source in the presence or absence of  $\text{CuI}$  at room temperature (Scheme 23).<sup>26</sup>

In 2016, Xu and Vicic reported the nickel-catalyzed difluoromethylation of aryl iodides, bromides, and

triflates with  $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$  (Scheme 24a).<sup>27</sup> Using  $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$  as the difluoromethyl source, Liu et al. successfully developed efficient  $\text{Cu}$ -catalyzed decarboxylative difluoromethylation reaction of aliphatic carboxylic acids (Scheme 24b)<sup>103</sup> and the first copper-catalyzed difluoromethylation of benzylic  $\text{C}(\text{sp}^3)\text{—H}$  bonds via the strategy of harnessing amidyl radicals derived from  $N$ -chloroamides (Scheme 24c).<sup>104</sup>



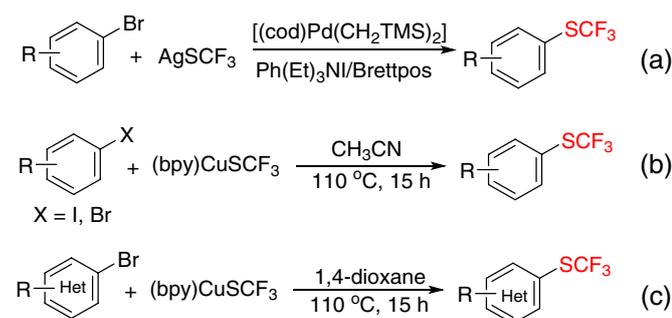
**Scheme 24** | Difluoromethylation with  $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ .

### Trifluoromethylthiolation

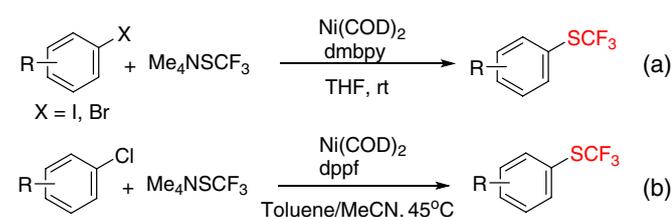
In 2011, Buchwald et al. developed a general method for synthesis of Ar-SCF<sub>3</sub> compounds through the Pd-catalyzed reaction of aryl bromides with AgSCF<sub>3</sub> (Scheme 25a).<sup>105</sup> Weng et al. reported that the cross-coupling reaction between aryl halides with (bpy)CuSCF<sub>3</sub> gave aryl trifluoromethyl thioethers in good yields (Scheme 25b).<sup>39</sup> Zhang and Weng subsequently reported that trifluoromethylthiolated heteroarenes could be prepared by direct trifluoromethylthiolation

of a series of heteroaryl bromides with (bpy)CuSCF<sub>3</sub> (Scheme 25c).<sup>106</sup>

Zhang and Vici described the Ni(COD)<sub>2</sub>/dmbpy catalytic system for nucleophilic trifluoromethylthiolation of aryl iodides and bromides with Me<sub>4</sub>NSCF<sub>3</sub> under mild reaction conditions (Scheme 26a).<sup>107</sup> Interestingly, when dppf was used as ligand instead of dmbpy, Schoenebeck et al. found that the nickel-based catalytic systems were also able to activate the C(sp<sup>2</sup>)-Cl bond for the trifluoromethylthiolation of aryl chlorides (Scheme 26b).<sup>108</sup> Computational and experimental studies suggest a Ni<sup>0</sup>/Ni<sup>II</sup> cycle involving oxidative addition of the C(sp<sup>2</sup>)-Cl bond and C(sp<sup>2</sup>)-SCF<sub>3</sub> reductive elimination.



**Scheme 25** | Trifluoromethylthiolation of aryl halides.



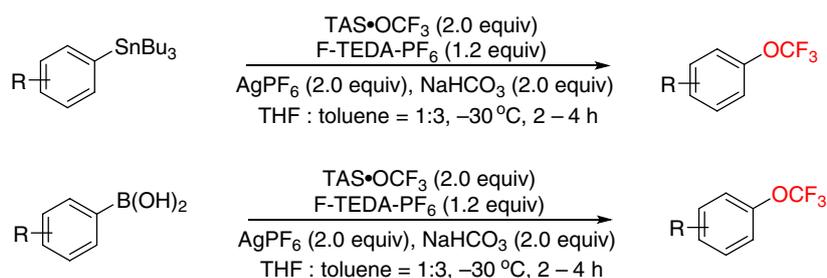
**Scheme 26** | Nickel-catalyzed trifluoromethylthiolation of aryl halides.

### Trifluoromethoxylation

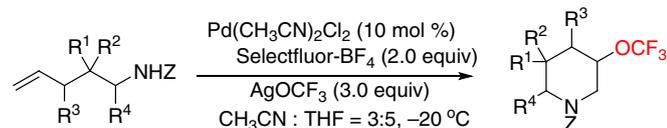
The introduction of the OCF<sub>3</sub> group into organic molecules is regarded as a significant but challenging value-added conversion due to the easily decomposing character of the trifluoromethyl anion and limited trifluoromethoxylating reagents. In 2011, Ritter et al. first reported silver-mediated trifluoromethoxylation of aryl stannanes and arylboronic acids using TAS•OCF<sub>3</sub> as OCF<sub>3</sub> source (Scheme 27).<sup>109</sup>

In 2015, Liu et al. established the first catalytic trifluoromethoxylation of unactivated alkenes by employing Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> as catalyst, AgOCF<sub>3</sub> as trifluoromethoxide source, and Selectfluor-BF<sub>4</sub> as oxidant (Scheme 28).<sup>110</sup> Mechanistic studies illustrated that the key intermediate Pd<sup>IV</sup>OCF<sub>3</sub> is relatively stable and undergoes faster reductive elimination than β-fluoride elimination for the formation of C-OCF<sub>3</sub> bond.

In 2017, Tang et al. developed a new trifluoromethoxy reagent TFMS for asymmetric bromotrifluoromethoxylation of alkenes.<sup>111</sup> This is the first example of a catalytic enantioselective trifluoromethoxylation reaction (Scheme 29). The discovery of the TFMS reagent brings new opportunities for direct



**Scheme 27** | Trifluoromethoxylation of aryl stannanes and arylboronic acids.



**Scheme 28** | Aminotrifluoromethoxylation reaction of unactivated alkenes.

trifluoromethoxylation. By employing TFMS as a nucleophilic trifluoromethoxylating reagent, Tang et al. successfully achieved azidotrifluoromethoxylation of styrenes, direct dehydroxytrifluoromethoxylation of alcohols, hydroxyltrifluoromethoxylation of epoxides, trifluoromethoxylation of aryl diazonium salts, and the direct C(sp<sup>2</sup>)-H trifluoromethylation of arenes and heteroarenes (Scheme 29).<sup>112-116</sup>

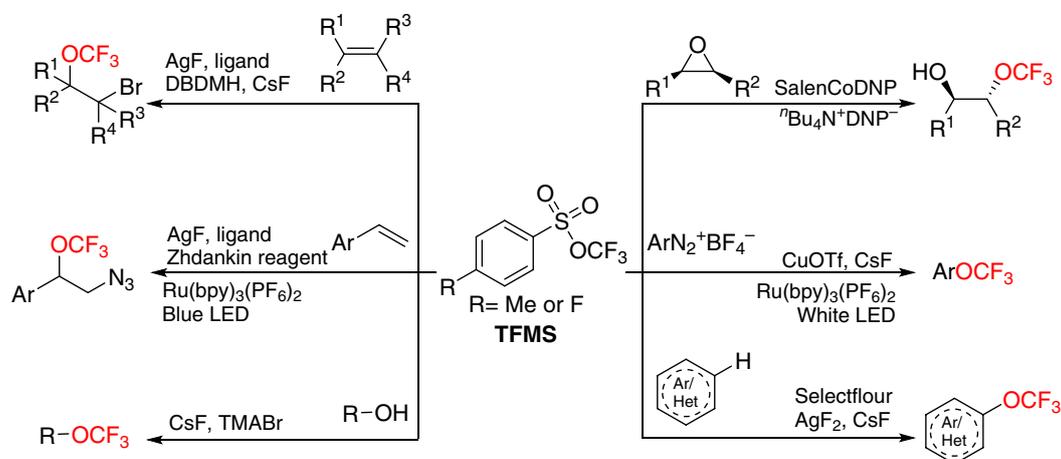
In 2018, Hu et al. reported a trifluoromethoxylation-bromination reaction of the in situ-generated arynes from 2-trimethylsilylphenyl triflate with TFBz using phenylethynyl bromide as the electrophilic bromine

source. This was the first example of trifluoromethoxylation-functionalization of arynes (Scheme 30).<sup>42</sup>

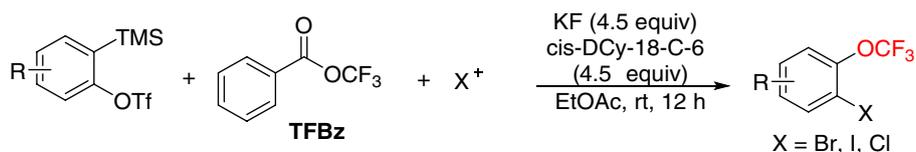
Umamoto et al. realized the regio- and stereoselective synthesis of trifluoromethoxylated alkenes from a series of alkynes by employing trifluoromethyl nonaflate (TFNf) as a nucleophilic trifluoromethoxy source (Scheme 31).<sup>44</sup>

### Radical fluorination and fluoroalkylation reactions

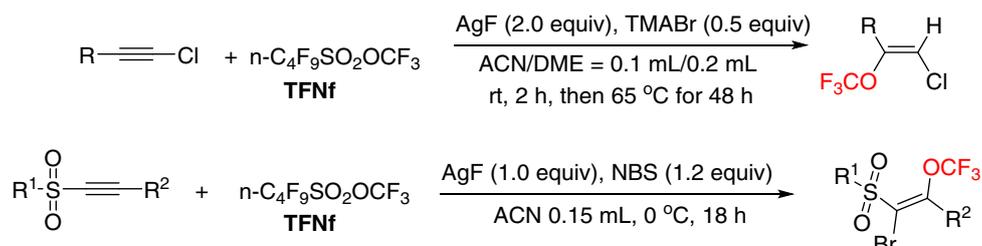
Radical reactions are undoubtedly experiencing a renaissance since the end of the last century. Advantages of radical reaction include: (1) the reactivity of stabilized radicals are predictable; (2) the chemo-, regio-, and stereoselectivity of radicals can be well controlled. One class of relatively stabilized alkyl radical species is the fluoroalkyl (R<sub>f</sub>) radicals: the combination of the σ-inductive effect and the π-donating effect of the fluorine atom contributes to the stability and ultimately the reactivity of the fluoroalkyl radicals. In this section, we specifically focus on the reactions where the R<sub>f</sub> radicals are involved in the key C-R<sub>f</sub> bond formation step.



**Scheme 29** | Trifluoromethoxylation with TFMS.



**Scheme 30** | Trifluoromethoxylation-halogenation of arynes.

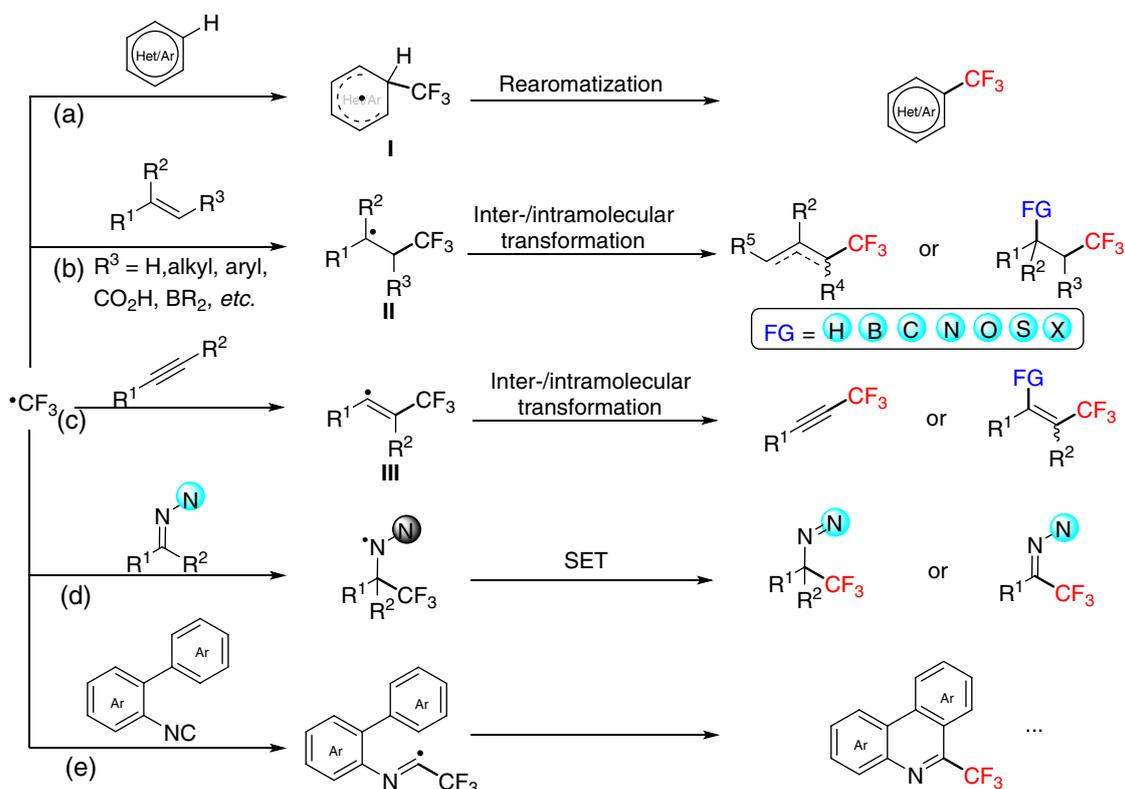


**Scheme 31** | Hydrotrifluoromethoxylation with TFNF.

### Trifluoromethylation

The flourishing development of radical trifluoromethylation mainly relies both on the design of new trifluoromethylating reagents that are readily accessible and the development of reaction conditions that are mild and easily operational. A number of strategies that could

initiate radical trifluoromethylation have been reported, including photochemical, electrochemical, thermal, metal, or metal-free catalysis, and photoredox catalysis.<sup>117</sup> The scope of arenes covers benzene, mono-/multisubstituted benzenes with electro-donating or withdrawing groups, and polyarenes. Meanwhile, a wide range of heteroarenes



**Scheme 32** | The addition of  $CF_3$  radical to unsaturated bonds.

successfully undergo radical trifluoromethylation smoothly. The generally accepted mechanism is the initiation of a radical precursor under suitable conditions to generate a  $\text{CF}_3$  radical, which reacts with the aromatic ring to provide a reactive radical intermediate **I** (Scheme 32a). The rearomatization process gives rise to the final products. The advantage for the radical aryl C-H trifluoromethylation is the atom- and step-economy without the need for pre-functionalized substrates such as (hetero)aryl halides and boronic acid derivatives.

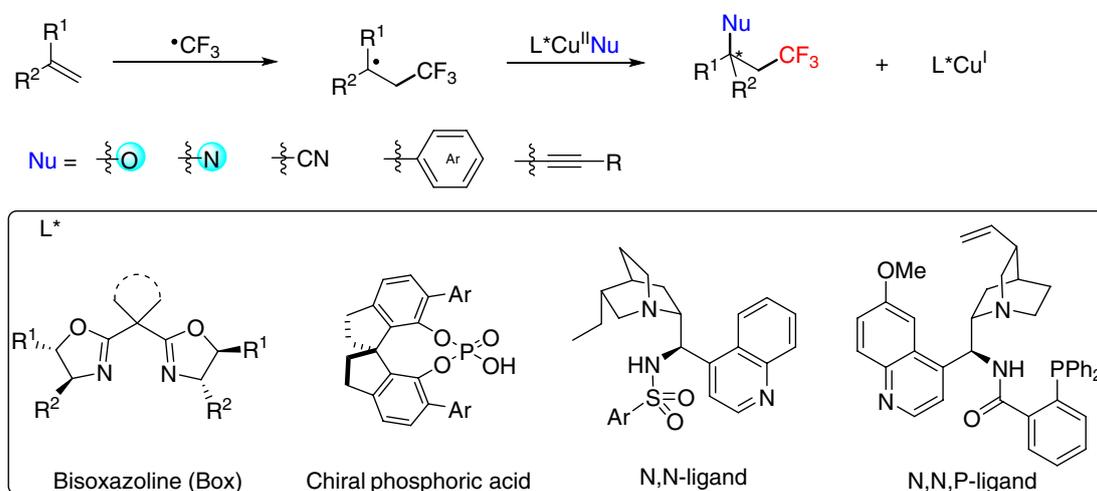
The radical trifluoromethylation of alkenes has emerged as a hot topic since its early development because it enables simultaneous incorporation of  $\text{CF}_3$  and an additional functional group at vicinal positions and allows the expedient synthesis of complex molecules from simple alkenes. As such, many elegant reviews have discussed the methods in alkenyl/allylic C-H trifluoromethylation,<sup>117c</sup> hydrotrifluoromethylation,<sup>117c</sup> trifluoromethylboration,<sup>118</sup> carbotrifluoromethylation,<sup>119</sup> oxytrifluoromethylation,<sup>120</sup> aminotrifluoromethylation,<sup>117e</sup> halotrifluoromethylation,<sup>121</sup> thiotrifluoromethylation,<sup>117c</sup> and trifluoromethylthio-trifluoromethylation,<sup>122</sup> and so on (Scheme 32b). Mechanistically, the reaction is initiated by the generation of a  $\text{CF}_3$  radical from diverse radical precursors. The  $\text{CF}_3$  radical adds easily to the alkene moiety to afford a highly reactive alkyl radical intermediate **II**. While the alkyl radical **II** might undergo direct radical addition, coupling, and substitution with a trapping reagent to deliver the final products, a radical-polar crossover reaction via oxidation to carbocation, reduction to carbanion, and combining with transition metal catalysis is also feasible. The regioselectivity is usually good since the  $\text{CF}_3$  radical would attack the less sterically-hindered site of the alkene moiety or the addition is driven by the formation of a stabilized alkyl radical **II**.

The  $\text{CF}_3$  radical reacts also with alkynes which is demonstrated in an early work on the iodotrifluoromethylation of alkenes. The mechanism is similar: the  $\text{CF}_3$  radical first

adds to the alkyne moiety, leading to a vinyl radical intermediate **III**, followed by a subsequent trapping process either in an inter- or intramolecular manner (Scheme 32c). Despite the difference in structure and property between alkyl radical **II** and vinyl radical **III**, the trapping reagents are similar to that of alkenes.<sup>123-125</sup>

While imines are not good radical acceptors, hydrazones are better ones and represent another class of unsaturated bonds to react with the  $\text{CF}_3$  radical. This is because the thus formed hydrazinyl radical **IV** derived from the addition of the  $\text{CF}_3$  radical to the hydrazone moiety could be stabilized via the formation of a two-center, three-electron  $\pi$  bond with the lone pair of the adjacent nitrogen atom (Scheme 32d).<sup>117d,126</sup> Besides, the  $\text{CF}_3$  radical readily reacts with the isocyanide group in cascade reactions for the construction of 6-trifluoromethylated phenanthridines or other compounds via the generation of an imidoyl radical and subsequent aromatic substitution (Scheme 32e).<sup>117b,127</sup>

It is only until recently that the trifluoromethyl radical has been harnessed in the enantioselective trifluoromethylation. The enantioselective radical 1,2-trifluoromethylation of alkenes has been disclosed by merging chiral copper catalysis with a radical addition process from 2013.<sup>128</sup> Buchwald developed a copper/chiral bisoxazoline ligand catalytic system for achieving the intramolecular enantioselective oxytrifluoromethylation of alkenes (Scheme 33).<sup>129</sup> Liu et al. from SIOC and others have elegantly disclosed a series of inter- and intramolecular enantioselective carbo-, azido-, and aminotrifluoromethylation of alkenes utilizing this catalytic system (Scheme 33).<sup>130</sup> At the same time, Liu et al. from SUSTech developed the amino-, oxy-, and carbotrifluoromethylation of alkenes by designing an array of chiral anionic ligands, such as chiral phosphoric acid, anionic N,N-ligand, and anionic N,N,P-ligand (Scheme 33).<sup>131-133</sup>

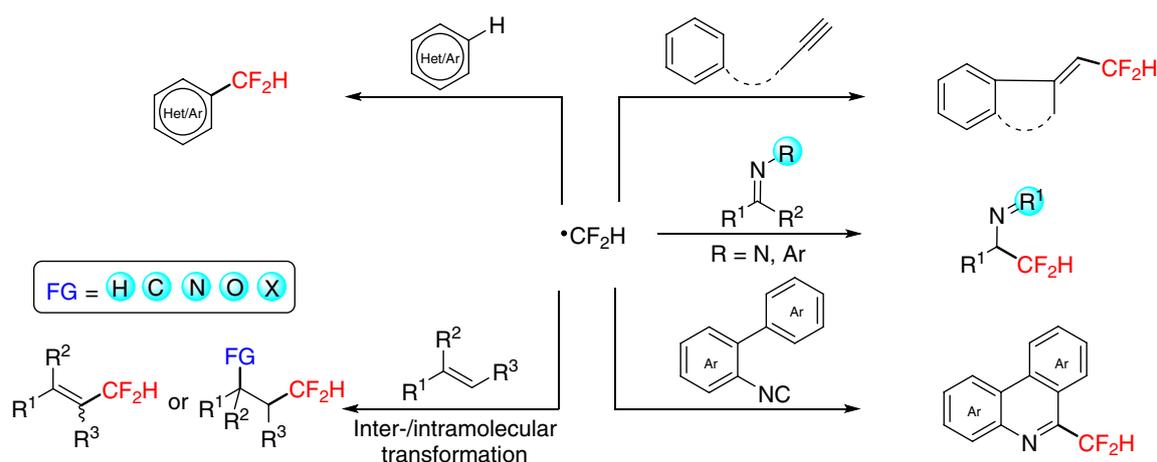


**Scheme 33** | The enantioselective radical trifluoromethylation reaction.

DOI: 10.31635/ccschem.022.202201935

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Link to VoR: <https://doi.org/10.31635/ccschem.022.202201935>



**Scheme 34** | The addition of  $\text{CF}_2\text{H}$  radical to unsaturated bonds.

### Difluoromethylation

The radical difluoromethylation reactions have also been well developed in the past decade. Similar to the  $\text{CF}_3$  radical, the  $\text{CF}_2\text{H}$  radical reacts readily with unsaturated bond systems (Scheme 34). The transition metal-mediated coupling of prefunctionalized arenes with an electrophilic difluoromethylating reagent provides a versatile tool in the synthesis of difluoromethylated arenes where the  $\text{CF}_2\text{H}$  radical is sometimes proposed to be involved.<sup>134</sup> In addition, the  $\text{CF}_2\text{H}$  radical also reacts with alkenes,<sup>135</sup> C=N bonds,<sup>136</sup> and isocyanides,<sup>30,137</sup> where the initiation step is the addition of a  $\text{CF}_2\text{H}$  radical to the unsaturated bonds, while the trapping reagents are similar to those of radical trifluoromethylation reactions.

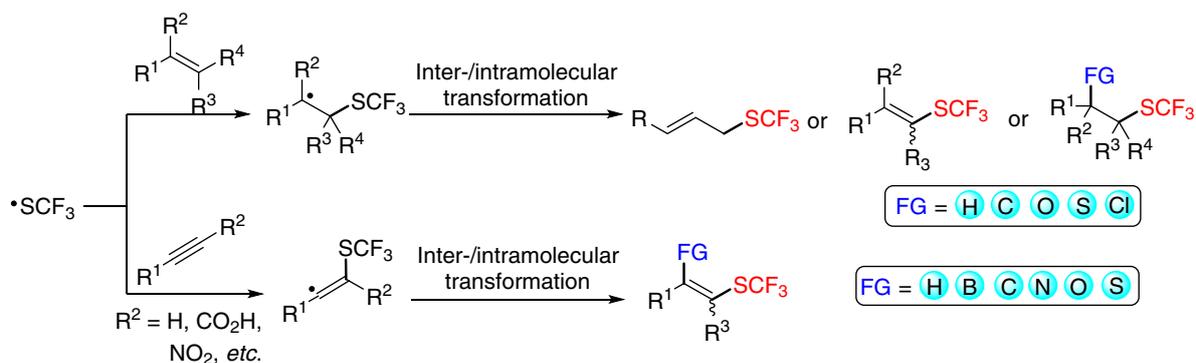
### Trifluoromethylthiolation

In 2014, Yin and Wang made an important breakthrough by using the bench-stable  $\text{AgSCF}_3$  as the radical source under oxidative conditions to achieve an intramolecular carbotrifluoromethylthiolation of alkenes. Numerous reports of radical trifluoromethylthiolation of alkenes and alkynes have been described based on new reagents

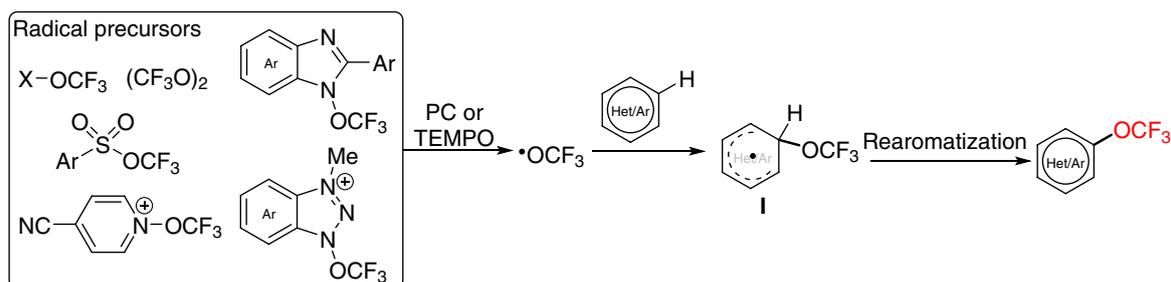
such as N- $\text{SCF}_3$  reagents (Scheme 35).<sup>138</sup> In addition to N- $\text{SCF}_3$  reagents, Qing et al. demonstrated that trifluoromethanesulfonic anhydride is also a suitable  $\text{SCF}_3$  radical precursor via a deoxygenative reduction process.<sup>139</sup> A gamut of trapping reagents has been accommodated, including hydrogen, chlorine, as well as carbon-, boron-, oxygen-, nitrogen-, and sulfur-based functional groups (Scheme 35).

### Trifluoromethoxylation

Compared with other fluoroalkylation reactions, the radical trifluoromethoxylation reaction has been less studied due to the relative rareness of the trifluoromethoxylation reagents. Nevertheless, a few radical C-H trifluoromethoxylation of arenes and heteroarenes have been reported recently. Mechanistically, these reactions resemble those of radical trifluoromethylation. The key step in these reactions is the addition of  $\text{OCF}_3$  radical to the aromatic rings, providing the highly reactive radical **I**, which undergoes rearomatization to give the desired trifluoromethoxylation product (Scheme 36).<sup>140</sup> Efforts in recent years have mainly been dedicated to the



**Scheme 35** | Addition of  $\text{SCF}_3$  radical to alkenes and alkynes.



**Scheme 36** | Radical trifluoromethoxylation reactions.

development of new radical trifluoromethoxylation reagents (N-OCF<sub>3</sub> and ArSO<sub>2</sub>OCF<sub>3</sub>).<sup>45–47</sup>

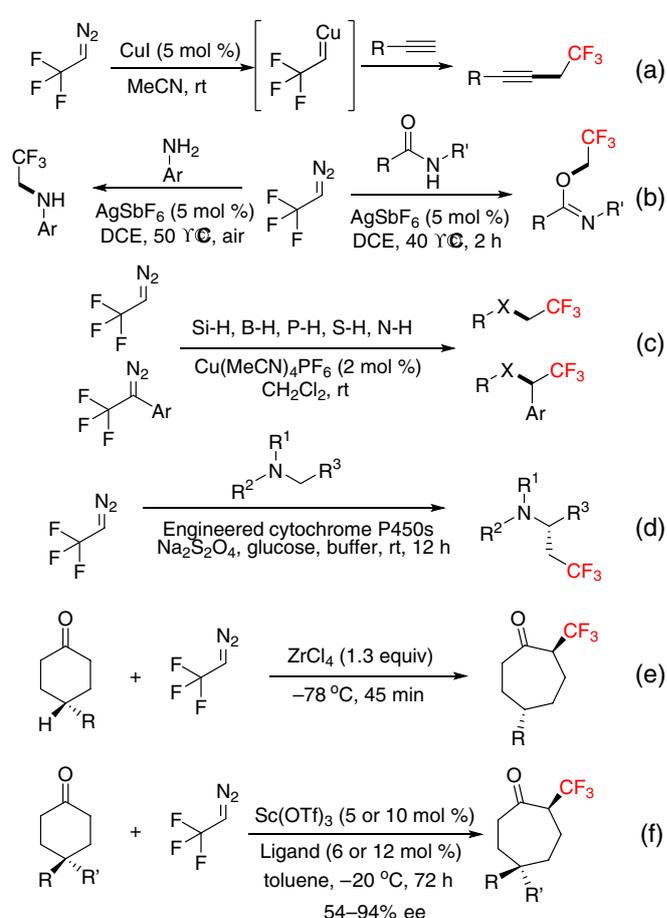
## Fluorinated carbene reactions

### Trifluoroethylation

CF<sub>3</sub>CHN<sub>2</sub> could serve as an efficient precursor to form trifluoromethyl carbene intermediate under transition metal catalysis or thermal conditions. In 2012, Ma et al. reported a copper-catalyzed trifluoroethylation reaction of terminal alkynes under mild conditions without the need for additional base or ligands (Scheme 37a).<sup>49</sup> In 2015, Wang et al. found that silver could perform as an efficient catalyst for the direct trifluoroethylation of anilines under simple conditions (Scheme 37b).<sup>141</sup> In 2016, Gouverneur et al. reported a more general trifluoroethylation reaction of heteroatom–hydrogen bonds under copper catalysis (Scheme 37c).<sup>142</sup> In 2019, Arnold et al. reported that engineered cytochrome P450 enzymes could catalyze the enantioselective trifluoroethylation of  $\alpha$ -amino C–H bonds (Scheme 37d). This study represents a notable example of applying biocatalysis for the synthesis of chiral organofluorine molecules from fluoroalkyl carbene intermediates.<sup>143</sup> In 2011, Morandi and Carreira reported a method for the preparation of  $\alpha$ -trifluoromethylated aldehydes and ketones by homologation of aldehydes and cyclohexanones with F<sub>3</sub>CCHN<sub>2</sub> which was generated in situ from F<sub>3</sub>CCH<sub>2</sub>NH<sub>2</sub>·HCl (Scheme 37e).<sup>144</sup> In 2022, an asymmetric version of such reaction was reported by Wang et al., thus providing an alternative method for the preparation of optically enriched trifluoromethylated compounds (Scheme 37f).<sup>145</sup>

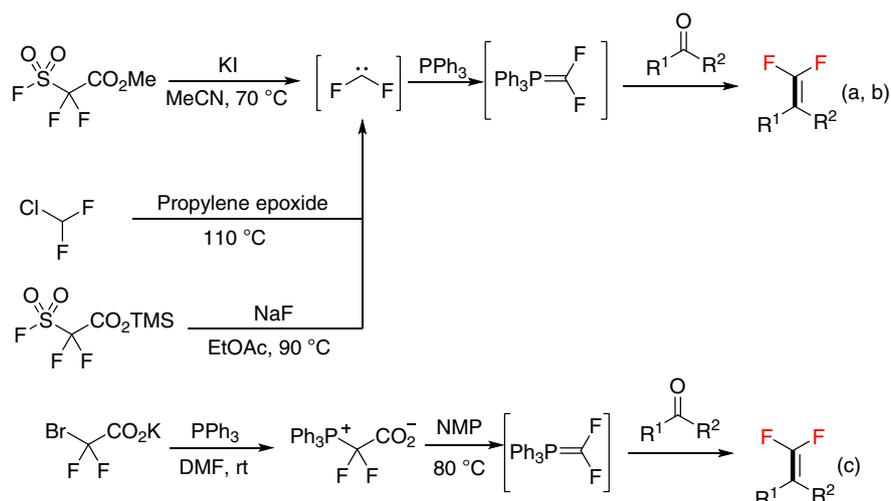
### gem-Difluoromethylenation

gem-Difluoroalkenes constitute a distinct class of organofluorine chemicals possessing ample applications in the fields of medicinal chemistry, the agrochemical industry, and materials science. Among various synthetic approaches, the difluorocarbene-enabled Wittig-type olefination reaction represents an attractive means in terms of scope, generality, and operational simplicity. In 2013,



**Scheme 37** | Catalytic trifluoroethylation reaction with CF<sub>3</sub>CHN<sub>2</sub>.

Dolbier et al. and Xiao et al. independently reported that FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>Me, FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>TMS, and ClCF<sub>2</sub>H could also work as viable difluorocarbene precursors in such difluoromethylenation reactions (Schemes 38a and 38b).<sup>146,147</sup> More importantly, Xiao's group isolated a stable and easily handled difluoromethylene phosphobetaine (Ph<sub>3</sub>P<sup>+</sup>CF<sub>2</sub>CO<sub>2</sub><sup>-</sup>) from BrCF<sub>2</sub>CO<sub>2</sub>K and PPh<sub>3</sub> (Scheme 38c),<sup>148</sup> which not only could undergo the Wittig reaction with aldehydes but could also function as a new difluorocarbene reagent in a series of reactions.<sup>57</sup>



**Scheme 38** | *gem*-Difluoromethylenation reaction of carbonyl compounds.

In 2015, Hu et al. and Wang et al. independently reported a novel *gem*-difluoromethylenation reaction via cross-coupling of difluorocarbene with diazo compounds under transition metal-free conditions (Scheme 39).<sup>149,150</sup> Both  $\text{TMSCF}_3$  and  $\text{TMSCF}_2\text{Br}$  could be employed as a difluorocarbene source, and a wide variety of diazo compounds including  $\alpha$ -diazoacetates, diaryldiazomethanes, diazirines and hydrazones could be transformed into the corresponding 1,1-difluoroalkenes.

Bi reported a general platform for the synthesis of heteroatom-substituted *gem*-difluoroalkenes from  $\text{CF}_3\text{CHN}_2$  (Scheme 40).<sup>53</sup> This protocol employs trifluoroacetaldehyde *N*-tfsylhydrazone (TFHZ-Tfs) as a safe and easy-to-handle  $\text{CF}_3\text{CHN}_2$  surrogate. The metal catalyst could decompose  $\text{CF}_3\text{CHN}_2$  to form  $\text{CF}_3$ -metallocarbene intermediate, which was then attacked by a nucleophile to give oxonium ylide. Final deprotonation and  $\beta$ -fluoride elimination under basic conditions lead to the *gem*-difluoromethylenylation products.

### Cyclopropanation with difluorocarbene

Amii et al. reported the use of sodium bromodifluoroacetate as difluorocarbene source to react with terminal alkenes, internal alkenes, vinyl boronates, vinyl carboxylic esters, and silyl enol ethers to give the corresponding *gem*-

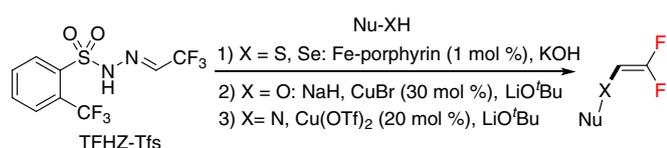
difluorocyclopropanes in good to high yields under thermal conditions (Scheme 41a).<sup>151</sup> In 2011, Olah et al. disclosed the use of  $\text{TMSCF}_3$  as a novel difluorocarbene source to *gem*-difluorocyclopropanes with a broad scope of alkenes (Scheme 41b).<sup>55</sup> A major advantage of this protocol is the relatively low reaction temperature due to the use of tetrabutylammonium triphenyldifluorosilicate (TBAT) or NaI as the activator. In addition, Mikami et al. has also demonstrated the use of (trifluoromethyl)zinc reagent  $[\text{Zn}(\text{CF}_3)_2(\text{DMPU})_2]$  as difluorocarbene precursor to undergo cyclopropanation with alkenes (Scheme 41c).<sup>152</sup> Notably, Goetz et al. from Pfizer conducted a systematic study on the large-scale *gem*-difluorocyclopropanation of butyl acrylate with various difluorocarbene precursors.<sup>153</sup> He developed a procedure that utilizes ethyl bromodifluoroacetate as difluorocarbene precursor to obtain the difluorocyclopropane acid on >100 kg scale, which is a key fluorinated building block for drug molecular synthesis (Scheme 41d).

### Cyclopropanation with fluoroalkyl carbene

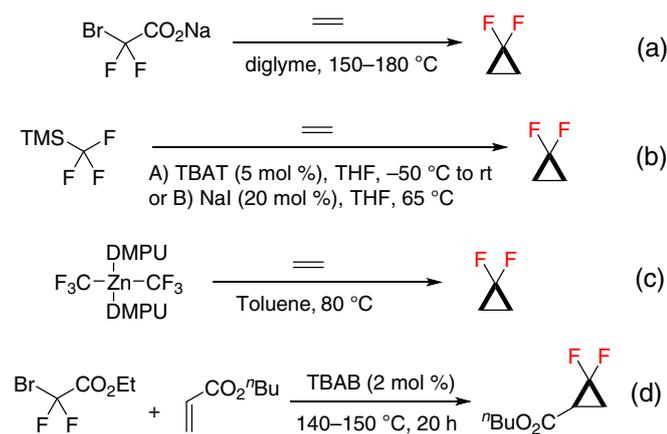
In 2010, Morandi and Carreira reported the cyclopropanation of styrenes with in situ-generated  $\text{CF}_3\text{CHN}_2$  catalyzed by an iron-porphyrin complex in aqueous media (Scheme 42a).<sup>48</sup> This protocol avoids the isolation of



**Scheme 39** | *gem*-Difluoromethylenation reaction of diazo compounds.

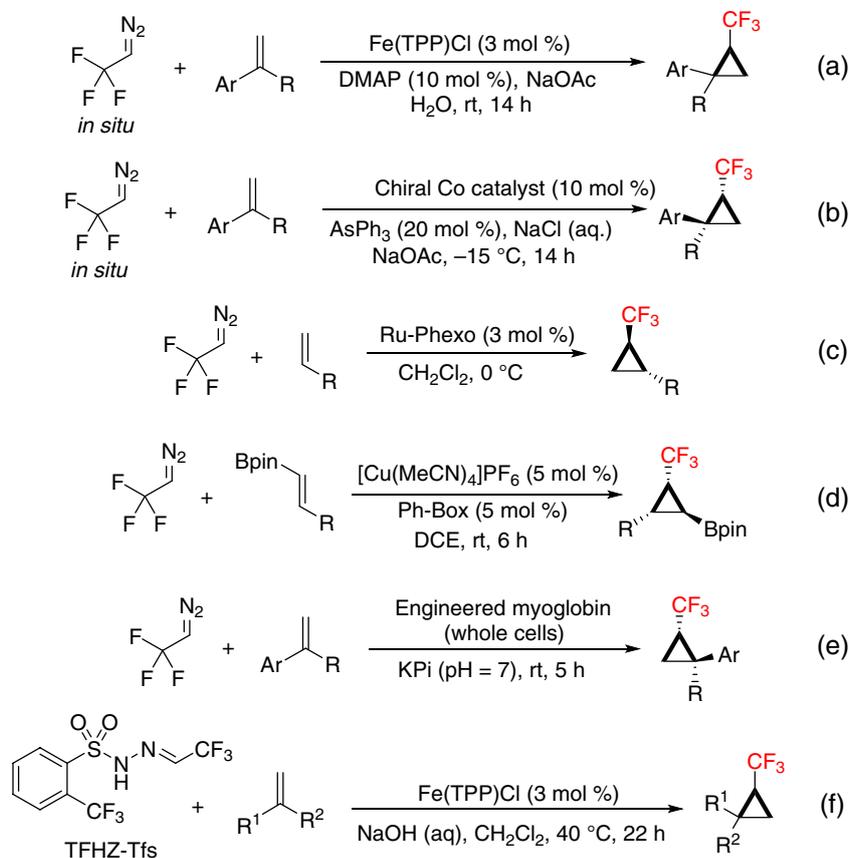


**Scheme 40** | *gem*-Difluoromethylenation reaction of heteroatoms.

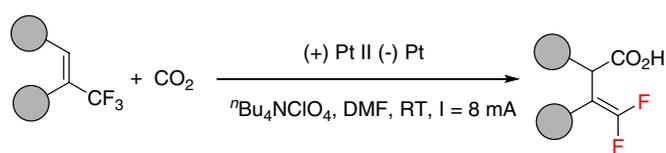


**Scheme 41** | *Cyclopropanation with difluorocarbene.*

toxic and gaseous  $\text{CF}_3\text{CHN}_2$  and triggered a significantly increased interest in the chemistry of  $\text{CF}_3\text{CHN}_2$  as a powerful trifluoromethyl carbene precursor in the following decade. Notably, Carreira et al. also developed a Co-catalyzed enantioselective version of the [2 + 1] cycloaddition reaction of styrenes with  $\text{CF}_3\text{CHN}_2$  (Scheme 42b).<sup>154</sup> Subsequently, Iwasa et al. reported a Ru-Pheox-catalyzed asymmetric cyclopropanation of  $\text{CF}_3\text{CHN}_2$  with styrenes, vinyl ethers, and vinyl amines in good yields with high stereoselectivities (Scheme 42c).<sup>155</sup> Very recently, Carreras et al. established a copper-bisoxazoline complex platform for the synthesis of trifluoromethyl cyclopropylboronates from  $\text{CF}_3\text{CHN}_2$  and alkenyl boronates (Scheme 42d).<sup>156</sup> While the above-mentioned protocols extensively explored the use of transition metal catalysis in the cyclopropanation of trifluoromethyl carbene, Fasan et al. developed a remarkable biocatalytic strategy for the synthesis of enantioenriched trifluoromethyl cyclopropanes from  $\text{CF}_3\text{CHN}_2$  and vinylarenes (Scheme 42e).<sup>157</sup> In 2019, Bi's group took advantage of TFHZ-Tfs as a stable and easily handled trifluorodiazooethane surrogate to undergo cyclopropanation reactions with alkenes in the presence of an iron catalysis (Scheme 42f).<sup>53</sup>



**Scheme 42** | *Cyclopropanation with  $\text{CF}_3\text{CHN}_2$  and fluoroalkyl hydrazones.*



**Scheme 43** | Electrochemical defluorinative carboxylation of  $\alpha$ -CF<sub>3</sub> alkenes.

## Defluorofunctionalization reactions

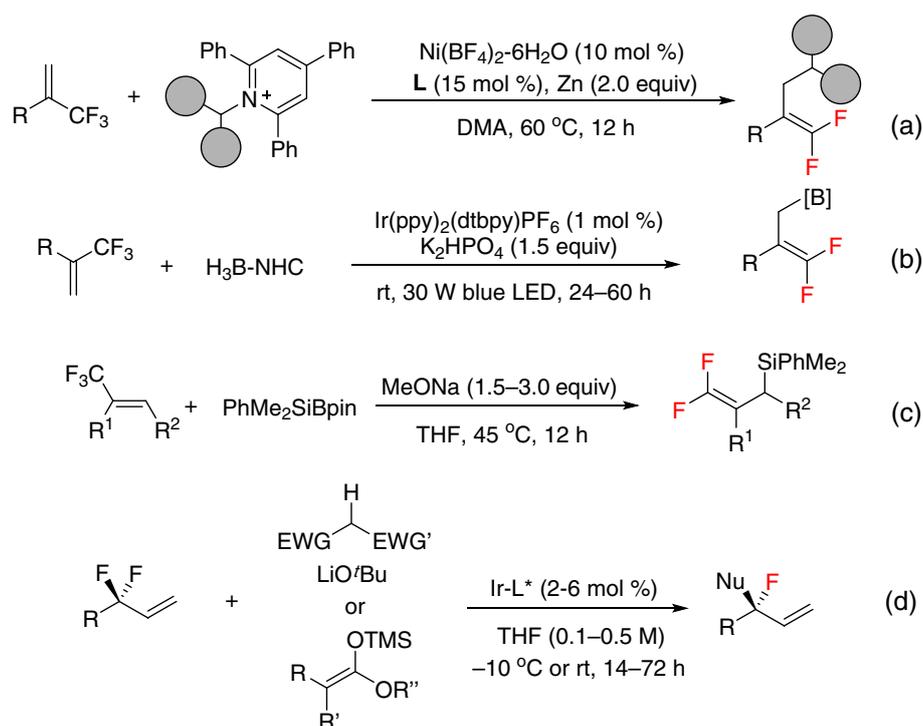
### C-F bond activation in C-CF<sub>3</sub>

Due to their electron-deficient property,  $\alpha$ -trifluoromethylstyrenes show unique and intriguing reactivities in their C-F bond activation, which inherently react with various nucleophiles on the  $\gamma$ -position carbon atom with respect to the fluorine substituents, leading to the formation of new bonds and cleavage of C-F bonds. In 2020, Zhou et al. reported an unprecedented electrochemical  $\gamma$ -carboxylation of  $\alpha$ -CF<sub>3</sub> alkenes with CO<sub>2</sub> to provide efficiently vinylacetic acids bearing a *gem*-difluoroalkene moiety (Scheme 43).<sup>158</sup>

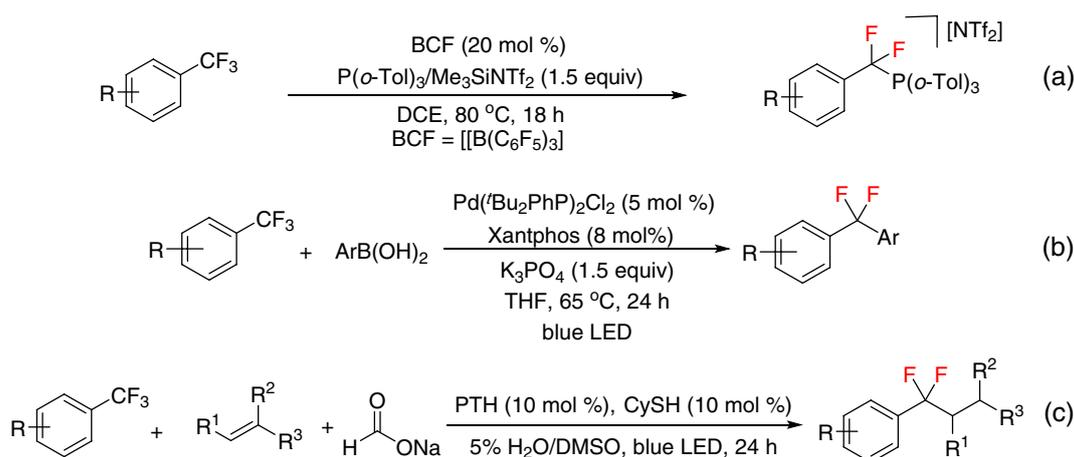
In 2020, Wang et al. disclosed a Ni- and Zn-mediated reductive allylic defluorinative cross-coupling reaction between  $\alpha$ -trifluoromethyl alkenes and secondary alkyl pyridinium salts. A series of *gem*-difluoroalkenes bearing various functional moieties with good compatibility could be afforded by the combination of reductive

C-N and C-F bond cleavage in the transformation (Scheme 44a).<sup>159</sup> In 2020, Yang et al. reported an elegant photoinduced SET process for direct B-H bond activation to access *gem*-difluoroalkenes organoboron compounds (Scheme 44b).<sup>160</sup> Notably, this photoinduced reaction takes advantage of the beneficial redox potentials of NHC-boranes to generate boron radicals, thus obviating the need for extra radical initiators, promoting C-F bond cleavage. In 2019, Shi et al. reported a transition-metal-free defluorosilylation of fluoroalkenes using silylboronates as silylating reagents (Scheme 44c).<sup>161</sup> This protocol shows a broad substrate scope, mild reaction conditions, and high yields as well as easy operation. In 2020, Hartwig et al. reported an Ir-catalyzed asymmetric defluoroalkylation of one of the two fluorine atoms in 3-substituted 3,3-difluoropropenes in excellent enantioselectivities, providing a convenient approach to access optically-enrich fluorinated quaternary carbon center (Scheme 44d).<sup>162</sup>

The direct construction of valuable fluorinated molecules from readily available trifluoromethyl aromatics through selective cleavage of the C-F bond is an attractive goal and has attracted more and more attention recently. In 2020, Young et al. developed a Frustrated Lewis pair-mediated substitution of trifluoromethylaromatics with neutral phosphine and pyridine bases (Scheme 45a).<sup>163</sup> This reaction could provide a broad range of difluoromethyl products by further functionalization through nucleophilic substitution, photoredox



**Scheme 44** | Allylic defluorinative reaction.



**Scheme 45** | C-F bond functionalizations of trifluoromethylaromatics.

coupling, as well as electrophilic transfer reactions. In addition to intramolecular defluorofunctionalization reactions, there are many intermolecular couplings via defluorofunctionalization reaction. In 2021, Zhang et al. reported visible light-promoted palladium-catalyzed defluoroarylation of trifluoromethylarenes with aryl boronic acids (Scheme 45b).<sup>164</sup> Wang and Jui developed a new catalytic strategy for selective functionalization of the strong C-F bonds in trifluoromethylaromatics via SET process (Scheme 45c).<sup>165</sup> In this protocol, a single electron reduction of Ar-CF<sub>3</sub> substrates leads to a difluorobenzyl radical through a C-F bond cleavage. And then the radical undergoes efficient intermolecular coupling with simple alkenes in a defluoroalkylation process where radical termination is achieved by a polarity reversal catalyst.

Wang et al. disclosed a general strategy for sequential carbon-fluorine (C-F) bond functionalizations of trifluoroacetamides and trifluoroacetates (Scheme 46).<sup>166</sup> This process begins with the activation of a carbonyl oxygen atom by a 4-dimethylaminopyridine-boryl radical, then a spin-center shift promotes the C-F bond cleavage. The two-stage process with controllable chemical selectivity can afford various fluorinated products.

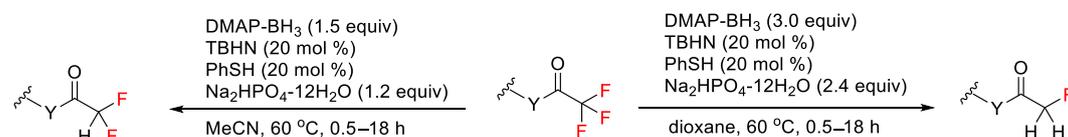
### C-F bond activation of BrCF<sub>2</sub>CO<sub>2</sub>R

The various deconstructive modes of halodifluoromethyl compounds, such as BrCF<sub>2</sub>CO<sub>2</sub>Et, ClCF<sub>2</sub>CO<sub>2</sub>Na, ClCF<sub>2</sub>H,

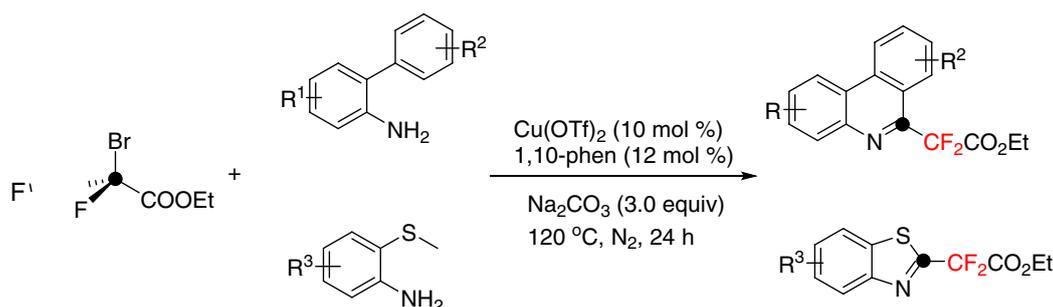
BrCF<sub>2</sub>CONRR as well as BrCF<sub>2</sub>P(O)OEt<sub>2</sub> via C-F bond cleavage, were developed for the generation of a variety of synthons to assemble more valuable products. In 2018, Song et al. reported a novel one-pot cascade reaction involving both quadruple cleavage and single cleavage of BrCF<sub>2</sub>COOEt with primary amines to construct valuable fluorine-containing heterocycles for the first time (Scheme 47), in which BrCF<sub>2</sub>COOEt plays dual roles as both C1 synthon and difluoromethylating reagents.<sup>167</sup>

The same group further designed and developed a novel atom recombination reaction with BrCF<sub>2</sub>COOEt as both C1 synthon and fluorinated reagent. This reaction was proposed to proceed via the C-F bond cleavage to generate a broad range of valuable 3-fluorinated oxindoles in a single-vessel in good to excellent yields (Scheme 48).<sup>168</sup> The transformation is catalyst-free and features ease of execution, broad substrate scope, and excellent functional group compatibility.

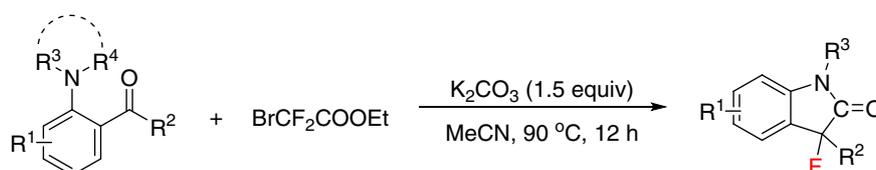
Song et al. further reported an efficient and general method for the assembly for 2-fluoroindoles, in which a wide range of 2-fluoroindole derivatives were accessed with high efficiency and chemoselectivity (Scheme 49).<sup>169</sup> In this protocol, BrCF<sub>2</sub>COOEt provided one carbon and one fluorine atom via cleavage of one C-N tertiary bond and formation of one new C-N bond and one C-C double bond with *ortho*-vinylanilines. Downstream transformations on 2-fluoroindoles led to various valuable bioactive molecules which demonstrated significant synthetic advantages over previous reports.



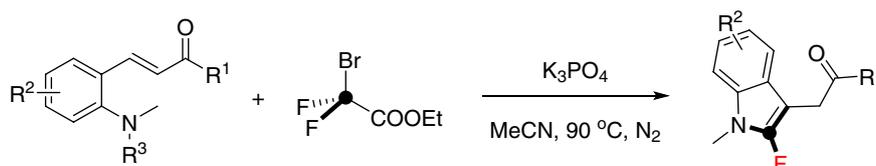
**Scheme 46** | C-F bond functionalizations of trifluoroacetamides and acetates.



**Scheme 47** | Using  $\text{BrCF}_2\text{CO}_2\text{Et}$  in the formation of fluorinated heteroaromatics.



**Scheme 48** | 3-Fluorinated oxindoles from 2-aminoarylketones and  $\text{BrCF}_2\text{CO}_2\text{Et}$ .



**Scheme 49** | 2-Fluoroindoles from ortho-vinylanilines and  $\text{BrCF}_2\text{CO}_2\text{Et}$ .

## Perspective

Owing to the importance of fluorine-containing compounds in many fields, the past decade has witnessed a surge of academic interest in the incorporation of the fluorine atom and fluoroalkyl groups into organic molecules. Despite great advances, several challenges still need to be addressed. (1) Most of the fluorinating and fluoroalkylating reagents require tedious synthesis, and some are air-/moisture-sensitive, which greatly retards their applications in the synthesis of fluorinated compounds in bulk. The development of more fluorinating and fluoroalkylating reagents with convenient methods in an economical manner are strongly needed. Moreover, the utilization of readily available inorganic fluoride salts as the fluorine source is also necessary. (2) The efficient and direct access to  $\text{ArOCF}_3$  has long been recognized as a formidable challenge in organic synthesis. Therefore, the development of reagents and reactions for the incorporation of trifluoromethoxy ( $\text{CF}_3\text{O}$ ) and other groups (such as  $\text{SF}_5$ ) into aromatic systems is highly desirable.

(3) Transition metal catalysis has played a vital role in the reported strategies, and the requirement of sustainability and economy calls for an increased focus on the development of earth-abundant transition metal catalysis (3d transition metals: from Ti to Cu) in a low catalytic loading. The merger of the recently developed photo- or electrocatalysis may convert the traditional harsh conditions into more mild conditions, leading to the development of environmentally benign strategies. In addition, more efforts need to be made toward the development of asymmetric synthesis of valuable enantioenriched fluorine-containing compounds. (4) The direct installation of fluorine or fluoroalkyl groups into bioactive molecules will continue to play an important role in the discovery of new drugs and agrochemicals. While many reported strategies for the incorporation of the fluorine atom rely on prefunctionalized substrates (alkenes, alkynes, carbonyls, organohalides, etc.), the direct C–H functionalization is undoubtedly an appealing approach since C–H bonds are ubiquitous in drug leads as well as many other bioactive compounds. Although a good site

selectivity has been observed in the radical C–H fluorooalkylation of heterocycles, the precise functionalization of simple aliphatic or aryl C–H bonds is still desirable.

## Acknowledgments

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