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A Fruitful Decade of Organofluorine Chemistry: New Reagents and Reactions

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Abstract

The development of synthetic methods for the introduction of fluorine atom and fluoroalkyl groups into organic molecules has gained increased attention. It was noteworthy that synthetic organic chemists recently jump 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.

Key Words: Fluorination; Fluoroalkylation; Reagent; Reaction; Fluorine Chemistry

1: Introduction

The fluorine atom has a very small size 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.¹ 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 the unique property, fluorinated compounds have found widespread applications in the preparation of pharmaceuticals, agrochemicals, and materials. It has been estimated that approximately 20% of pharmaceuticals and 50% of agrochemicals contain one or more fluorine atoms.² In addition, ¹⁸F-

labeled molecules are frequently used as imaging probes in positron emission tomography (PET) for diagnosis,³ 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_2), known as fluorite or fluorspar. Due to the inert reactivity of CaF_2 , Nature has hardly evolved a biosynthesis of fluorinated compounds. Therefore, natural products containing at least one fluorine atom are virtually absent, albeit with occasional occurrence.⁴ And almost all of organofluorine compounds in academia and industry were synthesized by chemists, thanks to the successful reaction of CaF_2 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 time 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 blooming 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 are very regretful that many excellent works were not included because of space limitation.

2: New fluorinating and fluoroalkylating reagents

2.1 Fluorinating reagents

2.1.1 Nucleophilic fluorinating reagents

The commonly used nucleophilic fluorinating reagents include metal fluoride salts (KF, CsF, and AgF), HF-based reagents ($\text{Et}_3\text{N}\cdot 3\text{HF}$ and $\text{pyridine}\cdot 9\text{HF}$), tetraalkylammonium fluorides and fluorinated hypervalent silicates. Over the past decade, several types of new nucleophilic fluorinating reagents have been developed (Figure 1). Hammond and Xu reported two novel HF-based reagents, $\text{DMPU}\cdot (\text{HF})_x$ ⁵ and $\text{KHSO}_4\cdot (\text{HF})_x$.⁶

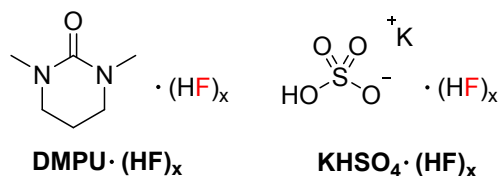


Figure 1. New nucleophilic fluorinating reagents

2.1.2 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_4 and its derivatives (e.g., DAST, Deoxo-Fluor, and XtalFluor). In 2010, Umemoto 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).⁷ 2-Pyridinesulfonyl fluoride (PyFluor) was developed by Doyle as an inexpensive and thermally stable deoxyfluorinating reagent.⁸ In 2011, Ritter reported a new deoxyfluorinating reagent PhenoFluor.⁹

In 2017, Hu reported the use of 3,3-difluoro-1,2-diarylcyclopropenes (CpFluors) as a class of novel deoxyfluorinating reagents with an all-carbon scaffold.¹⁰

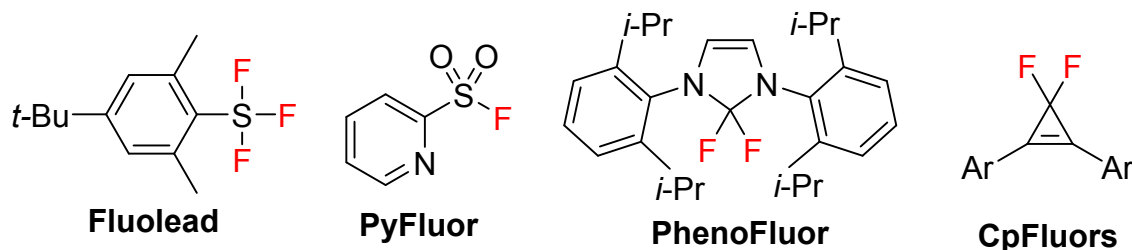


Figure 2. New deoxyfluorinating reagents

2.1.3 Electrophilic fluorinating reagents

The appearance of the commercially available and easy-to-handle electrophilic fluorinating reagents including NFSI, Selectfluor, *N*-fluoropyridinium salts (NFPY), and ArIF₂ has brought a breakthrough in synthetic fluorine chemistry. Over the past decade, a series of new electrophilic fluorinating reagents have been developed (Figure 3). Shibata¹¹ and Yang¹² independently reported the synthesis of substituted NFSI derivatives (**EF-I**). The chiral analogs of NFSI (**EF-II**) based on the *C*₂-symmetric chiral binaphthyl bis(sulfonimide) topology as a privileged motif were initially reported by Cahard, Ma, and Shibata.¹³ Gouverneur prepared a new class of chiral electrophilic fluorinating reagents **EF-III** based on the dicationic structural core of Selectfluor.¹⁴ In 2013, Stuart reported an air and moisture stable cyclic hypervalent iodine-based electrophilic fluorinating reagents **EF-IV**.¹⁵ Nevado synthesized chiral iodine(III) reagents **EF-V**.¹⁶

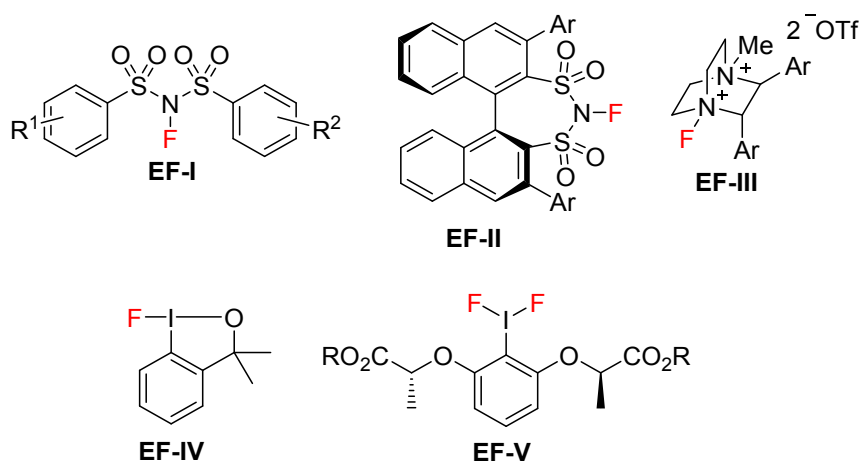


Figure 3. New electrophilic fluorinating reagents

2.2 Trifluoromethylating reagents

2.2.1 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, Lu and Shen reported trifluoromethyl-substituted sulfonium ylide as the electrophilic trifluoromethylating reagents (**ETF-I**) (Figure 4).¹⁷ In 2017, Umemoto reported powerful, thermally stable, one-pot-preparable and recyclable second-generation Umemoto's reagents (**Umemoto reagents II**).¹⁸ Ritter described in 2021 the Umemoto type reagent trifluoromethyl thianthrenium triflate (TT- $\text{CF}_3^+\text{OTf}^-$, **ETF-III**). TT- $\text{CF}_3^+\text{OTf}^-$ could serve not only as a competent electrophilic or a radical trifluoromethylating reagent but also as a nucleophilic trifluoromethylating reagent.¹⁹

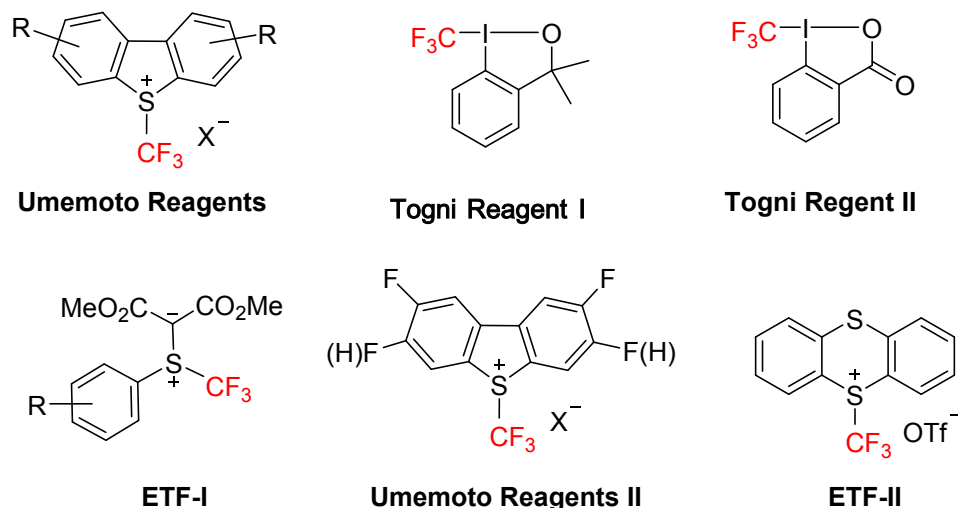


Figure 4. Electrophilic trifluoromethylating reagents.

2.2.2 Nucleophilic trifluoromethylating reagents

The most studied nucleophilic trifluoromethylating reagent was TMSCF_3 (Figure 5), so-called Ruppert-Prakash reagent. PhSO_2CF_3 and PhSOCF_3 could also serve as nucleophilic trifluoromethylating reagents in the presence of an alkoxide. Fluoroform (CF_3H) could also serve as a nucleophilic trifluoromethylating reagent. In 2011, Grushin and coworkers reported that reaction of fluoroform with $\text{CuCl}/\text{KO}^t\text{Bu}$ in DMF to give stable CuCF_3 after treatment with $\text{Et}_3\text{N} \cdot 3\text{HF}$ or $\text{Py} \cdot n\text{HF}$.²⁰

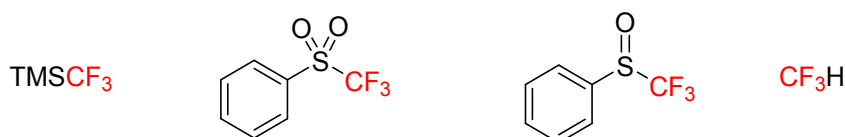


Figure 5. Nucleophilic trifluoromethylating reagents

2.2.3 Radical trifluoromethylating reagents

Even though electrophilic trifluoromethylating reagents could serve as 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 found that 1:1 adduct of CF_3I and tetramethylguanidine (TMG) forms a stable liquid $\text{TMG} \cdot \text{CF}_3\text{I}$, which acted as a radical trifluoromethyl reagent.²¹ Derivative of triflic acid or trifluoroacetic acid could also serve as trifluoromethyl radical precursor. One of the most studied radical trifluoromethyl reagent is $\text{CF}_3\text{SO}_2\text{Na}$ (Langlois' reagent). Trifluoromethanesulfonyl chloride ($\text{CF}_3\text{SO}_2\text{Cl}$) could also be used as a radical trifluoromethyl reagent,²² 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.²³ Baran described that $(\text{CF}_3\text{SO}_2)_2\text{Zn}$ was a more efficient radical trifluoromethylating reagent.²⁴ Trifluoroacetic anhydride could serve as a trifluoromethyl radical reagent in the presence of pyridine *N*-oxide under irradiation of blue light in combination with a photoredox catalyst.²⁵

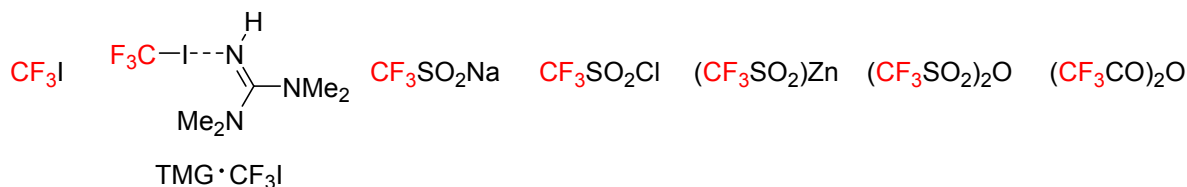


Figure 6. Radical trifluoromethylating reagents

2.3 Difluoromethylating reagents

Among all of nucleophilic difluoromethylating reagents, $\text{Me}_3\text{SiCF}_2\text{H}$ (Figure 7) was currently the most used nucleophilic difluoromethylating source. Difluoromethyl aryl sulfone ($\text{ArSO}_2\text{CF}_2\text{H}$) was a good alternative choice. In 2015, Shen 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.²⁶ An isolable and user-friendly zinc difluoromethyl reagent $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ was developed by Vicic.²⁷ In 2012, Baran reported the invention of a novel radical reagent $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ that was air-stable and free-flowing white powder.²⁸ Qing disclosed that (difluoromethyl)triphenylphosphonium bromide $[(\text{Ph}_3\text{PCF}_2\text{H})^+\text{Br}^-]$ might be the most easily available and handled radical difluoromethylating reagent under visible-light photoredox conditions.²⁹ Hu found that 2-[(difluoromethyl)sulfonyl]benzo[d]thiozole (**2-BT** $\text{SO}_2\text{CF}_2\text{H}$) was used as the precursor of difluoromethyl radical by visible-light photoredox catalysis.³⁰

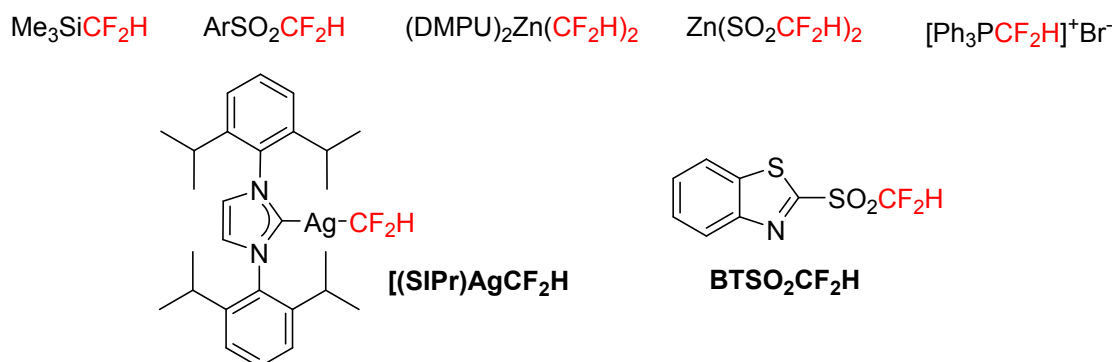


Figure 7. Difluoromethylating reagents

2.4 Monofluoromethylating reagents

Prakash reported in 2008 the first shelf-stable yet highly reactive electrophilic monofluoromethylating reagent *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**MEF-I**) (Figure 8).³¹ Shen reported the electrophilic monofluoromethylating reagents based on sulfonium ylide skeleton (**MEF-II**).³² Besides, two radical monofluoromethylating reagents $\text{CH}_2\text{FSO}_2\text{Na}$ ³³ and $(\text{CH}_2\text{FSO}_2)_2\text{Zn}$ ³⁴ have been reported by Hu and Baran respectively.

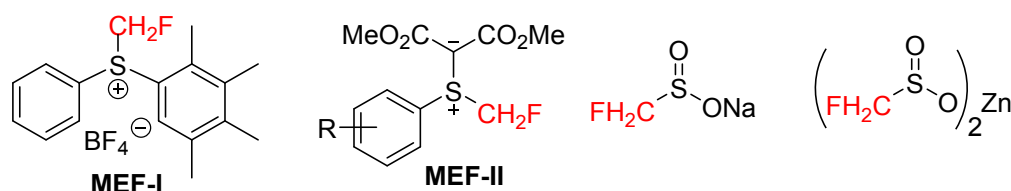


Figure 8. Monofluoromethylating reagents

2.5. Trifluoromethylthiolating reagents

2.5.1 Electrophilic trifluoromethylthiolating reagents

Before 2010, the electrophilic trifluoromethylthiolating reagent *N*-(trifluoromethylthio)phthalimide (**ESF-I**, Munavalli reagent)³⁵ was developed (Figure 9). In early 2013, Shibata reported a hypervalent iodonium ylide skeleton-based electrophilic trifluoromethylthiolating reagent (**ESF-II**).³⁶ Lu and Shen also reported in 2013 a new electrophilic trifluoromethylthiolating reagent (**ESF-III**, Lu-Shen reagent).³⁷ Later *N*-trifluoromethylthiosaccharin (**ESF-IV**, Shen reagent)³⁸ showcased unparalleled high electrophilicity. Furthermore, *N*-trifluoromethylthio bis(phenylsulfonyl)imide (**ESF-V**, Shen reagent II)³⁹ showed remarkably much higher electrophilicity.

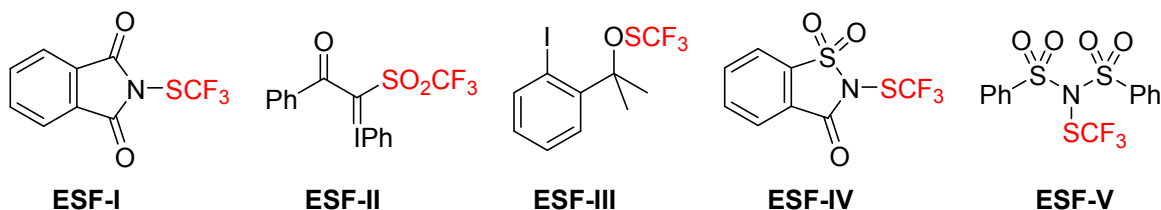


Figure 9. Electrophilic trifluoromethylthiolating reagents

2.5.2 Nucleophilic trifluoromethylthiolating reagents

AgSCF_3 and CuSCF_3 as well as Me_4NSCF_3 were widely used as the nucleophilic trifluoromethylthio sources (Figure 10). In 2012, Weng reported the two stable nucleophilic trifluoromethylthiolating reagents (L) CuSCF_3 (L = 2,2-bipyridine (bpy), 1,10-phenanthroline (phen)).⁴⁰ Likewise, in 2015, Vicic 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.⁴¹

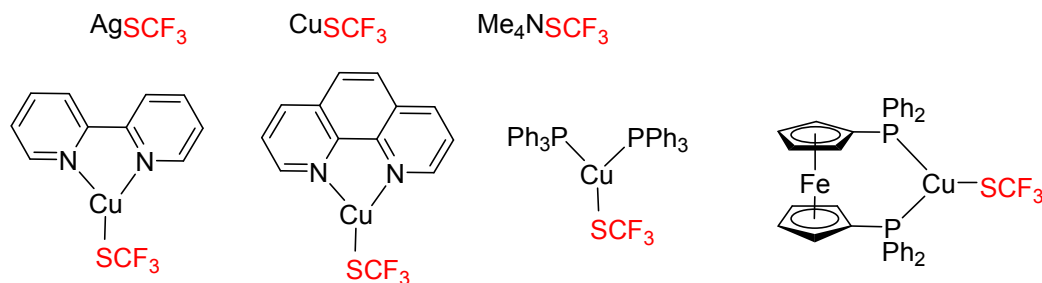
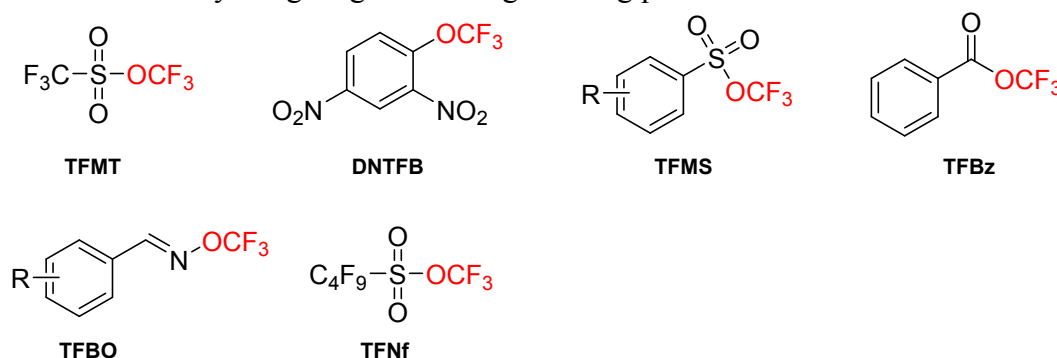
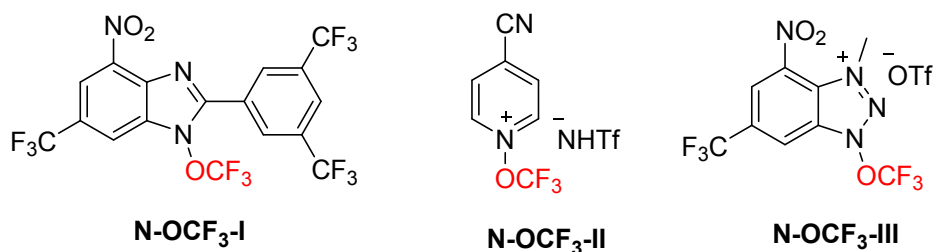


Figure 10. Nucleophilic trifluoromethylthiolating reagents**2.6. Trifluoromethoxylating reagents****2.6.1 Nucleophilic trifluoromethoxylating reagents**

In 2007, Kolomeitsev discovered that trifluoromethyl trifluoromethanesulfonate (**TFMT**, Figure 11) could generate CF_3O^- anion when treated with hard nucleophilic fluoride. In 2010, Langlois found that 2,4-dinitro(trifluoromethoxy)benzene (**DNTFB**) could be used as a new precursor of trifluoromethoxide anion. Tang discovered that trifluoromethyl sulfonates (**TFMS**) could be activated to release CF_3O^- in the presence of fluoride anions.⁴² Hu developed a new and practical trifluoromethoxylation reagent trifluoromethyl benzoate (**TFBz**).⁴³ In 2019, Tang reported a new nucleophilic trifluoromethoxylating reagent (*E*)-O-trifluoromethyl-benzaldoximes (**TFBO**).⁴⁴ Umemoto and Hammond discovered that trifluoromethyl nonafluorobutanesulfonate (**TFNf**) was a reactive trifluoromethoxylating reagent with high boiling point.⁴⁵

**Figure 11.** Nucleophilic trifluoromethoxylating reagents**2.6.2 Radical trifluoromethoxylating reagents**

In 2018, Ngai identified a benzimidazole bearing the $\text{N}-\text{OCF}_3$ moiety as a novel radical trifluoromethoxylating reagent under irradiation of blue LED (**N-OCF₃-I**, Figure 12).⁴⁶ Togni also discovered that trifluoromethoxypyridinium salt (**N-OCF₃-II**) was also radical trifluoromethoxylating reagent under the irradiation of blue light.⁴⁷ Furthermore, Ngai found that *N*-trifluoromethoxy triazolium salt (**N-OCF₃-III**) favors the selective generation of a single OCF_3 radical species after the SET reduction.⁴⁸

**Figure 12.** Radical trifluoromethoxylating reagents**2.7 Fluorinated carbene (difluorocarbene) reagents**

2.7.1 Fluoromethyl diazo and hydrazone reagents

Di- and trifluorodiazethane (XCF_2CHN_2 , $\text{X} = \text{F}, \text{H}$) is attractive precursor of XCF_2CH : carbene (Figure 13). In 2010, Carreira disclosed the *in-situ* generation of CF_3CHN_2 in a mixture of water and organic solvents.⁴⁹ In 2012, Ma developed a flow setup for the continuous gaseous CF_3CHN_2 generation/transformation sequence.⁵⁰ Subsequently, Mykhailiuk and Ma described the preparation of difluoromethyldiazo reagents.^{51,52} Zhang took advantage of trifluoroacetaldehyde toluenesulfonylhydrazone for the *in-situ* formation of CF_3CHN_2 .⁵³ Bi established trifluoroacetaldehyde *N*-triftoylhydrazones as bench-stable crystalline precursor to CF_3CHN_2 .⁵⁴

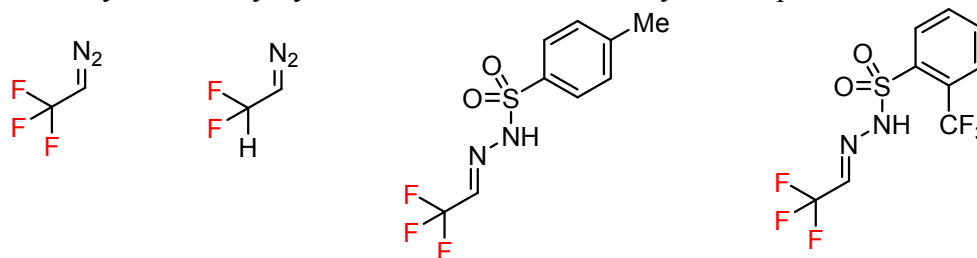


Figure 13. Fluoroalkyl diazo and hydrazone reagents

2.7.2 Difluorocarbene reagents

Difluorocarbene can be generated from many available and stable precursors. The earlier studies in this area focused on the use of environment-unfriendly or toxic reagents [such as CHXF_2 , CX_2F_2 ($\text{X} = \text{Cl}, \text{Br}$), Me_3SnCF_3 , or PhHgCF_3]. To overcome the problems, recent research has paid more attention to new surrogate molecules. Hu has centered on the development of (halodifluoromethyl)trimethylsilanes and difluoromethyltri(*n*-butyl)ammonium chloride (Figure 14) for the generation of difluorocarbene.⁵⁵⁻⁵⁷ Xiao demonstrated the reaction of $\text{BrCF}_2\text{CO}_2\text{K}$ and Ph_3P could smoothly afford the difluorocarbene precursor $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$ (PDFA).⁵⁸ Chen and Zhu 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 precursor. 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.⁵⁹

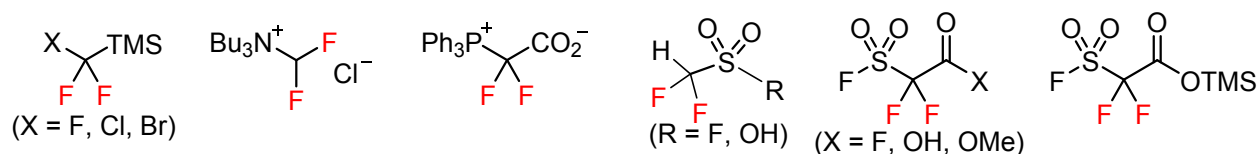


Figure 14. Difluorocarbene reagents

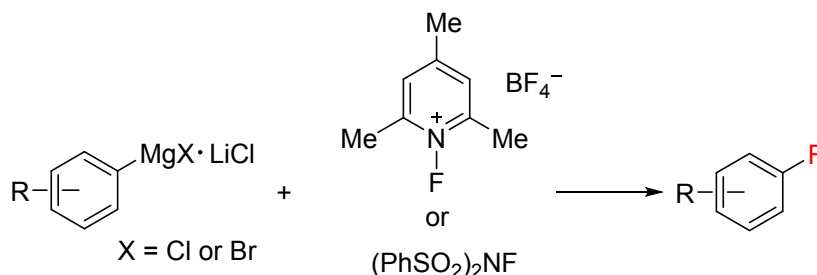
3: New fluorination and fluoroalkylation reactions

3.1 Electrophilic fluorination and fluoroalkylation reactions

3.1.1 Fluorination

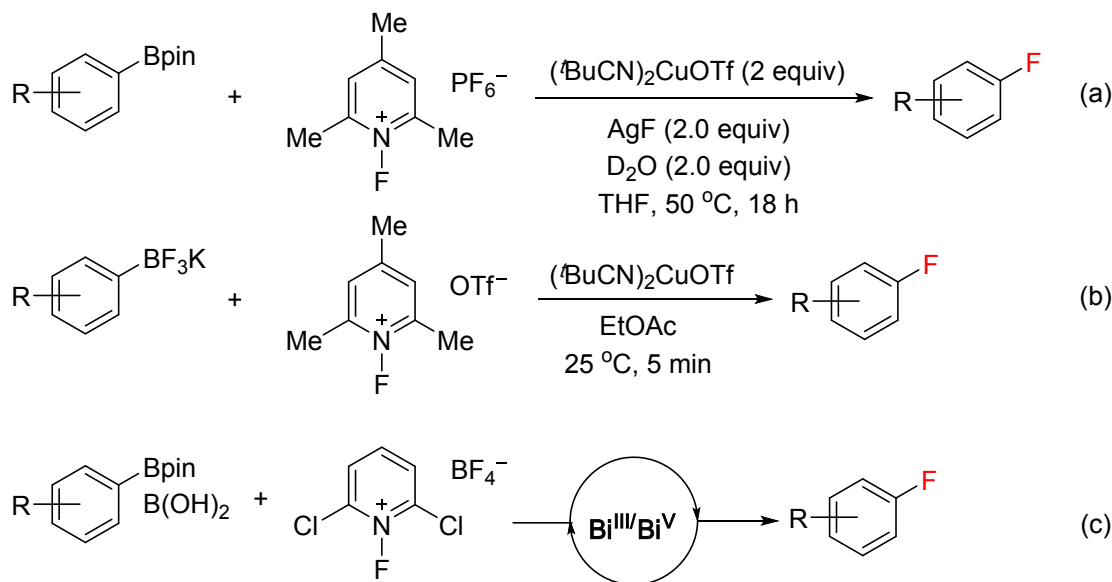
Aryl fluoride represents one of the most important structural motifs that are frequently found in many drug molecules. Classic methods for the preparation of aryl fluorides typically rely on the

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 electrophilic reagent. In 2010, Knochel and Beller independently reported reactions of (hetero)aryl magnesium reagents with *N*-fluorobenzenesulfonimide (NFSI) or *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (F-TMP-BF₄) to give the corresponding (hetero)aryl fluorides in high yields (Scheme 1).^{60,61}



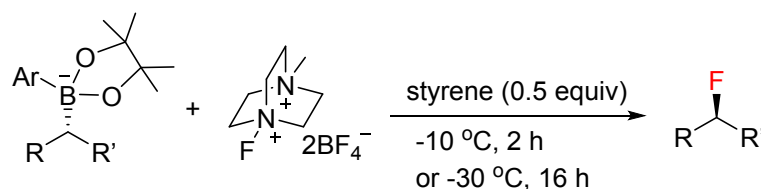
Scheme 1. Aryl fluoride formation from Grignard reagents

In 2013, Hartwig described the first copper-mediated fluorination of arylboronate esters using *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the electrophilic fluorine source (Scheme 2a).⁶² Shortly after, 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).⁶³ In 2020, Cornella 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).⁶⁴



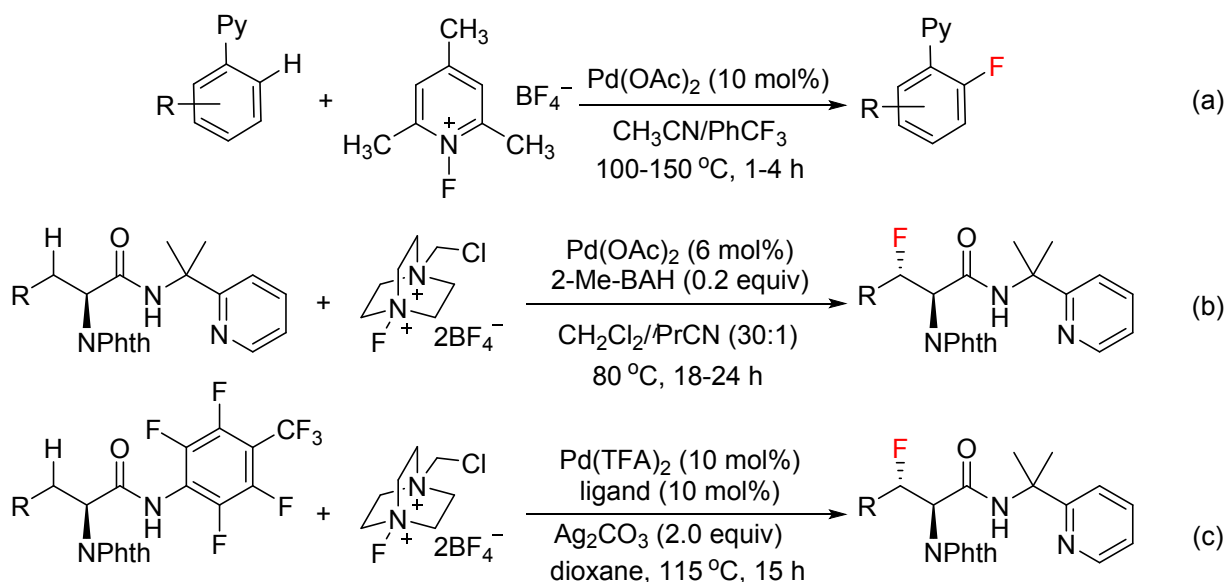
Scheme 2. Aryl fluoride formation from aryl boronic acids and derivatives

Aggarwal reported that “ate”-type lithium aryl alkyl boronate complexes reacted efficiently with Selectfluor in the presence of styrene to give stereospecifically alkyl fluorides with inversed configuration (Scheme 3).⁶⁵ It was proposed that the reaction proceeds via a polar S_E2_{inv} pathway and the role of styrene is to act as a radical scavenger to prohibit the SET pathway.



Scheme 3. Preparation of alkyl fluorides

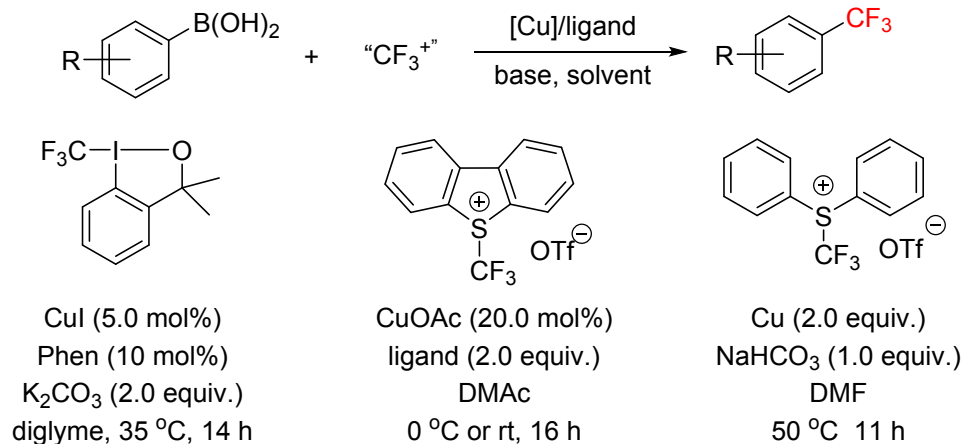
An alternative approach that using electrophilic fluorinating reagent is transition metal-catalyzed C-H fluorination. The first palladium-catalyzed directed arene *ortho* C-H bond fluorination was reported by Sanford in 2006 (Scheme 4a).⁶⁶ In 2015, Shi (Scheme 4b) and Yu (Scheme 4c) independently reported a Pd-catalyzed substrate-controlled methods for diastereoselective C(sp³)-H fluorination.^{67,68}



Scheme 4. Pd-catalyzed directed C-H fluorination

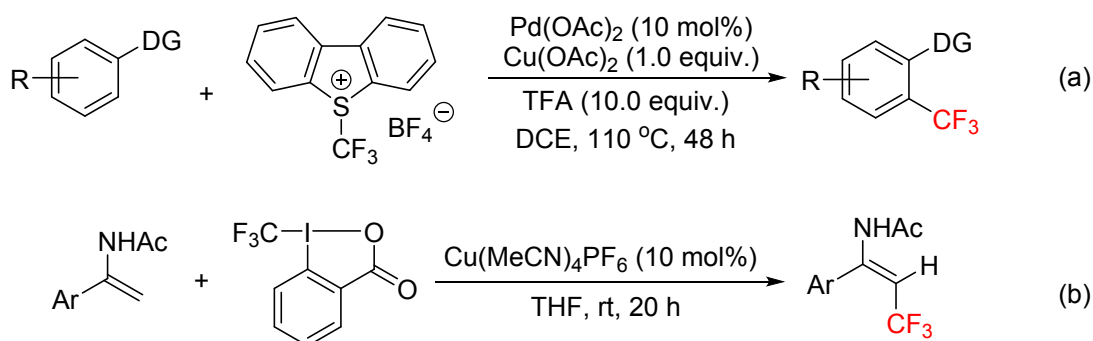
3.1.2 Trifluoromethylation

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).⁶⁹



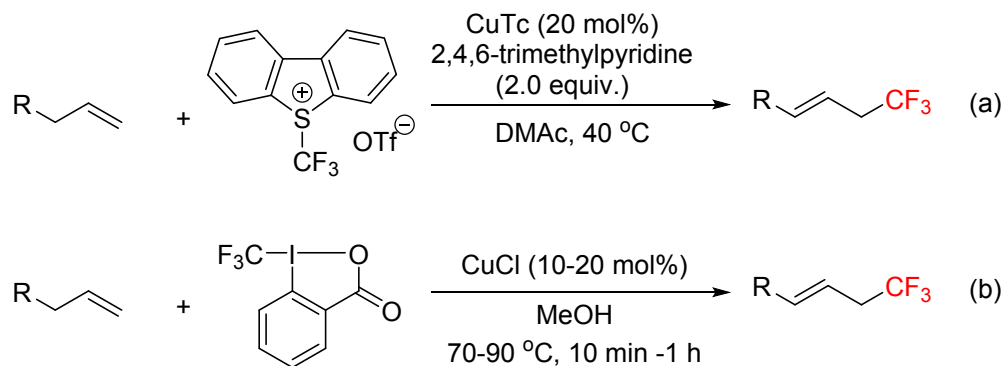
Scheme 5. Copper-mediated trifluoromethylation of aryl boronic acids

In 2010, Yu reported the first Pd(OAc)₂/Cu(OAc)₂ 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).⁷⁰ Not only aromatic C-H bonds, olefinic C-H bonds could be trifluoromethylated by an electrophilic trifluoromethylating reagent. In 2012, Loh found firstly that reactions of *N*-(1-phenylvinyl)acetamide with Togni's reagent II in the presence of 10 mol% Cu(MeCN)₄PF₆ occurred smoothly to give the *trans*-trifluoromethylated alkenes in good yields (Scheme 6b).⁷¹



Scheme 6. C-H trifluoromethylation

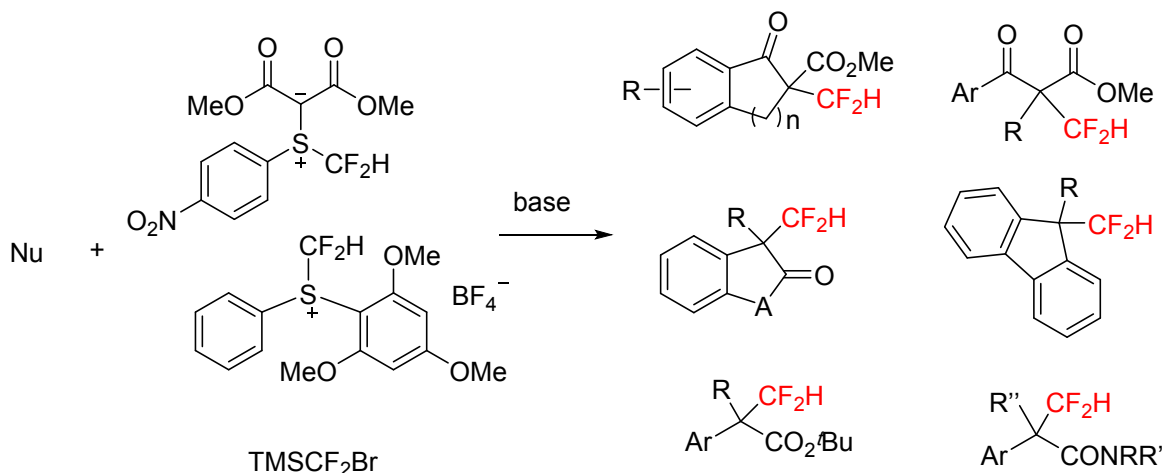
Allylic C-H bond also underwent C-H activation/trifluoromethylation, as groups of Liu and Wang reported simultaneously in 2011. In Liu's protocol, terminal alkenes reacted with Umemoto's reagent to give the trifluoromethylated products in high yields (Scheme 7a).⁷² Mechanistically, it was proposed that the reaction proceeds via a Heck-like four-membered-ring transition state. Likewise, Wang reported the similar allylic trifluoromethylation with Togni' reagent in good to excellent yields (Scheme 7b).⁷³



Scheme 7. Cu-catalyzed allylic C-H trifluoromethylation

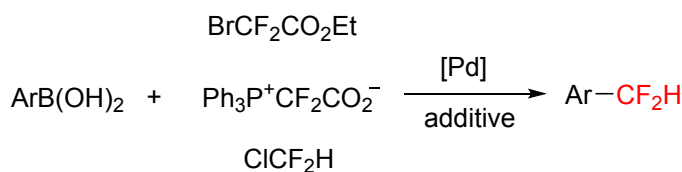
3.1.3 Difluoromethylation

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 β -ketoesters was first reported in 2018 by Shen using an isolated shelf-stable difluoromethyl-substituted ylide as difluoromethylating source and using Li_2CO_3 or LiO^tBu as the base (Scheme 8).⁷⁴ Mechanistic studies showed that the reaction occurred via a difluorocarbene intermediate and the lithium cation played an important role in alleviation the nucleophilicity of the oxygen in enolate. Likewise, in 2019, Liu and Hu reported that using *S*-(difluoromethyl)-*S*-phenyl-*S*-(2,4,6-trialkoxyphenyl) sulfonium salt⁷⁵ and TMSCF_2Br ,⁷⁶ respectively, as the difluorocarbene precursor could also achieve highly C-selective difluoromethylation of various soft carbon nucleophiles (Scheme 8).



Scheme 8. C-selective difluoromethylation of soft carbon nucleophiles

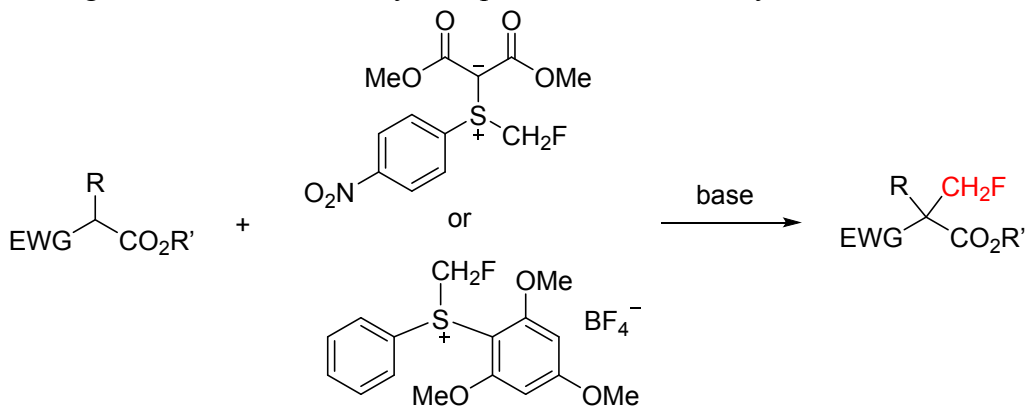
Transition metal catalysis could also mediate the coupling of a nucleophile such as boronic acid with the *in situ* generated difluorocarbene. Zhang reported in 2016 that palladium-catalyzed coupling of aryl boronic acids with $\text{BrCF}_2\text{CO}_2\text{Et}$, a difluorocarbene precursor, reacted smoothly to give difluoromethylated arenes in good yields (Scheme 9).⁷⁷ Shortly after, Xiao reported a similar reaction, in which $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$ (PDFA) was used as the difluorocarbene precursor.⁷⁸ In 2017, Zhang improved such reaction by using HCF_2Cl as the difluorocarbene precursor.⁷⁹



Scheme 9. Pd-catalyzed difluoromethylation of aryl boronic acids

3.1.4 Monofluoromethylation

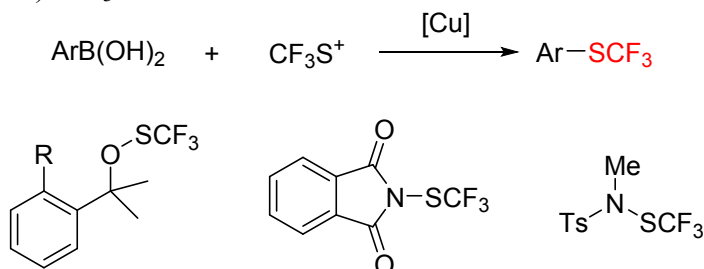
Monofluoromethyl group is a hard electrophile and the direct reaction of soft carbon nucleophiles with an electrophilic monofluoromethyl reagent often gave *o*-monofluoromethylated products. In 2017, Lu and Shen discovered that a monofluoromethyl sulfonium ylide was able to react with soft carbon nucleophile malonates to give C-monofluoromethylated products in excellent yields (Scheme 10).³² Likewise, Liu found that *S*-(monofluoromethyl)-*S*-phenyl-*S*-(2,4,6-trimethoxyphenyl) sulfonium salt is also a highly reactive electrophilic monofluoromethylating reagent which reacted with malonates, tetrahydroquinolinone carboxylate and pyrrolidinone carboxylate to give C-monofluoromethylated products in excellent yields.⁸⁰



Scheme 10. C-selective monofluoromethylation of soft carbon nucleophiles

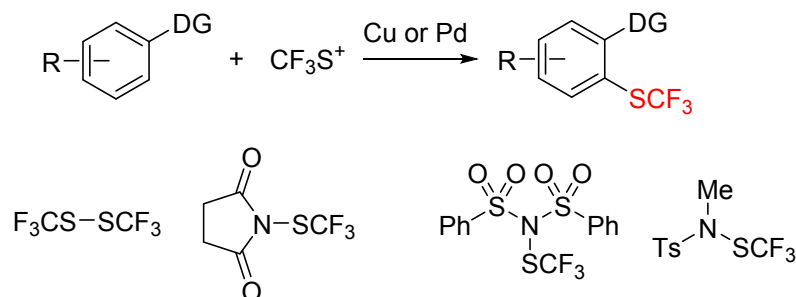
3.1.5 Trifluoromethylthiolation

The first copper-catalyzed coupling of aryl boronic acids with an electrophilic trifluoromethylthiolating reagent was reported by Shen in 2013 (Scheme 11).³⁷ In 2014, Rueping⁸¹ and Shen⁸² simultaneously reported a copper-catalyzed trifluoromethylthiolation of aryl boronic acids with *N*-trifluoromethylthiophthalimide (Manuvalli's reagent). In 2015, Billard reported the copper-catalyzed trifluoromethylthiolation of aryl boronic acids with the second-generation Billard's reagent TsN(Me)SCF₃.⁸³



Scheme 11. Cu-catalyzed trifluoromethylthiolation of aryl boronic acids

The first transition metal-catalyzed directed C-H trifluoromethylthiolation was reported by Daugulis using $\text{CF}_3\text{S}-\text{SCF}_3$ as the electrophilic trifluoromethylthiolating reagent (Scheme 12).⁸⁴ In 2015, Shen reported a palladium-catalyzed C-H trifluoromethylthiolation with *N*-trifluoromethylthiosuccinimide.⁸⁵ 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 directed C-H trifluoromethylthiolation using Shen's *N*-trifluoromethylthiosaccharin and $(\text{PhSO}_2)_2\text{NSCF}_3$, as the electrophilic trifluoromethylthiolating source respectively.⁸⁶

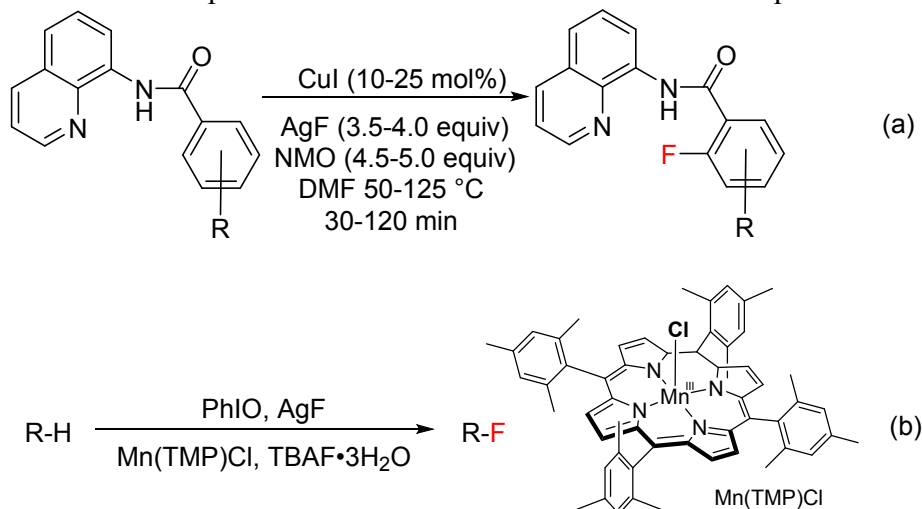


Scheme 12. Transition metal-catalyzed C-H trifluoromethylthiolation

3.2. Nucleophilic fluorination and fluoroalkylation reactions

3.2.1 Fluorination

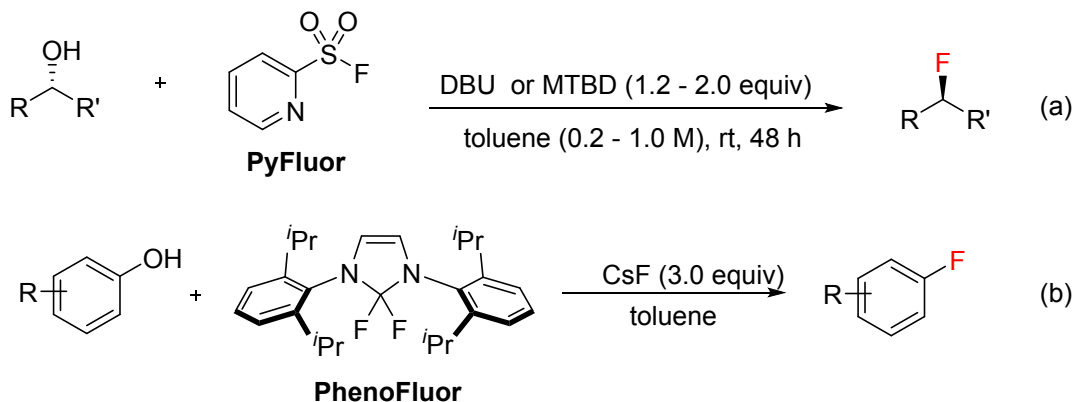
Daugulis reported the first Cu-catalyzed directed C-H fluorination of arenes with AgF in combination with the terminal oxidant *N*-methylmorpholine *N*-oxide (Scheme 13a).⁸⁷ This C-H fluorination was proposed to possibly proceed through C-F reductive elimination from a high-oxidation-state Cu^{III} fluoride complex. Direct sp^3 C-H fluorination is an efficient synthesis method for introducing fluorine atoms into alkanes. In 2012, Groves reported manganese catalyzed oxidative C-H bond fluorination using AgF (Scheme 13b).⁸⁸ This was the first catalytic method for selective and direct incorporation of fluoride ion into the unreactive sp^3 C-H bond.



Scheme 13. C-H fluorination

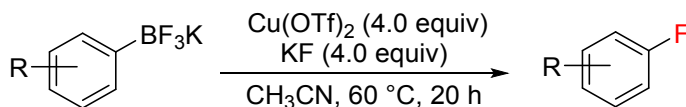
Deoxyfluorination of alcohols has found widespread applications due to the abundance and accessibility of alcohol-containing precursors. However, the traditional use of DAST for

deoxyfluorination is limited by the functional group tolerance and formation of the elimination side products. In 2015, Doyle reported a low-cost and highly thermal stable deoxyfluorination reagent PyFluor for deoxyfluorination of alcohols (Scheme 14a).⁸ Phenols are also an ideal starting material for fluorination reactions. In 2011, Ritter developed a new deoxyfluorination reagent PhenoFluor for *ipso*-fluorination of phenols to deliver aryl fluorides in one-step (Scheme 14b).⁹



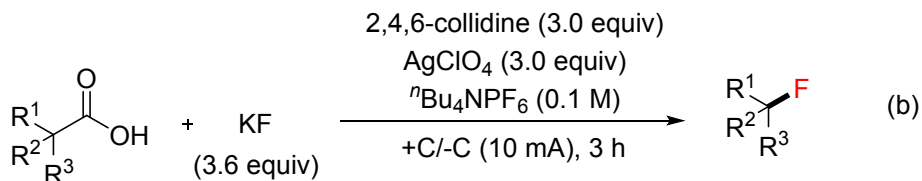
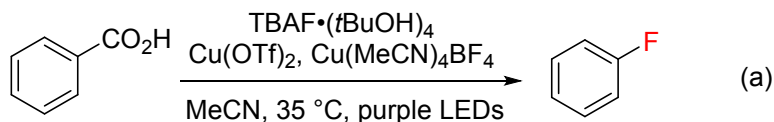
Scheme 14. Deoxyfluorination of hydroxy group

Aryl boron reagents are particularly attractive starting materials for C–F bond-forming reactions. In 2013, Sanford reported a remarkably mild and general fluorination method by Cu-mediated fluorination of aryltrifluoroborates with potassium fluoride (Scheme 15).⁸⁹ 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.



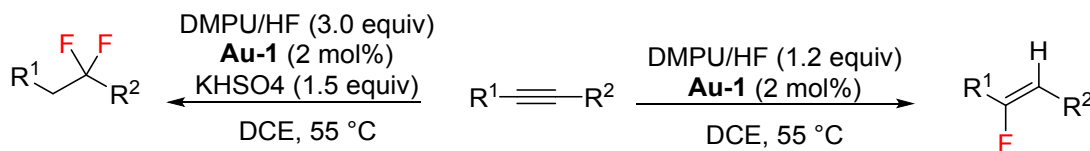
Scheme 15. Cu(OTf)₂-mediated fluorination of aryltrifluoroborates

Ritter developed a photoinduced decarboxylative fluorination of benzoic acid derivatives with fluoride (Scheme 16a).⁹⁰ The author proposed that copper has two roles in this reaction: one is to reduce the barrier of photo-induced 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 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).⁹¹



Scheme 16. Decarboxylative fluorination

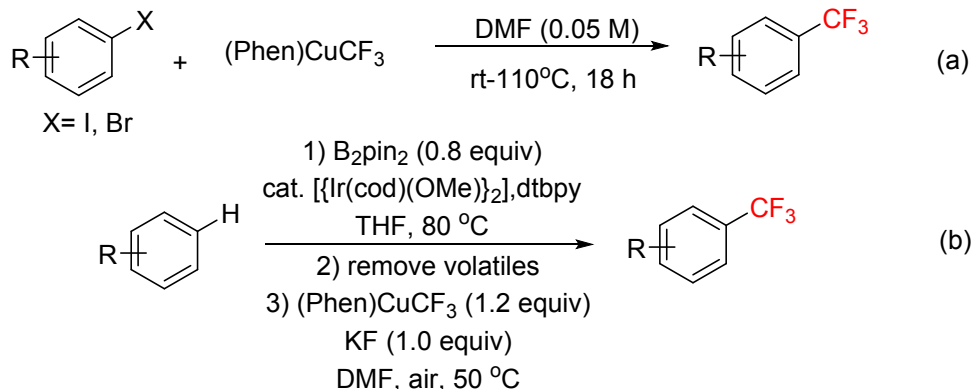
Pyridine/HF and triethylamine/HF have been explored extensively as nucleophilic fluorination reagents. Because of their strong alkalinity, they may interfere with many metal catalysts. In 2014, Xu reported that DMPU/HF could be used in the gold-catalyzed high regioselective mono- and dihydrofluorination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



Scheme 17. Hydrofluorination of alkynes

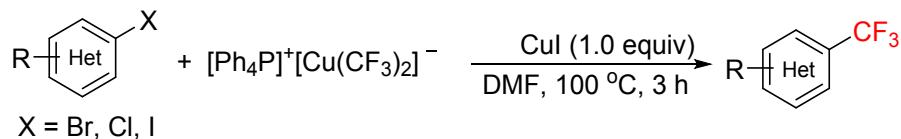
3.2.2 Trifluoromethylation

Copper-mediated/catalyzed cross-coupling reaction of electrophiles with nucleophilic trifluoromethylating reagents has proven to be an efficient strategy for the construction of C(sp²)-CF₃ bonds. TMS-CF₃ is widely used as the nucleophilic trifluoromethyl source. The trifluoromethylation proceeded through the *in situ* generated CuCF₃ intermediate via transmetalation of the nucleophilic CF₃ moiety to copper. Over the past decade, several well-defined trifluoromethylated copper (I) complexes were prepared and evaluated in trifluoromethylation reactions. In 2011, Hartwig developed an isolable and stable trifluoromethylcopper(I) reagent [(phen)CuCF₃] for trifluoromethylations of aryl iodides and bromides in DMF at room temperature to 110 °C (Scheme 18a).⁹² Hartwig also successfully achieved one-pot C-H trifluoromethylation of arenes *via* the formation of an arylboronate ester *in situ* (Scheme 18b).⁹³ Arene was first converted to aryl boronate esters in the presence of Ir catalyst followed by copper-mediated oxidative trifluoromethylation with [(phen)CuCF₃].



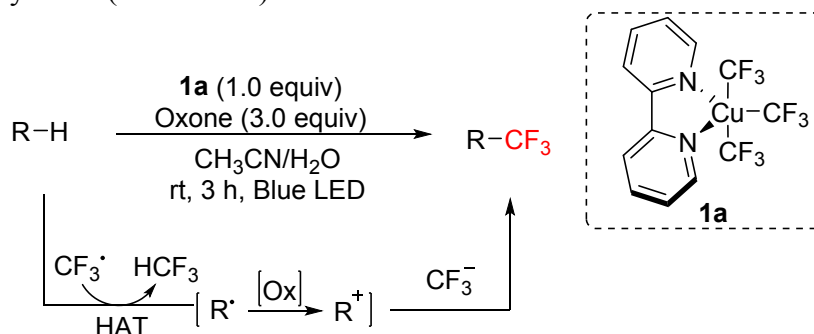
Scheme 18. Trifluoromethylation with (phen)CuCF₃

It was suggested that [Cu(CF₃)₂][−] might act as the reservoir for the generation of active “CuCF₃”. To verify the conjecture that whether and how the active “CuCF₃” were produced from bistrifluoromethylated cuprate [Cu(CF₃)₂][−], Shen prepared a stable bistrifluoromethylated cuprate [Ph₄P]⁺[Cu(CF₃)₂][−] and tested its reactivity. It was found that the active “CuCF₃” generated from [Ph₄P]⁺[Cu(CF₃)₂][−] **1** and CuI was highly reactive to allow the trifluoromethylation of activated heteroaryl bromides and chlorides (Scheme 19).⁹⁴



Scheme 19. Trifluoromethylation of activated heteroaryl halides

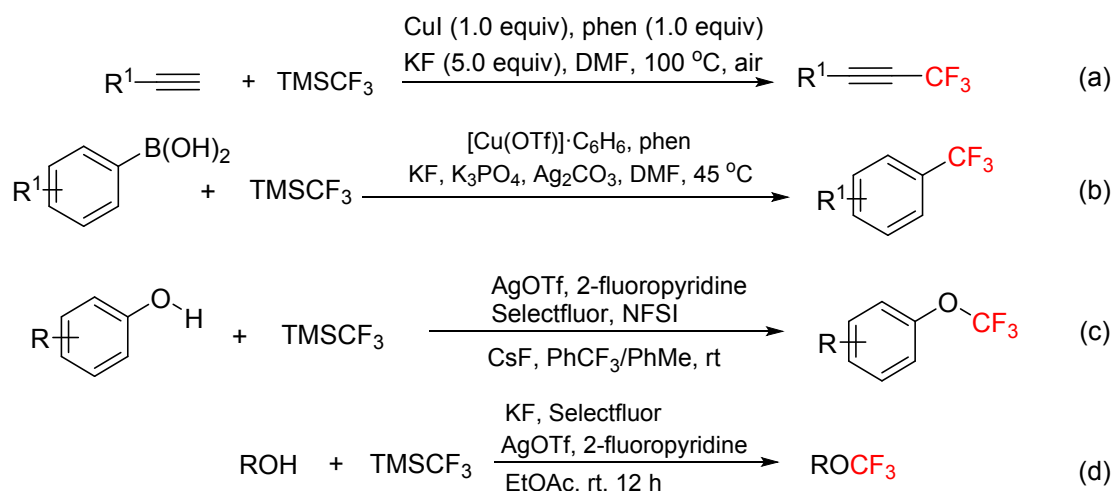
The C(sp²)-H trifluoromethylation reaction has been extensively investigated for the installation of trifluoromethyl groups into arenes, heteroarenes, olefins, and aldehydes. However, C(sp³)-H trifluoromethylation was rarely reported, especially for those unactivated alkanes. In 2021, Hong described a mild and efficient method for the direct C(sp³)-H trifluoromethylation of the unactivated alkanes by using [bpyCu(CF₃)₃] as the initiator for the visible-light-promoted reaction, trifluoromethyl radical source for hydrogen atom transfer (HAT), and trifluoromethyl anion source for trifluoromethylation (Scheme 20).⁹⁵



Scheme 20. Direct C(sp³)-H trifluoromethylation of unactivated alkanes.

In 2010, Qing proposed the concept of oxidative trifluoromethylation: the reaction of a nucleophilic substrate with a nucleophilic trifluoromethylating reagent in the presence of an

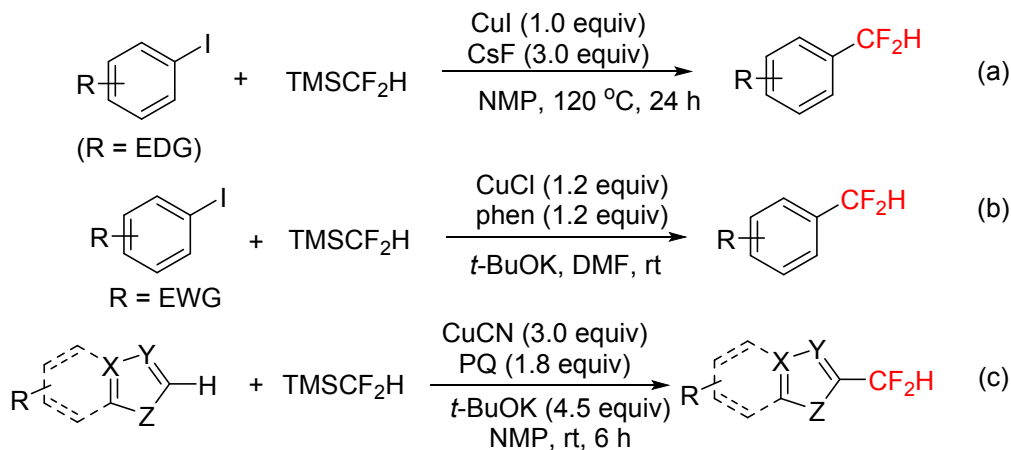
oxidants.⁹⁶ The first oxidative trifluoromethylation was applied to alkynes using TMSCF_3 as nucleophilic trifluoromethyl source for the formation of trifluoromethylated acetylenes (Scheme 21a).⁹⁷ Subsequently, the first copper-mediated oxidative trifluoromethylation of aryl boronic acids was developed (Scheme 21b).⁹⁸ An efficient method for the preparation of aryl(alkyl) trifluoromethyl ethers by AgOTf -mediated oxidative trifluoromethylation phenols(alcohols) with TMSCF_3 using Selectfluor as the oxidant at room temperature was also developed (Scheme 21c-d).⁹⁹⁻¹⁰⁰ Especially, trifluoromethylation of various primary, secondary, tertiary alcohols and a series of structurally complex medicinal molecules with a hydroxy group proceeded efficiently under mild reaction conditions.



Scheme 21. Oxidative trifluoromethylation.

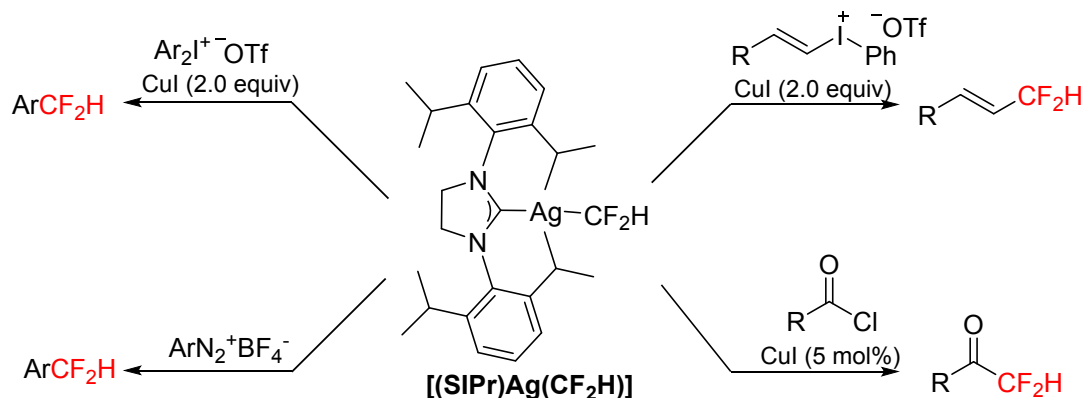
3.2.3 Difluoromethylation

In 2012, Hartwig reported a copper-mediated difluoromethylation of aryl iodides with TMSCF_2H (Scheme 22a).¹⁰¹ Nevertheless, the electron-deficient aryl iodides were not suitable for this transformation. Then in 2014, Qing 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).¹⁰² In 2018, copper-mediated C–H oxidative difluoromethylation of heteroarenes using TMSCF_2H as difluoromethyl source was developed by Qing (Scheme 22c).¹⁰³ It is worth noting that the CF_2H 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.



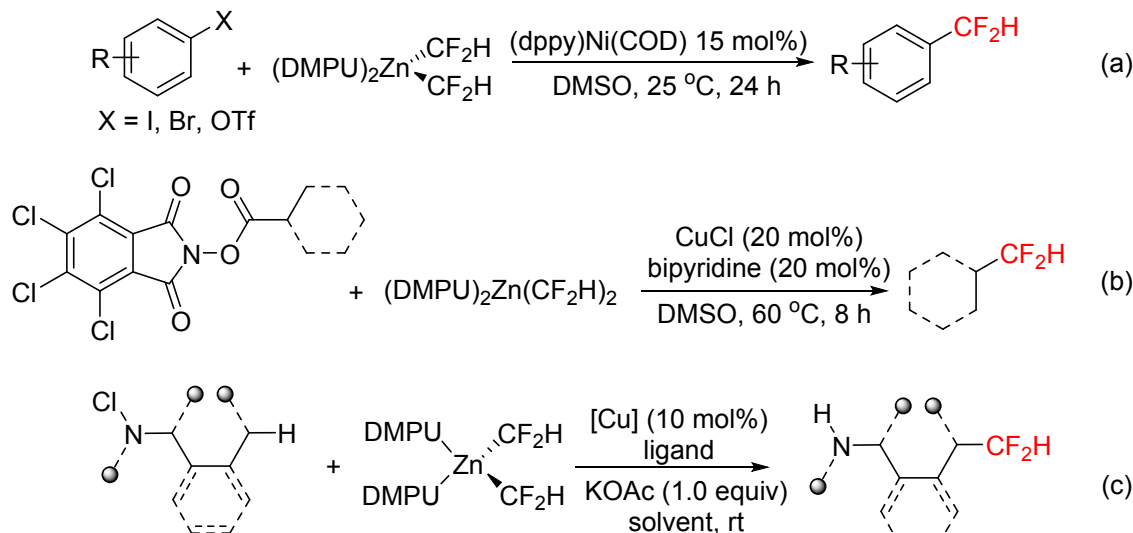
Scheme 22. Direct difluoromethylation with TMSCF_2H .

In 2015, Shen achieved successfully 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 CuI at room temperature (Scheme 23).²⁶



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

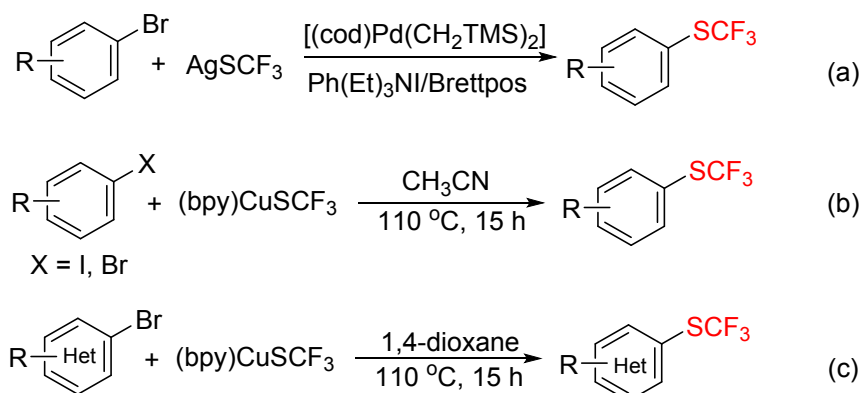
In 2016, Vicic reported the nickel-catalyzed difluoromethylation of aryl iodides, bromides, and triflates with $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ (Scheme 24a).²⁷ Using $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ as difluoromethyl source, Liu successfully developed efficient Cu-catalyzed decarboxylative difluoromethylation reaction of aliphatic carboxylic acids (Scheme 24b),¹⁰⁴ 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).¹⁰⁵



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

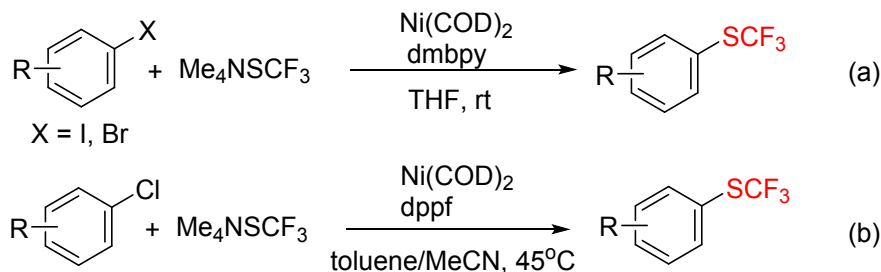
3.2.4 Trifluoromethylthiolation

In 2011, Buchwald developed a general method for synthesis of Ar-SCF₃ compounds through the Pd-catalyzed reaction of aryl bromides with AgSCF₃ (Scheme 25a).¹⁰⁶ Weng reported that the cross-coupling reaction between aryl halides with (bpy)CuSCF₃ gave aryl trifluoromethyl thioethers in good yields (Scheme 25b).⁴⁰ Weng subsequently reported that trifluoromethylthiolated heteroarenes could be prepared by direct trifluoromethylthiolation of a series of heteroaryl bromides with (bpy)CuSCF₃ (Scheme 25c).¹⁰⁷



Scheme 25. Trifluoromethylthiolation of aryl halides.

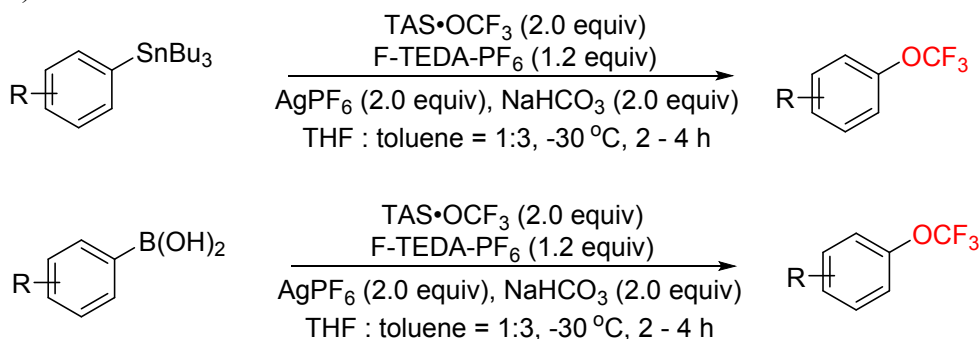
Vicic described the Ni(COD)₂/dmbpy catalytic system for nucleophilic trifluoromethylthiolation of aryl iodides and bromides with Me₄NSCF₃ under mild reaction conditions (Scheme 26a).¹⁰⁸ Interestingly, when dppf was used as ligand instead of dmbpy, Schoenebeck found that the nickel-based catalytic systems were also able to activate C(sp²)-Cl bond for the trifluoromethylthiolation of aryl chlorides (Scheme 26b).¹⁰⁹ Computational and experimental studies suggest a Ni⁰/Ni^{II} cycle involving oxidative addition of the C(sp²)-Cl bond and C(sp²)-SCF₃ reductive elimination.



Scheme 26. Nickel-catalyzed trifluoromethylthiolation of aryl halides.

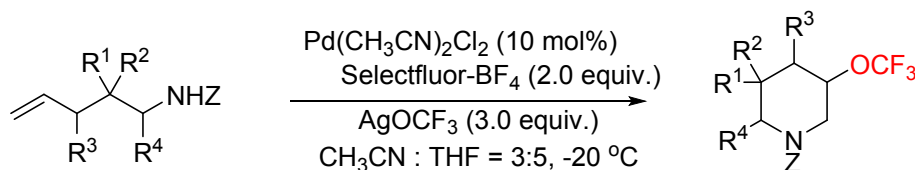
3.2.5 Trifluoromethoxylation

The introduction of OCF₃ group into organic molecules is regarded as a significant value-added but challenging conversion due to the easily decomposing character of the trifluoromethyl anion and limited trifluoromethoxylating reagents. In 2011, Ritter first reported silver-mediated trifluoromethoxylation of aryl stannanes and arylboronic acids using TAS•OCF₃ as OCF₃ source (Scheme 27).¹¹⁰



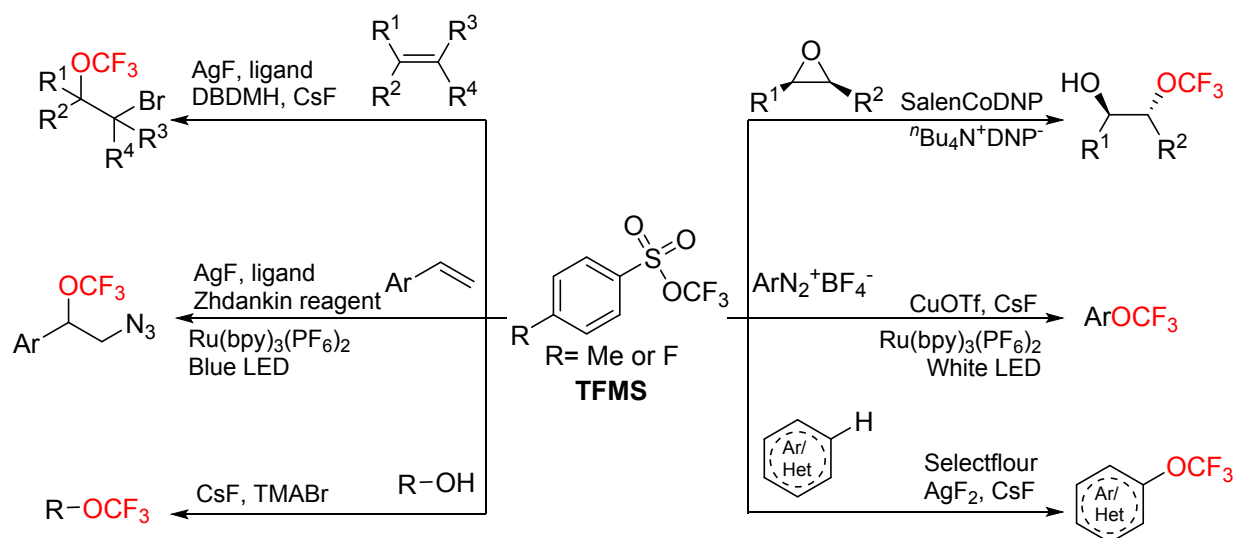
Scheme 27. Trifluoromethoxylation of aryl stannanes and arylboronic acids.

In 2015, Liu established the first catalytic trifluoromethoxylation of unactivated alkenes by employing Pd(CH₃CN)₂Cl₂ as catalyst, AgOCF₃ as trifluoromethoxide source, and Selectfluor-BF₄ as oxidant (Scheme 28).¹¹¹ Mechanistic studies illustrated that the key intermediate Pd^{IV}OCF₃ is relative stable, and undergoes faster reductive elimination than β-fluoride elimination for the formation of C-OCF₃ bond.



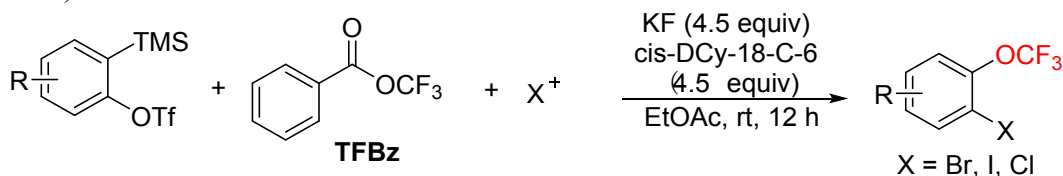
Scheme 28. Aminotrifluoromethoxylation reaction of unactivated alkenes.

In 2017, Tang developed a new trifluoromethoxy reagent TFMS for asymmetric bromotrifluoromethoxylation of alkenes. This is the first example of catalytic enantioselective trifluoromethoxylation reaction (Scheme 29).¹¹² The discovery of TFMS reagent brings new opportunities for the direct trifluoromethoxylation. By employing TFMS as a nucleophilic trifluoromethoxylating reagent, Tang successfully achieved azidotrifluoromethoxylation of styrenes,¹¹³ direct dehydroxytrifluoromethoxylation of alcohols,¹¹⁴ hydroxyltrifluoromethoxylation of epoxides,¹¹⁵ trifluoromethoxylation of aryl diazonium salts,¹¹⁶ and the direct C(sp²)-H trifluoromethylation of arenes and heteroarenes (Scheme 29).¹¹⁷



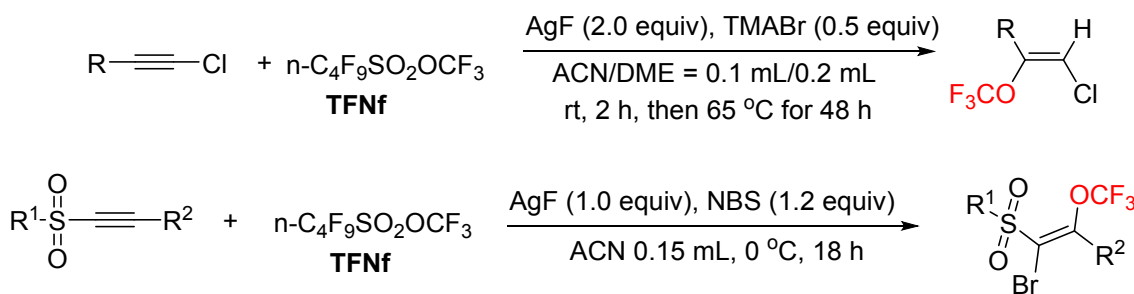
Scheme 29. Trifluoromethoxylation with TFMS.

In 2018, Hu 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).⁴³



Scheme 30. Trifluoromethoxylation-halogenation of arynes.

Unemoto and Hammond 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).⁴⁵



Scheme 31. Hydrotrifluoromethoxylation with TFNf.

3.3 Radical fluorination and fluoroalkylation reactions

The radical reactions are undoubtedly experiencing a renaissance since the end of 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_f) radicals: the combination of σ inductive effect and π donating effect of 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_f radicals are involved in the key C– R_f bond formation step.

3.3.1 Trifluoromethylation

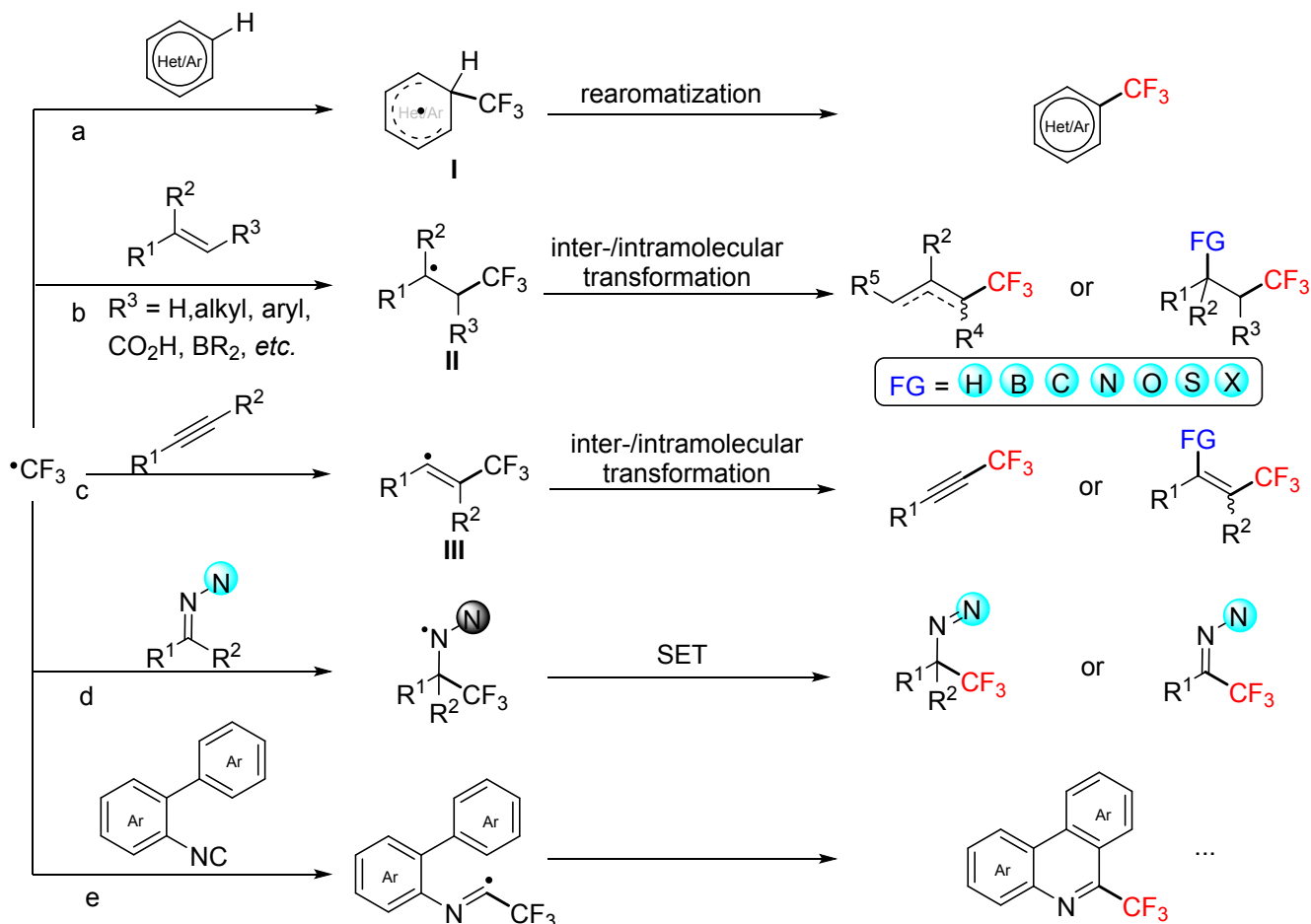
The flourishing development of radical trifluoromethylation mainly relies both on the design of new trifluoromethylating reagents that are readily accessible and the development of reaction conditions that are mild and easily-operational. A number of strategies that could initiate the radical trifluoromethylation have been reported, including photochemical, electrochemical, thermal, metal or metal-free catalysis, and photoredox catalysis.¹¹⁷ The scope of arenes covers benzene, mono-/multi-substituted benzenes with electro-donating or withdrawing-groups, and polyarenes. Meanwhile, a wide range of heteroarenes successfully undergo radical trifluoromethylation smoothly. The generally accepted mechanism is the initiation of a radical precursor under suitable conditions to generate a CF_3 radical, which reacts with the aromatic ring to provide a reactive radical intermediate **I** (Scheme 32a). The rearomatization process would give rise to the final products. The advantage for the radical aryl C–H trifluoromethylation is the atom- and step-economy without the need for prefunctionalized 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 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,^{118c} hydrotrifluoromethylation,^{118c} trifluoromethylboration,¹¹⁹ carbotrifluoromethylation,¹²⁰ oxytrifluoromethylation,¹²¹ aminotrifluoromethylation,^{118e} halotrifluoromethylation,¹²² thiotrifluoromethylation,^{118c} and trifluoromethylthio-trifluoromethylation,¹²³ *etc* (Scheme 32b). Mechanistically, the reaction is initiated by the generation of a CF_3 radical from diverse radical precursors. The 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 process 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 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 CF_3 radical reacts also with alkynes which is demonstrated in an early work on the iodotrifluoromethylation of alkenes. The mechanism is similar: the 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 different structure and property between alkyl radical **II** and vinyl radical **III**, the trapping reagents are similar to that of alkenes.¹²⁴⁻¹²⁶

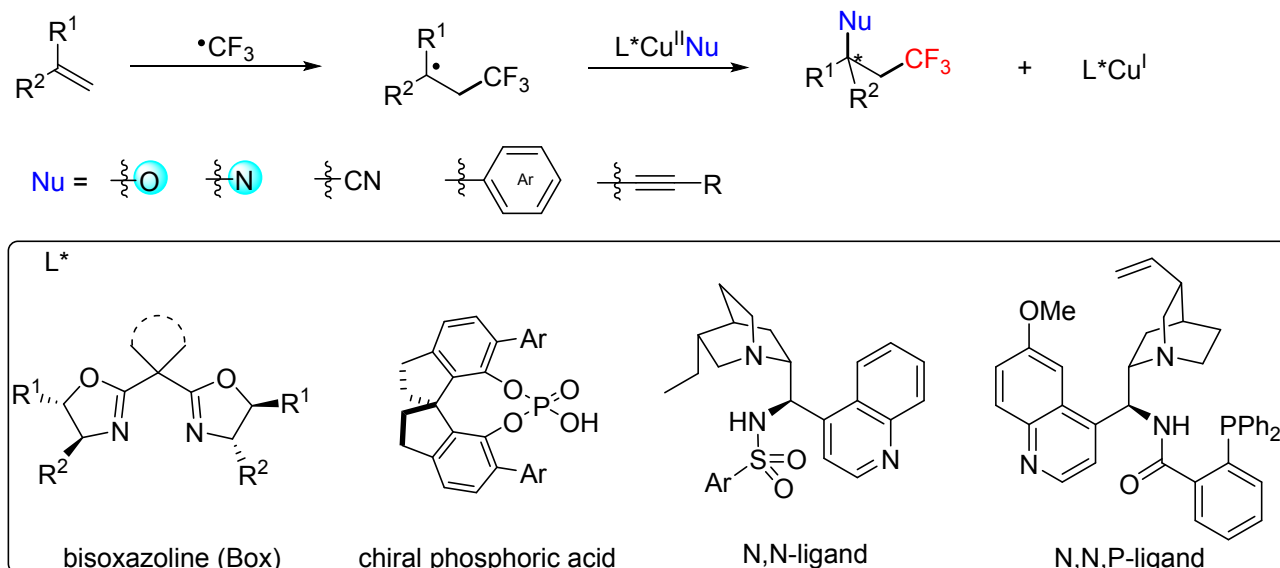
While imines are not good radical acceptors, hydrazones are better ones and represent another class of unsaturated bonds to react with the CF_3 radical. This is because the thus formed hydrazinyl radical **IV** derived from the addition of the CF_3 radical to the hydrazone moiety could be stabilized via the formation of a two-center, three-electron π bond with the lone pair of the adjacent nitrogen

atom (Scheme 32d).^{118d,127} Besides, the 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).^{118b,127}



Scheme 32. The addition of CF_3 radical to unsaturated bonds

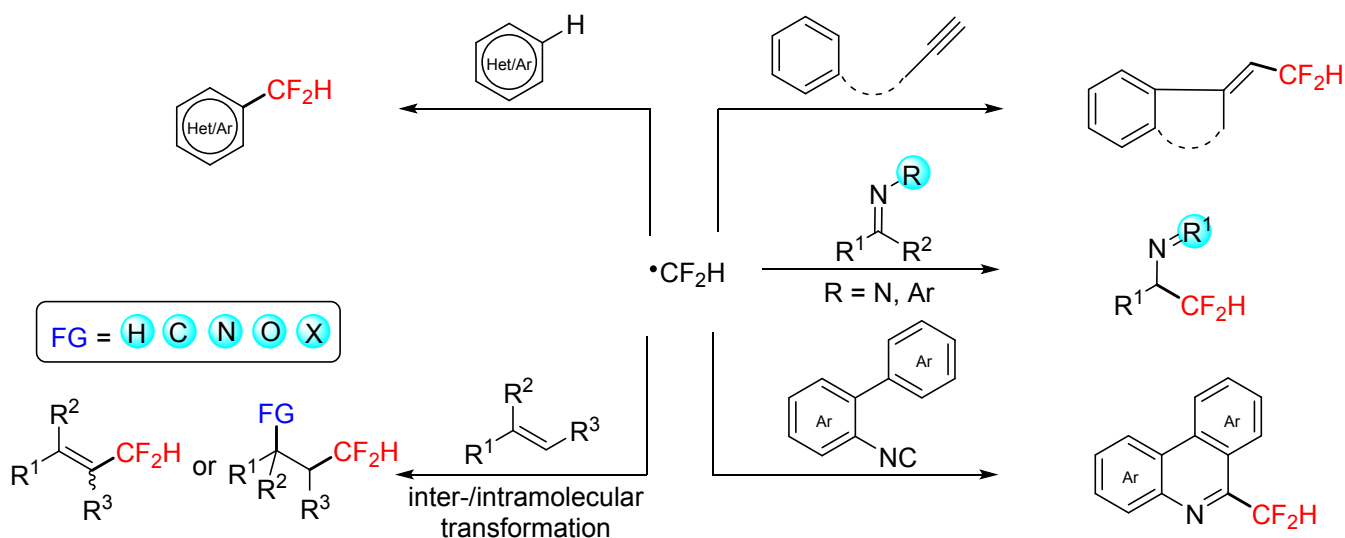
It is only until recently that the trifluoromethyl radical has been harnessed in the enantioselective trifluoromethylation. The enantioselective radical 1,2-trifluoromethylation of alkenes has been disclosed by merging chiral copper catalysis with radical addition process from 2013.¹²⁹ Buchwald developed a copper/chiral bisoxazoline ligand catalytic system for achieving the intramolecular enantioselective oxytrifluoromethylation of alkenes (Scheme 33).¹³⁰ G. Liu from SIOC and others has elegantly disclosed a series of inter- and intramolecular enantioselective carbo-, azido- and aminotrifluoromethylation of alkenes utilizing this catalytic system (Scheme 33).¹³¹ At the same time, X.-Y. Liu from SUSTech developed the amino-, oxy-, and carbotrifluoromethylation of alkenes by designing an array of chiral anionic ligands, such as chiral phosphoric acid,¹³² anionic N,N-ligand,¹³³ and anionic N,N,P-ligand (Scheme 33).¹³⁴



Scheme 33. The enantioselective radical trifluoromethylation reaction

3.3.3. Difluoromethylation

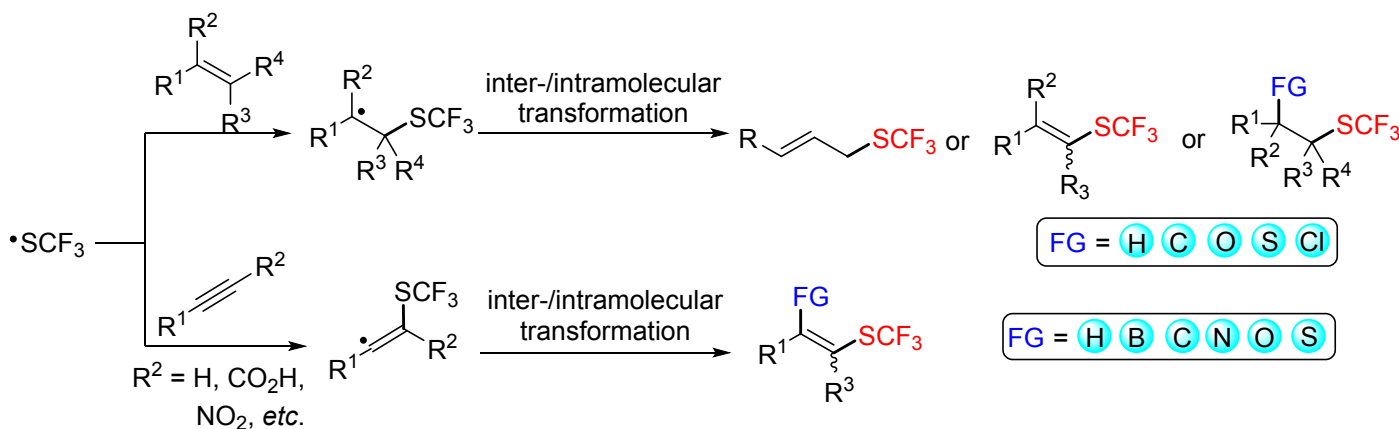
The radical difluoromethylation reactions have also been well developed in the past decade. Similar to the CF_3 radical, the CF_2H radical reacts readily with unsaturated bond systems (Scheme 34). The transition metal-mediated coupling of prefunctionalized arenes with an electrophilic difluoromethylating reagent provides a versatile tool in the synthesis of difluoromethylated arenes where the CF_2H radical is sometimes proposed to be involved.¹³⁵ In addition, the CF_2H radical also reacts with alkenes,¹³⁶ $\text{C}=\text{N}$ bonds,¹³⁷ and isocyanides,^{30,138} where the initiation step is the addition of a CF_2H radical to the unsaturated bonds, while the trapping reagents are similar to those of radical trifluoromethylation reactions.



Scheme 34. The addition of CF_2H radical to unsaturated bonds

3.3.4 Trifluoromethylthiolation

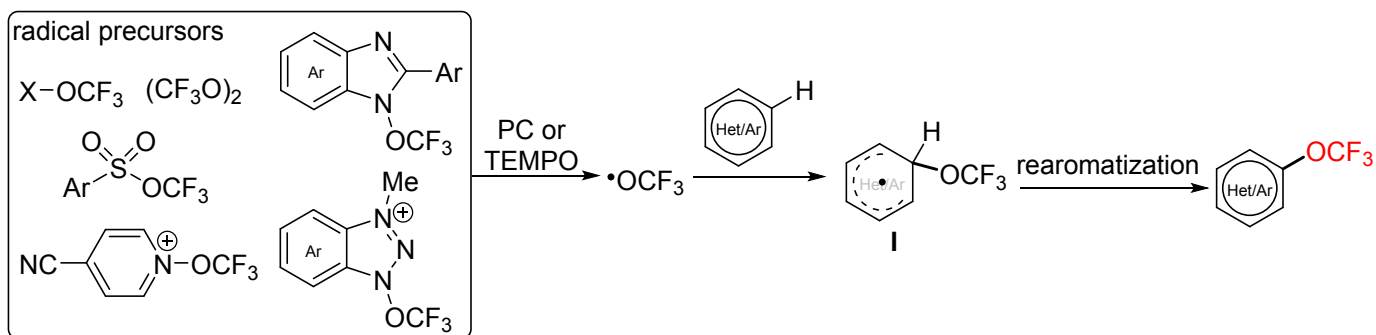
In 2014, Wang made an important breakthrough by using the bench-stable AgSCF_3 as the radical source under oxidative conditions to achieve an intramolecular carbotrifluoromethylthiolation of alkenes.¹³⁹ Numerous reports of radical trifluoromethylthiolation of alkenes and alkynes have been described based on new reagents such as N-SCF_3 reagents (Scheme 35). In addition to N-SCF_3 reagents, Qing demonstrated that trifluoromethanesulfonic anhydride is also a suitable SCF_3 radical precursor via a deoxygenative reduction process.¹⁴⁰ 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).



Scheme 35. Addition of SCF_3 radical to alkenes and alkynes

3.3.5 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 that of radical trifluoromethylation. The key step in these reactions is the addition of OCF_3 radical to the aromatic rings, providing the highly reactive radical **I**, which undergoes the rearomatization to give the desired trifluoromethoxylation product (Scheme 36).¹⁴¹ Efforts in the last few years has been mainly dedicated to the development of new radical trifluoromethoxylation reagents (N-OCF_3 and $\text{ArSO}_2\text{OCF}_3$).^{46–48}

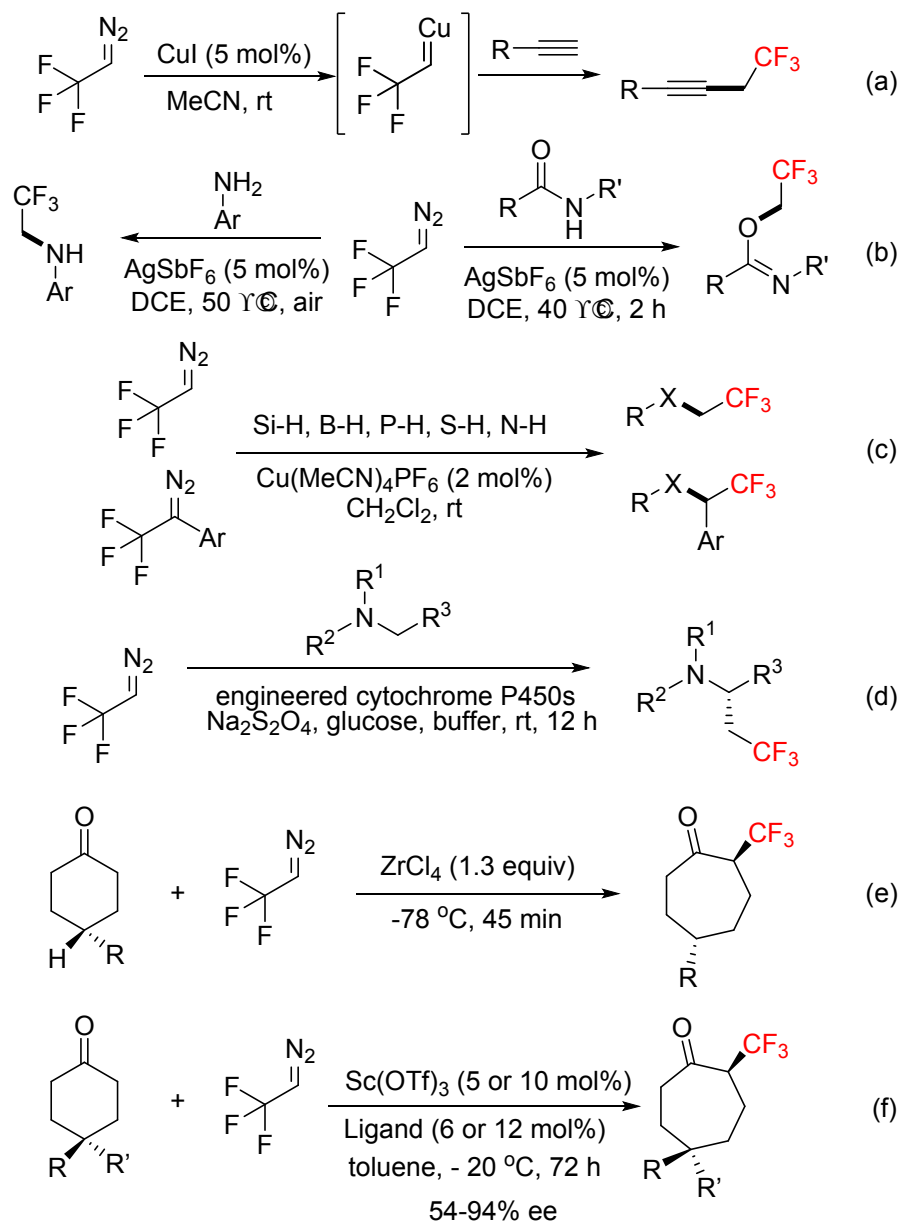


Scheme 36. Radical trifluoromethoxylation reactions

3.4 Fluorinated carbene reactions

3.4.1 Trifluoroethylation

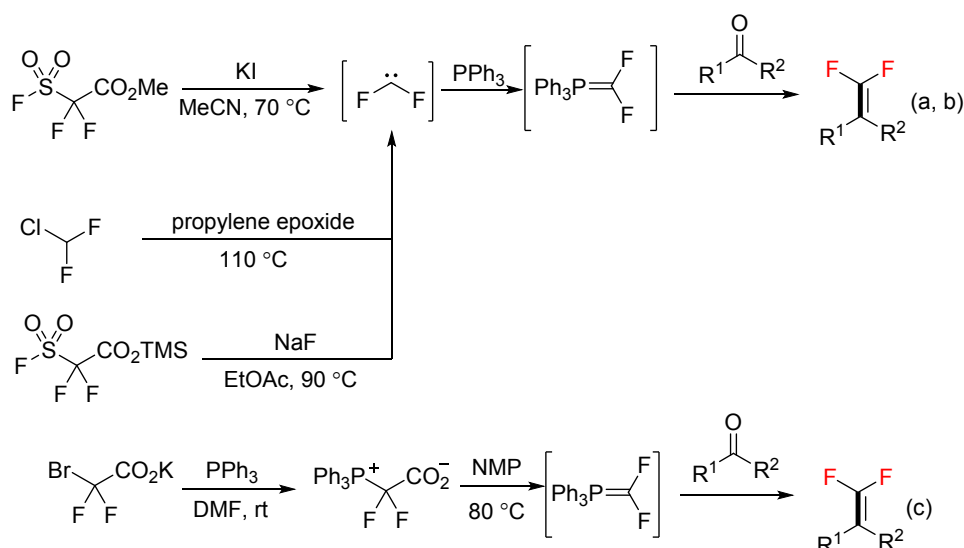
2,2,2-Trifluorodiazethane (CF_3CHN_2) could serve as an efficient precursor to form trifluoromethyl carbene intermediate under transition metal catalysis or thermal conditions. In 2012, Ma reported a copper-catalyzed trifluoroethylation reaction of terminal alkynes under mild conditions without the need for additional base or ligand (Scheme 37a).⁵⁰ In 2015, Wang found that silver could perform as an efficient catalyst for the direct trifluoroethylation of anilines under simple conditions (Scheme 37b).¹⁴² In 2016, Gouverneur reported a more general trifluoroethylation reaction of heteroatom–hydrogen bonds under copper catalysis (Scheme 37c).¹⁴³ In 2019, Arnold reported that engineered cytochrome P450 enzymes could catalyze the enantioselective trifluoroethylation of α -amino C–H bonds (Scheme 37d).¹⁴⁴ This study represents a notable example of applying biocatalysis for the synthesis of chiral organofluorine molecules from fluoroalkyl carbene intermediates. In 2011, Carreira reported a method for the preparation of α -trifluoromethylated aldehydes and ketones by homologation of aldehydes and cyclohexanones with F_3CCHN_2 which was generated in situ from $\text{F}_3\text{CCH}_2\text{NH}_2\cdot\text{HCl}$ (Scheme 37e).¹⁴⁵ In 2022, an asymmetric version of such reaction was reported by Wang, thus providing an alternative method for the preparation of optically enriched trifluoromethylated compounds (Scheme 37f).¹⁴⁶



Scheme 37. Catalytic trifluoroethylation reaction with CF_3CHN_2

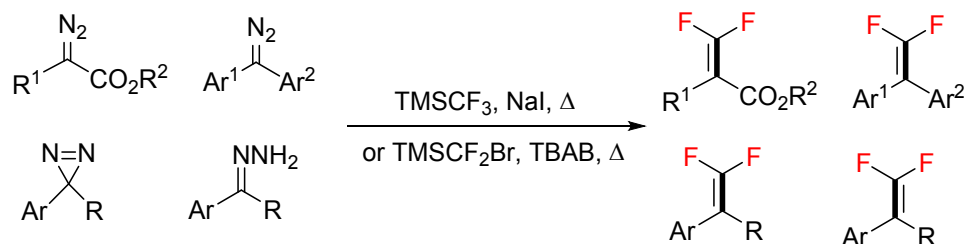
3.4.2 *gem*-Difluoromethylenation

gem-Difluoroalkenes constitute a distinct class of organofluorine chemicals possessing ample applications in the field of medicinal chemistry, agrochemical industry, and materials science. Among various synthetic approaches, difluorocarbene-enabled Wittig-type olefination reaction represents an attractive means in terms of scope, generality and operation simplicity. In 2013, Dolbier and Xiao independently reported that $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}$, $\text{FSO}_2\text{CF}_2\text{CO}_2\text{TMS}$, and ClCF_2H could also work as viable difluorocarbene precursors in such difluoromethylenation reactions (Scheme 38 a and b).¹⁴⁷⁻¹⁴⁸ More importantly, Xiao's group isolated a stable and easily handling difluoromethylene phosphobetaine ($\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$) from $\text{BrCF}_2\text{CO}_2\text{K}$ and PPh_3 (Scheme 38c),¹⁴⁹ which not only could undergo Wittig reaction with aldehydes, but also function as a new difluorocarbene reagent in a series of reactions.⁵⁸



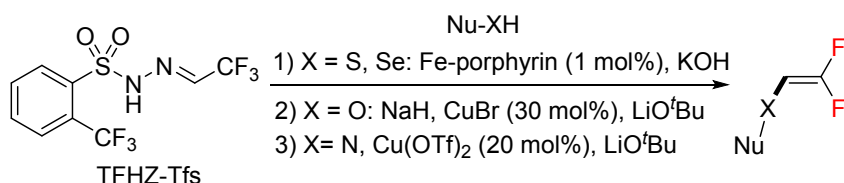
Scheme 38. *gem*-Difluoromethylenation reaction of carbonyl compounds

In 2015, Hu and Wang independently reported a novel *gem*-difluoromethylenation reaction via cross-coupling of difluorocarbene with diazo compounds under transition metal-free conditions (Scheme 39).¹⁵⁰⁻¹⁵¹ Both TMSCF_3 and TMSCF_2Br could be employed as difluorocarbene source and a wide variety of diazo compounds including α -diazoacetates, diaryldiazomethanes, diazirines and hydrazones could be transformed into the corresponding 1,1-difluoroalkenes.



Scheme 39 *gem*-Difluoromethylenation reaction of diazo compounds

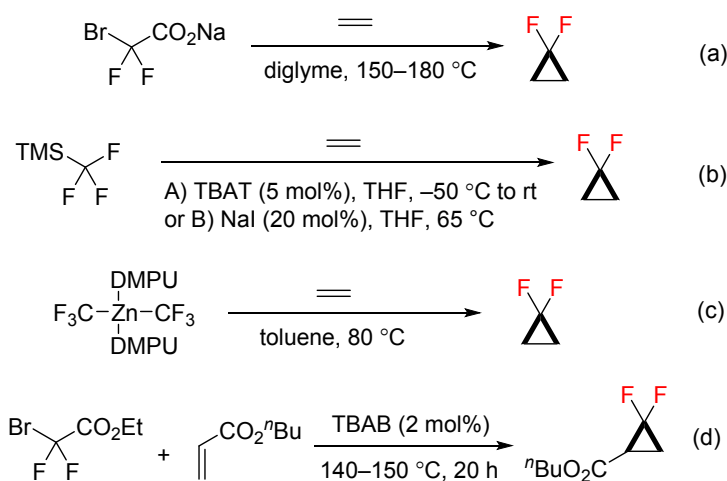
Bi reported a general platform for the synthesis of heteroatom-substituted *gem*-difluoroalkenes from trifluorodiazethane (CF_3CHN_2) (Scheme 40).⁵⁴ This protocol employs trifluoroacetaldehyde *N*-tfsylhydrazone (TFHZ-Tfs) as a safe and easy-to-handle CF_3CHN_2 surrogate. The metal catalyst could decompose CF_3CHN_2 to form CF_3 -metallcarbenoid intermediate, which was then attacked by a nucleophile to give oxonium ylide. Final deprotonation and β -fluoride elimination under basic conditions could lead to the *gem*-difluoromethylenylation products.



Scheme 40. *gem*-Difluoromethylenation reaction of heteroatoms

3.4.3 Cyclopropanation with difluorocarbene

Amii 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).¹⁵² In 2011, Hu and Prakash disclosed the use of TMSCF_3 as a novel difluorocarbene source to *gem*-difluorocyclopropanes with a broad scope of alkenes (Scheme 41b).¹⁵³ A major advantage of this protocol is the relatively low reaction temperature by using TBAT (tetrabutylammonium triphenyldifluorosilicate) or NaI as the activator. In addition, Mikami 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).¹⁵⁴ Notably, Goetz from Pfizer conducted a systematic study on the large-scale *gem*-difluorocyclopropanation of butyl acrylate with various difluorocarbene precursors.¹⁵⁵ He developed a procedure that utilized 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).

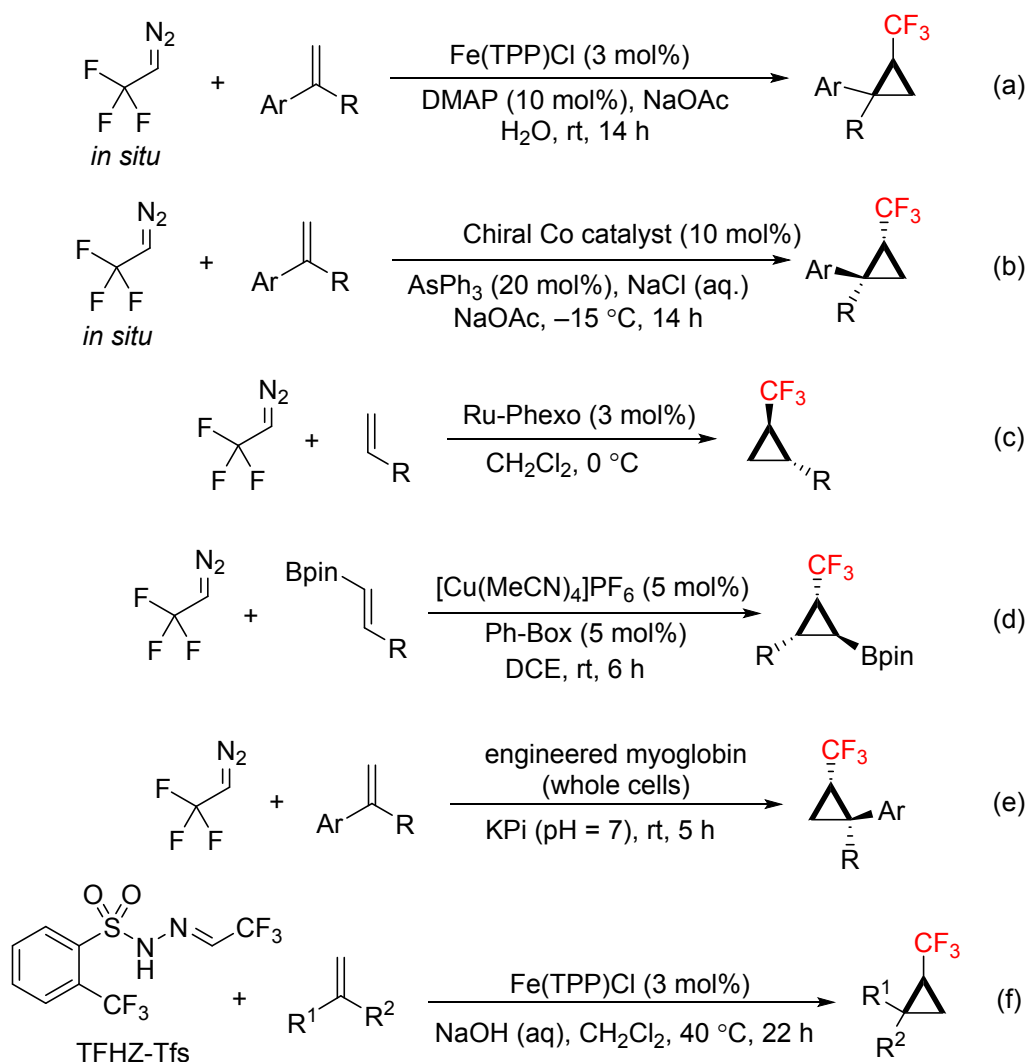


Scheme 41 Cyclopropanation with difluorocarbene

3.4.4 Cyclopropanation with Fluoroalkyl Carbene

In 2010, Carreira reported the cyclopropanation of styrenes with *in situ* generated CF_3CHN_2 catalyzed by an iron–porphyrin complex in aqueous media (Scheme 42a).⁴⁹ This protocol avoids the isolation of toxic and gaseous CF_3CHN_2 and triggers a significantly increasing interest on the chemistry of CF_3CHN_2 as a powerful trifluoromethyl carbene precursor in the following decade. Notably, Carreira also developed a Co-catalyzed enantioselective version of the [2 + 1] cycloaddition reaction of styrenes with CF_3CHN_2 (Scheme 42b).¹⁵⁶ Subsequently, Iwasa reported a Ru-Pheox-catalyzed asymmetric cyclopropanation of CF_3CHN_2 with styrenes, vinyl ethers and vinyl amines in good yields with high stereoselectivities (Scheme 42c).¹⁵⁷ Very recently, Carreras established a copper-bisoxazoline complex platform for the synthesis of trifluoromethyl cyclopropylboronates from CF_3CHN_2 and alkenyl boronates (Scheme 42d).¹⁵⁸ While the above-mentioned protocols extensively explored the use of transition metal catalysis in the cyclopropanation of trifluoromethyl carbene, Fasan developed a remarkable biocatalytic strategy for the synthesis of enantioenriched trifluoromethyl cyclopropanes from CF_3CHN_2 and

vinylarenes (Scheme 42e).¹⁵⁹ In 2019, Bi's group took advantage of trifluoroacetaldehyde *N*-tfsylhydrazone (TFHZ-Tfs) as a stable and easily handling trifluorodiazooethane surrogate to undergo cyclopropanation reactions with alkenes in the presence of an iron catalysis (Scheme 42f).⁵⁴

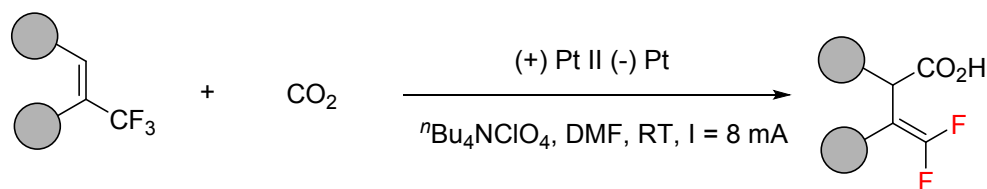


Scheme 42. Cyclopropanation with CF₃CHN₂ and fluoroalkyl hydrazone

3.5 Defluorofunctionalization reactions

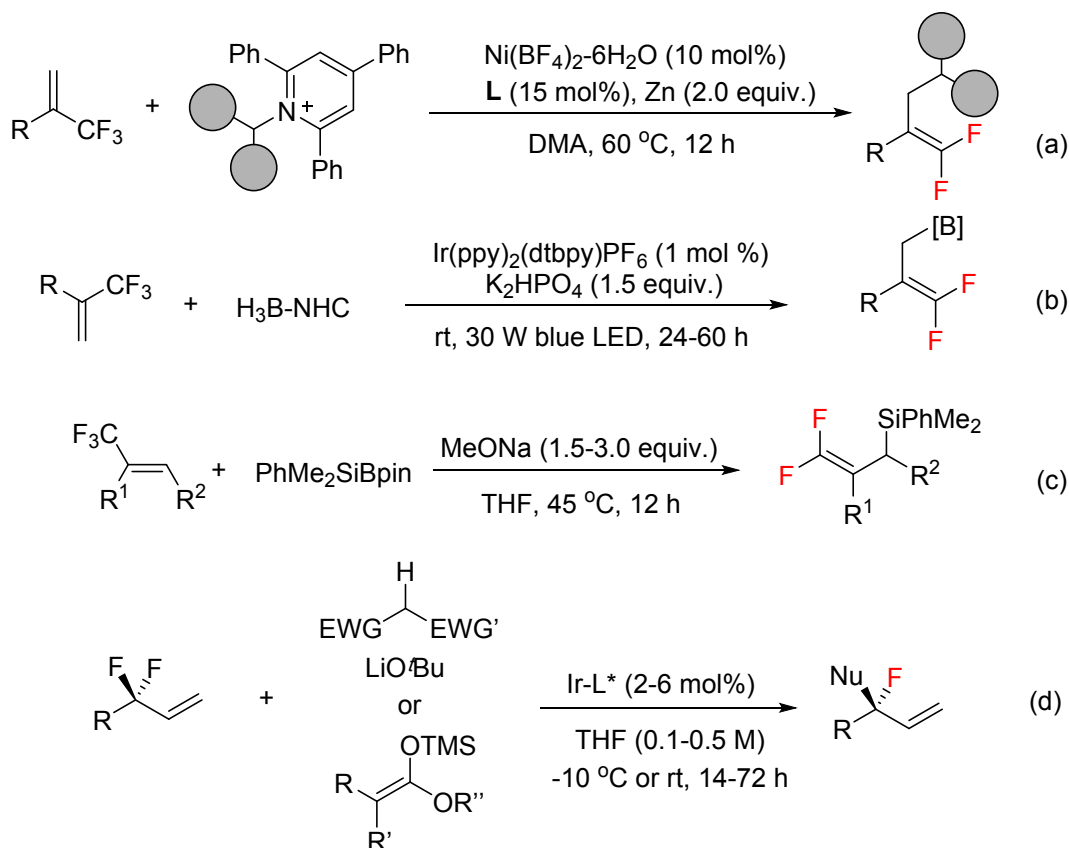
3.5.1 C-F bond activation in C-CF₃

Due to their electron-deficient property, α -trifluoromethylstyrenes show unique and intriguing reactivities in their C-F bond activation, which inherently react with various nucleophiles on the γ -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 reported an unprecedented electrochemical γ -carboxylation of α -CF₃ alkenes with CO₂ to provide efficiently vinylacetic acids bearing a *gem*-difluoroalkene moiety (Scheme 43).¹⁶⁰



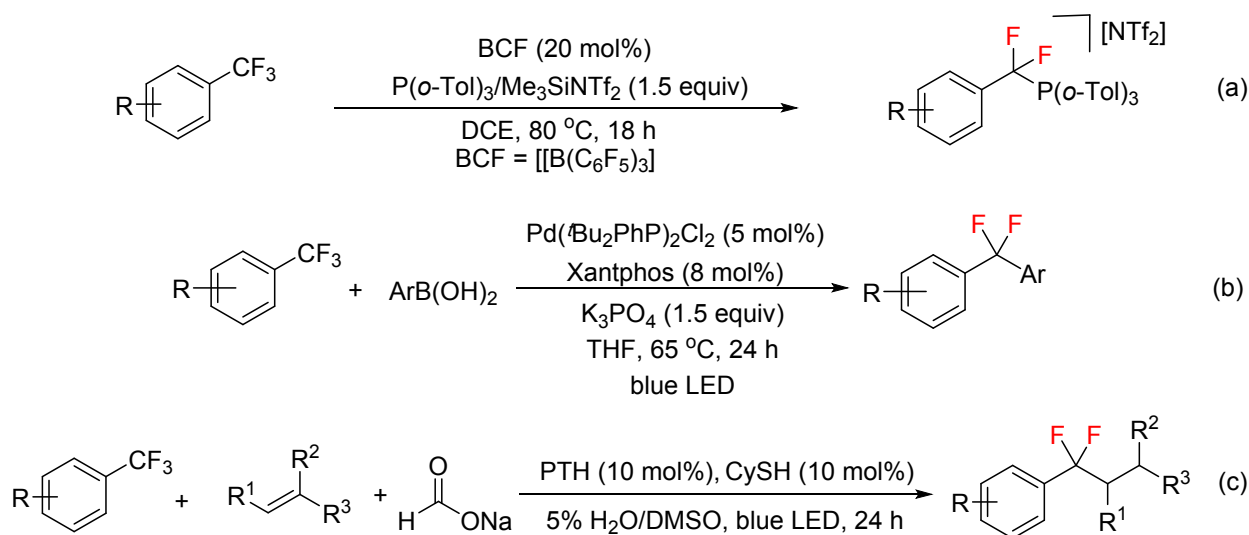
Scheme 43. Electrochemical defluorinative carboxylation of α -CF₃ alkenes

In 2020, Wang disclosed a Ni- and Zn-mediated reductive allylic defluorinative cross-coupling reaction between α -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).¹⁶¹ In 2020, Yang reported an elegant photoinduced SET process for direct B-H bond activation to access *gem*-difluoroalkenes organoboron compounds (Scheme 44b).¹⁶² Notably, this photoinduced reaction takes advantage of the beneficial redox potentials of NHC-boranes to generate boron radical, thus obviating the need for extra radical initiators, promoting C-F bond cleavage. In 2019, Shi reported a transition-metal-free defluorosilylation of fluoroalkenes using silylboronates as silylating reagents (Scheme 44c).¹⁶³ This protocol shows a broad substrate scope, mild reaction conditions, high yields as well as easy operation. In 2020, Hartwig reported a 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).¹⁶⁴



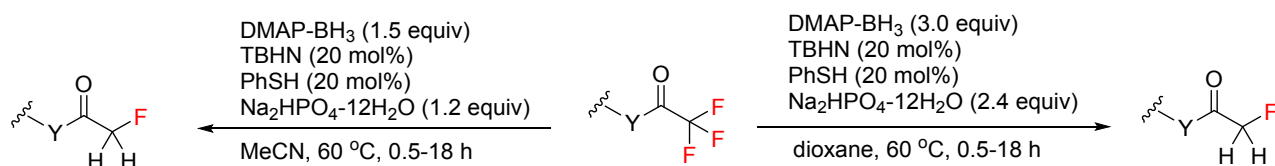
Scheme 44. Allylic defluorinative reaction

The direct construction of valuable fluorinated molecules from readily available trifluoromethyl aromatics through selective cleavage of C-F bond is an attractive goal and has attracted more and more attention recently. In 2020, Young developed a Frustrated Lewis pair-mediated substitution of trifluoromethyl aromatics with neutral phosphine and pyridine bases (Schemes 45a).¹⁶⁵ This reaction could provide a broad range of difluoromethyl products by further functionalization through nucleophilic substitution, photoredox coupling, as well as electrophilic transfer reactions. In addition to intramolecular defluorofunctionalization reactions, there are many intermolecular couplings via defluorofunctionalization reaction. In 2021, Zhang reported visible light-promoted palladium-catalyzed defluoroarylation of trifluoromethylarenes with aryl boronic acids (Scheme 45b).¹⁶⁶ Jui developed a new catalytic strategy to selective functionalization of the strong C-F bonds in trifluoromethyl aromatics via SET process (Scheme 45c).¹⁶⁷ In this protocol, single electron reduction of Ar-CF₃ substrates leads to 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.



Scheme 45. C-F bond functionalizations of trifluoromethyl aromatics

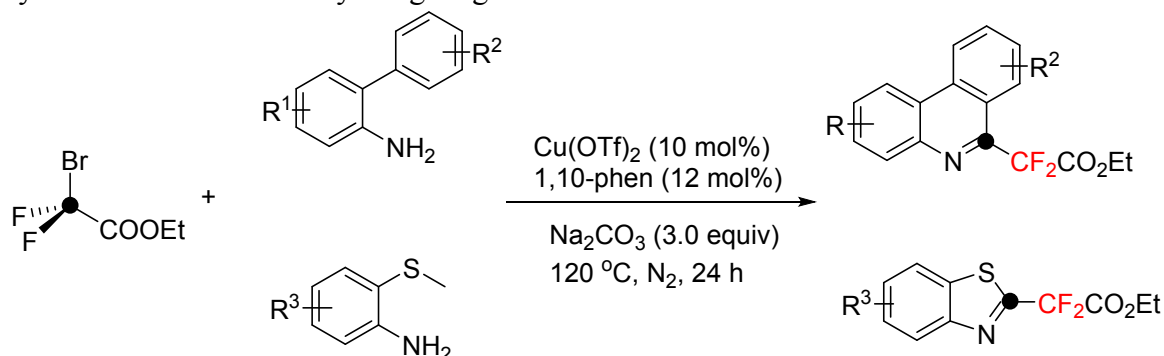
Wang disclosed a general strategy for sequential carbon-fluorine (C-F) bond functionalizations of trifluoroacetamides and trifluoroacetates (Scheme 46).¹⁶⁸ This process begins with the activation of a carbonyl oxygen atom by a 4-dimethylaminopyridine-boryl radical, then a spin-center shift (SCS) promotes the C-F bond cleavage. The two-stage process with controllable chemical selectivity can afford various fluorinated products.



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

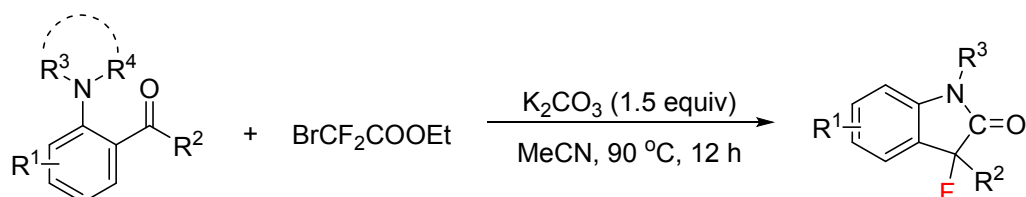
3.5.2 C-F bond activation of BrCF₂CO₂R.

The various deconstructive modes of halodifluoromethyl compounds, such as BrCF₂CO₂Et, ClCF₂CO₂Na, ClCF₂H, BrCF₂CONRR as well as BrCF₂P(O)OEt₂ via C-F bond cleavage were developed for the generation of a variety of synthons to assemble more valuable products. In 2018, Song reported a novel one-pot cascade reaction involving both quadruple cleavage and single cleavage of BrCF₂COOEt with primary amines to construct valuable fluorine-containing heterocycles for the first time (Scheme 47),¹⁶⁹ in which BrCF₂COOEt plays dual roles as both C1 synthon and difluoromethylating reagents.



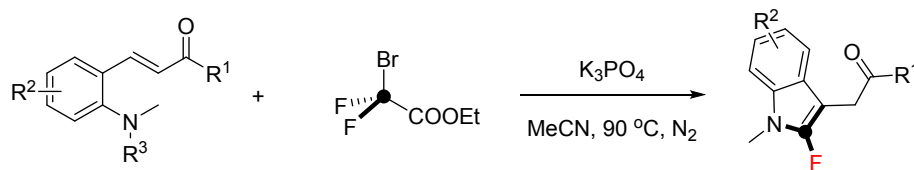
Scheme 47. Using BrCF₂CO₂Et in the formation of fluorinated heteroaromatics

The same group further designed and developed a novel atom recombination reaction with BrCF₂COOEt as both C1 synthon and fluorinated reagent. This reaction was proposed to proceed via 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).¹⁷⁰ The transformation features catalyst-free, ease of execution, broad substrate scope and excellent functional group compatibility.



Scheme 48. 3-Fluorinated oxindoles from 2-aminoarylketones and BrCF₂COOEt.

Song 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).¹⁷¹ In this protocol, BrCF₂COOEt 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 lead to various valuable bioactive molecules which demonstrated significant synthetic advantages over previous reports.



Scheme 49. 2-Fluoroindoles from *ortho*-vinylanilines and BrCF₂COOEt.**4: Perspective**

Owing to the importance of fluorine-containing compounds in many fields, the past decade has witnessed a surge of academic interests in the incorporation of the fluorine atom and fluoroalkyl groups into organic molecules. Despite these great progresses, several challenges should be addressed. (1) Most of the fluorinating and fluoroalkylating reagents required 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 economic manner are strongly needed. Moreover, the utilization of readily available inorganic fluoride salts as the fluorine source is also highly demanded. (2) The efficient and direct access to ArOCF₃ has long been recognized as a formidable challenge in organic synthesis. Therefore, the development of reagents and reactions for the incorporation of trifluoromethoxy (CF₃O) and other groups (such as SF₅) 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 on an increased focus to the development the 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 potential development of environmental benign strategies. Besides, more efforts should 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 of the incorporation of the fluorine atom rely on the 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 fluoroalkylation of heterocycles, the precise functionalization on simple aliphatic or aryl C–H bonds is still desirable.

5: Acknowledgements

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TOC Graphic

