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Promising reagents for difluoroalkylation

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This review describes recent advances in difluoroalkylation reactions using different substrates. Generally speaking, RCF₂ radical is generally proposed in the mechanism of these reactions. At present, the most used difluoroalkylation reagent is RCF₂X, which can be reduced by metal, photocatalyst or bases to RCF₂ radical. Various substrates such as alkenes, alkynes, amines and so on could well be applied to these difluoroalkylation reactions.

1. Introduction

Because of their special physicochemical properties, difluorinated compounds have an important role in agrochemicals, pharmaceuticals, and materials sciences.^{1–3} Therefore, the development of efficient and simple methods for the introduction of difluoroalkyl groups has received more and more attention in recent years.^{4–8} At present, various reagents such as HCF₂Cl,⁹ BrCF₂P(O)(OEt)₂,¹⁰ TMSCF₂Br,^{11,12} HFPO,¹³ CF₃ZnBr₂·CH₃CN,⁵ FSO₂CF₂CO₂H¹⁴ and so on^{4,15–18} are used for difluoroalkylation reactions. But some side reactions such as dimerization, protonation and other unknown byproducts accompany the difluoroalkylation reaction when some of these reagents especially metal species are employed. As early as 2001, the Chen group realized the fluoroalkylation of aromatic compounds with per(poly)fluoroalkyl chlorides mediated by sodium dithionite. The single-electron transfer (SET) mechanism was proposed for the fluoroalkylation reaction.^{18b} Difluoroalkyl halides as a class of efficient and readily available reagents for difluoroalkylation reactions have become the most widely used in organic synthesis in recent years. In 2018, the Zhang group summarized transition-metal-catalyzed difluoroalkylation with difluoroalkyl halides *via* cross-coupling.⁴ According to the pathways by which the difluoroalkyl halides react, they classified these reactions into four categories: nucleophilic difluoroalkylation, electrophilic difluoroalkylation, radical difluoroalkylation and difluoromethylation by metal–difluorocarbene coupling. There have been some other reviews about difluoroalkylation (CF₂R) reactions,^{4,6,19–22} and these reactions will not be described in this review. Besides metal-catalyzed difluoroalkylation reactions, difluor-

alkylation reactions which are conducted under metal-free conditions also have made much progress in recent years, and these reactions will be described in this review. This review mainly describes the difluoroalkylation reactions reported in the last three years. According to the different substrates, we classify these difluoroalkylation reactions into eight types.

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2. Difluoroalkylation with alkenes

2.1. Carbodifluoroalkylation with alkenes

In the past few years, a significant renaissance of photocatalysis in the field of organic chemistry has been seen^{7,23–33} since the pioneer works reported by MacMillan³⁴ and Yoon³⁵ in 2008. With the assistance of visible light, RCF₂X could serve as an important synthon for difluoroalkylation reactions in organic chemistry. The reduction of RCF₂X in the presence of a photocatalyst was one of the most common strategies for the formation of RCF₂ radical. Because of its high reactivity, RCF₂

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Scheme 1 The difluoroalkylation/cyclization reaction of *N*-(but-2-enyl)indoles.

radical could react with various substrates to construct complicated molecules *via* difluoroalkylation reactions.^{36–41}

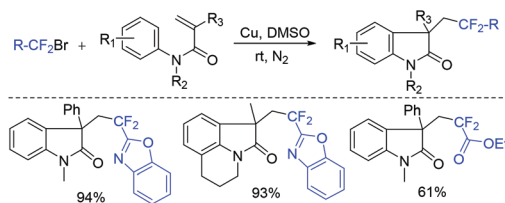
In 2018, the Li group demonstrated that difluoroalkylated pyrrolo[1,2-*a*]indoles with a quaternary carbon center can be efficiently synthesized *via* difluoroalkylation and cyclization cascade reaction of *N*-(but-2-enyl)indoles with BrCF_2R (Scheme 1).⁴² In the presence of visible light, products with good to high yields were generated. A plausible reaction mechanism is outlined in Scheme 1. Initially, RCF_2 radical was generated from the oxidation of excited photocatalyst $[\text{Ir}^{3+}]$ with RCF_2Br . The addition of RCF_2 radical to **1** produced intermediate **2**. Subsequently, intermediate **3** was formed from intramolecular radical cyclization of intermediate **2** on C2 of the indole ring. Then oxidation of intermediate **3** by the $[\text{Ir}^{4+}]$ complex occurred to deliver intermediate **4** and the $[\text{Ir}^{3+}]$ catalyst. Finally, deprotonation of this cationic intermediate **4** by base afforded the final product.

This visible light induced radical addition/cyclization strategy could also be applied for the reaction of biaryl vinyl ethers with $\text{BrCF}_2\text{CO}_2\text{Et}$ (Scheme 2).⁴³ 6-Fluoroalkylchromenes with moderate to good yields were obtained. Control experiments indicated that RCF_2 radical might be involved in the mechanism, and a radical addition to the carbon–carbon double bond might occur prior to the cyclization process.

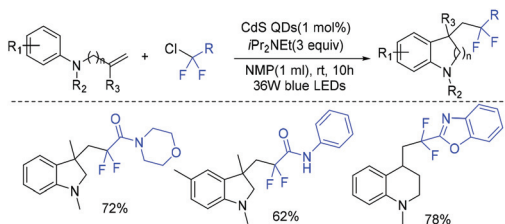
The copper-mediated difluoromethylenation of *N*-arylacrylamides with benzo-1,3-oxazolic difluoromethyl-



Scheme 2 The radical addition/cyclization of biaryl vinyl ethers.



Scheme 3 The copper-catalyzed difluoromethylenation of *N*-arylacrylamides.



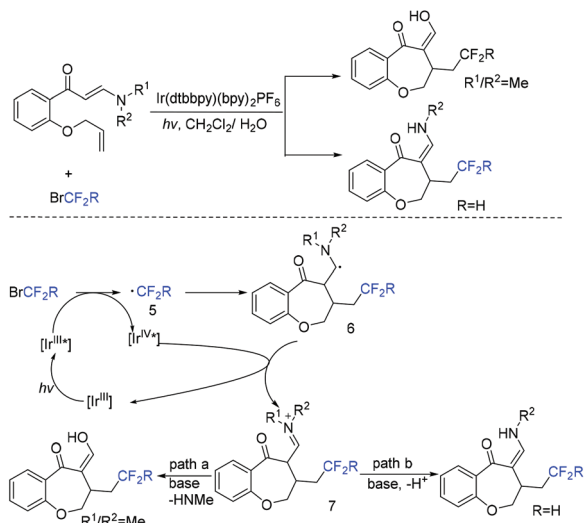
Scheme 4 The cadmium sulfide quantum-dot-photocatalyzed cascade cyclization of unactivated olefins.

bromide was described by the Jiang group (Scheme 3).⁴⁴ RCF_2 radical, which was generated from $\text{Cu}(0)$ -mediated SET with RCF_2Br , could add to the terminal $\text{C}=\text{C}$ double bond of *N*-arylacrylamide and then underwent intramolecular radical cyclization to form the desired product.

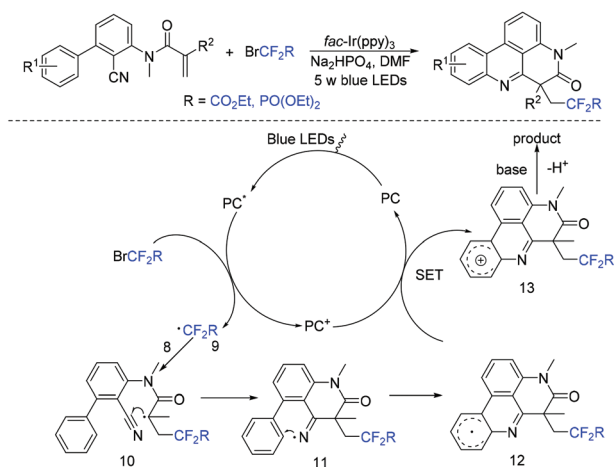
In 2019, Feng and coworkers reported the cadmium sulfide quantum-dot-photocatalyzed cascade cyclization of ethyl chlorodifluoroacetate with unactivated olefins (Scheme 4).⁴⁵ Control experiments showed that a radical intermediate was involved in this reaction. Visible-light-absorbing CdS QDs which could transform difluoromethyl chlorides to difluoromethyl radical played an important role in this strategy.

The Yang group found that CF_2 -containing benzoxepine derivatives can be synthesized from visible-light-induced external radical-triggered annulation.⁴⁶ In addition, different products were obtained if the substituents on the nitrogen were different. A plausible mechanism is outlined in Scheme 5. Initially, the excited state $[\text{Ir}(\text{dtbbpy})(\text{bpy})_2\text{PF}_6]^*$ which was generated under visible-light irradiation was oxidized by $\text{BrCF}_2\text{CO}_2\text{Et}$ to generate $[\text{Ir}(\text{iv})(\text{dtbbpy})(\text{bpy})_2\text{PF}_6]^+$ complex and RCF_2 radical species **5**. Subsequently, radical intermediate **6** was formed *via* sequential radical addition between RCF_2 radical and the propenyl group of the substrate. Then intermediate **6** was oxidized by $[\text{Ir}(\text{iv})(\text{dtbbpy})(\text{bpy})_2\text{PF}_6]^+$ to form iminium intermediate **7** with the concurrent regeneration of $[\text{Ir}(\text{dtbbpy})(\text{bpy})_2\text{PF}_6]$. Finally, the corresponding product was generated from the hydrolyzation of iminium ion **7** by water (path a). Additionally, when nitrogen was monosubstituted iminium ion, the corresponding enamine was formed *via* the deprotonation and tautomerization reaction (path b).

The Sun group found *N*-arylacrylamides could also react with $\text{BrCF}_2\text{CO}_2\text{R}$ smoothly for assembly of difluoroalkylphenanthridine derivatives induced by visible light (Scheme 6).⁴⁷



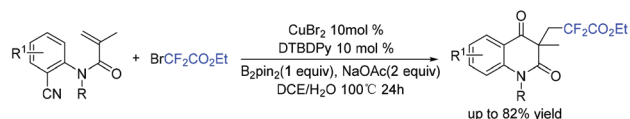
Scheme 5 The synthesis of CF₂-containing benzoxepine derivatives.



Scheme 6 The assembly of difluoroalkylphenanthridine derivatives.

Besides, fluoroalkylating reagents CF₃SO₂Cl and BrCF₂PO(OEt)₂ were also well applicable to this reaction. Fluoroalkyl radical which was generated from oxidative quenching of the excited state PC* by the fluorine reagents was proposed in the mechanism. The subsequent intermolecular radical addition to the C=C double bond of *N*-arylacrylamides **8** afforded the radical intermediate **10**, followed by intramolecular radical addition to the cyano group affording iminyl radical **11**. Subsequently the homolytic aromatic substitution process, oxidation and deprotonation reaction occurred in sequence to afford the final products.

In 2018, the Shi group developed a facile method to construct diverse difluorinated quinoline-2,4-diones *via* Cu-catalyzed direct difluoromethylation of activated alkenes through a difluoromethyl radical addition/cyclization reaction (Scheme 7). It is noteworthy that visible-light photoredox catalysis was also effective for this reaction.⁴⁸

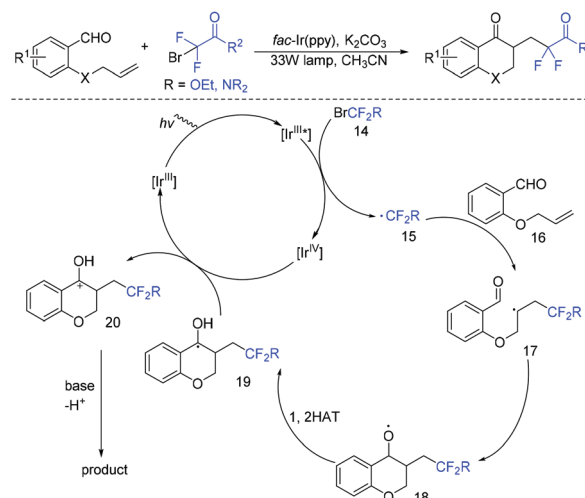


Scheme 7 The synthesis of difluorinated quinoline-2,4-diones catalyzed by copper.

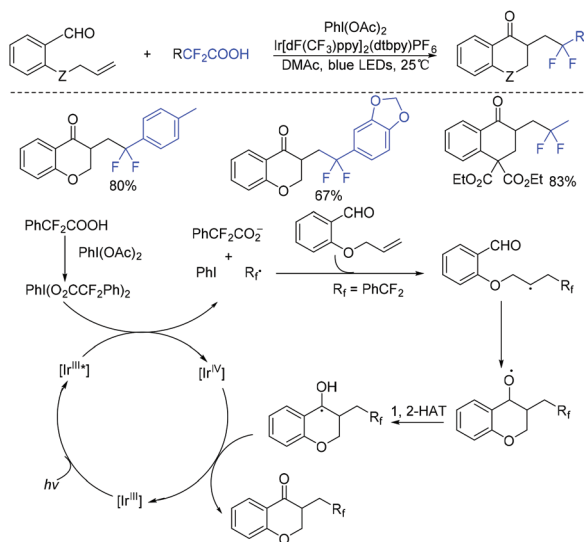
Chroman-4-ones are an important motif in medicinal compounds and biologically active molecules.^{49–51} In 2019, the Zhou group described a visible-light photoredox-catalyzed radical cascade cyclization of alkenyl aldehydes with BrCF₂COR for the synthesis of various difluoroacetylated chroman-4-ones (Scheme 8).⁵² The addition reaction of fluoroalkyl radical **15** to **16** afforded the intermediate **17**, which then underwent intramolecular cyclization to give the intermediate **18**. Subsequently, 1,2-H shift of E resulted in intermediate **19**. Then, intermediate **19** was oxidized by Ir(IV) to afford carbocation **20**, which was converted to the desired product by deprotonation.

Difluoroacetic acids were also found to be good difluoroalkyl radical precursors for decarboxylative difluoroalkylation.^{53–57} In 2019, the Zhu group realized visible-light-induced acyldifluoroalkylation of alkenyl aldehydes with difluoroacetic acids (Scheme 9).⁵⁸ PhI(OAc)₂ should be added as the oxidant, which could react with the excited state Ir(III)* and difluoroacetic acids *via* SET process to give difluoromethyl radical.

The group of Tu and Jiang found that fluoroalkylated (*Z*)-1-indenones could be efficiently synthesized *via* hydrofluoroalkylation of 1,6-enynes with ethyl bromodifluoroacetate in the presence of photocatalysts.⁵⁹ THF behaved as a hydrogen source in this transformation. The proposed mechanism is shown in Scheme 10. Oxidation of Ir*(III) by fluoroalkyl bromides resulted in fluoroalkyl radical **21**. The addition of radical **21** to 1,6-enynes generated radical **22**, which was followed by cyclization to produce vinyl radical **23**. Finally, radical



Scheme 8 The cyclization of alkenyl aldehydes with BrCF₂COR.



Scheme 9 The acyldifluoroalkylation of alkenyl aldehydes with difluoroacetic acids.

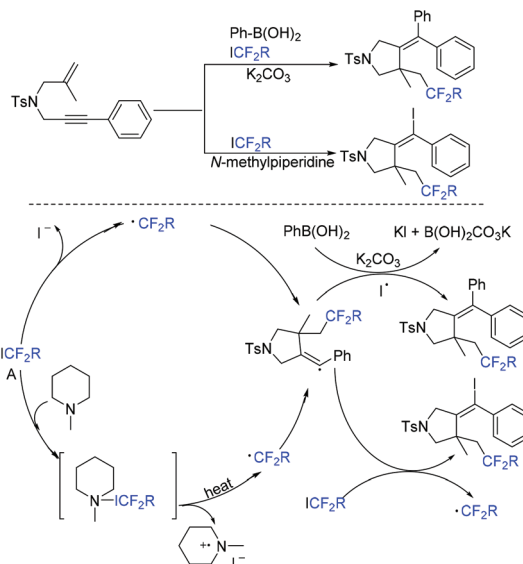


Scheme 10 The synthesis of fluoroalkylated (Z)-1-indenones.

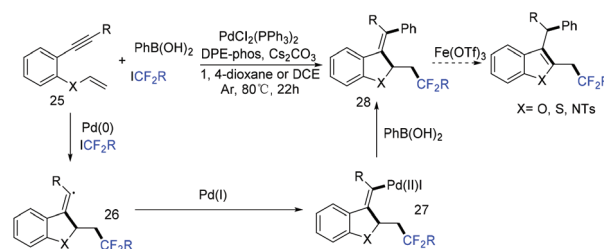
23 abstracted hydrogen from THF to provide the desired product. In addition, fluoroalkyl and halo groups were all incorporated into 1-indenone skeleton when copper catalysis was used instead of photocatalysis.

The Liang group found that 1,6-enynes were good substrates for difluoroalkylation with $\text{ICF}_2\text{CO}_2\text{Et}$ (Scheme 11).⁶⁰ In the absence of metal catalysts, two different difluoroalkylated cyclization products with various functional groups and high stereoselectivity were obtained under the condition that only base was used. The properties of the bases were key factors to give different difunctionalized cyclization products. The reaction of base with $\text{ICF}_2\text{CO}_2\text{Et}$ to afford $\text{CF}_2\text{CO}_2\text{Et}$ radical *via* EDA complex was suggested in the catalytic cycle.

The palladium-catalyzed three-component cascade difluoroalkylation and arylation of 1,6-enynes with ethyl difluoro-



Scheme 11 The difluoroalkylation of 1,6-enynes with $\text{ICF}_2\text{CO}_2\text{Et}$.



Scheme 12 The synthesis of fluoroalkylated (Z)-1-indenones.

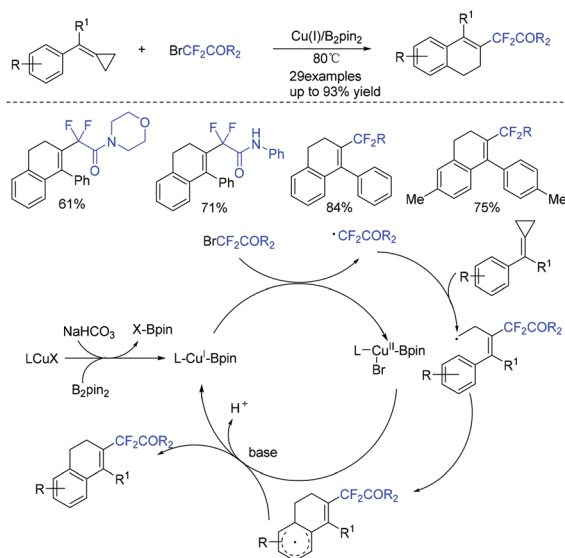
iodoacetate and phenylboronic acid was realized by the Zhang group (Scheme 12).⁶¹ The products can be converted into CF_2 -containing benzofurans, benzothiophenes and indoles through an $\text{Fe}(\text{OTf})_3$ -catalyzed isomerization. Reduction of $\text{ICF}_2\text{CO}_2\text{Et}$ with $\text{Pd}(0)$ to form $\text{CF}_2\text{CO}_2\text{Et}$ radical, transmetalation process between the intermediate 27 and phenylboronic acid process were proposed in the reaction mechanism.

Difluoroacyl heterocyclic compounds have been found in various biologically active compounds and agrochemicals.^{62,63} Much effort has been devoted to these compounds.^{64–68} In 2019, the copper-mediated radical cyclization of naphthalenyl iododifluoromethyl ketones with olefins was demonstrated by the Wu group (Scheme 13),⁶⁹ providing difluoroacyl compounds with moderate yields. Mechanistic investigations implied that difluorinated radical intermediate which was generated from the reduction of RCF_2I by $\text{Cu}(0)$ was involved in the reaction pathway.

In 2019, the Wang group described the copper/ B_2pin_2 -catalyzed difluoroalkylation of methylenecyclopropanes with bromodifluorinated acetates and acetamides (Scheme 14).⁷⁰ Various substrates reacted well in this system. Both the catalyst and an inert atmosphere are necessary for the success of this reaction. A tandem radical process involving ring-opening/intramolecular cyclization was proposed in the catalytic cycle.



Scheme 13 The copper-mediated radical cyclization of naphthalenyl iododifluoromethyl ketones.



Scheme 14 The copper/ B_2pin_2 -catalyzed difluoroalkylation of methylenecyclopropanes.

The first difunctionalization of unactivated alkenes through desulfonylation-initiated distal alkenyl migration was reported by the Wang group. Previously unknown 3,3-difluoro-5-styrylpiperidin-2-one derivatives bearing a quaternary stereocenter can be efficiently synthesized using this method (Scheme 15).⁷¹ A radical mechanism was suggested for this transformation. Initially, fluoroalkyl radical **29** and Cu(II) species are generated from the oxidation of Cu(I) species by $BrCF_2R_3$ through a SET process. Then fluoroalkyl radical **29** selectively attacks the less sterically hindered terminal alkene to give the transient alkyl radical **30**. The addition reaction of the RCF_2 radical **30** to the internal double bond occurred to generate the cyclized radical **31**. Radical **31** will undergo rapid desulfonylation to form the key *N*-centered radical **32**. Finally, an annulation proceeded rapidly and delivered the products 3,3-difluoro-5-styrylpiperidin-2-ones.

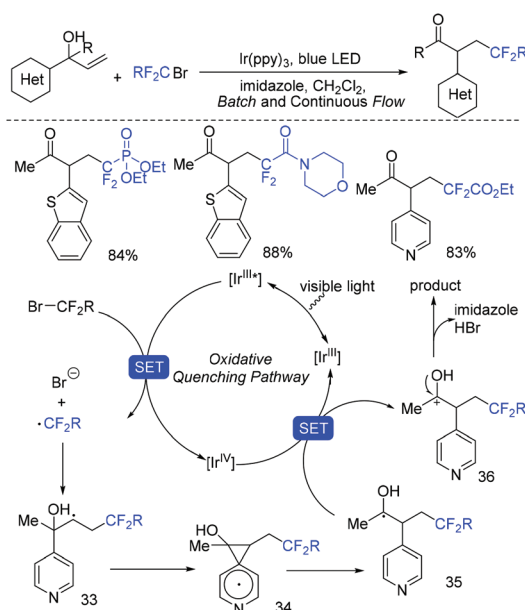
A novel photocatalytic 1,2-heterocycle migration reaction of allylic alcohols with $BrCF_2CO_2Et$ was described by the Noel



Scheme 15 The difunctionalization of unactivated alkenes through desulfonylation.

group, affording various β -difluorinated α -aryl heterocyclic ketones (Scheme 16).⁷² The application of continuous flow allowed shorter reaction times, higher selectivity and opportunities to scale the chemistry. The addition of CF_2CO_2Et radical generated from the oxidation of *fac*-[Ir(ppy)₃]⁺ to the olefin generated intermediate **33**. Then 1,2-heterocycle migration of **33** resulted in **35**, which was further converted to the desired product *via* oxidation. The Cu_2O -catalyzed phosphonyldifluoromethylation and ethoxycarbonyldifluoromethylation of allylic alcohols through a radical 1,2-aryl migration was also realized by the Xiong group (Scheme 17).⁷³

Without the need of photocatalyst, a light-mediated Truce-Smiles arylation rearrangement mediated by an organic base



Scheme 16 The photocatalytic difluoromethylation of allylic alcohols.

Scheme 17 The Cu_2O -catalyzed difluoromethylation of allylic alcohols.

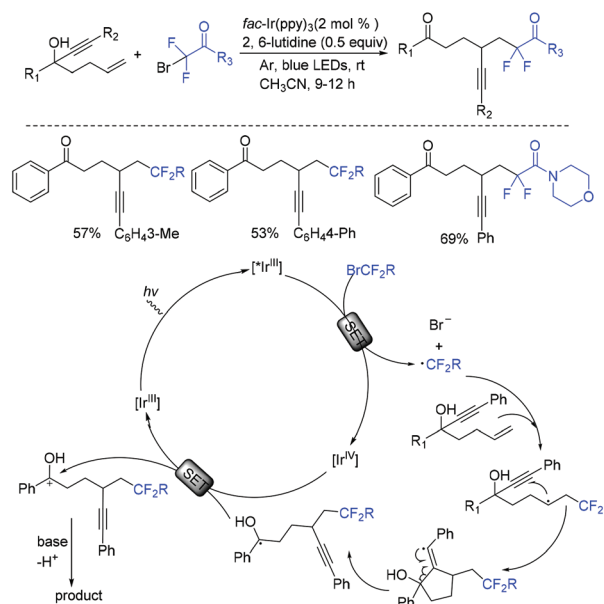
Scheme 18 The light-mediated arylative rearrangement.

was described by the group of Duong and Greaney (Scheme 18).⁷⁴ This transformation simultaneously introduced an aryl ring and a difluoroacetate moiety across unactivated alkenes. A radical mechanism was proposed for this reaction. Different from previous reports, $\text{CF}_2\text{CO}_2\text{Et}$ radical could be generated from the reduction of $\text{BrCF}_2\text{CO}_2\text{Et}$ by TEMDA induced by visible light. The addition reaction of $\text{CF}_2\text{CO}_2\text{Et}$ radical to alkenes **37** resulted in radical **38**. Then, Truce-Smiles aryl shift with extrusion of SO_2 and hydrogen atom transfer occurred in sequence to afford the desired product.

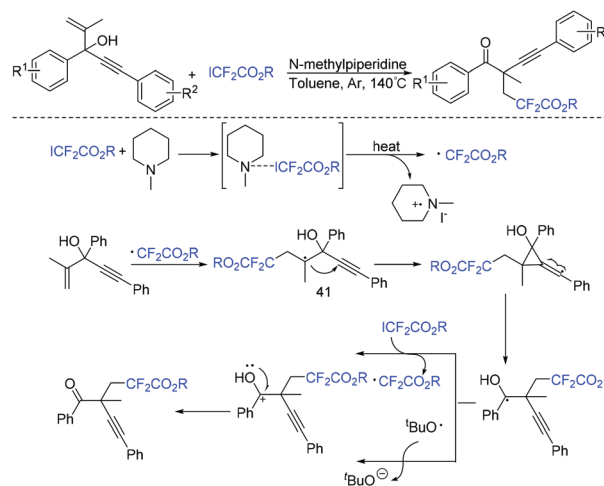
The visible-light-mediated tandem radical difluoroalkylation and alkylation of unactivated alkenes with BrCF_2COR was realized by the Zhu group (Scheme 19).⁷⁵ However, an aliphatic alkynyl substrate was not suitable for this transformation because of the rearrangement of the starting material and undesired decomposition. The C–C bond activation *via* intramolecular 1,4-alkynyl migration was involved in the mechanism.

Another organic base-promoted difluoroalkylation reaction of 1,4-enynes with $\text{ICF}_2\text{CO}_2\text{Et}$ was realized by yje Liang group.⁷⁶ Various functional groups were compatible with this reaction. A possible mechanism is outlined in Scheme 20. The direct interaction of *N*-methylpiperidine with $\text{ICF}_2\text{CO}_2\text{Et}$ was proposed to form $\text{CF}_2\text{CO}_2\text{Et}$ radical. Alkynyl radical migration of **41** was also proposed in the mechanism.

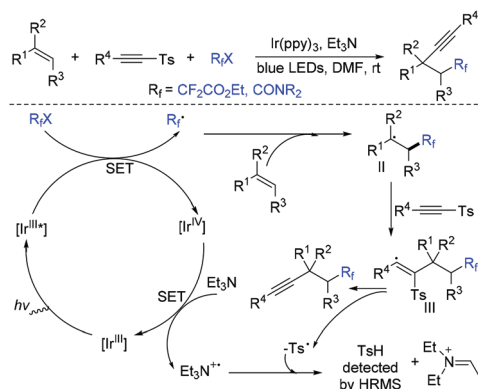
The first intermolecular alkynyl-difluoroalkylation of unactivated alkenes *via* visible-light-induced three-component reac-



Scheme 19 The light-mediated difluoroalkylation and alkylation of unactivated alkenes.

Scheme 20 The base-promoted difluoroalkylation reaction of 1,4-enynes with $\text{ICF}_2\text{CO}_2\text{Et}$.

tion of difluoroalkyl halides, unactivated alkenes and alkynyl sulfones was realized by the Zhu group (Scheme 21).⁷⁷ This reaction provides a simple and efficient route to the construction of synthetically valuable β -difluoroalkylated alkynes. The reaction of Ir^{III} and R_fX occurred to form difluoroalkyl radical, which was followed by addition to alkenes to afford intermediate II. Then the addition of intermediate II to alkynyl sulfones and β -elimination occurred in sequence to produce the final product. It is worthwhile to note that Et_3N plays multiple roles such as a base and a reductant in this reaction. Additionally, $\text{Ir}(\text{II})/\text{Ir}(\text{III})$ pathway was also possible for this transformation.



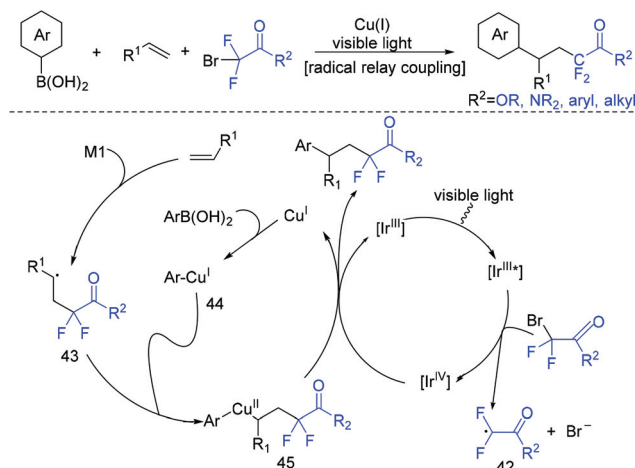
Scheme 21 The alkynyl-difluoroalkylation of unactivated alkenes.

As is well known, allenes are highly reactive substrates and play an important role in organic chemistry.^{78,79} A nickel-catalyzed 1,4-carbofluoroalkylation of 1,3-enynes with boronic acids and fluoroalkyl halides to access structurally diverse fluoroalkylated allenes was reported by the Wang group (Scheme 22).⁸⁰ The use of nickel to generate fluoroalkyl radicals from $\text{BrCF}_2\text{CO}_2\text{Et}$ (rate-determining step) and reductive elimination were proposed for this reaction.

Besides 1,3-enynes, alkenes are also good substrates to react with boronic acids and fluoroalkyl halides, producing γ -arylation of carbonyl compounds. The Shu group found that the employment of copper and visible-light catalysis was essential for this reaction.⁸¹ The mechanism is shown in Scheme 23. The reduction of $\text{BrCF}_2\text{CO}_2\text{Et}$ with excited $\text{Ir}^*(\text{III})$ photocatalyst would give radical intermediate **42** and the oxidized photocatalyst $\text{Ir}(\text{IV})$. **42** would be trapped by alkenes to



Scheme 22 The nickel-catalyzed 1,4-carbofluoroalkylation of 1,3-enynes.



Scheme 23 The process of γ -arylation of carbonyl compounds.

generate a new alkyl radical intermediate **43**. In the presence of a base, the arylcopper intermediate **44** was delivered from the reaction of $\text{Cu}(\text{I})$ with aryl boronic acid, which was followed by recombination with **43** to give **45**. Then, **45** would undergo reductive elimination to give the final product with the concurrent regeneration of $\text{Ir}(\text{III})$ and $\text{Cu}(\text{I})$ species.

In 2019, the perfluoroalkylative pyridylation of alkenes *via* 4-cyanopyridineboryl radicals was developed by the Li group (Scheme 24).⁸² Density functional theory calculations and experimental studies suggested that the 4-cyanopyridineboryl radicals generated from 4-cyanopyridine and $\text{B}_2(\text{pin})_2$ played an important role in the catalytic cycle, which not only activates C–X bond homolysis but also serves as a pyridine precursor. The selective cross-coupling of the resulting alkyl radicals generated from the addition reaction of RCF_2 radicals to alkenes and 4-cyanopyridineboryl radicals delivered the corresponding product with a quaternary carbon center.

In 2019, another three-component reaction of fluoroalkyl halides, alkenes and arenes was reported by the Liang group.⁸³ An unprecedented three-component direct C–H addition was achieved in the challenging *meta*-selective fashion catalyzed by Ru. Control experiments and computational analyses were carried out to investigate the mechanism. The plausible catalytic cycle is outlined in Scheme 25. Initially, carboxylate-assisted C–H ruthenation occurred to give **46**, which was followed by the reaction with fluoroalkyl halide and alkenes *via* SET to afford **47** and radical **48**. Subsequently, the newly formed radical bond added to the *para*-position of the C–Ru bond, leading to species **49**, which was followed by rearomatization to give ruthenacycle **50**. Finally, the *meta*-functional-



Scheme 24 The perfluoroalkylative pyridylation of alkenes.

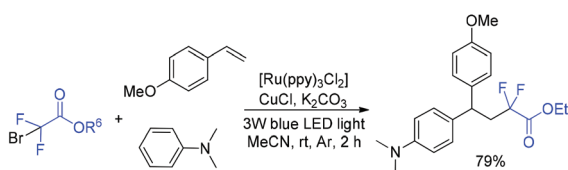


Scheme 25 The three-component reaction of fluoroalkyl halides, alkenes and arenes.

zation product was delivered by demetalation, with the release of ruthenium(II) complex.

In 2018, the Li group found that the 1,2-alkylarylation reaction of styrenes, α -carbonylalkyl bromides and *N,N*-disubstituted anilines could be conducted in the presence of photoredox and copper cooperative catalysis (Scheme 26).⁸⁴ In addition to Friedel-Crafts alkylation, this reaction provided a new access for the C–H alkylation of *N,N*-disubstituted anilines with high *para*-selectivity. Carbonylalkyl bromides such as primary, secondary and tertiary α -bromoalkyl ketone esters, malonic esters and cycloalkane were all good partners for this reaction. The product with 79% yield was obtained when $\text{BrCF}_2\text{CO}_2\text{Et}$ was employed. $\text{CF}_2\text{CO}_2\text{Et}$ radical which was generated from the reduction of $\text{BrCF}_2\text{CO}_2\text{Et}$ with the excited state $\text{Ru}(\text{bpy})_3^{*2+}$ was proposed in the mechanism.

Recently, the asymmetric three-component Minisci reaction of quinolines or pyridines with α -bromocarbonyl compounds



Scheme 26 C(sp³)–Br/C(sp²)–H functionalization mediated by photoredox and copper cooperative catalysis.



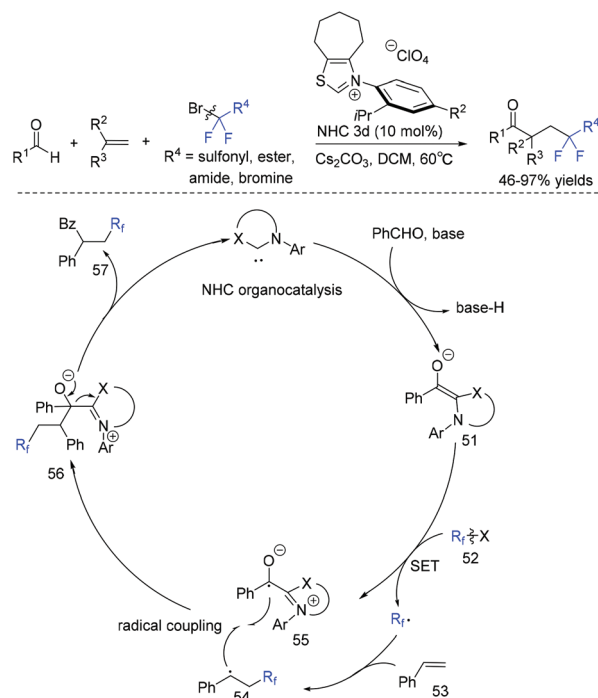
Scheme 27 Alkenes for difluoromethyl radical addition.

and enamides mediated by dual photoredox and chiral Brønsted acid catalysis was presented by Studer and coworkers (Scheme 27).⁸⁵ A range of valuable chiral γ -amino acid derivatives are obtained with good to excellent enantioselectivities. But when $\text{BrCF}_2\text{CO}_2\text{Et}$ was used in this system, only 42% yields and 69 : 31 er value was isolated.

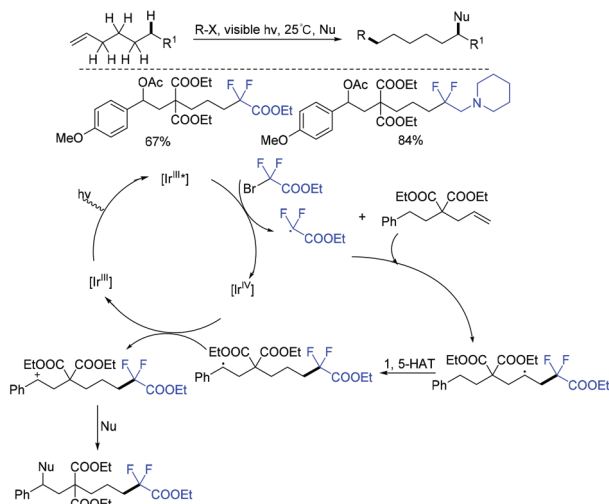
The group of Li and Han demonstrated that *N*-heterocyclic carbene (NHC) could also catalyze radical difluoroalkylation of olefins.⁸⁶ The dearomative difunctionalization of indoles could be readily achieved *via* this reaction. The mechanism is presented in Scheme 28. Firstly, the reaction of NHC catalyst, aldehyde and base occurred to give Breslow intermediate 51, which was followed by SET with fluoroalkyl reagent RCF_2X to afford fluoroalkyl radical and a persistent ketyl radical 55. Subsequently, radical 54 generated from the addition of fluoroalkyl radical to styrene was trapped by radical 55 through a radical–radical cross-coupling pathway to form intermediate F. Finally, the fluoroketone product was obtained with the release of NHC.

2.2. Hydrodifluoroalkylation with alkenes

In 2018, visible-light-induced 1,6-difunctionalizations of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ were realized by the Nevado group



Scheme 28 The *N*-heterocyclic carbene-catalyzed radical difluoroalkylation of olefins.



Scheme 29 The visible-light-induced 1,6-difunctionalization of alkenes.

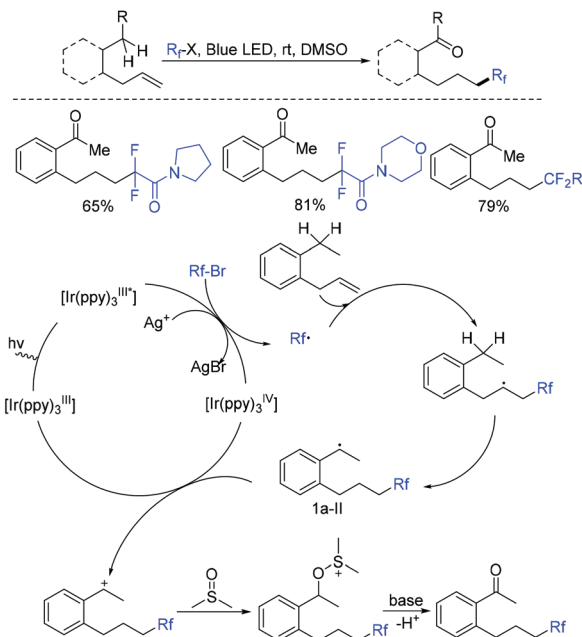
(Scheme 29).⁸⁷ The addition reaction of $\text{CF}_2\text{CO}_2\text{Et}$ radical which was generated from the reduction of $\text{BrCF}_2\text{CO}_2\text{Et}$ by $[\text{Ir}]^{\text{III}*}$ with double bond afforded a vicinal radical intermediate. Subsequently, a remote benzylic radical was generated *via* 1,5-HAT, which can be trapped with O- or C-nucleophiles to produce new Csp³–O and Csp³–Csp² bonds at room temperature.

In the same year, a series of difluoroalkylated ketones or aldehydes was obtained by the group of Luo and Cheng *via* Cu-catalyzed oxidation of alcohols with $\text{BrCF}_2\text{CO}_2\text{Et}$ (Scheme 30).⁸⁸ The catalytic oxidation of alcohols and difluoroalkylation of alkenes were concurrently realized in this reaction, enabling a highly efficient and attractive method for organic synthesis. Similarly, radical difluoroalkylation of alkenes, intramolecular 1,5- or 1,6-HAT, SET oxidation and deprotonation reactions were proposed in the mechanism.

Besides alcohols, the group of Ma and Li demonstrated that difluoroalkylated ketones could also be synthesized *via* visible-light-mediated cascade remote oxyfluoroalkylation of alkenes employing dimethyl sulfoxide as the oxidant and solvent (Scheme 31).⁸⁹ From the plausible mechanism we can see that the alkene fluoroalkylation-initiated remote benzyl C–H bond activation *via* 1,5-H migration in a highly controlled site-selective



Scheme 30 The Cu-catalyzed oxidation of alcohols with $\text{BrCF}_2\text{CO}_2\text{Et}$.

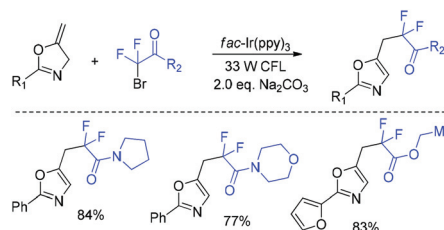


Scheme 31 The Cu-catalyzed oxidation of alcohols with $\text{BrCF}_2\text{CO}_2\text{Et}$.

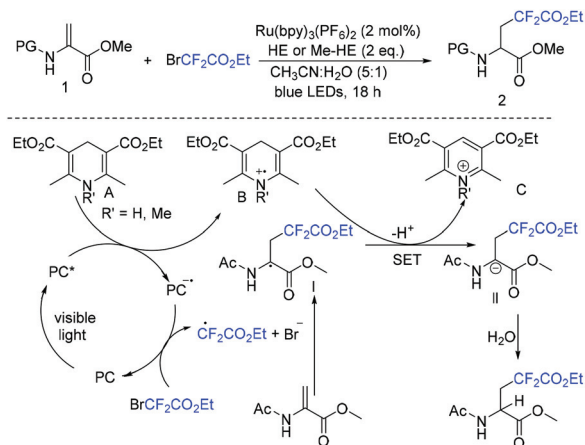
tive manner and Kornblum reaction with dimethyl sulfoxide as the oxidant played a key role in this reaction.

The group of Zhou and Chen realized the reaction of methylene-2-oxazolines with difluoroalkylating reagents *via* a photoredox strategy (Scheme 32).⁹⁰ Difluoroalkylated oxazoles with diverse functionalities were prepared using this method. Tandem radical addition of $\text{CF}_2\text{CO}_2\text{Et}$ radical and subsequent oxidative aromatization steps were proposed in the reaction mechanism.

The photoredox-catalyzed reaction of α,β -dehydroamino acids and peptides with $\text{BrCF}_2\text{CO}_2\text{Et}$ was demonstrated by the Mancheño group, providing various of non-natural amino acids and peptides (Scheme 33).⁹¹ Additionally, arylsulfonyl chlorides or various *N*-(acyloxy)phthalimides (NHPI esters) were also effective for this reaction. In the catalytic cycle, PC^* was reduced by Hantzsch ester to form PC^{*-} and HE-radical cation. Then PC^{*-} reacted with $\text{BrCF}_2\text{CO}_2\text{Et}$ to produce $\text{CF}_2\text{CO}_2\text{Et}$ radical and the photocatalyst PC. Subsequently, the addition reaction of $\text{CF}_2\text{CO}_2\text{Et}$ radical and the double bond of the α,β -dehydroamino acid resulted in radical I, which was followed by reduction and protonation reaction to provide the desired product.



Scheme 32 The difluoroalkylation of alkenes.



Scheme 33 The photoredox-catalyzed reaction of α,β -dehydroamino acids and peptides with $\text{BrCF}_2\text{CO}_2\text{Et}$.

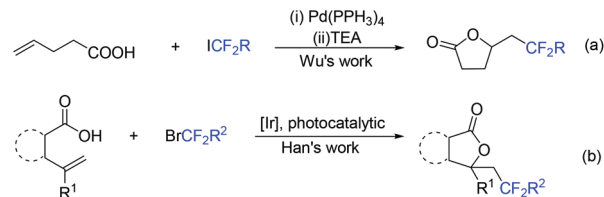
2.3. Heterodifluoroalkylation with alkenes

Due to its thermodynamic stability and kinetic inertness, it is challenging to utilize CO_2 for organic synthesis. Many methods have been developed to harness CO_2 for the synthesis of various organic compounds up to now.^{92–99} In 2018, a selective difluoroalkylation of allyl amines with carbon dioxide *via* visible-light photoredox catalysis was developed by the Yu group.¹⁰⁰ Various 2-oxazolidinones with difluoroalkyl groups were generated. A plausible mechanism is outlined in Scheme 34. $\text{Ru}(\text{I})$ which was generated from the reductive quenching of excited photocatalyst $\text{Ru}(\text{II})^*$ by DABCO reduces BrCF_2R to CF_2R radical. Then carbamate **58** which was generated from **59** and CO_2 *in situ* reacted with CF_2R radical to give benzylic radical **60**. Then oxidation of **60** by excited $\text{Ru}(\text{II})^*$ and intramolecular cyclization of **61** occurred in sequence to afford the final product **62**.

The cyclization of alkenyl carboxylic acids with difluoroalkyl reagents for the synthesis of difluoroalkylated lactones has



Scheme 34 The difluoroalkylation of allyl amines with carbon dioxide.



Scheme 35 The cyclization of alkenyl carboxylic acids with difluoroalkyl reagents.

been established in recent years. The Wu group developed a palladium-catalyzed reaction for the synthesis of difluoroalkylated lactones (Scheme 35a).¹⁰¹ In 2017, the iridium-catalyzed photoredox lactonization for the synthesis of difluoroalkylated lactones was realized by the Han group (Scheme 35b).¹⁰² In 2018, the group of Li realized the copper(I)-catalyzed difluoroalkylation of alkenyl carboxylic acids under mild reaction conditions (Scheme 36).¹⁰³ The highly valued CF_2 -containing lactones were delivered in moderate to excellent yields. A radical-involved pathway was proposed for this catalytic reaction. Firstly, an initial SET from $\text{Cu}(\text{I})\text{Ln}$ **63** to RCF_2Br occurred to generate RCF_2 radical and $\text{Cu}(\text{II})$. Subsequently, the addition reaction of RCF_2 radical to unsaturated carboxylic acid delivered the difluoroalkyl radical intermediate **64**. Then, the carbocation intermediate **65** was formed by oxidation of **64**, concurrently regenerating the active copper(I) catalyst. Finally, the desired product was obtained through an intramolecular nucleophilic attack (Scheme 36, path a). Another pathway involving the $\text{Cu}(\text{III})$ intermediate **66** followed by the reductive elimination under basic conditions to generate the final product was also possible (Scheme 36, path b). In the same



Scheme 36 The copper-catalyzed cyclization of alkenyl carboxylic acids with difluoroalkyl reagents.



Scheme 37 The copper-catalyzed cyclization of unsaturated carboxylic acids.

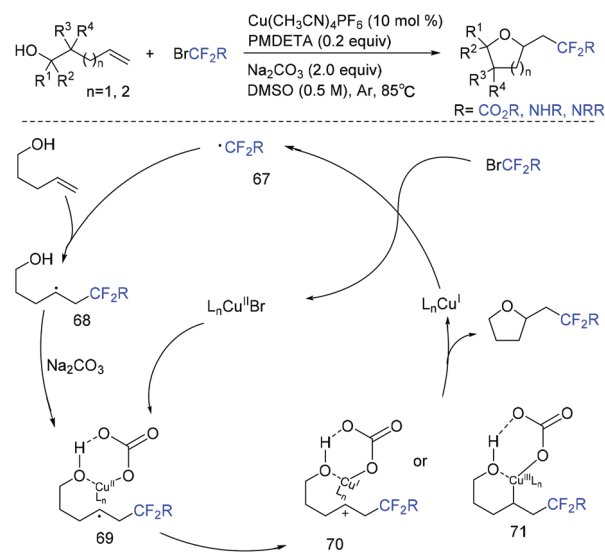
year, another copper-catalyzed difluoroalkylation of alkenyl carboxylic acids for the synthesis of lactone was also reported by the Wang group (Scheme 37).¹⁰⁴ A Cu(I)/Cu(II) mechanism was suggested for this transformation.

The Yang group demonstrated that bromodifluoromethylphosphonates are also good reagents for the construction of difluoroalkylated lactones (Scheme 38).¹⁰⁵ The reaction of bromodifluoromethylphosphonates with alkenyl acids was smoothly carried out in the presence of visible light. Besides acids, alcohols and sulfonamides were also suitable for this system. CF₂P-containing heterocycles can be obtained efficiently. Similar to the production process of RCF₂ radical, the oxidative quenching process of the excited *fac*-[Ir(ppy)₃]* with diisopropyl bromodifluoromethylphosphate *via* SET to afford CF₂PO(OⁱPr)₂ radical was involved in the reaction mechanism.



Scheme 38 The reaction of bromodifluoromethylphosphonates with alkenyl acids.

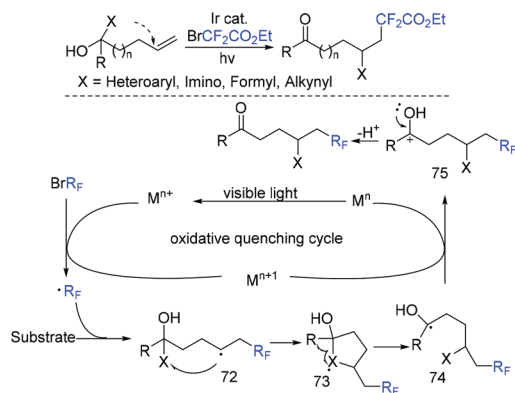
Copper-catalyzed intramolecular oxydifluoroalkylation of hydroxyl-containing alkenes for the synthesis of various fluorinated tetrahydrofurans was also described by the group of Wang and Guo.¹⁰⁶ Besides ethyl bromodifluoroacetate, other functionalized difluoroalkylated bromides were also well employed in this system. The proposed mechanism of this reaction is shown in Scheme 39. First, RCF₂ radical **67** and Cu(II) intermediate were generated from the oxidation of Cu(I) by ethyl bromodifluoroacetate. The addition reaction of radical **67** and alkenes occurred to generate intermediate **68**, which was trapped by Cu(II) in the presence of base Na₂CO₃ to form intermediate **69**. Then two possible intermediates **70** or **71** may be formed. The desired product can be generated from **70** *via* nucleophilic attack of activated alcohol toward carbon cation species. Alternatively, intermediate **71** which undergoes reductive elimination could also deliver the desired product. These two pathways are possible simultaneously. In 2019, this group demonstrated that when amine-containing olefins were used as substrates instead of hydroxyl-containing alkenes, diverse difluorinated nitrogen-containing polycycles were obtained (Scheme 40).¹⁰⁷ Oxidation of Cu(I) species by BrCF₂CO₂Et through a SET to afford an electrophilic RCF₂ radical and Cu(II) species was also described in the proposed mechanism. Recently, the photoredox-catalyzed oxydifluoroalkylative cyclization of alkenes using R₃I was also reported by the Luo group.¹⁰⁸



Scheme 39 The copper-catalyzed intramolecular oxydifluoroalkylation of hydroxyl-containing alkenes.



Scheme 40 The synthesis of difluorinated nitrogen-containing polycycles.

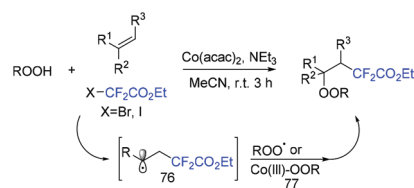


Scheme 41 The synthesis of difluorinated alkyl ketones.

Distal functional group migration was also observed in the reaction of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ (Scheme 41).¹⁰⁹ In combination with visible-light photocatalysis, difluorinated alkyl ketones were readily obtained with high yields. Besides heteroaryl group, imino, formyl, and alkynyl groups were also well tolerated in this system. Radical addition, functional group migration and oxidation reaction were proposed in the plausible mechanism.

The Song group found that the copper/ B_2pin_2 system was effective for difluoroalkylation-thiolation of arylalkenes (Scheme 42).¹¹⁰ B_2pin_2 as an organic reductant played an important role in this transformation, which enables the simultaneous installation of a $\text{C}(\text{sp}^3)\text{-C}(\text{F}_2\text{R})$ bond and a $\text{C}(\text{sp}^3)\text{-S}(\text{R})$ bond by utilizing two electrophilic substrates. Radical trapping experiments suggested that the $\text{CF}_2\text{CO}_2\text{Et}$ radical was involved in the reaction mechanism.

The three-component difluoroalkylation-peroxidation of alkenes with difluorohaloactates and hydroperoxides catalyzed by $\text{Co}(\text{acac})_2$ was developed by the Li group (Scheme 43).¹¹¹ Various β -peroxydifluoroalkyl derivatives were accessed efficiently *via* this strategy. In addition, other halides were also tolerated in this reaction, giving the alkylation-peroxidation products. $\text{CF}_2\text{CO}_2\text{Et}$ radical generated from the reduction of $\text{BrCF}_2\text{CO}_2\text{Et}$ by $\text{Co}(\text{II})$ added to alkenes to form radical **76**. Then *tert*-butylperoxy radical or cobalt *tert*-butylperoxy **77** which were generated from the reaction of cobalt(III) species



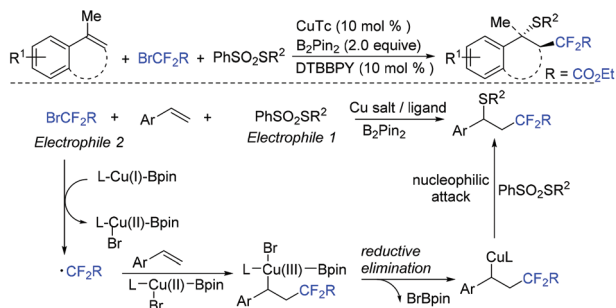
Scheme 43 The three-component difluoroalkylation-peroxidation of alkenes with difluorohaloactates and hydroperoxides.



Scheme 44 The difluoroalkylation-thiolation of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ and RSH.

with hydroperoxide react with radical **76** to afford the desired product.

In 2019, the difluoroalkylation-thiolation of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ and RSH mediated by iron was developed by the Cai group (Scheme 44).¹¹² $\text{Csp}^3\text{-Csp}^3$ and $\text{Csp}^3\text{-S}$ bonds were simultaneously formed in this reaction. FeCl_2 which can be used to activate thiols *via* Fe/S complex has been documented.¹¹³ A possible reaction mechanism was proposed as shown in Scheme 44. A radical intermediate **79** and an oxidized photocatalyst $\text{fac-Ir}^{4+}(\text{ppy})_3$ were generated from the oxidation of $\text{fac-Ir}^{3+}(\text{ppy})_3$ with $\text{BrCF}_2\text{CO}_2\text{Et}$. Then the radical **79** added to styrene **80**, giving a benzyl radical intermediate **81**. On the other hand, the reaction of $\text{Fe}(\text{II})$ with 4-methylbenzenethiol delivered an iron-sulfur intermediate **82** in the presence of a base, which was followed by recombination with **81** to produce intermediate **84**. Finally, a SET occurred between **84** and $\text{fac-Ir}^{4+}(\text{ppy})_3$, providing the desired product, along with the liberation of FeCl_2 . In the same year, the same group¹¹⁴ found that three-component difluoroalkylamination of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ and amines could also be realized under similar reaction conditions (Scheme 45). Besides thiols and amines, alcohol was also found to be suitable for this type of reaction by the Nishikata group (Scheme 46).¹¹⁵ The copper-mediated radical and cation crossover mechanism was involved in the reaction pathway.



Scheme 42 The light-mediated Truce-Smiles rearrangement.



Scheme 45 The difluoroalkylation–thiolation of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ and amines.

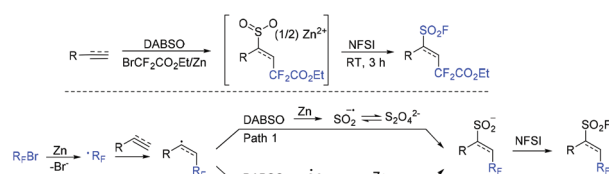


Scheme 46 The difluoroalkylation–thiolation of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ and alcohols.

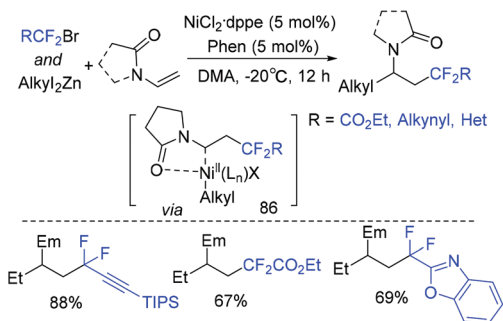
1,4-Diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct (DABSO) as an inexpensive and readily available reagent has been widely used in organic transformations.^{116–118} In 2019, Chen and coworkers achieved a zinc-mediated intermolecular reductive radical fluoroalkylsulfination of unsaturated C–C bonds with fluoroalkyl bromides and DABSO (Scheme 47).¹¹⁹ Alkenes and alkynes were all tolerated in this reaction, affording the product with moderate yields. Preliminary mechanistic investigations revealed that a sulfur dioxide anion radical species reduced by Zn from SO_2 was involved in this reaction.

Due to side reactions, nickel-catalyzed dialkylation of alkenes remains underdeveloped. In 2019, a nickel-catalyzed three-component difluoroalkylation–alkylation of *N*-vinyl-2-pyrrolidinone with difluoroalkyl bromides and dialkylzinc reagents was reported by the Zhang group (Scheme 48).¹²⁰ *N*-Vinylloxazolidinone and *N*-vinylacetamide can also be applied to this system. $\text{BrCF}_2\text{COOEt}$ was used for this reaction, the corresponding product being obtained in 51% yield. Two mechanisms initiated by Ni(I) or Ni(II) were possible for this reaction. As a key intermediate, radical **86** was generated in both mechanisms.

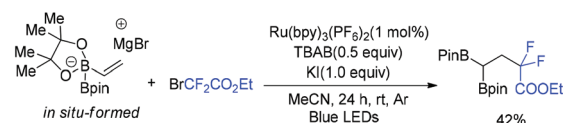
The Shi group found that $\text{CF}_2\text{CO}_2\text{Et}$ radical was also a good partner to react with alkenyl diboronate complexes (Scheme 49).¹²¹ In the presence of Ru photocatalyst, *gem*-bis(boryl)alkanes were formed from the reaction of alkenyl dibor-



Scheme 47 The difluoroalkylation–thiolation of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ and alcohols.



Scheme 48 The difluoroalkylation–thiolation of alkenes with $\text{BrCF}_2\text{CO}_2\text{Et}$ and alcohols.



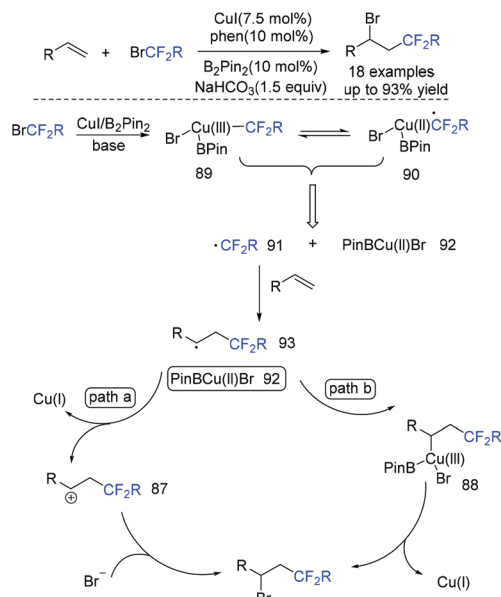
Scheme 49 The reaction of alkenyl diboronate complexes with $\text{BrCF}_2\text{CO}_2\text{Et}$.

onate with diverse alkyl halides. Alkyl radicals added efficiently to the alkenyl diboronate complexes. Then the adduct radical anions undergo radical–polar crossover and 1,2-boryl-anion shift from boron to the α -carbon to afford the final product.

In 2018, the difluoroacetylation of alkenes using ethyl bromodifluoroacetate ($\text{BrCF}_2\text{CO}_2\text{Et}$) catalyzed by copper was reported by the Zhu group (Scheme 50).¹²² In the presence of a base, $\text{BrCF}_2\text{CO}_2\text{Et}$ was reduced by the complex of $\text{CuI}/\text{B}_2\text{Pin}_2$ to generate CF_2COOEt radical **91** along with Cu(II) **92**. Then, radical **91** added to the terminal carbon of alkenes to give carbon radical intermediate **E**, which can be oxidized by **92**, trapped by bromide ion to afford the desired product. Alternatively, intermediate **93** coupled with **92** to afford Cu(III) complex which was followed by reductive elimination to afford product with the release of Cu(I) . This pathway was also possible.

The He group demonstrated that organophosphine was a good catalyst for atom transfer radical addition of alkenes with ethyl iododifluoroacetate (Scheme 51).¹²³ Substrate-controlled selectivity was observed in this difluoroacetylation. When styrenes were subjected to this system, a Heck-type difluoroalkylated product was furnished. Difluoroalkylated alkanes were obtained when alkenes were used. A noncovalent interaction between the phosphine catalyst and carbon–iodine bond was suggested for this reaction.

The base-controlled selective (phenylsulfonyl)difluoromethylation of alkenes with $\text{PhSO}_2\text{CF}_2\text{I}$ was observed by the Wang group (Scheme 52).¹²⁴ Both atom transfer radical addition and Heck-type products could be obtained *via* simply tuning the organic or inorganic bases in the presence of visible light. The oxidative quenching of $^*\text{Ru(bpy)}_3^{2+}$ with $\text{PhSO}_2\text{CF}_2\text{I}$ was proposed in the mechanism. Both types of products can be formed *via* two pathways.



Scheme 50 The copper-catalyzed difluoroacetylation of alkenes.

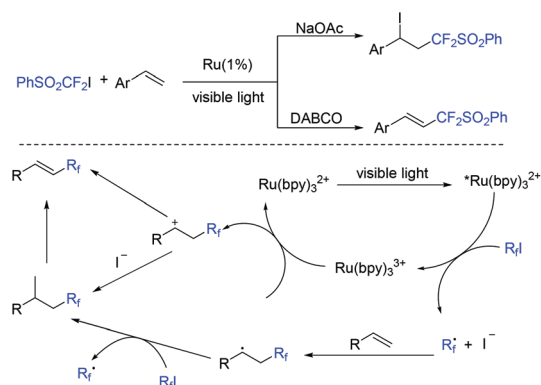


Scheme 51 The organophosphine-catalyzed difluoroalkylation of alkenes.

The photoredox-catalyzed oxydifluoroalkylation of alkenes with $\text{BrCF}_2\text{CO}_2\text{R}$ using dimethyl sulfoxide (DMSO) as an oxidant was reported by Tang and coworkers (Scheme 53).¹²⁵ From the proposed mechanism we can see that AgTFA as the additive assisted the formation of $\text{CF}_2\text{CO}_2\text{R}$ radical *via* oxidative quenching of $^*\text{Ir}(\text{ppy})_3$ with $\text{BrCF}_2\text{CO}_2\text{R}$. The final products were isolated *via* Kornblum oxidation of carbocation **100** with DMSO.

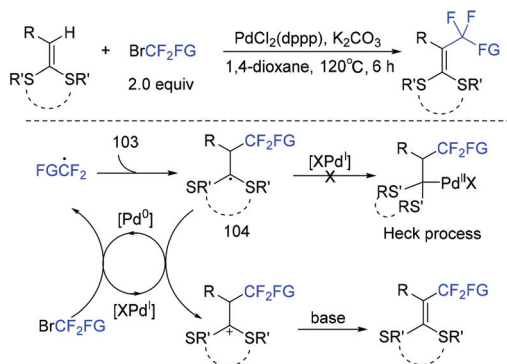
2.4. Other difluoroalkylation with alkenes

The palladium-mediated vinylic C–H difluoroalkylation of ketene dithioacetals with $\text{BrCF}_2\text{CO}_2\text{Et}$ was realized by the

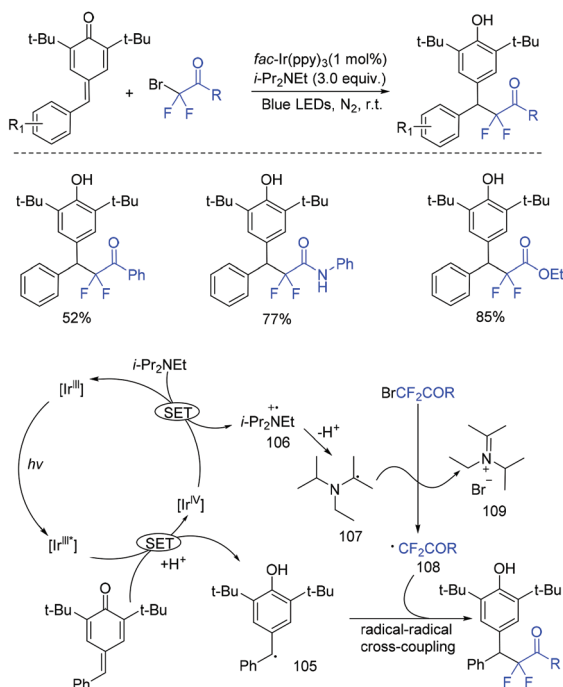
Scheme 52 The (phenylsulfonyl)difluoromethylation of alkenes with $\text{PhSO}_2\text{CF}_2\text{I}$.Scheme 53 The photoredox-catalyzed oxydifluoroalkylation of alkenes with $\text{BrCF}_2\text{CO}_2\text{R}$ using dimethyl sulfoxide.

group of Wang and Zhu in 2018 (Scheme 54).¹²⁶ Two SET processes were involved in the reaction mechanism. Owing to the unique structural characters of ketene dithioacetals, a $\text{Pd}(0)/\text{Pd}(I)$ catalytic cycle was proposed for this reaction, which was different from the known palladium catalyzed Heck-type reaction of alkenes with fluoroalkyl bromides.

Xu and coworkers reported a visible-light-induced cross-coupling reaction of *para*-quinone methides (*p*-QMs) with difluoroalkylating reagents (Scheme 55).¹²⁷ A series of difluoroalkylated diarylmethane compounds with pharmaceutical potential was accessed. From the plausible mechanism we can see that the excited photocatalyst, $^*\text{fac-Ir}(\text{ppy})_3$, was primarily quenched by *p*-QMs to afford the diarylmethane radical intermediates, which was followed by a radical–radical cross-coupling reaction with difluoroalkyl radicals to deliver the final product. Amine could react as reductant with both $\text{Ir}(IV)$ and



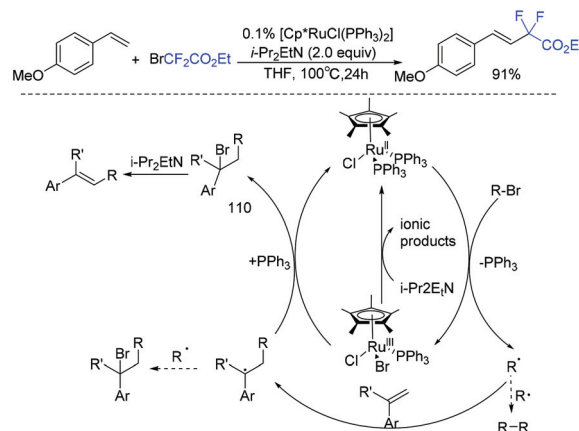
Scheme 54 The palladium-mediated C–H difluoroalkylation of ketene dithioacetals.



Scheme 55 The visible-light-induced difluoroalkylation reaction of *p*-QMs.

$\text{BrCF}_2\text{CO}_2\text{Et}$ to produce $\text{Ir}(\text{III})$ and $\text{CF}_2\text{CO}_2\text{Et}$ radical respectively.

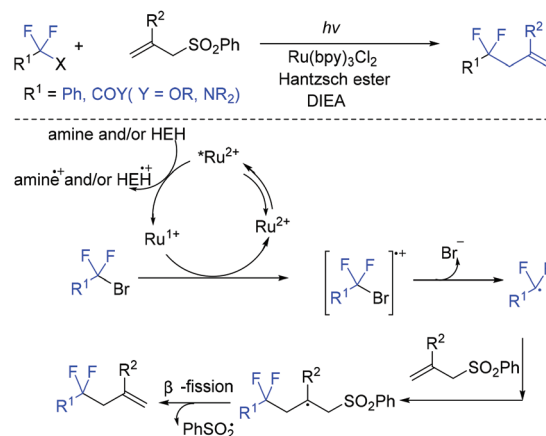
Muñoz-Molina and Perez found that $[\text{Cp}^*\text{RuCl}(\text{PPh}_3)_2]$ complex showed good catalytic activity for the Heck-type alkenylation of alkyl bromides (Scheme 56).¹²⁸ Tertiary, secondary, and primary alkyl bromides could all react smoothly in this reaction. The corresponding product could be obtained in 91% yield when $\text{BrCF}_2\text{CO}_2\text{Et}$ was used. Hünig's base played an important role for this transformation. Preliminary mechanistic studies support the participation of alkyl radicals in the reaction. The mechanism is outlined in Scheme 56. Initially, the formation of carbon-centered radicals by a SET process was induced by the half-sandwich ruthenium(II) complex, which was followed by the anti-Markovnikov addition with the



Scheme 56 The Ru complex-catalyzed Heck-type alkenylation.

olefin to deliver another radical species. Then the new radical species reduced the ruthenium(III) center to ruthenium(II), with the release of intermediate **110**. Finally, the desired product was obtained *via* base-induced elimination reaction. Additionally, the amine acts as a reductant to regenerate the $\text{Ru}(\text{II})$ catalyst from $\text{Ru}(\text{III})$.

The visible-light-induced coupling of difluoromethyl halides with allyl sulfones for the synthesis of 4,4-difluoroalkenes was reported by the Ryu group (Scheme 57).¹²⁹ With the help of catalytic $\text{Ru}(\text{bpy})_3\text{Cl}_2$, diisopropylethylamine, and Hantzsch ester, the reaction proceeded effectively within 2 h. In the catalytic cycle, $\text{Ru}(\text{I})$ was reduced by HEH and/or amine from the photoexcited $\text{Ru}(\text{II})^*$ *via* a SET process. Then another SET process occurred between $\text{Ru}(\text{I})$ and $\text{BrCF}_2\text{CO}_2\text{Et}$ to generate $\text{CF}_2\text{CO}_2\text{Et}$ radical, which was followed by an addition reaction with C and β -fragmentation to furnish the product. In 2020, the Yao group found that the decarboxylative allylation of α,α -difluoroarylacetic acids with allyl sulfones can also be catalyzed by silver in water.¹³⁰ Preliminary mechanistic investigations suggest that a radical process and β -elimination might be involved.



Scheme 57 The visible-light-induced coupling of difluoromethyl halides with allyl sulfones.



Scheme 58 The photoinduced decarboxylative difunctionalization of maleic anhydride with amine and fluorinated alkyl iodides.

The photoinduced decarboxylative difunctionalization of maleic anhydride with amine and fluorinated alkyl iodides was reported by the Zhang group (Scheme 58).¹³¹ A variety of fluorinated alkyl halides and amines reacted smoothly in this reaction. The difluoroalkyl radical which was generated from oxidative quenching reaction between fluorinated alkyl iodides and excited Ru(II)* was also possible in this reaction.

Coumarins are an important class of heterocyclic compounds which display a wide range of biological activities.^{132–135} In 2019, the same group found that difluoroalkylation of *ortho*-hydroxycinnamic esters with BrCF₂CO₂Et can proceed smoothly through a visible-light-induced cascade radical cyclization process (Scheme 59). A variety of 3-fluoroalkylated coumarins were successfully prepared under mild conditions. Similarly, RCF₂ radical species was also proposed in the reaction cycle.¹³⁶

3. Difluoroalkylation with alkynes

3.1. Carbodifluoroalkylation with alkynes

In 2015, the Fu group reported the visible-light-promoted aryl-difluoroacetylation of alkynes with ethyl bromodifluoroacetate for the synthesis of 3-difluoroacetylated coumarins (Scheme 60).⁴⁰ A wide range of functional groups was tolerated in this reaction. A tandem radical cyclization process which involved RCF₂ radical was proposed for this reaction.

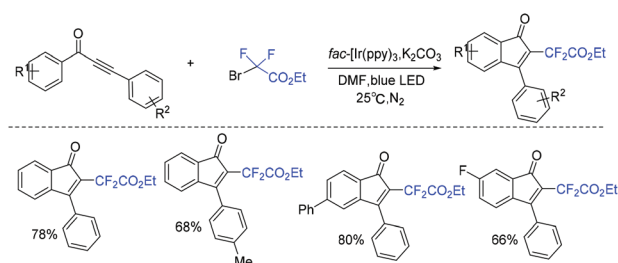
A mild and efficient photocatalytic protocol for the synthesis of difluoroacetylinones *via* the reaction of 1,3-diarylpropynones with ethyl bromodifluoroacetate was established by Rastogi and coworkers (Scheme 61).¹³⁷ The visible-light-catalyzed difluoroacetylation of 1,3-diarylpropynones followed by intramolecular radical cyclization was proposed for this reaction.



Scheme 59 The difluoroalkylation of *ortho*-hydroxycinnamic esters.



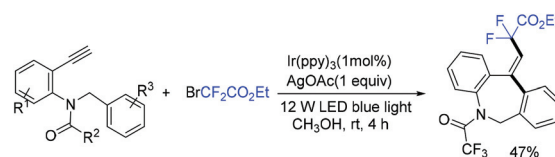
Scheme 60 The visible-light-promoted aryldifluoroacetylation of alkynes with ethyl bromodifluoroacetate.



Scheme 61 The synthesis of difluoroacetylinones *via* the reaction of 1,3-diarylpropynones with ethyl bromodifluoroacetate.

In the presence of Ir(ppy)₃ as photocatalyst, the group of Li and Hu found that *N*-benzyl-*N*-(2-ethynylaryl)amides were good partners to react with ethyl bromodifluoroacetate for the synthesis of substituted dibenzazepines (Scheme 62).¹³⁸ Two carbon-centered functional groups are introduced across the C≡C bond in a single reaction. The Xu group found that this reaction can also smoothly proceed in the presence of organic photocatalysts (cat-PMP) (Scheme 63).¹³⁹ Fluoroalkyl radical which formed from the reduction of BrCF₂CO₂Et by excited-state cat-PMP* was proposed in the catalytic cycle. Then intermolecular addition of fluoroalkyl radical RCF₂ to *N*-benzyl-*N*-(2-ethynylaryl)amides occurred to provide radical **112**, which was followed by intramolecular addition to form intermediate **114**. Intermediate **114** was oxidized by cat-PMP⁺⁺ to afford **115**. Finally, intermediate **115** undergoes deprotonation to furnish the desired product. On the other hand, another possible pathway (path b) was also possible for this reaction.

Copper-catalyzed cascade radical addition/dearomative spirocyclization of biaryl ynones to access difluoromethylated spiro [5.5]trienones was first realized by the Zhu group (Scheme 64).¹⁴⁰



Scheme 62 The synthesis of substituted dibenzazepines catalyzed by Ir(ppy)₃.



Scheme 63 The synthesis of substituted dibenzazepines catalyzed by organic photocatalysts.



Scheme 64 The copper-catalyzed cascade radical addition/dearomatization spirocyclization of biaryl ynones.

This reaction is useful for the construction of spiro compounds. When Ag was employed as catalyst, monofluoromethylated and phosphorated spiro[5.5]trienones were also obtained using diethylphosphite as substrate. Fluoroalkyl radical was proposed in the reaction mechanism. A vinyl radical **117** was formed *via* the addition of RCF_2 radical to C–C triple bond, then 6-*exo-trig* cyclization occurred to afford intermediate **119** which is oxidized by M^{n+1} to form oxocarbenium ion **120**. After demethylation, the desired product was obtained.



Scheme 65 The cobalt-promoted cyclization of fluoroalkyl radical with C–C triple bond.

In 2019, the group of Ackermann and Li demonstrated that cobalt was a good catalyst to promote the cyclization of fluoroalkyl radical with C–C triple bond (Scheme 65).¹⁴¹ Various fluorinated chromenes were synthesized *via* cobalt-catalyzed difluoroalkylation/Giese radical conjugate cyclization manifold with various alkyne-tethered cyclohexadienones and halogenated fluorinating reagents. Similar to copper catalyst, the Co catalyst could also reduce ethyl bromodifluoroacetate to produce difluoroalkyl radical. Subsequently, the addition of difluoroalkyl radical with alkynes resulted in alkenyl radical **127**. Then intermediate **127** undergoes an intramolecular Giese radical conjugate addition to afford the key intermediate **128**, which was followed by reduction by Zn, along with hydrolysis, providing the desired product, with the release of the active $\text{Co(I)}\text{Ln}$ complex.

Cyclopropenes having unique rigid structure and variable reactivity have attracted much interest.^{142–145} In 2019, the Ma group¹⁴⁶ reported the first highly enantioselective Rh^{II} -catalyzed cyclopropenation reaction of unactivated internal alkynes with a difluorodiazaoethane reagent (PsDFA) (Scheme 66). A broad range of enantioenriched unsaturated three-membered carbocycles can be obtained smoothly. Subsequently, various reactions such as crosscouplings, hydrogenation, Diels–Alder reaction, and Pauson–Khand reaction could occur to demonstrate the synthetic utility of the strained carbocycles.



Scheme 66 The palladium-catalyzed difluoroalkylation reaction of *N*-propargylamides.

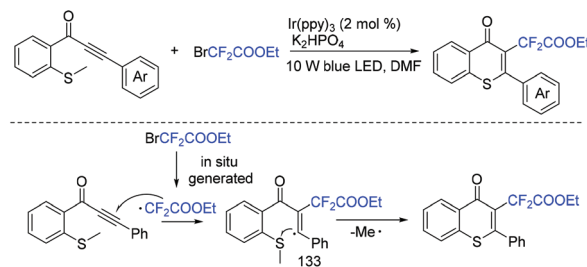
3.2. Hydrodifluoroalkylation with alkynes

The group of Wang and Zhao found that the hydrodifluoroalkylation of alkynes with ethyl bromodifluoroacetate could proceed smoothly mediated by copper.¹⁴⁷ Metabisulfite as reduction agent should be used for this reaction to suppress the homocoupling of terminal alkynes. It can be seen from Scheme 67 that CF_2COOEt radical was generated from the reaction of $\text{BrCF}_2\text{COOEt}$ and Cu(I) *via* SET process. Then addition reaction with (phenylethynyl)copper **130**, hydrogen abstraction from solvents and protonation by moisture occurred in sequence to give the final product.

3.3. Heterodifluoroalkylation with alkynes

A facile method for the synthesis of C2-tetrasubstituted indolin-3-ones *via* copper-catalyzed redox cycloisomerization of nonprefunctionalized nitroalkynes with $\text{BrCF}_2\text{CO}_2\text{Et}$ was achieved by the Song group (Scheme 68).¹⁴⁸ Using diboron as the reductant, this reaction proceeded in a one-pot protocol forming a fluorine-containing non-carbon quaternary center. One of the oxygens from NO_2 was captured by B_2pin_2 with the aid of Na_2CO_3 . Another oxygen in NO_2 was transformed into C=O bond of C2-tetrasubstituted indolin-3-ones.

In 2019, the same group developed a visible-light-promoted cyclization of methylthiolated alkynones with $\text{BrCF}_2\text{CO}_2\text{Et}$ for the synthesis of 2-substituted thiochromones.¹⁴⁹ The desired products could be accessed with moderate to good yields *via* $\text{C(sp}^2\text{)-S}$ bond formation and $\text{C(sp}^3\text{)-S}$ cleavage. Besides $\text{CF}_2\text{CO}_2\text{Et}$ group, phosphoryl, sulfenyl, and acyl groups are also well tolerated in this method. The reaction mechanism is depicted in Scheme 69. Firstly, the fluoroalkyl radical was generated from the corresponding conditions. Then the C-C triple bond in alkynones was attacked by fluoroalkyl radical to give vinyl radical **133**. Finally, 6-*exo-trig* cyclization of **133** with the

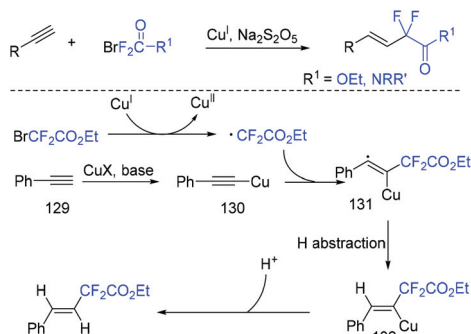


Scheme 69 The cyclization of methylthiolated alkynones with $\text{BrCF}_2\text{CO}_2\text{Et}$ for the synthesis of 2-substituted thiochromones.

SMe moiety gave the desired product along with the release of methyl radical.

The carbon radical intermediates generated from the electrophilic radical addition of $\text{CF}_2\text{CO}_2\text{Et}$ radical with alkynes can be trapped by an oxygen nucleophile to form difluoro-substituted heterocycles.^{40,150,151} In 2018, a palladium-catalyzed difluoroalkylation reaction of *N*-propargylamides with ethyl iododifluoroacetate for the synthesis of difluoromethyl oxazoles and oxazolines was reported by the Liang group (Scheme 70).¹⁵² A $\text{Pd(0)/Pd(I)/Pd(II)}$ cycle was proposed for the reaction mechanism. Additionally, perfluoroalkyl iodides were also suitable for the generation of perfluoroalkyl heterocycles.

An efficient cobalt-catalyzed difluoroalkylation of alkynes/alkenes for the construction of fluorinated hydrocarbons was described by Jacobi von Wangelin and coworkers.¹⁵³ However, alkyl-substituted terminal alkynes were not effective in this system. This was the first cobalt-catalyzed reaction with high stereoselectivity. The proposed reaction mechanism is shown



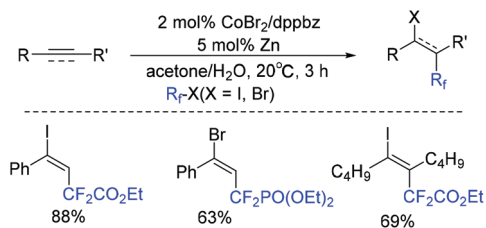
Scheme 67 The copper-catalyzed hydrodifluoroalkylation of alkynes with ethyl bromodifluoroacetate.



Scheme 68 The synthesis of C2-tetrasubstituted indolin-3-ones.



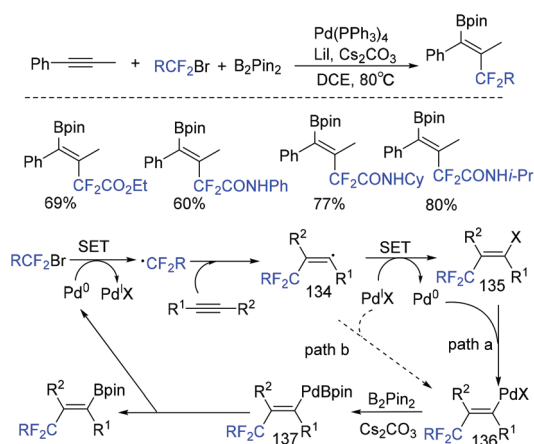
Scheme 70 The palladium-catalyzed difluoroalkylation reaction of *N*-propargylamides.



Scheme 71 The cobalt-catalyzed difluoroalkylations of alkynes/alkenes.

in Scheme 71. Different from related cobalt-catalyzed reductive couplings and Heck-type reactions, terminal halogen atom transfer mediated by Co catalyst was involved in the radical chain mechanism, which avoided the use of a stoichiometric sacrificial reductant. The $R_f\text{Co}^{\text{III}}\text{X}$ complex which delivered the free R_f radical and mediated the halogen atom transfer to the terminal vinyl radical played an important role in the catalytic cycle.

In 2018, a palladium-mediated three-component reaction of alkynes with fluoroalkyl halides and diboron reagents was developed by the group of Zhu and Bai (Scheme 72).^{154a} Both internal and terminal alkynes were tolerated in this reaction, providing the functionalized 1,2-fluoroalkylboronated alkenes with excellent regio- and stereoselectivity. In the catalytic cycle, a SET process was also proposed between fluoroalkyl halides and $\text{Pd}(0)$ to afford RCF_2 radical and $\text{Pd}(\text{I})$ species. Then the addition reaction of RCF_2 radical and alkynes took place to give vinyl radical. Then oxidative addition and base-assisted transmetalation with B_2pin_2 delivering the alkenyl(boryl)palladium intermediate **137** and reductive elimination of **137** occurred successively to give the desired product (path a). Alternatively, path b featuring the direct reaction of vinyl radical I with $\text{Pd}(\text{I})$ was also possible. But this pathway was less likely. The palladium-catalyzed *trans*-fluoroalkylation-borylation of alkynes with fluoroalkyl iodides and B_2pin_2 was also realized by the Zhang group.^{154b}



Scheme 72 The palladium-mediated three-component reaction of alkynes with fluoroalkyl halides and diboron reagents.



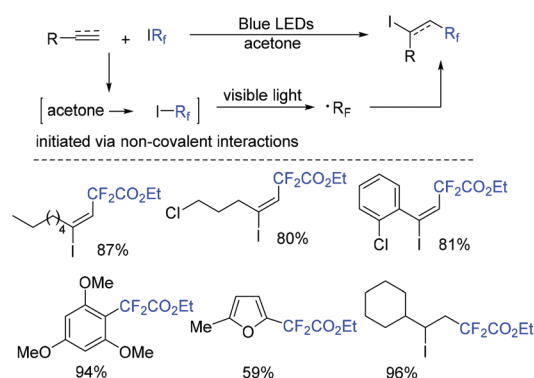
Scheme 73 The copper-catalyzed difluoroalkylation reaction of alkynes with ethyl iododifluoroacetate.

In 2018, the Liang group found that air-stable SCF_3 and SeCF_3 reagents could act as free-radical initiators of ethyl iododifluoroacetate *via* reduction reaction (Scheme 73).¹⁵⁵ In the presence of air-stable SCF_3 and SeCF_3 reagents, the difluoroalkylation reaction of alkynes with ethyl iododifluoroacetate proceeded smoothly. β -Proton elimination was successfully avoided. Besides alkynes, alkenes were also suitable in this reaction. A $\text{Cu}(\text{I})$ – $\text{Cu}(\text{II})$ – $\text{Cu}(\text{III})$ mechanism was described for this reaction.

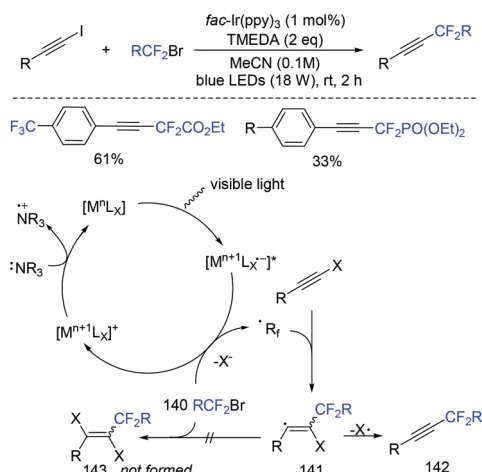
A photocatalyst-free fluoroalkylation reaction of alkynes with fluoroalkyl iodides was developed by the He group (Scheme 74).¹⁵⁶ It is worth noting that the noncovalent interactions between acetone and fluoroalkyl iodides could assist the formation of fluoroalkyl radical. Additionally, (hetero) arenes and alkenes were also tolerated in this transformation.

3.4. Other difluoroalkylation with alkynes

In 2019, the visible-light-induced alkynyl-difluoroalkylation of alkynyl halides with fluoroalkyl halides to access a diverse range of fluoroalkylalkynes was described by the Cho group (Scheme 75).¹⁵⁷ Controlled experiments suggested a radical mechanism was possible. SET from *fac*- $\text{Ir}(\text{ppy})_3^*$ to fluoroalkyl



Scheme 74 The photocatalyst-free fluoroalkylation reaction of alkynes with fluoroalkyl iodides.



Scheme 75 The visible-light-induced alkynyl-difluoroalkylation of alkynyl halides with fluoroalkyl halides.

halide generated the oxidized photocatalyst $fac\text{-Ir(ppy)}_4$ and the RF_2 radical. The $fac\text{-Ir(ppy)}_4$ could be reduced by TMEDA to form $fac\text{-Ir(ppy)}_3$ complex. Then vinyl radical **141** was formed *via* the addition reaction of RCF_2 radical and alkynyl halide, which could be converted to the final product *via* dehalogenation.

In 2019, a palladium-catalyzed ligand-free difluoroalkylation of alkynes with iododifluoroacetones for the construction of difluorinated 1,3-enynes was developed by the Wu group (Scheme 76).¹⁵⁸ The radical addition of RCOCF_2 radical which was generated from reduction of iododifluoroacetones with $\text{Pd(PPh}_3)_4$ to alkynes and subsequent Sonogashira coupling with the same alkynes were involved in the reaction mechanism.

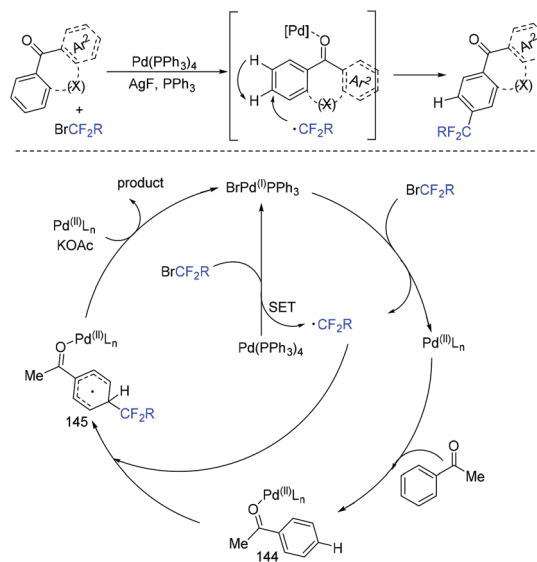


Scheme 76 The construction of difluorinated 1,3-enynes.

4. Difluoroalkylation with arene

In 2018, an efficient *para*-selective C–H difluoromethylation of aromatic ketones catalyzed by tetrakis(triphenylphosphine)palladium(0) was developed by the Zhao group (Scheme 77).¹⁵⁹ Additionally, several well-known drugs such as oxybenzone, ketoprofen, zaltoprofen, and propafenone were also well tolerated in this system. The role of AgF was unclear, it being likely to assist the palladium complex in activating the aromatic ring. A mechanistic study suggested that a highly *para*-selective difluoromethylation reaction may result from the palladium complex coordinated to the carbonyl group. SET between Pd(I) and $\text{BrCF}_2\text{CO}_2\text{Et}$ took place to afford $\text{CF}_2\text{CO}_2\text{Et}$ radical and Pd(II) . Then $\text{CF}_2\text{CO}_2\text{Et}$ radical coupled with complex **144** which came from the coordination of Pd(II) intermediate with aromatic ketone to give intermediate **145**. Subsequently, intermediate **145** was converted to the final product *via* SET process and aromatization, with the liberation of Pd(I) catalyst. Almost at the same time, similar work was described by the group of Xu and Lou (Scheme 78).¹⁶⁰

In 2019, Li and coworkers found that *para*-selective C–H difluoroalkylation of aromatic carbonyls could also be induced by visible light.¹⁶¹ In the presence of Ir(ppy)_3 as the catalyst and 1,10-phenanthroline as the additive, various products could be obtained efficiently. The proposed mechanism is



Scheme 77 The *para*-selective C–H difluoromethylation of aromatic ketones.



Scheme 78 The *para*-selective C–H difluoromethylation of aromatic ketones.



Scheme 79 The *para*-selective C–H difluoromethylation of aromatic ketones.

shown in Scheme 79. Concurrently, irradiation of $\text{Ir}^{\text{III}}(\text{ppy})_3$ resulted in excited $\text{Ir}^{\text{III}}(\text{ppy})_3^*$, which could be oxidized by $\text{BrCF}_2\text{CO}_2\text{Et}$ via a SET process with the formation of $\text{CF}_2\text{CO}_2\text{Et}$ radical and $\text{Ir}^{\text{IV}}(\text{ppy})_3$. Then the *para*-selective addition of $\text{CF}_2\text{CO}_2\text{Et}$ radical to aryl carbonyls occurred to produce intermediate **146**, which could be converted to radical anion intermediate **147** by the reverse process of deprotonation. Finally, intermediate **147** was oxidized by Ir^{IV} to give the product via rearomatization. In the same year, similar reactions of visible-light-induced difluoroalkylation of aromatic aldehydes were developed by the Xu group (Scheme 80).¹⁶²

Using ruthenium(II) as a catalyst, *para*-selective C–H difluoromethylation of ketoxime ethers was also realized by the Zhao group, providing the corresponding *para*-difluoromethylated products in moderate to good yield (Scheme 81).¹⁶³ Mechanistic studies showed that chelation-assisted cycloruthenation may play an important role in the *para* selectivity of the difluoromethylation of ketoxime ethers. Different from Zhao's work, *meta*-C–H alkylation of arenes catalyzed by Ru was described by Ackermann in the presence of visible light (Scheme 82a).¹⁶⁴ Both tertiary and secondary alkyl bromides were compatible with this reaction. When $\text{BrCF}_2\text{CO}_2\text{R}$ was employed, the product was isolated in 48% yield. Recently, the Ru-catalyzed *meta*-C–H bond difluoroalkylation of 2-phenoxy-pyridines was realized by the Cui group (Scheme 82b).¹⁶⁵



Scheme 80 The *para*-selective C–H difluoromethylation of aromatic aldehydes.



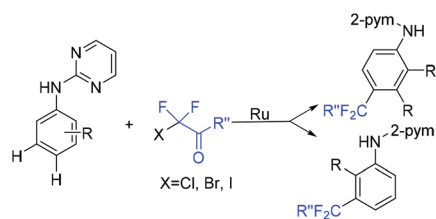
Scheme 81 The *para*-selective C–H difluoromethylation of ketoxime ethers.



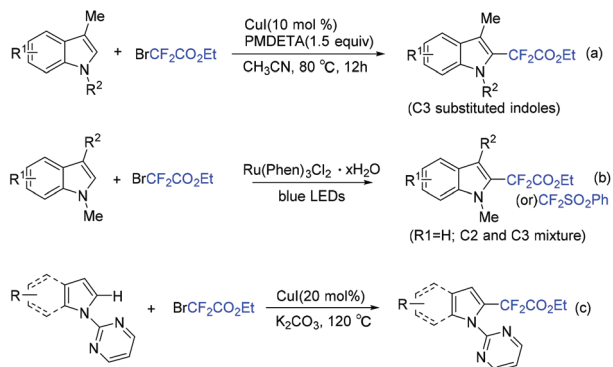
Scheme 82 The *meta*-C–H alkylation of arenes catalyzed by Ru.

The ruthenium(II)-catalyzed *para*- and *meta*-selective C–H difluoroalkylation of aniline derivatives with $\text{BrCF}_2\text{CO}_2\text{Et}$ was reported by the Liang group (Scheme 83).¹⁶⁶ Mechanistic investigation implied that the key factor of the *para*-selective difluoroacetylation derived from the cycloruthenation that occurred at N–H and C–H simultaneously. The electronic effects of carboxylate ligands along with a base determined the selectivity. This reaction rendered readily the modification of anilines as well as the structural motifs of biologically active compounds. Notably, *meta*-substituted products were obtained when $\text{ClCF}_2\text{CO}_2\text{Et}$ and $\text{BrCF}_2\text{CO}_2\text{Et}$ were applied to this reaction.

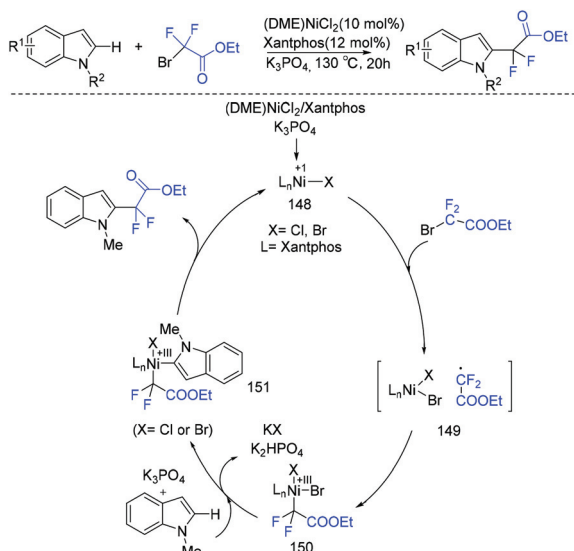
Use of Cu (Scheme 84a)¹⁶⁷ and Ru (Scheme 84b)¹⁶⁸ to catalyze difluoroalkylation of heteroarenes, including indoles, with $\text{BrCF}_2\text{CO}_2\text{R}$ was also realized by several groups. However, a mixture of C-2 and C-3 difluoroalkylation was observed in these methods. Therefore, C-3 substituted indoles were usually applied to achieve selective C(2)–H difluoroalkylation. The Shi



Scheme 83 The ruthenium(II)-catalyzed *para*- and *meta*-selective C–H difluoroalkylation of aniline derivatives.



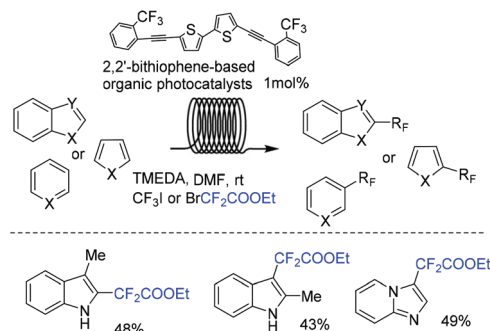
Scheme 84 The difluoroalkylation of heteroarenes.



Scheme 85 The nickel-catalyzed C(2)-H difluoroalkylation of C-3 unsubstituted indoles.

group realized copper-catalyzed C-2 difluoromethylation of indoles and pyrroles with $\text{BrCF}_2\text{CO}_2\text{Et}$. But a pyrimidyl group should be present as a directing group (Scheme 84c).¹⁶⁹ In 2018, the nickel-catalyzed regioselective C(2)-H difluoroalkylation of C-3 unsubstituted indoles with $\text{BrCF}_2\text{CO}_2\text{R}$ was successfully achieved by the Punji group (Scheme 85).^{170a} Assistance of a directing group at the indoles was not necessary. A possible mechanism is described in Scheme 85. First, the Ni precursor might be reduced by Xantphos and base to active Ni(I) catalyst **148**, which was followed by the reaction with $\text{BrCF}_2\text{CO}_2\text{R}$ to afford intermediate **149**. Then intermediate **149** underwent radical rebound to generate Ni(III) species **150**, which was converted to intermediate **151** via C(2)-H activation of indole.^{170b} Finally, the product was formed via reductive elimination of **151**, with the regeneration of the active catalyst. A parallel Ni(0)/Ni(II) path was also possible.

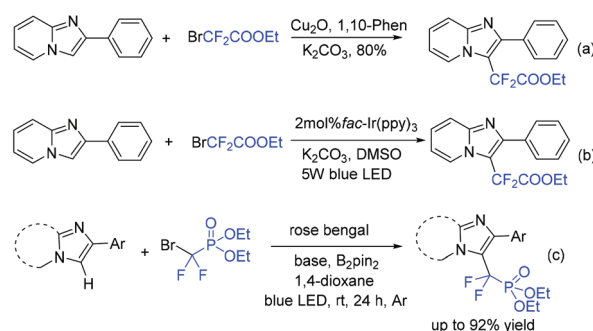
With the aid of DFT calculations, Noël and coworkers synthesized a series of substituted bithiophene derivatives as



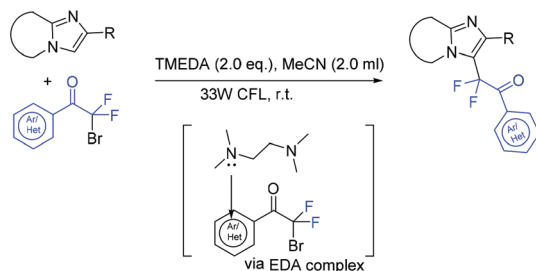
Scheme 86 The visible-light-induced C-H functionalization of heteroarenes.

novel and inexpensive organic photocatalysts (Scheme 86).¹⁷¹ The activity of these photocatalysts was proved to be comparable with that of other commonly used organic or transition-metal photocatalysts in C-H functionalization of heteroarenes. Additionally, reaction proceeded in continuous-flow photomicroreactor affording the product with moderate to excellent yields within a few minutes. Both reductive and oxidative quenching pathways were proposed in the mechanism.

Imidazopyridines are important structures in numerous bioactive molecules and pharmaceuticals.^{172,173} Difluoroalkylation of imidazopyridines with $\text{BrCF}_2\text{CO}_2\text{Et}$ and a Cu-based catalyst was reported by the Hajra group (Scheme 87a).¹⁷⁴ In 2017, the Fu group¹⁷⁵ demonstrated that an Ir photocatalyst was effective for this reaction (Scheme 87b). A variety of desired products with high functional group tolerance were obtained. $\text{CF}_2\text{CO}_2\text{Et}$ radical derived from the reaction of $\text{BrCF}_2\text{CO}_2\text{Et}$ and photoexcited state $[\text{fac-Ir(III)}(\text{ppy})_3]^*$ under light irradiation was proposed for this transformation. Besides imidazopyridines, benzo[d]isoxazoles were also proved to be suitable for Ir-photocatalyzed difluoroalkylation reaction.¹⁷⁶ The first organophotoredox-catalyzed difluoromethylenephosphonation of imidazoheterocycles was reported by the Hajra group (Scheme 87c).¹⁷⁷ Bis (pinacolato)diboron (B_2pin_2) played an important role for this reaction via activation of imidazoheterocycles. The Xu group demonstrated that visible-light-induced difluoroalkylation of imidazopyridines could also be realized in the absence of cata-



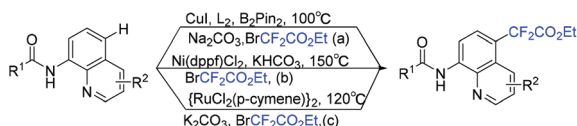
Scheme 87 The difluoroalkylation of imidazopyridines.



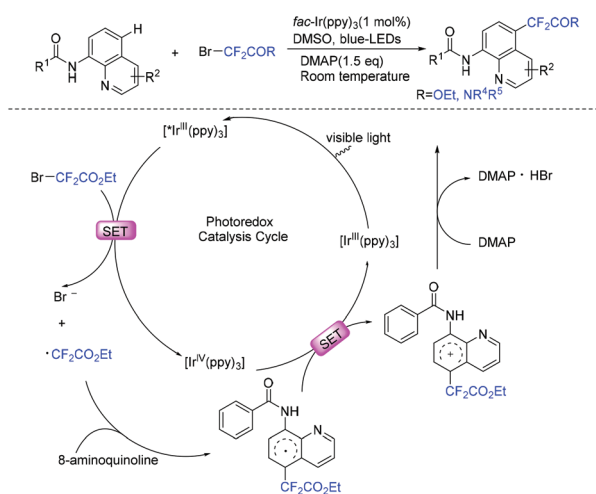
Scheme 88 The visible-light-induced difluoroalkylation of imidazopyridines *via* EDA.

lyst (Scheme 88).¹⁷⁸ An energy transfer of bromodifluoroaryl ketones *via* visible light irradiation affording the excited intermediate bromodifluoroaryl ketones and a rapid C–Br bond homolysis to generate the difluoroacyl radical species **I** *via* excited intermediate bromodifluoroaryl ketones were proposed for this reaction.

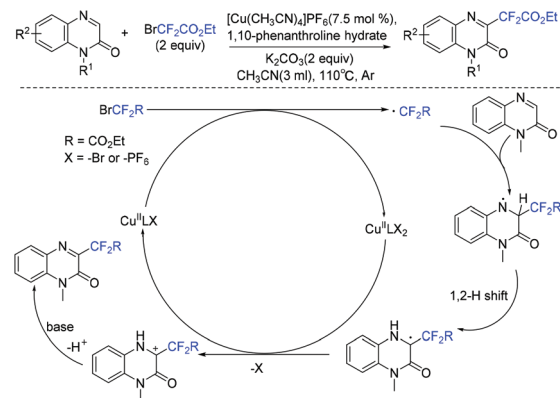
8-Aminoquinoline was also proved to be a good substrate for difluoroalkylation with difluoromethyl bromide reagent. For example, the Cu (Scheme 89a),¹⁷⁹ Ni (Scheme 89b)¹⁸⁰ and Ru (Scheme 89c)¹⁸¹ mediated difluoromethylation of 8-aminoquinoline has been achieved by the Wu, Wang and Zhao groups separately. In 2019, the visible-light-induced difluoroalkylation of 8-aminoquinolines at room temperature was realized by Sun and coworkers (Scheme 90).¹⁸² $\text{CF}_2\text{CO}_2\text{Et}$ radical



Scheme 89 The Cu-, Ni-, Ru-catalyzed difluoroalkylation of 8-aminoquinolines.



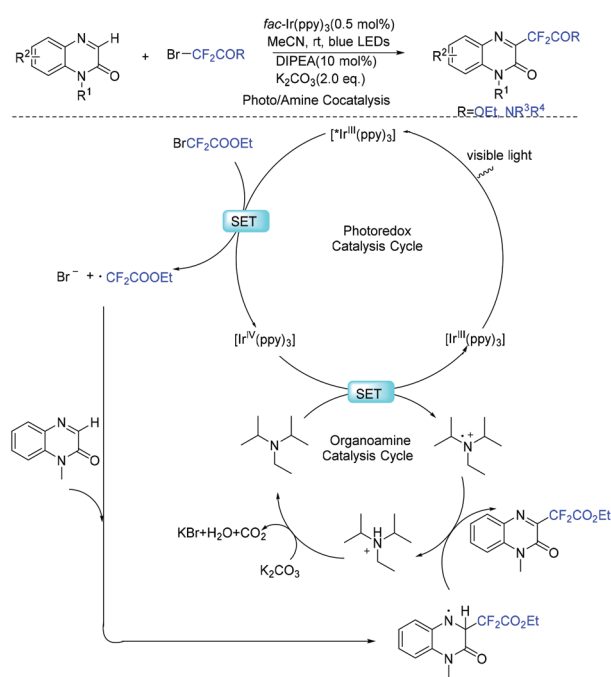
Scheme 90 The visible-light-induced difluoroalkylation of 8-aminoquinolines.



Scheme 91 The copper-catalyzed direct C-3 difluoroacetylation of quinoxalinones.

which was generated from oxidative quenching of excited $\text{Ir}(\text{ppy})_3^*$ by $\text{BrCF}_2\text{CO}_2\text{Et}$ was proposed in this reaction.

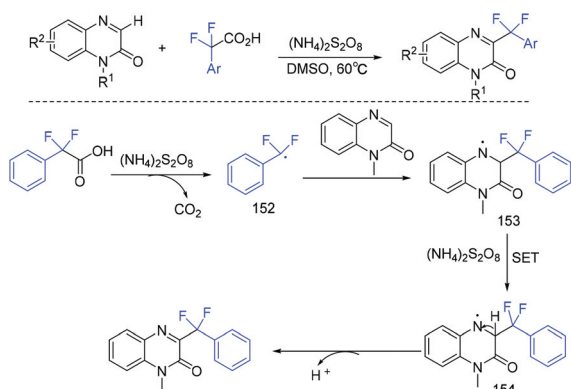
Quinoxalin-2-one derivatives are useful molecules and appear in many bioactive molecules.^{183–186} In 2019, a copper-catalyzed direct C-3 difluoroacetylation of quinoxalinones with ethyl bromodifluoroacetate was demonstrated by Zhang and coworkers (Scheme 91).¹⁸⁷ In 2019, the visible-light- and organoamine-cocatalyzed difluoroalkylation of quinoxalinones with functionalized difluoromethyl bromides was also realized by the Sun group (Scheme 92).¹⁸⁸ Catalytic amount of DIPEA should be added for the success of this transformation. RCF_2 radical generated from the reduction of RCF_2Br was proposed for both of these reactions.



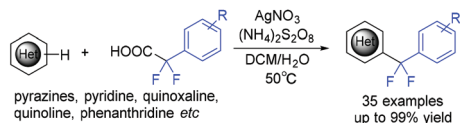
Scheme 92 The visible-light- and organoamine-cocatalyzed difluoroalkylation of quinoxalinones.

In the same year, the decarboxylative difluoroarylmethylation of quinoxalin-2(1*H*)-ones with α,α -difluoroarylacetic acids was described by the Zhang group (Scheme 93).¹⁸⁹ The CF_2 group of α,α -difluoroarylacetic acids was crucial in this transformation. The decarboxylation process between α,α -difluorophenylacetic acid and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ occurred to generate the Rf radical with the liberation of CO_2 . The Wan group demonstrated that difluoroarylacetic acids could also react well with other N-heteroarenes (Scheme 94).¹⁹⁰ Using Ag catalyst, N-heteroarenes such as pyrazines, pyridine, quinoxaline, quinoline, and phenanthridine reacted smoothly in this reaction. The SET between difluoroacetic acid and $\text{Ag}(\text{II})$ which was generated from the oxidation of $\text{Ag}(\text{I})$ by $(\text{NH}_4)_2\text{S}_2\text{O}_8$ occurred to produce the corresponding nucleophilic aryl difluoromethyl radical.

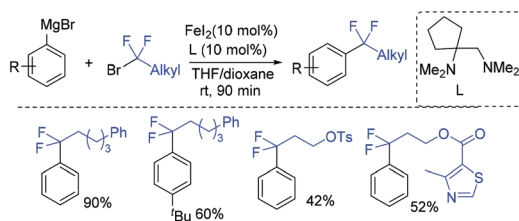
The first iron-catalyzed cross-coupling of Grignard reagents with fluoroalkyl halides was demonstrated by the Zhang group (Scheme 95).¹⁹¹ A diamine, in which a butylene was substi-



Scheme 93 The decarboxylative difluoroarylmethylation of quinoxalin-2(1*H*)-ones.



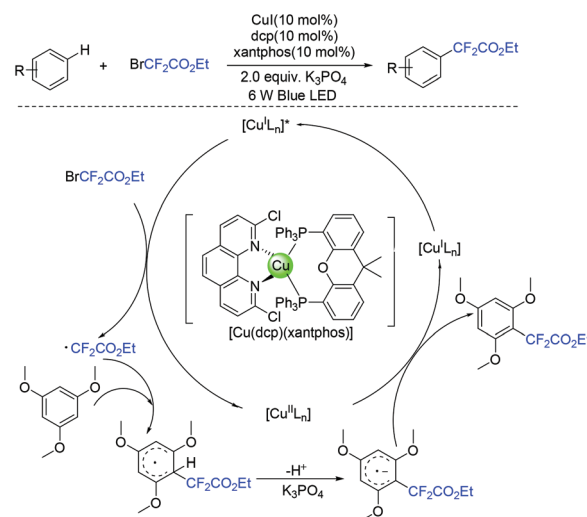
Scheme 94 The decarboxylative difluoroarylmethylation of N-heteroarenes.



Scheme 95 The cross-coupling of Grignard reagents with fluoroalkyl halides.

tuted at one carbon atom of the ethylene backbone in TMEDA, can improve the catalytic efficiency and suppress the side reactions of defluorination, because of the changes of iron complex from five-coordinate to more electron-deficient four-coordinate.

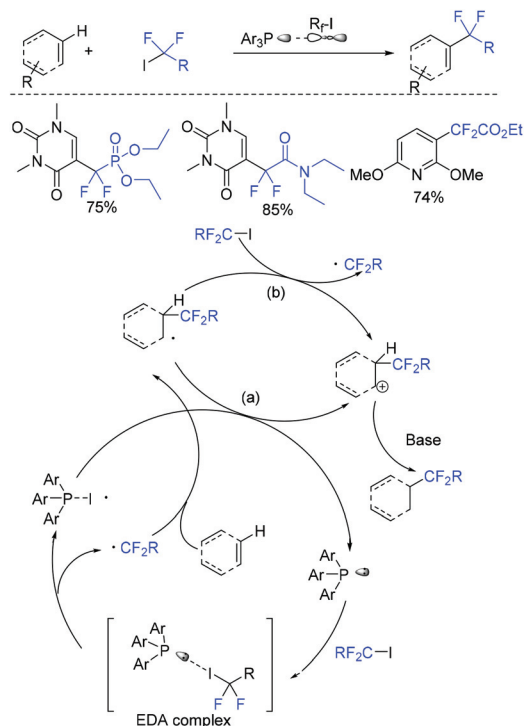
In 2019, the visible-light-induced difluoroalkylation of arenes with difluoroalkylation reagents ($\text{BrCF}_2\text{CO}_2\text{Et}$ or $\text{BrCF}_2\text{CONR}_1\text{R}_2$) was realized by the Liu group (Scheme 96).¹⁹² The *in situ* formation of cuprous photocatalyst from cuprous iodide, an imine ligand and a triaryl phosphine ligand was a key factor for this reaction. Difluoromethyl radicals which were generated *via* SET from the excited photocatalyst to difluoroalkylation reagents was suggested in the difluoroalkylation. In the same year, Hisaeda and coworkers found that these reactions can also be realized in the presence of cobalt catalyst (Scheme 97).¹⁹³ Driven by controlled-potential electrolysis and visible-light irradiation in dimethyl sulfoxide, a wide range of electron-rich arenes and N-, O-, and S-containing heteroarenes



Scheme 96 Visible-light-induced difluoroalkylation of arenes.



Scheme 97 The Co-catalyzed difluoroalkylation of arenes.

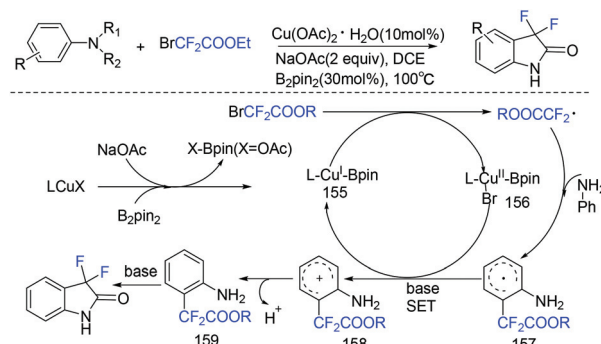


Scheme 98 The triaryl phosphine-catalyzed difluoroalkylation of arenes.

reacted smoothly. Mechanistic studies revealed that a radical pathway mediated by homolytic cleavage of the cobalt(III) was involved in the mechanism. In the presence of triaryl phosphine as the catalyst, the visible-light-promoted difluoroalkylation reaction of arenes or heterocycles with difluoroalkyl iodide was presented by the Zhang group (Scheme 98).¹⁸⁰ Mechanistic investigation implied that a radical-chain process that was initiated by an electron donor–acceptor complex formed from difluoroalkyl iodide and phosphine was involved in this reaction.

An efficient method for the synthesis of 3,3-difluoro-2-oxindoles *via* copper/B₂pin₂-catalyzed C–H difluoroacetylation–cycloamidation of anilines with ethyl bromodifluoroacetate was realized by the Song group (Scheme 99).¹⁹⁴ In this strategy, amino groups act as directing groups, providing *ortho*-difluoroacetylated products regioselectively. In the presence of a base, LCu(I)–Bpin species **155** was generated between LCuX(I) and B₂pin₂. Then BrCF₂CO₂R was reduced by species **155** to give a CF₂CO₂R radical. Subsequently CF₂CO₂R radical reacted with aniline to deliver intermediate **157** directed by amino groups. Finally, the 3,3-difluoro-2-oxindole derivatives were obtained after a SET pathway and intramolecular cycloamidation between ester and amino groups.

In the same year, the Zhang group reported a visible-light-induced photoredox difluoromethylation–amidation of anilines with bromodifluoroacetate (Scheme 100).¹⁹⁵ A broad range of difluorooxindoles was obtained *via* this process. However, aniline was not suitable for this system owing to the



Scheme 99 The copper/B₂pin₂-catalyzed C–H difluoroacetylation–cycloamidation of anilines.



Scheme 100 The visible-light-induced photoredox difluoromethylation–amidation of anilines.

formation of a large amount of *para*-difluoroacetylated aniline. In the catalytic cycle, the reaction of bromodifluoroacetate and excited state of the photocatalyst $^*[\text{Ir}(\text{ppy})_3]$ was also proposed for this transformation to afford RCF₂ radical. The Sun group found that 2-(1*H*-pyrrol-1-yl)anilines and 2-(1*H*-indol-1-yl)anilines were also good substrates to react with bromodifluoroacetate, providing various fluorinated pyrrolo[1,2-*d*]benzodiazepine derivatives.¹⁹⁶

Because of the steric disadvantage as well as entropy, the use of aryl-substituted anilines for this difluoromethylation transformation was challenging. The Li group realized the copper-catalyzed C–H [3 + 2] annulation of *N*-aryl- or alkyl-substituted anilines with bromodifluoroacetate (Scheme 101).¹⁹⁷ The corresponding 3,3'-disubstituted oxindole products with moderate to good yields were assembled. In 2019, the Pd-cata-



Scheme 101 The copper-catalyzed annulation of *N*-substituted anilines.



Scheme 102 The copper-catalyzed annulation of *N*-substituted anilines.

lyzed two-component C–H difluoroalkylation cyclization cascade reaction of 1-(2-aminophenyl)pyrrole derivatives was realized by the Liu group (Scheme 102).¹⁹⁸ A variety of difluoroalkylated pyrrolobenzodiazepine derivatives were obtained in good yields. Two possible pathways which involved radical intermediates were proposed for this transformation.

5. Difluoroalkylation with alkyl C–H bond

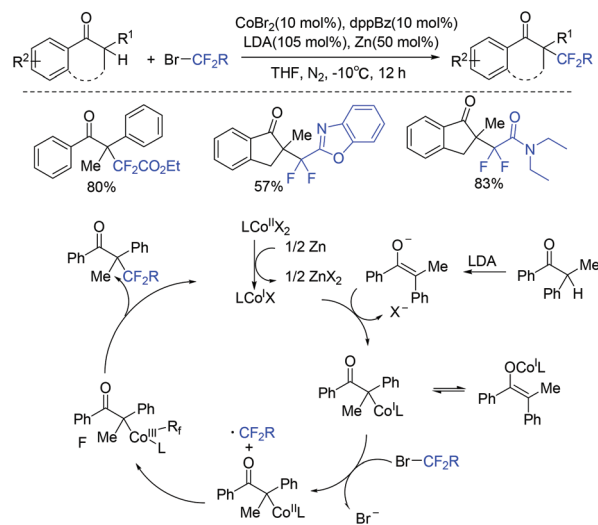
Because of the high bond dissociation energy and lack of “active” HOMO or LUMO orbitals to interact with transition metal catalytic centers, it is more difficult to functionalize a C(sp³)–H bond.^{199–204} However, rapid progress has been achieved in recent years.^{133,205–210} Ketones are some of the most commonly used substrates for fluoroalkylation reactions.^{211,212} However, defluorination reactions often occur to form fluoroalkene compounds. In order to prevent defluorination reactions, tertiary ketones are usually necessary. In 2018, the group of Lu and Xiao described enantioselective radical difluoroalkylation reactions of β -ketoesters using an asymmetric photoredox and nickel catalysis cascade (Scheme 103).²¹³ But the corresponding product was isolated with moderate yield and enantioselectivity (55% yield, 83:17 er) when BrCF₂CO₂R was used. In addition, perfluoroalkylation of β -ketoesters was also realized in this system. The reductive quenching of Ir(III)* with the Ni complex was proposed in the catalytic cycle. CF₂CO₂Et radical was generated from the reduction of XCF₂CO₂Et by Ir(II).



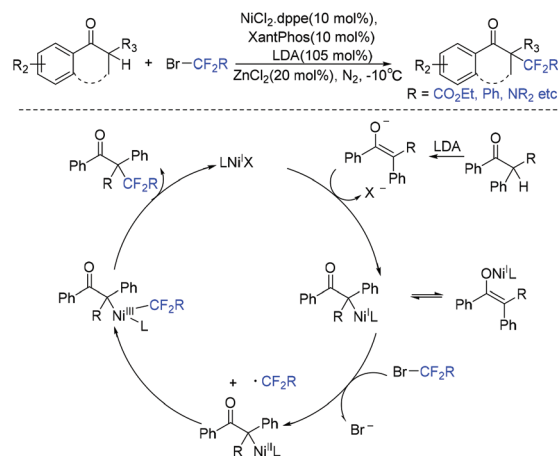
Scheme 103 The difluoroalkylation reactions of β -ketoesters.

In 2018, the cobalt-catalyzed difluoroalkylation of tertiary aryl ketones for facile synthesis of quaternary alkyl difluorides was disclosed by the Wang group (Scheme 104).²¹⁴ Preliminary mechanistic investigations indicated that a difluoroalkyl radical was involved in a Co(I)/Co(III) catalytic cycle. Zn metal could reduce the Co(II) to the catalytically active Co(I) species. Nickel was also found to be efficient for this type of reaction by the same group the following year (Scheme 105).²¹⁵ But only tertiary aryl ketones were suitable for this difluoroalkylation reaction. A Ni(I)/Ni(III) catalytic cycle was proposed for this reaction. If a secondary ketone was employed, a tetrafluoroalkylated monofluoroalkene product was formed through defluorination.

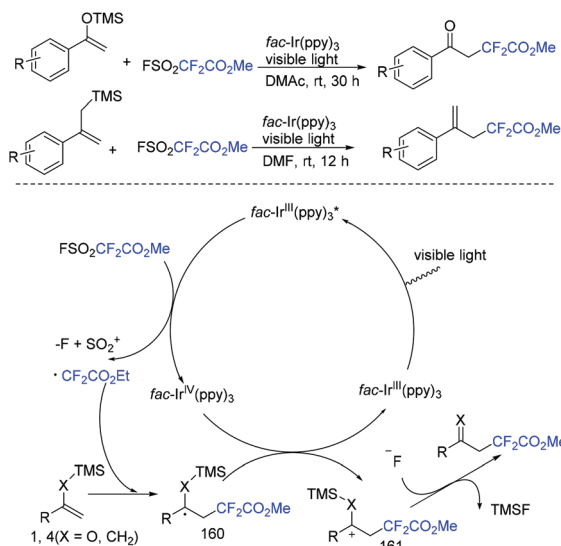
In 2018, the methoxycarbonyldifluoromethylation of trimethylsilyl enol ethers and allyltrimethylsilanes with FSO₂CF₂CO₂Me induced by visible light was developed by the



Scheme 104 The cobalt-catalyzed difluoroalkylation of tertiary aryl ketones.



Scheme 105 The nickel-catalyzed difluoroalkylation of tertiary aryl ketones.



Scheme 106 The methoxycarbonyldifluoromethylation of trimethylsilyl enol ethers.

Qing group (Scheme 106).²¹⁶ Aromatic ketones and aliphatic ketones were all compatible with this transformation. The oxidative quenching of $fac\text{-Ir}^{\text{III}}(\text{ppy})_3^*$ with $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}$ took place to give $\text{CF}_2\text{CO}_2\text{Me}$ radical and $fac\text{-Ir}^{\text{IV}}(\text{ppy})_3$ was proposed for this reaction. Additionally, fluoride anion could assist the desilylation of **161** to provide the target products.

6. Difluoroalkylation with isocyanide

In 2013, the first visible-light-promoted isocyanide insertion was described by the Yu group (Scheme 107).²¹⁷ Various 6-alkylated phenanthridine derivatives were obtained with good to excellent yields. Fluoroalkyl radical which was generated from the reduction of ethyl bromodifluoroacetate by $\text{Ir}(\text{ppy})_3^*$ added with isocyanide to provide radical **162**. Subsequently, radical **162** underwent intramolecular hemolytic



Scheme 107 The visible-light-promoted isocyanide insertion.

aromatic substitution to give radical intermediate **163**. Then radical intermediate **163** was followed by oxidation and deprotonation reaction to release the desired product.

The Song group realized the sodium sulfite-involved photocatalytic radical cascade cyclization of 2-isocyanoarylthioethers (Scheme 108).²¹⁸ 2- CF_2 -containing benzothiazoles can be efficiently prepared using this methodology. Different from previous reports, sodium sulfite should be added in the photocatalytic cycle to reduce Ir^{IV} into Ir^{III} .

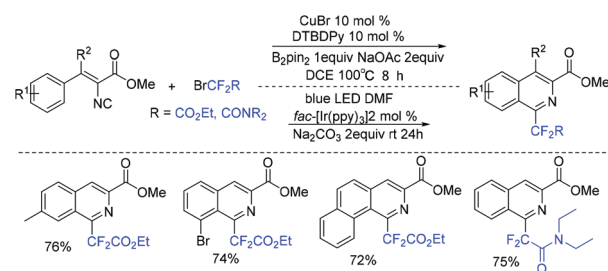
A $\text{Cu}/\text{B}_2\text{pin}_2$ system-promoted cyclization reaction of vinyl isocyanides with bromodifluoroacetic derivatives for the synthesis of 1-difluoroalkylated isoquinolines was reported by the Shi group (Scheme 109).²¹⁹ Preliminary mechanistic studies revealed that a tandem radical cyclization process was involved in this transformation. In addition, this transformation can also be induced by visible light.

7. Difluoroalkylation with amine

In 2018, the Song group found that $\text{BrCF}_2\text{CO}_2\text{Et}$ played a dual role as a C1 synthon and a difluoroalkylating reagent in the reaction of $\text{BrCF}_2\text{CO}_2\text{Et}$ with primary amines (Scheme 110).²²⁰ Difluorocarbene which was generated from the reaction of $\text{BrCF}_2\text{CO}_2\text{Et}$ with Na_2CO_3 via decarboxylation and debromination processes was involved in the catalytic cycle. Based on



Scheme 108 The photocatalytic radical cascade cyclization of 2-isocyanoarylthioethers.



Scheme 109 The $\text{Cu}/\text{B}_2\text{pin}_2$ -promoted cascade cyclization of vinyl isocyanides.



Scheme 110 The reaction of $\text{BrCF}_2\text{COOEt}$ with primary amines.



Scheme 111 The synthesis of 2,4-disubstituted 1,3,5-triazines.

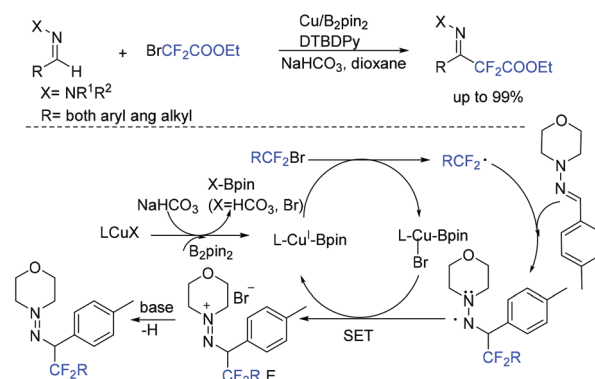
experimental observations and DFT calculations, they found that base played an active role in the formation of the key intermediate isocyanides generated from primary amines and difluorocarbene. The same group found that ethyl bromodifluoroacetate could also serve as a C1 synthon to access 2,4-disubstituted 1,3,5-triazines (Scheme 111).²²¹ Both symmetric and unsymmetric 2,4-disubstituted 1,3,5-triazines could be obtained with only small amounts of toxic inorganic wastes generated. Based on experimental results, it was speculated that difluorocarbene ($:\text{CF}_2$) was actually generated from $\text{BrCF}_2\text{CO}_2\text{Et}$ with the assistance of base. Then difluorocarbene ($:\text{CF}_2$) reacted with amidine to afford intermediate **165**, which was defluorinated to imine intermediate **166** under basic conditions. Subsequently, intermediate **167** was generated from the reaction of intermediate **166** with another amidine. Finally the corresponding products were formed through intramolecular nucleophilic addition of **167** and elimination of one molecule of ammonia.

8. Difluoroalkylation with $\text{C}=\text{N}$

In 2016, the CuI (Scheme 112a)²²² and $\text{Pd}_2(\text{dba})_3$ (Scheme 112b)²²³ catalyzed difluoroalkylations of hydrazones were realized by the Monteiro group. The Ir (Scheme 112c)²²⁴ and Au (Scheme 112d)²²⁵ catalyzed difluoroalkylation of hydrazones induced by visible light was also presented by the Zhu and Hashmi groups separately. The $\text{Cu(II)/B}_2\text{pin}_2$ -catalyzed



Scheme 112 The difluoroalkylation of hydrazones catalyzed by various metals.



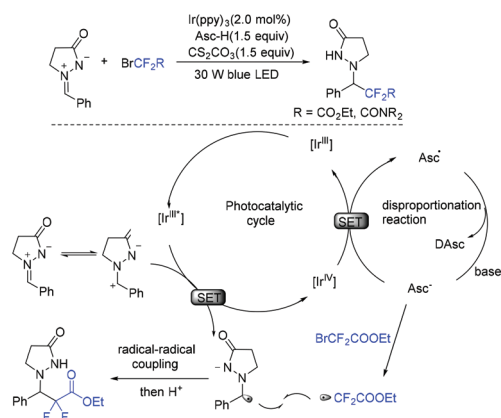
Scheme 113 The $\text{Cu/B}_2\text{pin}_2$ -catalyzed difluoroalkylation of hydrazones.

difluoroalkylation of hydrazones with difluoroalkyl bromides using diboron as reductant was reported the Song group (Scheme 113).²²⁶ Both aromatic and aliphatic hydrazones were suitable for this reaction. A difluoroalkyl radical *via* a SET pathway was suggested in the reaction mechanism. Additionally, the catalytic diboron reagent was a key factor in this transformation.

The direct three-component difluoroalkylation reaction between aldehydes, hydrazines, and halodifluoromethylated reagents catalyzed by visible-light organic photoredox was realized by Wang and coworkers (Scheme 114).²²⁷ A reductive quenching of photoexcited PC^* species with the hydrazine *in situ* generated from aldehyde and hydrazine to form the strong reductant PC^- and radical intermediate **168** was proposed for this reaction.

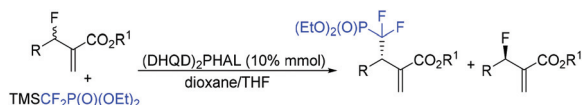
In 2019, a visible-light-induced difluoroalkylation of N,N -cyclicazomethine imine with BrCF_2R was successfully realized by the Yang group (Scheme 115).²²⁸ Mechanistic investigations showed that a reductive radical–radical coupling pathway and oxidation of ascorbic acid with Ir(IV) to form ascorbyl radical were involved in the mechanism.

Scheme 114 The three-component difluoroalkylation reaction between aldehydes, hydrazines and halodifluoromethylated reagents.

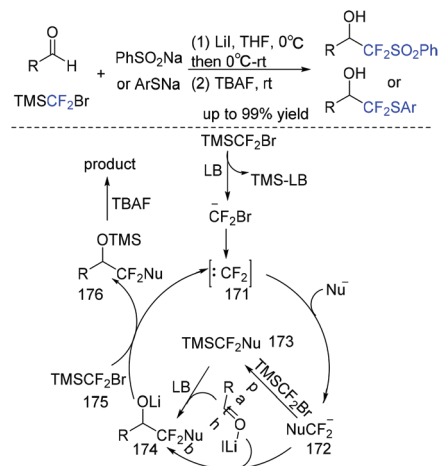


Scheme 115 The difluoroalkylation of *N,N*-cyclicazomethine imine.

The first base-catalyzed enantioselective phosphoryl-difluoromethylation was described by the Vilotijevic group (Scheme 116).²²⁹ By the use of diethyl(difluoro(trimethylsilyl)methyl)phosphonate reagent as a latent pronucleophile, the enantiomers of the product can be readily accessed. A kinetic resolution was involved in the reaction process. But the yield of the reaction was not very high.



Scheme 116 Enantioselective substitution of allylic fluorides.



Scheme 117 The (phenylsulfonyl)difluoromethylation of aldehydes.

9. Difluoroalkylation with C=O

In the past decade, tremendous efforts have been made in (phenylsulfonyl/arylthio)difluoromethylation of aldehydes.^{230–234} Among these reactions, the nucleophilic addition of $\text{PhSO}_2\text{CF}_2^-$ or PhSCF_2^- anion to carbonyl compounds (such as aldehydes) was the most popular method. In 2019, the Hu group found that TMSCF_2Br was good partner for nucleophilic (phenylsulfonyl/arylthio)difluoromethylation of aldehydes and $\text{PhSO}_2\text{Na}(\text{ArSNa})$ (Scheme 117).²³⁵ The preparation of $\text{PhSO}_2\text{CF}_2\text{X}$ or PhSCF_2X ($\text{X} = \text{H}, \text{Br}, \text{TMS}$) reagents was avoided in this three-component reaction. The *in situ* generation of difluorocarbene *via* the reaction of TMSCF_2Br with a Lewis base activator ($\text{LB} = \text{PhSO}_2^-, \text{PhS}^-,$ or **174**) was proposed in the reaction mechanism. Then the reaction of difluorocarbene with $\text{PhSO}_2\text{Na}(\text{ArSNa})$ occurred to form the corresponding $\text{PhSO}_2\text{CF}_2(\text{PhSCF}_2)$ anions. Finally, the desired difluoromethylated products were obtained *via* nucleophilic addition of $\text{PhSO}_2\text{CF}_2(\text{PhSCF}_2)$ anions to aldehydes.

10. Conclusions

The difluoroalkylation reaction has made much progress in the last few years. In this review, we summarized the advances of difluoroalkylation reactions in the last three years. The most commonly used difluoroalkylation reagent was RCF_2X . Generally speaking, RCF_2 radical which was usually generated from the reduction of RCF_2X was the active intermediate in most cases. When alkenes or alkynes were used as substrates, reactions were usually initiated by radical addition to the carbon-carbon unsaturated bonds; then the final products can be isolated in different ways. Visible-light-induced and metal-catalyzed difluoroalkylations were all realized. Some electron-rich bases could also be used to induce the formation of RCF_2 radical for these reactions *via* EDA complex. At present, the most efficient photocatalyst was metal [Ir]. In the absence of visible light, copper was proved to be one of the most effective

catalysts in metal catalyzed difluoroalkylation. In consideration of green chemistry and cost efficiency, a cheap photocatalyst or even catalyst-free difluoroalkylation reaction is more desirable. Asymmetric difluoroalkylation is also worth further study. Additionally, multicomponent reaction for the introduction of RCF₂ group also needs to be further explored. We anticipate that this review will open new avenues for the development of difluoroalkylation reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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