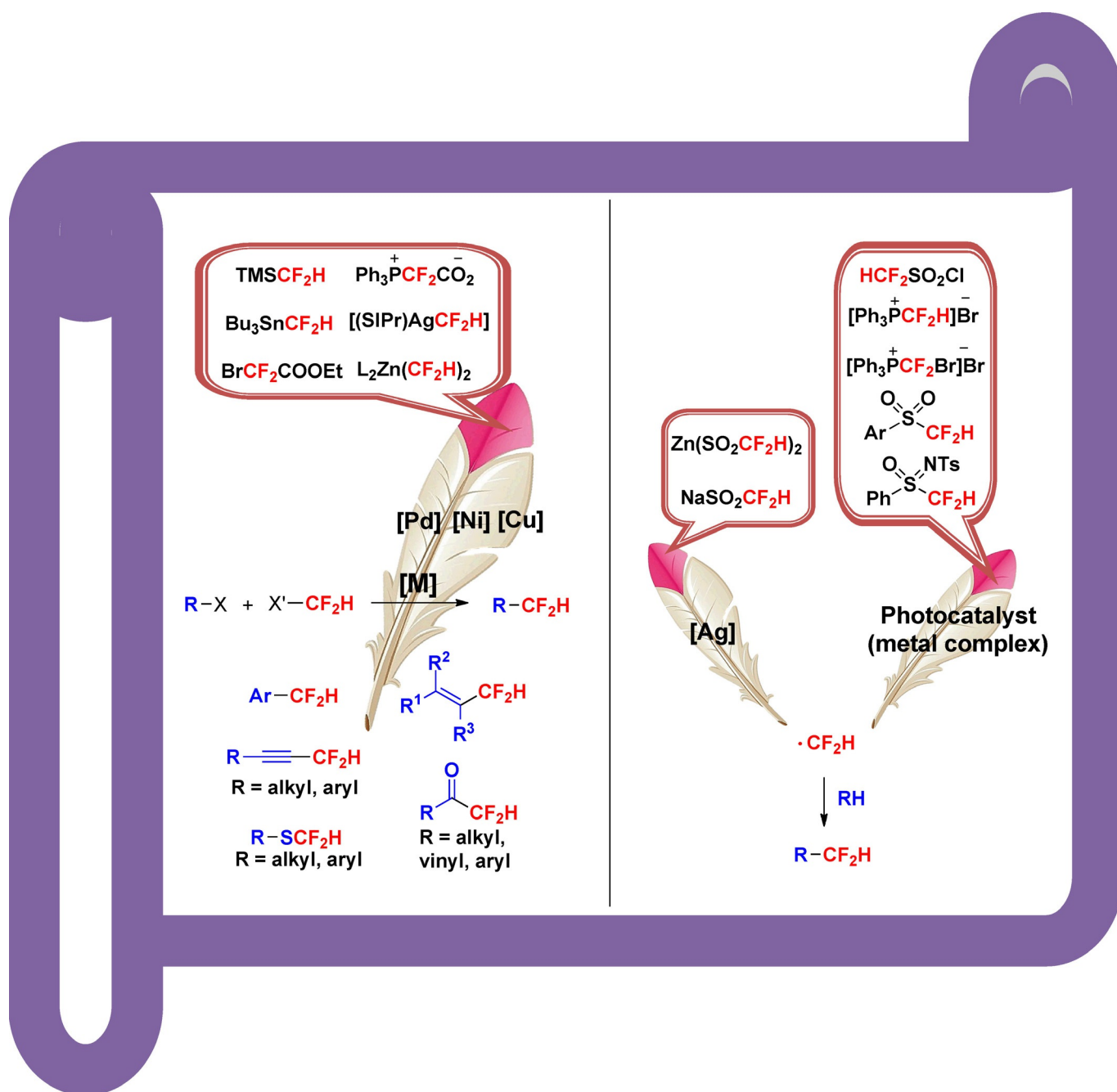


Synthetic Methods

Metal-Catalyzed Direct Difluoromethylation Reactions

Jian Rong, Chuanfa Ni, and Jinbo Hu^{*[a]}



Abstract: Owing to the excellent performance of fluorinated compounds in the areas of pharmaceuticals, agrochemicals, and materials chemistry, organic chemists have made great efforts towards the selective incorporation of fluorine or fluorinated moieties into organic molecules through nucleophilic, electrophilic, radical, and metal-catalyzed pathways. Impressive progress in fluorination and perfluoroalkylation

(especially trifluoromethylation) reactions has been made over the past few decades. However, methods for incorporating lightly fluorinated groups (such as $-\text{CF}_2\text{H}$) are still underdeveloped, in spite of their important applications in pharmaceuticals and agrochemicals. This Focus Review summarizes recent developments in metal-catalyzed direct difluoromethylation reactions.

1. Introduction

Because of the unique intrinsic properties of fluorine, such as high electronegativity and small atomic radius, the incorporation of fluorine or fluorinated moieties into biologically active compounds can enhance their lipophilicity and resistance towards oxidation, thereby improving their membrane permeability, metabolic stability, and bioavailability.^[1] Among the various fluorinated moieties (especially lightly fluorinated groups), the difluoromethyl group ($-\text{CF}_2\text{H}$) is of great importance because it can act as a more-lipophilic isostere of carbinol, thiol, hydroxamic acid, or amide groups.^[2] The CF_2H group is weakly acidic and is capable of hydrogen-bonding interactions to improve the binding selectivity of biologically active compounds.^[2] As a consequence, the difluoromethyl group has been widely utilized in the design of various pharmaceuticals and agrochemicals (Figure 1).^[2b,3] Compared to the highly developed methods for trifluoromethylation,^[4] difluoromethylation is still underdeveloped, probably owing to the lack of efficient sources of the difluoromethyl group and stable difluoromethyl–metal complexes. Conventionally, difluoromethylated compounds are prepared through the deoxyfluorination of aldehydes with sulfur tetrafluoride, *N,N*-diethylaminosulfur trifluoride (DAST), bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor), and other related reagents.^[1] However, the limitations of these methods are apparent, such as the need for harsh reaction conditions and poor functional-group tolerance, and these limitations have restricted their wide utilization. On the other hand, metal-catalyzed direct difluoromethylation reactions have many advantages, such as fewer synthetic steps, milder reaction conditions, and broader substrate scope, which make them suitable for late-stage difluoromethylation reactions. This Focus Review summarizes the direct difluoromethylation reactions that use transition metals in both stoichiometric and catalytic amounts.^[5] The transition metals in difluoromethylation reactions play various roles, including stabilizing the difluoromethyl anion (as difluoromethyl carriers), promoting the formation of difluoromethyl free radicals (such as tran-

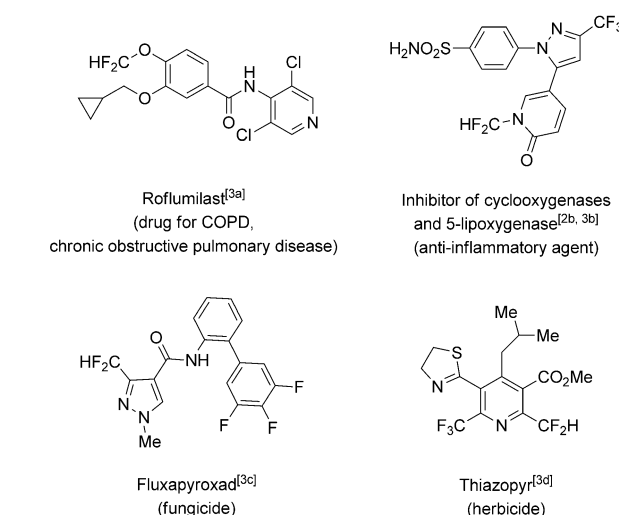
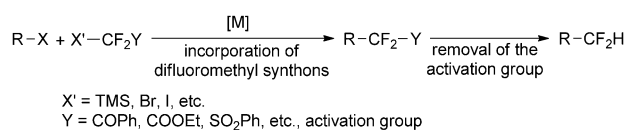


Figure 1. Representative pharmaceuticals and agrochemicals that contain a difluoromethyl group.

sition-metal photoredox catalysts), and facilitating the formation of $\text{HF}_2\text{C}-\text{C}$ and $\text{HF}_2\text{C}-\text{X}$ bonds (through the reductive elimination of difluoromethyl–metal complexes).

During the pursuit of efficient methods for difluoromethylation, some readily available difluoromethyl synthons, such as HCF_2COPh , $\text{TMSCF}_2\text{COOEt}$, $\text{Et}_3\text{SiCF}_2\text{COOEt}$, $\text{BrCF}_2\text{COOEt}$, $\text{FSO}_2\text{CF}_2\text{COOH}$, $\text{TMSCF}_2\text{SO}_2\text{Ph}$, $\text{BrCF}_2\text{SO}_2\text{Ph}$, and $\text{ICF}_2\text{SO}_2\text{Ph}$, have been developed and used in metal-mediated difluoromethylation reactions. These reactions proceed through the incorporation of difluoromethyl synthons into the target compounds, followed by the removal of the activating groups (Scheme 1).^[6–21] However, these metal-mediated stepwise (indirect) difluoromethylation reactions are beyond the scope of this review. This Focus Review focuses on recent developments in metal-catalyzed direct difluoromethylation reactions, that is, reactions that involve the direct transfer of a CF_2H group.

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Scheme 1. Metal-mediated stepwise difluoromethylation reactions. TMS = trimethylsilyl.

2. Metal-Catalyzed Difluoromethylation

2.1. Difluoromethyl–Metal Complexes

The first example of a difluoromethyl–transition-metal complex, $[(\text{CO})_5\text{Mn}(\text{CF}_2\text{H})]$, was reported by Calderazzo's group in 1967.^[22a] Eisenberg and co-workers also reported the structurally well-defined complexes $[\text{IrCl}(\text{OCOCF}_2\text{Cl})(\text{CF}_2\text{H})(\text{CO})(\text{PPh}_3)_2]$ and $[\text{IrCl}_2(\text{CF}_2\text{H})(\text{CO})(\text{PPh}_3)_2]$.^[22j–l] Since these reports, there has been a long-standing interest in the preparation of $[\text{M}–\text{CF}_2\text{H}]$ complexes to explore the capability of the difluoromethyl group in coordinating with transition metals.^[22b–s] It has been found that the difluoromethyl ligand can exhibit a rich coordination chemistry that allows the ligation of different transition metals; some representative $[\text{M}–\text{CF}_2\text{H}]$ complexes are shown in Figure 2. However, most of these complexes were not stable enough to be isolated and fully characterized. Compared to their corresponding $[\text{M}–\text{CF}_3]$ complexes, the $\text{M}–\text{C}$ bonds in $[\text{M}–\text{CF}_2\text{H}]$ complexes are typically weaker and more reactive. For example, the $[\text{CuCF}_2\text{H}]$ complex is much more reactive than the $[\text{CuCF}_3]$ complex and decomposes more readily.^[22d,e]

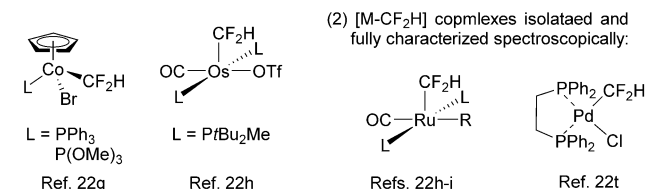
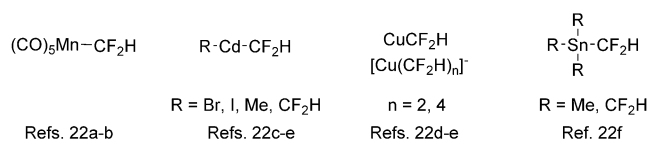
2.2. Metal-Mediated Cross-Coupling Difluoromethylation

Investigations of these difluoromethyl–transition-metal complexes found that they could be used to directly transfer

a CF_2H group onto an organic compound (Scheme 2).^[22c,e] Burton and Hartgraves reported that the reaction of metallic cadmium with CF_2HI in DMF produced a mixture of $[\text{Cd}(\text{CF}_2\text{H})_2]$ and $[\text{Cd}(\text{CF}_2\text{H})\text{I}]$ in a 25:75 ratio and 91% overall yield (based on ^{19}F NMR spectroscopic analysis). They found that this mixture could be used for the difluoromethylation of allyl bromide and 3-chlorobut-1-yne (Scheme 2a).^[22e] (Difluoromethyl)zinc could be prepared in a similar manner to (difluoromethyl)cadmium, but it required a much longer reaction time (Scheme 2b).^[22e] (Difluoromethyl)copper could be prepared by transmetalation between (difluoromethyl)cadmium and copper(I) bromide or chloride (Scheme 2c).^[22e] The as-prepared (difluoromethyl)copper species was highly reactive, and it readily decomposed at temperatures above -30°C .

Interestingly, these difluoromethyl–metal (metal = Cd, Zn, Cu) species exhibited significant differences in reactivity in di-

(1) $[\text{M}–\text{CF}_2\text{H}]$ complexes not isolated and fully characterized:



(3) $[\text{M}–\text{CF}_2\text{H}]$ complexes isolated and characterized by X-ray crystallography:

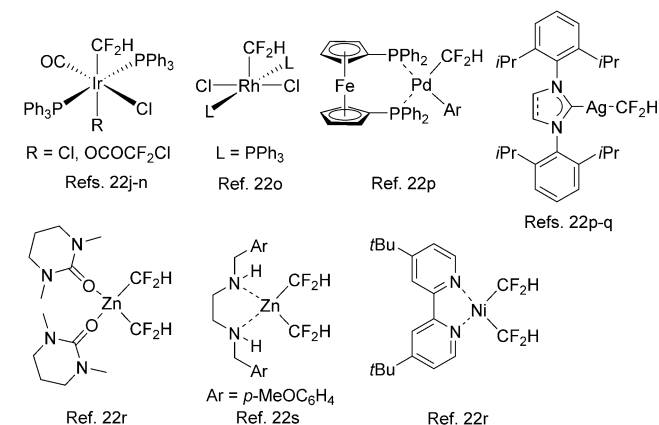


Figure 2. Representative $[\text{M}–\text{CF}_2\text{H}]$ complexes. Tf = trifluoromethanesulfonyl.

Jian Rong was born in Yichang, Hubei province, China, in 1990 and obtained a double BSc degree in chemistry and biology from Central China Normal University, where he worked with Professor Wen-Jing Xiao. In 2012, he continued his study as a PhD candidate at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS), with Professor Jinbo Hu. His current research interests include selective fluoroalkylation and photoredox catalysis.

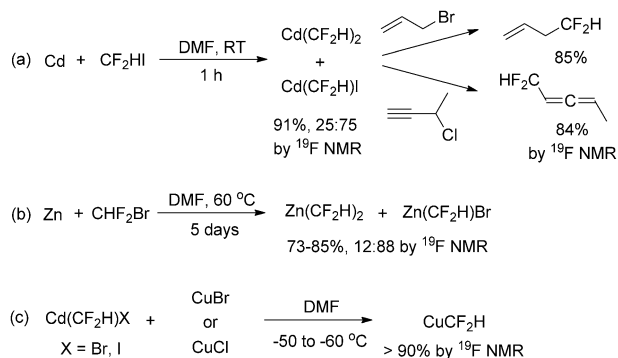


Chuanfa Ni obtained his BSc degree in chemistry from Shandong Normal University in 2003. After graduate work (2003–2009) at the Shanghai Institute of Organic Chemistry (SIOC) under the supervision of Professor Jinbo Hu and postdoctoral work (2009–2012) at the University of Southern California under the supervision of Professor G. K. Surya Prakash, he joined the Hu group at SIOC as an Associate Research Professor in 2012.



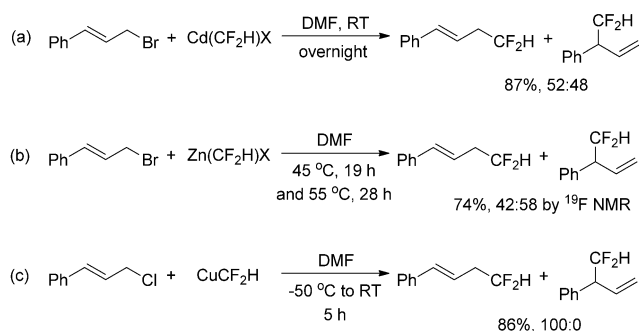
Jinbo Hu was born in Zhejiang, China, in 1973. After he completed his BS (Hangzhou University) and MS (Chinese Academy of Sciences) degrees, he undertook his PhD work from 1997 to 2002 at the University of Southern California with Professors G. K. S. Prakash and G. A. Olah. After postdoctoral work at USC, he accepted a Research Professorship at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) in early 2005, where he is currently the Head of the CAS Key Laboratory of Organofluorine Chemistry. He was the recipient of the RSC Fluorine Prize 2009 and the Novartis Chemistry Lectureship 2015–2016. His current research interests include synthetic methods for selective fluorination, defluorination, and fluoroalkylation, and fluorinated materials.





Scheme 2. Preparation of difluoromethyl cadmium, zinc, and copper reagents.

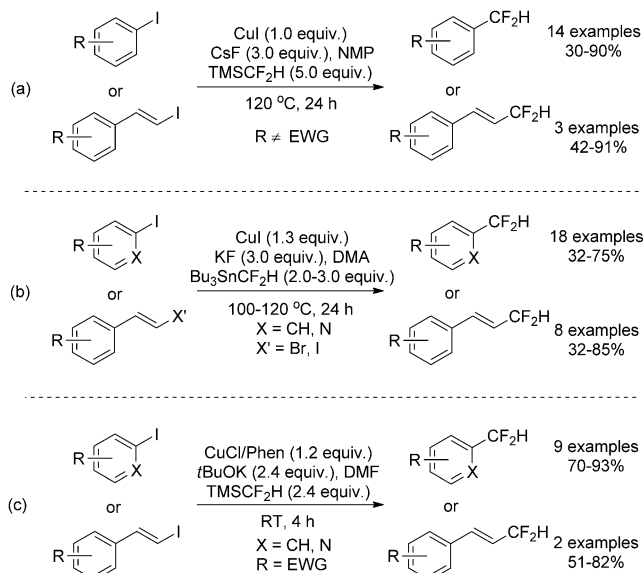
fluoromethylation reactions (Scheme 3).^[22e] For example, in the reaction with cinnamyl halide, $[\text{HCF}_2\text{ZnX}]$ was much less reactive than $[\text{HCF}_2\text{CdX}]$. After heating $[\text{HCF}_2\text{ZnX}]$ with cinnamyl bromide in DMF for 19 hours at 45 °C and then for 28 hours at



Scheme 3. Reactivity of difluoromethyl cadmium, zinc, and copper reagents.

55 °C, 18% of $[\text{HCF}_2\text{ZnX}]$ still remained. $[\text{HCF}_2\text{ZnX}]$ is a less-toxic difluoromethylating reagent and so is more attractive for synthetic applications, even though it is less reactive than $[\text{HCF}_2\text{CdX}]$. Notably, the $[\text{CuCF}_2\text{H}]$ species that was prepared by transmetalation between $[\text{HCF}_2\text{CdX}]$ and CuX ($\text{X} = \text{Br}, \text{Cl}$) was even more reactive than $[\text{HCF}_2\text{CdX}]$ and $[\text{HCF}_2\text{ZnX}]$, with high regioselectivity for the linear product, presumably owing to its aggregation in solution (and thus higher steric hindrance) than $[\text{HCF}_2\text{CdX}]$. Despite the relatively low stability of $[\text{CuCF}_2\text{H}]$, it is a useful difluoromethyl-transfer reagent for allyl halides.^[22e]

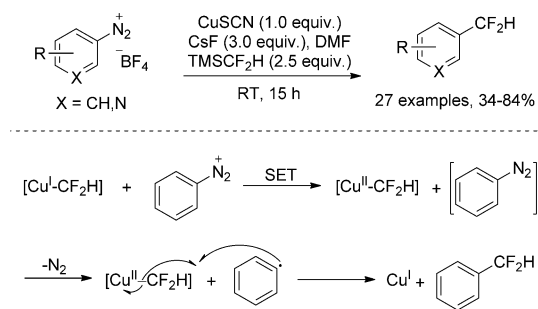
Because of the high toxicity of the (difluoromethyl)cadmium reagent and the low reactivity of the (difluoromethyl)zinc reagent, the less-toxic and relatively reactive (difluoromethyl)copper reagent had attracted much attention in coupling reactions. In 2012, Fier and Hartwig reported the copper-mediated difluoromethylation of aryl and vinyl iodides (Scheme 4a).^[23] TMSCF_2H , which could be prepared by the reduction of TMSCF_3 with NaBH_4 on a large scale, was used as the difluoromethyl source.^[24] This procedure was applicable to the difluoromethylation of electron-rich and electron-neutral aryl and vinyl iodides in high yields. However, it was not suitable for electron-deficient aryl iodides and was incompatible with sub-



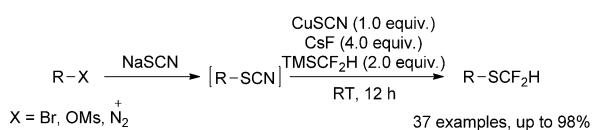
Scheme 4. Copper-mediated difluoromethylation of aryl and vinyl halides. EWG = electron-withdrawing group, NMP = *N*-methylpyrrolidone, DMA = dimethylacetamide, Phen = phenanthroline.

strates that contained a carbonyl group. In the reaction, an excess amount of TMSCF_2H (5 equiv) was required, presumably to facilitate the formation of the $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ intermediate, which acted as a stable "reservoir" of reactive $[\text{Cu}(\text{CF}_2\text{H})]$. In the same year, Prakash and co-workers developed a copper-mediated difluoromethylation of (hetero)aryl iodides and β -styryl halides by employing tributyl(difluoromethyl)stannane ($\text{Bu}_3\text{SnCF}_2\text{H}$) as the difluoromethyl source (Scheme 4b).^[25] One advantage associated with the use of $\text{Bu}_3\text{SnCF}_2\text{H}$ was the improvement of the difluoromethylation reaction with electron-deficient (hetero)aryl and vinyl iodides and substrates that contained a carbonyl group. DFT calculations revealed that DMF as the reaction solvent strongly stabilized the $[\text{CuCF}_2\text{H}]$ species. In 2014, Qing and co-workers reported the copper-mediated difluoromethylation of electron-poor aryl iodides with TMSCF_2H at room temperature (Scheme 4c).^[26] In Qing's reaction system, a more-soluble activator (*t*BuOK) and an extra ligand (phenanthroline) were used, which not only decreased the amount of TMSCF_2H required (to 2.4 equiv), but also dramatically lowered the reaction temperature (to room temperature). As a consequence, electron-deficient (hetero)aryl and vinyl iodides were smoothly difluoromethylated in good-to-excellent yields, thereby constituting an important complement to Hartwig's work.

In 2014, Goossen and co-workers reported a Sandmeyer difluoromethylation reaction of (hetero)arene diazonium salts in which TMSCF_2H was used as the reagent (Scheme 5).^[27] Mechanistic investigation through radical-inhibition experiments and radical-trapping experiments confirmed that the reaction proceeded through a radical pathway. This method provided a new synthetic alternative to difluoromethyl arenes from readily available aryl amines. In 2015, the same group developed a copper-mediated difluoromethylthiolation of alkyl bromides/mesylates and arene diazonium salts with TMSCF_2H (Scheme 6).^[28] This reaction provided new opportunities for the



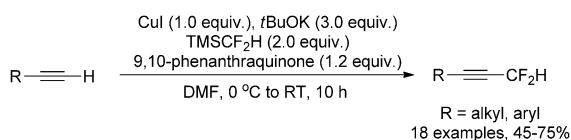
Scheme 5. Sandmeyer difluoromethylation of (hetero)arene diazonium salts and proposed reaction mechanism. SET = single-electron transfer.



Scheme 6. Copper-mediated difluoromethylation of alkyl bromides, mesylates, and arene diazonium salts with TMSCF₂H. Ms = methanesulfonyl.

synthesis of difluoromethyl thioethers from widely available starting materials, such as alkyl halides, alcohols, and aryl amines.

In 2015, Qing and co-workers reported a copper-mediated oxidative difluoromethylation of terminal alkynes with TMSCF₂H in the presence of 9,10-phenanthraquinone as the oxidant (Scheme 7).^[29] This method efficiently allowed the synthesis of difluoromethylated alkynes. Notably, the amounts of both CuI (2.0 equiv) and *t*BuOK (3.0 equiv) were crucial to the success of this reaction.

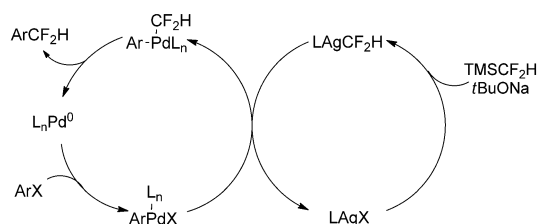
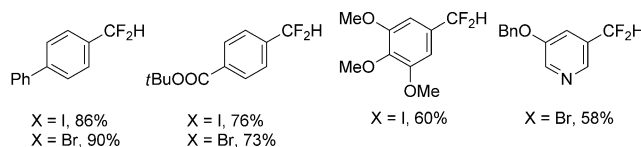
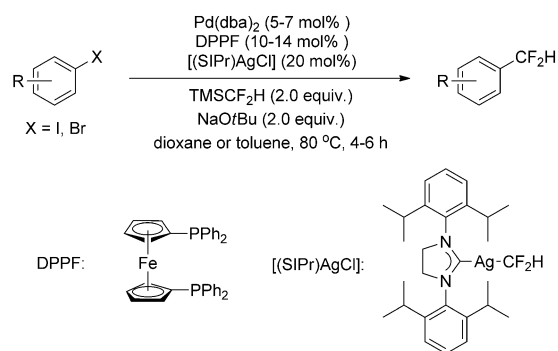


Scheme 7. Copper-mediated oxidative difluoromethylation of terminal alkynes with TMSCF₂H.

2.3. Metal-Catalyzed Cross-Coupling Difluoromethylation

The above-mentioned examples are all non-catalytic methods for difluoromethylation that require stoichiometric amounts of the metals. In this regard, metal-catalyzed difluoromethylation reactions are clearly more attractive.

In 2014, Shen and co-workers reported a cooperative dual palladium/silver catalyst for the direct difluoromethylation of aryl bromides and iodides with TMSCF₂H (Scheme 8).^[22p] This bimetallic catalytic system consisted of two cooperative transmetalation reactions, Si-to-Ag transmetalation and then Ag-to-Pd transmetalation, both of which proceeded faster than the direct Si-to-Pd transmetalation. To confirm the cooperative



Scheme 8. A cooperative dual palladium/silver catalyst system for the direct difluoromethylation of aryl bromides and iodides and proposed reaction mechanism. dba = dibenzylideneacetone.

effect of palladium and silver, two key intermediates, [(SIPr)Ag(CF₂H)] and [(DPPF)Pd(Ph)(CF₂H)], were prepared and their corresponding elemental steps were studied. Notably, reductive elimination from a (difluoromethyl)palladium complex was much faster than that from the analogous (trifluoromethyl)palladium complex.

As a logical extension of this work, in 2015, Shen and co-workers developed the Pd-catalyzed difluoromethylation of di-, tri-, and tetrasubstituted vinyl bromides, triflates, tosylates, and nonaflates by using the isolated [(SIPr)Ag(CF₂H)] (Figure 3) as a difluoromethyl source at room temperature (Scheme 9).^[30] To avoid activation of the allylic C–F bond in the difluoromethylated alkene products under basic conditions, well-defined, air-stable [(SIPr)Ag(CF₂H)] was used instead of the (SIPr)AgCl/TMSCF₂H/*t*BuONa system. The bromo group in the vinyl bromide and vinyl triflate substrates remained unaffected, thus indicating that vinyl bromides and vinyl triflates were much

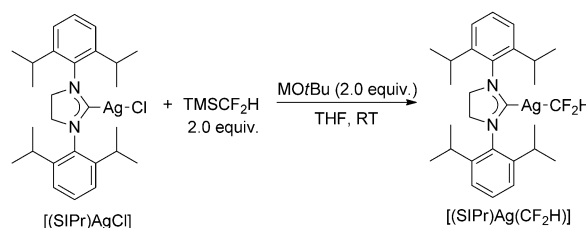
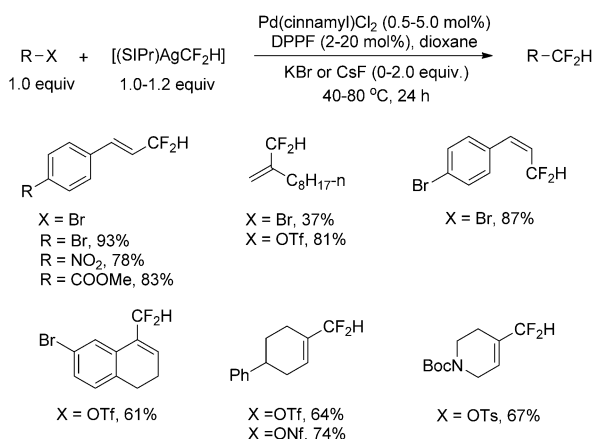


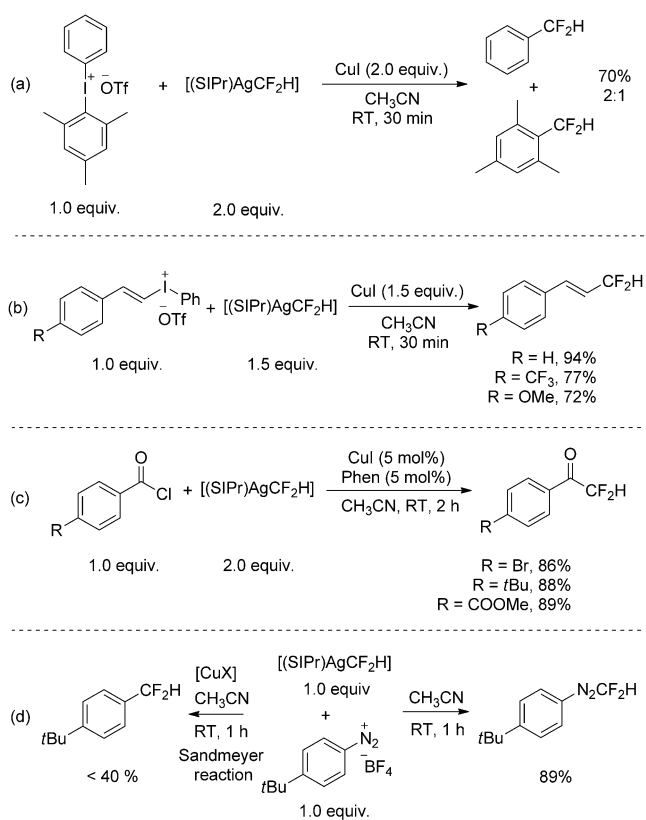
Figure 3. Preparation of [(SIPr)AgCl].



Scheme 9. Pd-catalyzed difluoromethylation of di-, tri-, or tetrasubstituted vinyl bromides, triflates, tosylates, and nonaflates with [(SIPr)Ag(CF₂H)]. Boc = *tert*-butyloxycarbonyl.

more reactive than aryl bromides in this reaction. In the cases of triflates, tosylates, and nonaflates, the addition of KBr could improve the reaction, presumably because the bromide anion could promote the conversion of [(DPPF)Pd(vinyl)(OTf)] into [(DPPF)Pd(vinyl)Br], thereby accelerating the transmetalation step in the catalytic cycle.

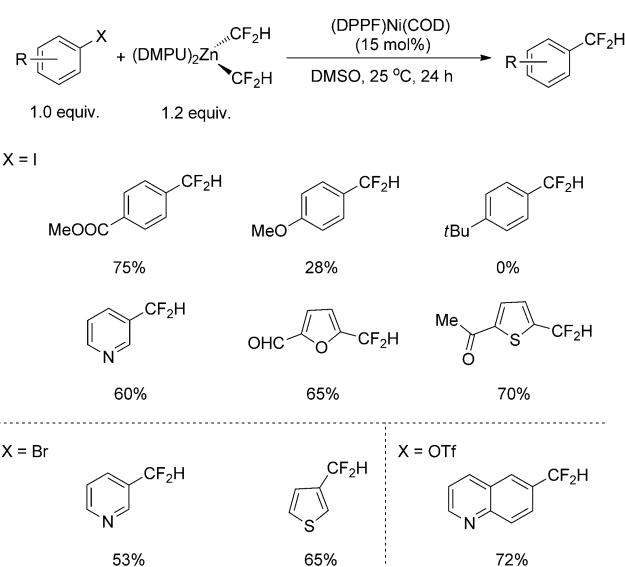
Shortly afterwards, Shen's group reported the difluoromethylation of iodonium salts and acid chlorides with [(SIPr)Ag(CF₂H)] in the presence of CuI at room temperature



Scheme 10. Difluoromethylation of diaryliodonium salts, vinyl(aryl)iodonium salts, aryldiazonium salts, and acid chlorides.

(Scheme 10a–c).^[22a] A stoichiometric amount of copper was required for the difluoromethylation of diaryliodonium salts and vinyl(aryl)iodonium salts (Scheme 10a and b). In the cases of unsymmetrical diaryliodonium salts, less-hindered aryl groups were slightly favored over hindered substituents, whereas, in the cases of vinyl(aryl)iodonium salts, the difluoromethylation reaction occurred selectively at the vinyl groups to give the difluoromethylated alkenes. Acid chlorides were more reactive than iodonium salts, and only a catalytic amount of copper was required for the reaction (Scheme 10c). Nevertheless, the difluoromethylation of aryldiazonium salts was quite different (Scheme 10d).^[22a] When copper salts were used as promoters, the expected Sandmeyer difluoromethylation product was obtained in less than 40% yield. Interestingly, when the reaction was performed in the absence of the copper salt, the formation of difluoromethylated azo compounds without extruding N₂ was much faster than the denitrogenative Sandmeyer reaction, and stable azo compounds were obtained in high yields.

In early 2016, Xu and Vici developed a Ni-catalyzed difluoromethylation of aryl halides and triflates by using a stable (difluoromethyl)zinc reagent (Scheme 11).^[22f] [(DMPU)₂Zn(CF₂H)₂]



Scheme 11. Ni-catalyzed difluoromethylation of aryl iodides, bromides, and triflates with a (difluoromethyl)zinc reagent. cod = 1,5-cyclooctadiene.

was isolated in high yield as a free-flowing solid from the reaction between diethylzinc and ICF₂H in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU; Figure 4). This (difluoromethyl)zinc reagent was stable for months in the solid state under an inert atmosphere. By using the known

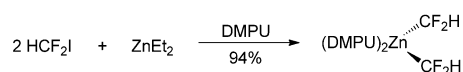
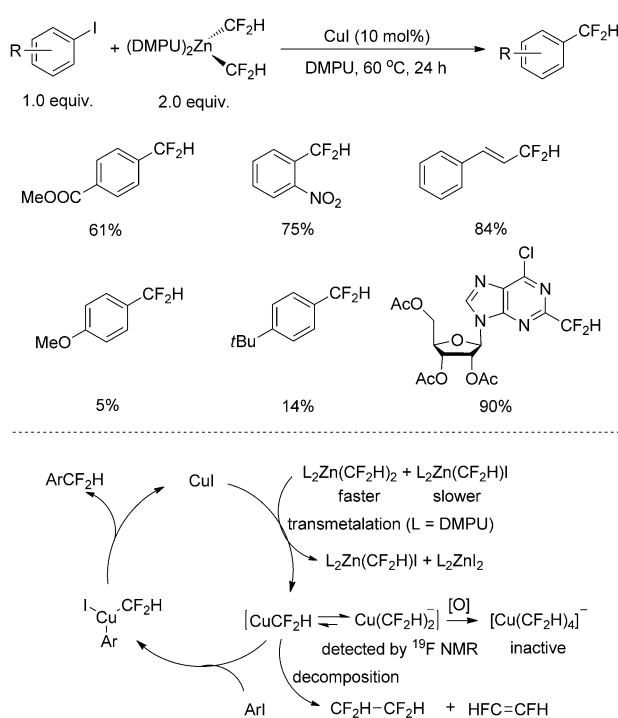


Figure 4. Preparation of [(DMPU)₂Zn(CF₂H)₂].

[(DPPF)Ni(cod)] as a precatalyst, the difluoromethylation of aryl iodides with [(DMPU)₂Zn(CF₂H)₂] could be achieved. Electron-deficient substrates worked well in this reaction. However, the yields decreased sharply when electron-rich substrates were used. In addition to aryl iodides, aryl bromides and triflates were also compatible in this reaction.

Very recently, Mikami's group reported a copper-catalyzed difluoromethylation of aryl iodides by using (difluoromethyl)-zinc reagent (DMPU)₂Zn(CF₂H)₂ (Scheme 12).^[31] No extra ligand



Scheme 12. Copper-catalyzed difluoromethylation of aryl iodides with a (difluoromethyl)zinc reagent and proposed reaction mechanism. Ac = acetyl.

on the copper catalyst or activator for the (difluoromethyl)zinc reagent were required. This method was effective for aryl iodides that contained electron-withdrawing substituents, but was ineffective for electron-rich aryl iodides. The oxidative addition of electron-rich aryl iodides was relatively slow and the [CuCF₂H] species that was formed by transmetalation from (DMPU)₂Zn(CF₂H)₂ readily decomposed. It has been found that the transmetalation of the CF₂H group from [(DMPU)₂Zn(CF₂H)₂] was much faster than that from [(DMPU)₂Zn(CF₂H)I].

Simultaneously, Mikami and co-workers also reported the palladium-catalyzed difluoromethylation of (hetero)aryl halides with (TMEDA)₂Zn(CF₂H)₂ (Figure 5). Aryl halides that contained both electron-withdrawing groups and electron-donating groups were compatible with this cross-coupling reaction (Scheme 13).^[225] Besides aryl iodides, other organohalides, including aryl bromides, vinyl bromides, and aryl chlorides, were also compatible in this reaction. The stability and reactivity of the (difluoromethyl)zinc reagent could be tuned by changing the ligand, and the Zn-to-Pd transmetalation of the difluoro-

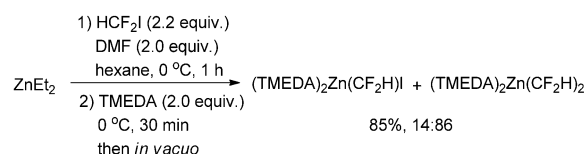
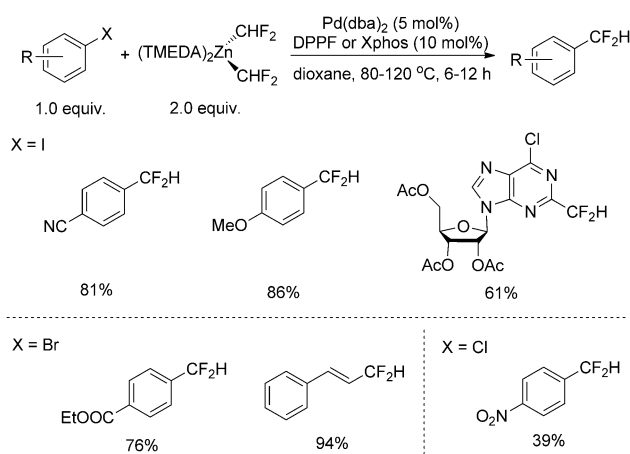


Figure 5. Preparation of [(TMEDA)₂Zn(CF₂H)₂]. TMEDA = tetramethylethylenediamine.



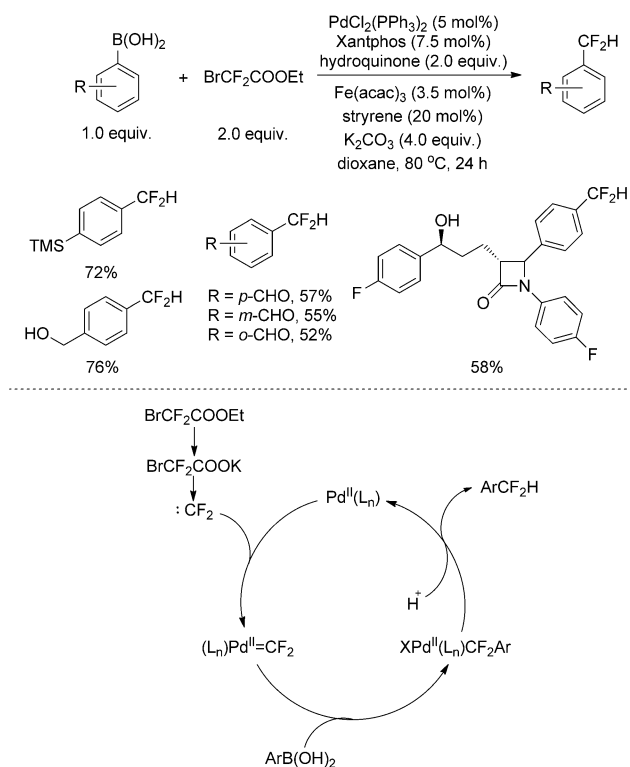
Scheme 13. Palladium-catalyzed Negishi cross-coupling reaction of aryl halides with (TMEDA)₂Zn(CF₂H)₂. XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

methyl group was highly efficient, even in the absence of an activator.

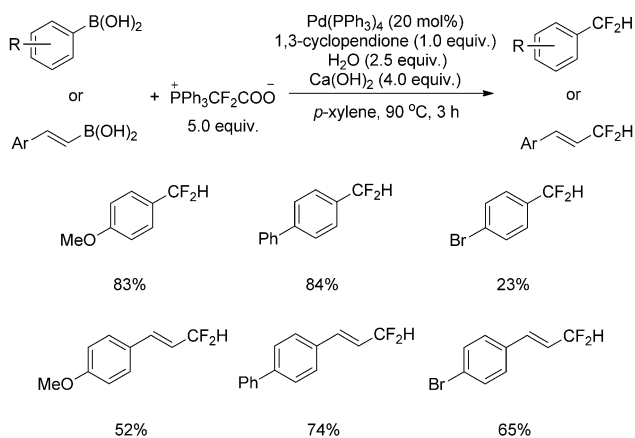
In addition to (difluoromethyl)silane, (difluoromethyl)silver, and (difluoromethyl)zinc reagents, difluorocarbenes, which can be used to form (difluoromethyl)metal complexes after protonation of the corresponding metal–difluorocarbene complexes, have also found application in transition-metal-catalyzed difluoromethylation.

In 2015, Zhang and co-workers reported the Pd-catalyzed difluoromethylation of arylboronic acids with ethyl bromodifluoroacetate (Scheme 14).^[32] A wide range of arylboronic acids with various substituents, including base- and nucleophile-sensitive functional groups, such as silyl, formyl, and carbinol groups, were all compatible with this reaction. The difluoromethylation of an ezetimibe derivative without protecting the free hydroxy group also proceeded smoothly. According to the mechanistic study, although no direct or strong evidence was found to support the involvement of a Pd=CF₂ complex, the proposed Pd^{II}-involved difluorocarbene pathway could offer a reasonable explanation for this difluoromethylation reaction.

In 2016, Xiao and co-workers reported the Pd-catalyzed difluoromethylation of boronic acids with difluoromethylene phosphobetaine reagent Ph₃P⁺CF₂COO⁻ (PDFA) to furnish (difluoromethyl)arenes and (difluoromethyl)olefins (Scheme 15).^[33] Electron-rich and electron-neutral arylboronic acids gave much-higher yields than electron-deficient aryl substrates. The difluoromethylation of various vinylboronic acids also worked well, with the formation of only a single stereoisomer of the



Scheme 14. Pd-catalyzed difluoromethylation of arylboronic acids with bromodifluoroacetate and proposed reaction mechanism. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, acac = acetylacetonate.



Scheme 15. Pd-catalyzed difluoromethylation of boronic acids with $\text{Ph}_3\text{P}^+\text{CF}_2\text{COO}^-$ (PDFA).

desired products. It was found that $[\text{Pd}(\text{PPh}_3)_4]$ could react with PDFA directly to give the $[\{\text{Pd}(\text{CF}_2)(\text{PPh}_3)_3\}]$ complex, which might be produced by trimerization of the $[\text{Pd}=\text{CF}_2]$ monomer (Figure 6). The $[\{\text{Pd}(\text{CF}_2)(\text{PPh}_3)_3\}]$ complex could also be used in the difluoromethylation of boronic acids, although the yield was low (6%). The detrimerization of the trimer into monomers might be difficult, or the trimer may have decomposed into other side products. In their mechanistic study, the authors proposed a mechanism that involved the formation and

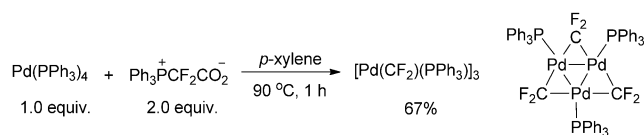
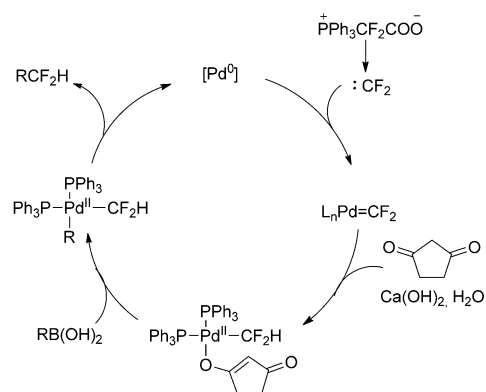


Figure 6. Synthesis of $[\{\text{Pd}(\text{CF}_2)(\text{PPh}_3)_3\}]$.

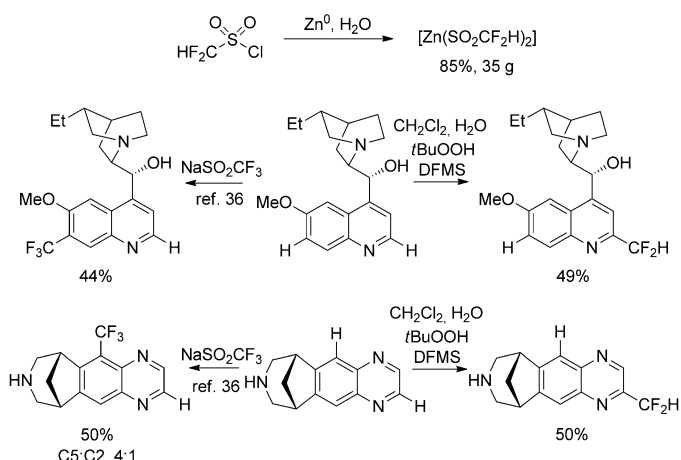
transformation of a $[\text{Pd}=\text{CF}_2]$ complex as a key intermediate (Scheme 16).



Scheme 16. Proposed reaction mechanism for the Pd-catalyzed difluoromethylation of boronic acids with PDFA.

2.4. Metal-Catalyzed Radical Difluoromethylation

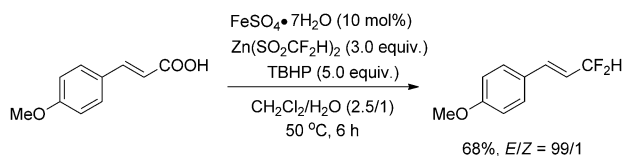
In 2012, Baran's group reported the invention of zinc difluoromethanesulfinate, $[\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2]$ (DFMS), as a new difluoromethylating reagent for the difluoromethylation of organic substrates through a radical process.^[34,35] $[\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2]$ was readily prepared through the reduction of difluoromethanesulfonyl chloride ($\text{HCF}_2\text{SO}_2\text{Cl}$) by zinc. Heteroaromatic groups could be selectively difluoromethylated by using $[\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2]$ in the presence of *t*BuOOH as an oxidant (Scheme 17). The authors proposed that the reaction occurred through a radical process,



Scheme 17. Difluoromethylation with $[\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2]$ (DFMS).

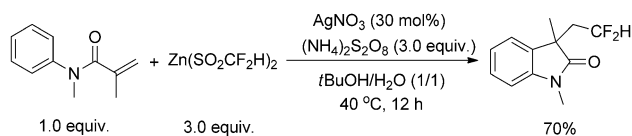
in which the CF_2H radical possessed nucleophilic character. $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ could also be used in the difluoromethylation of thiols and enones.

In 2013, Liu and co-workers reported an iron-catalyzed decarboxylative difluoromethylation of α,β -unsaturated carboxylic acids with $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$, which proceeded through a radical mechanism (Scheme 18).^[37] This approach provided a new



Scheme 18. Iron-catalyzed decarboxylative difluoromethylation of α,β -unsaturated carboxylic acids with $[\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2]$. TBHP = *tert*-butyl hydroperoxide.

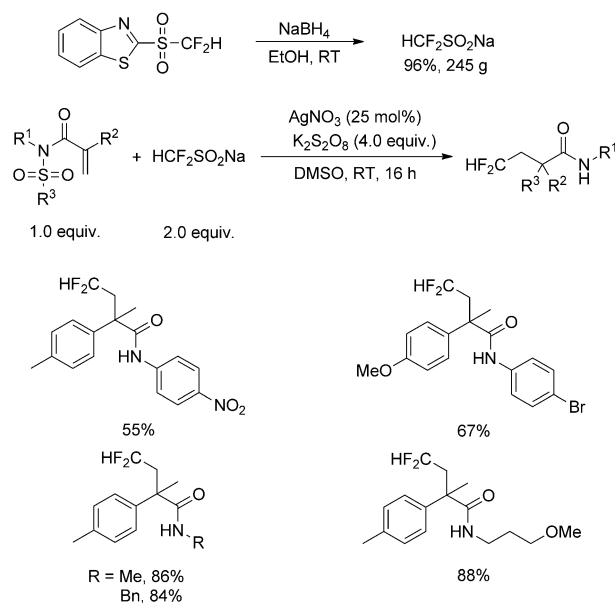
strategy for the stereospecific synthesis of HCF_2 -substituted *E* alkenes through a radical-addition/elimination process. However, this method was limited to electron-rich α,β -unsaturated carboxylic acids, as electron-deficient aryl-substituted acrylic acids gave very low yields of the desired products. In addition, alkyl-substituted acrylic acids failed to give the desired difluoromethylated alkene products. In 2014, Tan and co-workers reported a silver-catalyzed difluoromethylation/cyclization reaction of *N*-arylacrylamides with $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ (Scheme 19).^[38] This reaction provided an efficient method for synthesizing HCF_2 -substituted oxindoles through a radical-addition/cyclization process.



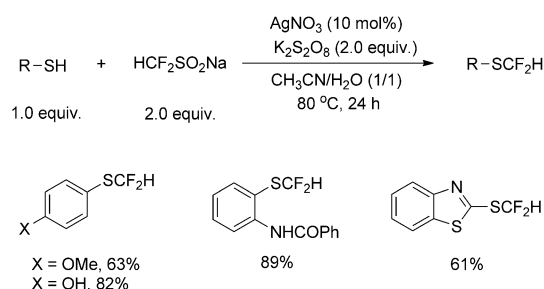
Scheme 19. Silver-catalyzed difluoromethylation/cyclization reaction of *N*-arylacrylamides with $[\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2]$.

In 2015, we developed a new method for the synthesis of $\text{HCF}_2\text{SO}_2\text{Na}$ through a concise reduction of the corresponding benzo[*d*]thiazol-2-yl sulfone by using NaBH_4 . This reaction provided a simple and efficient synthesis of $\text{HCF}_2\text{SO}_2\text{Na}$ that could be performed on a large scale with facile purification. By using $\text{HCF}_2\text{SO}_2\text{Na}$ as a difluoromethyl radical precursor and $\text{K}_2\text{S}_2\text{O}_8$ as the oxidant, the silver-catalyzed cascade difluoromethylation/aryl-migration/ SO_2 -extrusion of conjugated *N*-arylsulfonylated amides delivered α -aryl- β -difluoromethyl amides (Scheme 20).^[39] $\text{HCF}_2\text{SO}_2\text{Na}$ has been shown to be a good reagent for radical difluoromethylation and may have broad application in the radical difluoromethylation of different substrates in the future.

Recently, Yi and co-workers developed the silver-catalyzed difluoromethylation of (hetero)aryl thiols with $\text{HCF}_2\text{SO}_2\text{Na}$ as a difluoromethyl radical precursor and $\text{K}_2\text{S}_2\text{O}_8$ as an oxidant



Scheme 20. Silver-catalyzed cascade difluoromethylation/aryl-migration/ SO_2 -extrusion of conjugated *N*-arylsulfonylated amide with $\text{HCF}_2\text{SO}_2\text{Na}$.



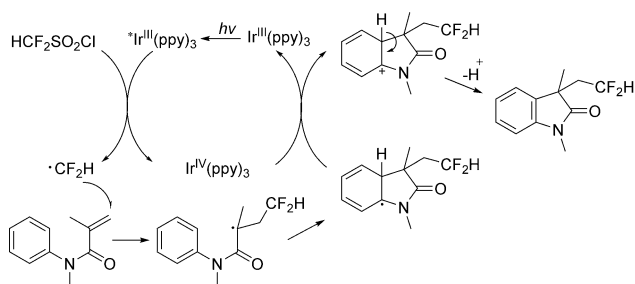
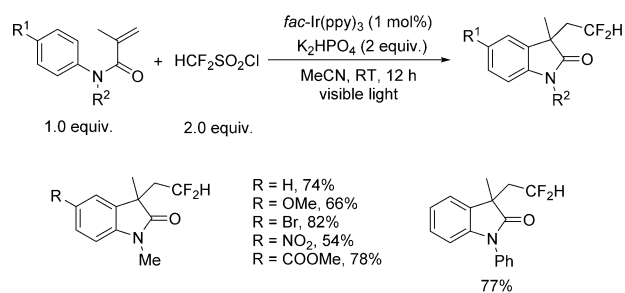
Scheme 21. Silver-catalyzed difluoromethylation of (hetero)aryl thiols with $\text{HCF}_2\text{SO}_2\text{Na}$.

(Scheme 21).^[40] This reaction exhibited good tolerance to various functional groups, including hydroxy and amide groups.

2.5. Difluoromethylation by Photoredox Catalysis with Transition-Metal Complexes

In recent years, by taking advantage of the highly tunable redox potentials of excited transition-metal complexes, visible-light-induced photoredox catalysis has emerged as a powerful synthetic tool for both bond-activation and construction processes that are usually difficult to realize by using conventional methods.^[41] In addition, visible-light-induced photoredox catalysis has emerged as an “eco-friendly” approach because it employs mild reaction conditions and has a broad functional-group tolerance. In particular, great progress has been made in photoredox radical fluoroalkylation reactions with transition-metal complexes as catalysts, including difluoromethylation.^[42]

In 2014, Dolbier's group reported the difluoromethylation/cyclization reaction of *N*-arylacrylamides with difluoromethanesulfonyl chloride ($\text{HCF}_2\text{SO}_2\text{Cl}$; Scheme 22),^[43] in which the CF_2H

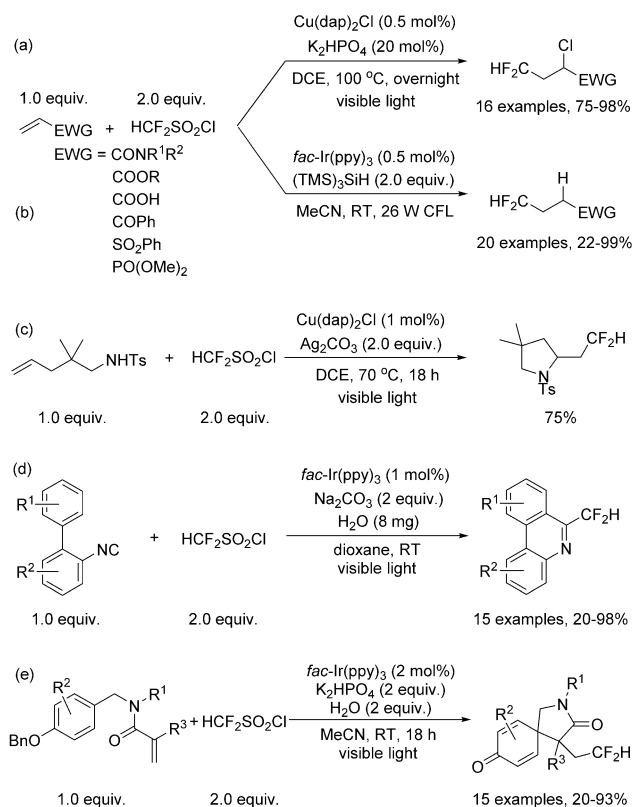


Scheme 22. Visible-light-catalyzed photoredox difluoromethylation/cyclization of *N*-arylacrylamides with $\text{HCF}_2\text{SO}_2\text{Cl}$ and proposed reaction mechanism. ppy = 2-phenylpyridine.

radical was generated from $\text{HCF}_2\text{SO}_2\text{Cl}$ by using photoredox catalysis with a transition-metal catalyst, $\text{fac-Ir}(\text{ppy})_3$, under mild conditions. Electron-rich and electron-deficient *N*-arylacrylamides were both tolerated in this transformation. Other fluoroalkyl radicals, such as CF_3 , C_4H_9 , CF_2COOMe , CH_2F , and CH_2CF_3 radicals, could also be introduced into *N*-arylacrylamides by using the same method with the corresponding fluoroalkanesulfonyl chloride ($\text{R}_f\text{SO}_2\text{Cl}$).

The judicious choice of transition-metal photoredox catalyst allowed the difluoromethylation reaction with $\text{HCF}_2\text{SO}_2\text{Cl}$ under photoredox catalysis to be applied to atom-transfer radical addition (ATRA) reactions of electron-deficient alkenes (Scheme 23 a),^[44] the hydro-difluoromethylation of electron-deficient alkenes (Scheme 23 b),^[45] the intramolecular amino-difluoromethylation of unactivated alkenes (Scheme 23 c),^[46] the difluoromethylation/cyclization reaction of biphenyl isocyanides (Scheme 23 d),^[47] and the intramolecular difluoromethylation of *N*-benzylacrylamides, coupled with a dearomatizing spirocyclization reaction (Scheme 23 e)^[48] among others.^[49] Radical difluoromethylation cascade reactions by using photoredox catalysis with a transition-metal catalyst have been considered to be a powerful approach for the construction of complex organic skeletons that contain a difluoromethyl group.

(Bromodifluoromethyl)phosphonium bromide, which can be readily prepared from the reaction between PPh_3 and CF_2Br_2 , is typically used as a precursor of difluorocarbene.^[50] In early 2016, Qing and co-workers reported a visible-light-induced hydro-difluoromethylation reaction of alkenes with (bromodifluoromethyl)phosphonium bromide in which they used water and THF as hydrogen sources (Scheme 24).^[51] In the presence of an iodide salt, the formation of bromo-bromodifluoromethylated and hydro-bromodifluoromethylated products was sup-

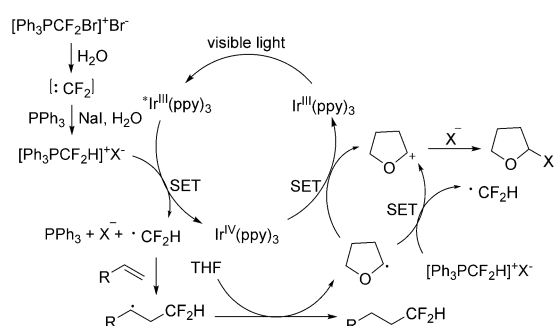
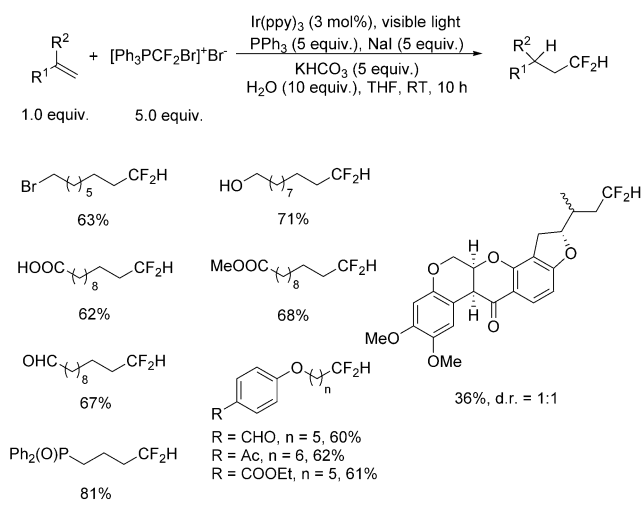


Scheme 23. Visible-light-catalyzed photoredox radical difluoromethylation cascade reactions with $\text{HCF}_2\text{SO}_2\text{Cl}$. dap = 2,9-bis(4-methoxyphenyl)-1,10-phenanthroline, DCE = 1,2-dichloroethane.

pressed, and so the difluoromethylated alkane was formed selectively.

(Difluoromethyl)triphenylphosphonium bromide, which can be prepared from the reaction between PPh_3 , CF_2Br_2 , THF and water, has been used as a precursor of difluoromethylene phosphonium ylide.^[52] Recently, Qing and co-workers reported its new application as a source of difluoromethyl radicals in the bromo-difluoromethylation and difluoromethylation of alkenes by using photoredox catalysis (Scheme 25).^[53] The use of a catalytic amount of the copper salt effectively inhibited the hydro-difluoromethylation of the alkenes and controlled the selective generation of bromo-difluoromethylated products, although its exact role in the reaction remained unclear. Recently, the oxydifluoromethylation of styrenes with (difluoromethyl)triphenylphosphonium bromide by using visible-light-induced photoredox catalysis was reported by the same group (Scheme 26).^[54]

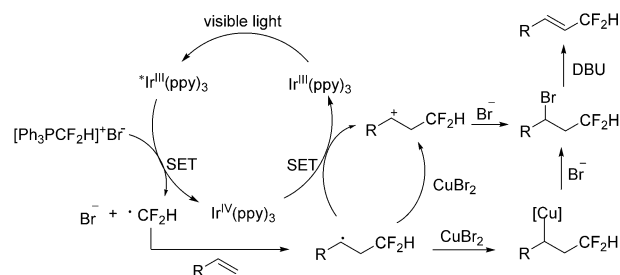
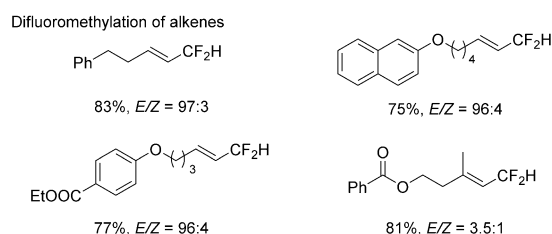
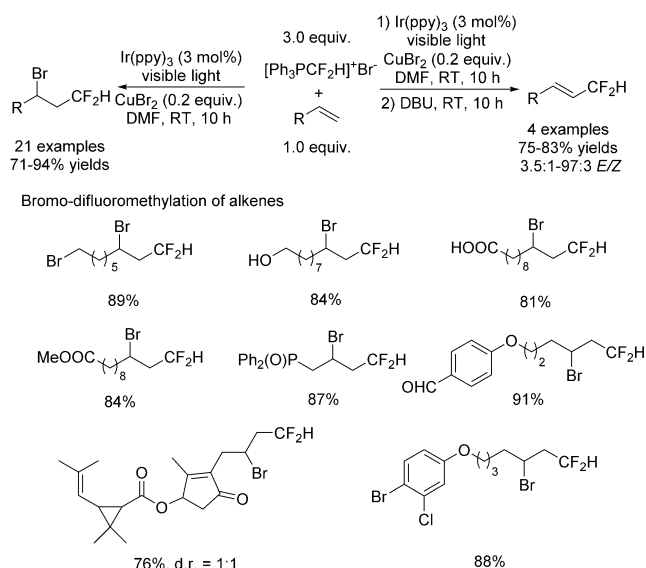
Fluoroalkyl sulfones are air-stable and readily available, and they have been widely used for the incorporation of diverse fluoroalkyl groups into organic molecules.^[55] However, the use of fluoroalkyl sulfones and their derivatives for radical fluoroalkylation through cleavage of the $\text{R}_f\text{-SO}_2$ (R_f = fluoroalkyl) bond to form C-centered R_f radicals is challenging, owing to the limitations of conventional radical initiators or single-electron-transfer (SET) reductants. Recently, our group reported the use of difluoromethyl sulfone as a new difluoromethyl radical precursor under visible-light-induced photoredox catalysis. The



Scheme 24. Visible-light-induced hydro-difluoromethylation of alkenes with (bromodifluoromethyl)phosphonium bromide and proposed reaction mechanism.

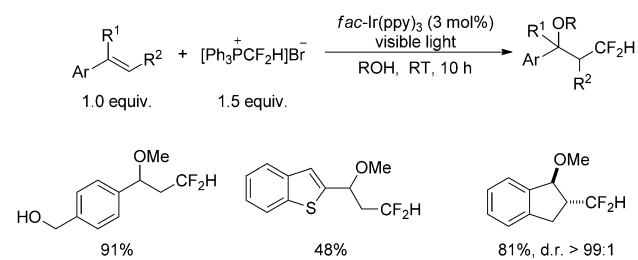
high efficiency of this method was demonstrated by the radical difluoromethylation of various isocyanides as excellent radical acceptors to afford difluoromethylated phenanthridine derivatives (Scheme 27).^[56] Furthermore, monofluoromethyl, 1,1-difluoroethyl, (phenyl)difluoromethyl, (benzoyl)difluoromethyl, and trifluoromethyl radicals could also be incorporated into isocyanides by using the same strategy with the corresponding fluoroalkyl sulfone ($\text{R}_f\text{SO}_2\text{Ar}$). This method demonstrates a new synthetic application of fluorinated sulfones, and it also provides a new approach to fluoroalkyl radicals. Very recently, we extended the application of this fluoroalkylation method to the oxydifluoromethylation of aryl alkenes with difluoromethyl sulfone by using visible-light-induced photoredox catalysis, and other fluoroalkylation reactions of aryl alkenes with the corresponding fluoroalkyl sulfone ($\text{R}_f\text{SO}_2\text{Ar}$) were also viable by using the same procedure (Scheme 28).^[57] Fu et al. developed the radical oxydifluoromethylation of olefinic amides with difluoromethyl sulfone for the synthesis of CF_2H -containing benzoxazines and oxazolines by using visible-light-induced photoredox catalysis (Scheme 29).^[58]

N-Tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine was initially developed by our group as a useful difluorocarbene source.^[59] Recently, it has been found that this difluoromethylsulfoximine reagent can also serve as a source of CF_2H radicals under photoredox conditions.^[56,60] Akita, Koike, and co-workers utilized

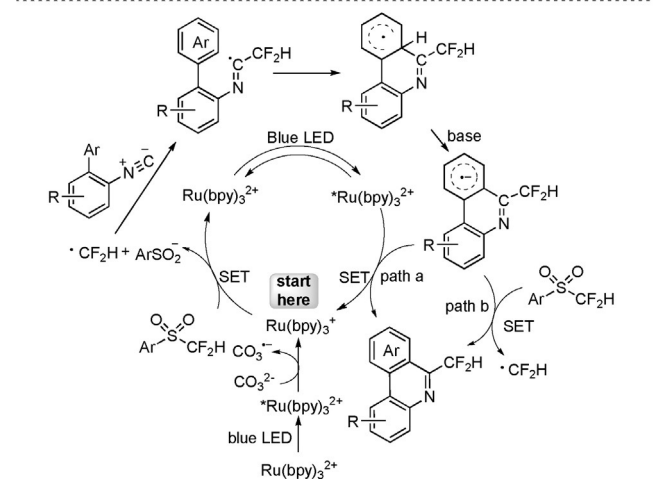
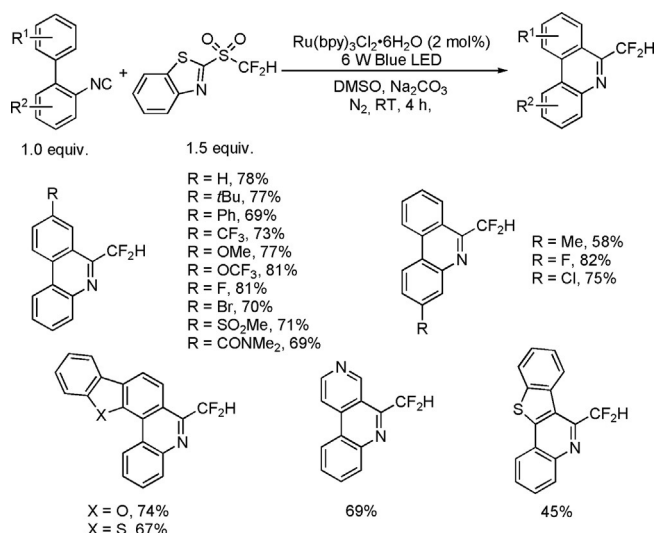


Scheme 25. Bromo-difluoromethylation and difluoromethylation of alkenes with (difluoromethyl)triphenylphosphonium bromide by using photoredox catalysis and proposed reaction mechanism. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

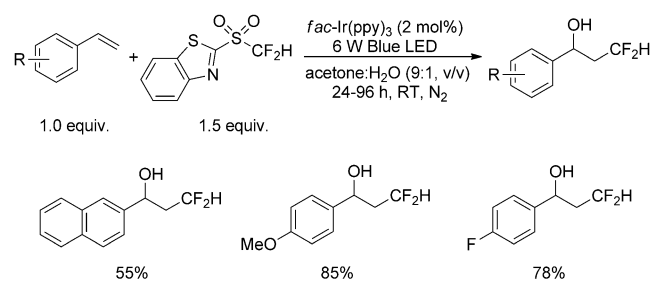
this reagent to achieve the oxydifluoromethylation of alkenes (Scheme 30).^[60] Electron-rich alkenes, electron-deficient alkenes, and more-complex alkene substrates, such as vinyl estrone and



Scheme 26. Oxydifluoromethylation of styrenes with (difluoromethyl)triphenylphosphonium bromide by using visible-light-induced photoredox catalysis.

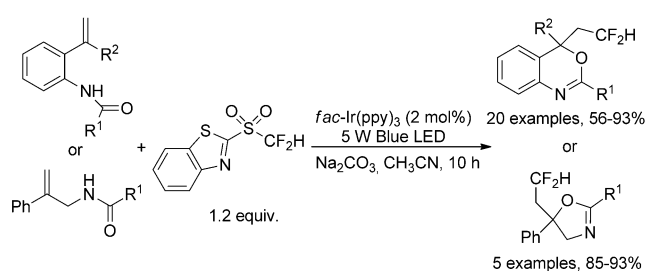


Scheme 27. Radical difluoromethylation of isocyanides with difluoromethyl sulfone by using visible-light-induced photoredox catalysis and proposed reaction mechanism. bpy = 2,2'-bipyridyl, LED = light-emitting diode.

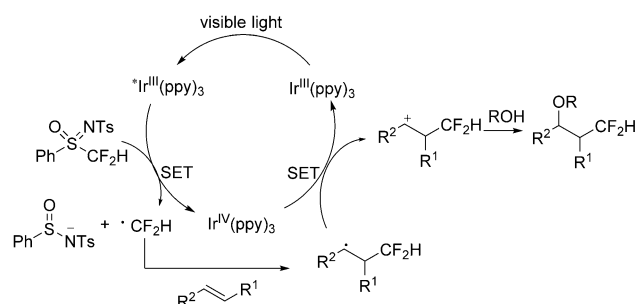
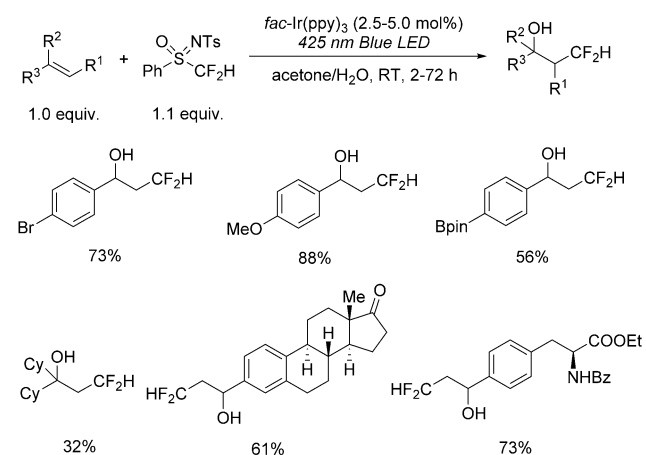


Scheme 28. Oxydifluoromethylation of aryl alkenes with difluoromethyl sulfone by using visible-light-induced photoredox catalysis.

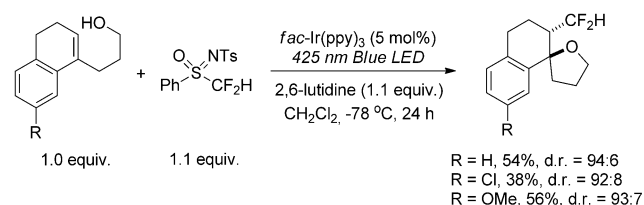
vinyl-*N*-benzoyl-*L*-tyrosine ethyl ester, were all compatible in this reaction. When alcohols and carboxylic acids were used instead of water as *O*-nucleophiles, the oxydifluoromethylation of alkene also proceeded smoothly. In addition, a diastereoselective oxydifluoromethylation reaction of aryl-fused cycloalkenylalkanols with difluoromethyl sulfoximine by using photoredox catalysis has also recently been developed (Scheme 31).^[61]



Scheme 29. Oxydifluoromethylation of olefinic amides with difluoromethyl sulfone by using visible-light-induced photoredox catalysis.



Scheme 30. Visible-light-induced photoredox-catalyzed oxydifluoromethylation of alkenes with *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine and proposed reaction mechanism. Bz = benzoyl.



Scheme 31. Diastereoselective oxydifluoromethylation of aryl-fused cycloalkenylalkanols with difluoromethyl sulfoximine by using photoredox catalysis.

3. Conclusion

Although significant advances have been made in metal-catalyzed difluoromethylation reactions (since 2014) and stoichio-

metric metal-mediated difluoromethylation reactions (since 2012), metal-catalyzed difluoromethylation remains an underdeveloped technique, especially compared to the analogous trifluoromethylation reaction. Only a few transition metals, including copper, palladium, and nickel, have been successfully used in metal-mediated or metal-catalyzed difluoromethylation reactions. In future, more attention should be devoted to the development of $[M-CF_2H]$ complexes of other metals, such as iron, rhodium, and gold. The long-standing challenges associated with difluoromethylation still remain, such as the lack of efficient sources of difluoromethyl groups and the limited reactivity of many difluoromethyl–metal complexes. Further efforts should be put into the development of more-efficient difluoromethyl sources and difluoromethyl–metal complexes with tunable reactivity.

Acknowledgements

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Keywords: difluoromethylation · fluorine · fluoroalkylation · homogeneous catalysis · transition metals

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