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State of Knowledge in Photoredox-Catalysed Direct Difluoromethylation

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Jiaxu Feng,^{a,b} Xiaodong Jia,^a Shuyue Zhang,^a Kui Lu,^{a,b,*} and Dominique Cahard^{c,*}

The direct introduction of diverse fluorinated motifs into feedstock molecules and advanced intermediates is widely studied in pharmaceutical research and drug development. Among the emerging motifs, the difluoromethyl CF_2H is isosteric and isopolar to hydroxy and thiol, while acting as lipophilic hydrogen donor. These properties prompted the recent remarkable progress made in direct difluoromethylation. In this context, photoredox catalysis serving difluoromethylation is a powerful strategy for the construction of CF_2H -containing organic compounds. This review describes the recent developments in visible-light-mediated radical difluoromethylation by means of easily accessible sources of CF_2H radical donors with emphasis for mechanistic considerations.

1. Introduction

Organofluorine compounds are widely distributed in the pharmaceutical, agricultural and functional materials sectors given their beneficial biological, physical, and chemical properties.¹ Among the significant fluorinated structural motifs nowadays regularly encountered, the difluoromethyl group (CF_2H) occupies a place of choice. Several reasons motivate the installation of the CF_2H motif into a wide variety of target compounds; indeed, its steric and electrostatic parameters match very well with those of hydroxy and thiol functions, hydrogen bonding donor capacity is preserved albeit weaker than the more polar hydroxy and thiol functions, lipophilicity is increased as well as the metabolic stability.² With this in mind, it is not surprising that selective positioning of the CF_2H group into complex molecules has become a flourishing research area in organic synthesis, medicinal chemistry and also materials science. Within recent

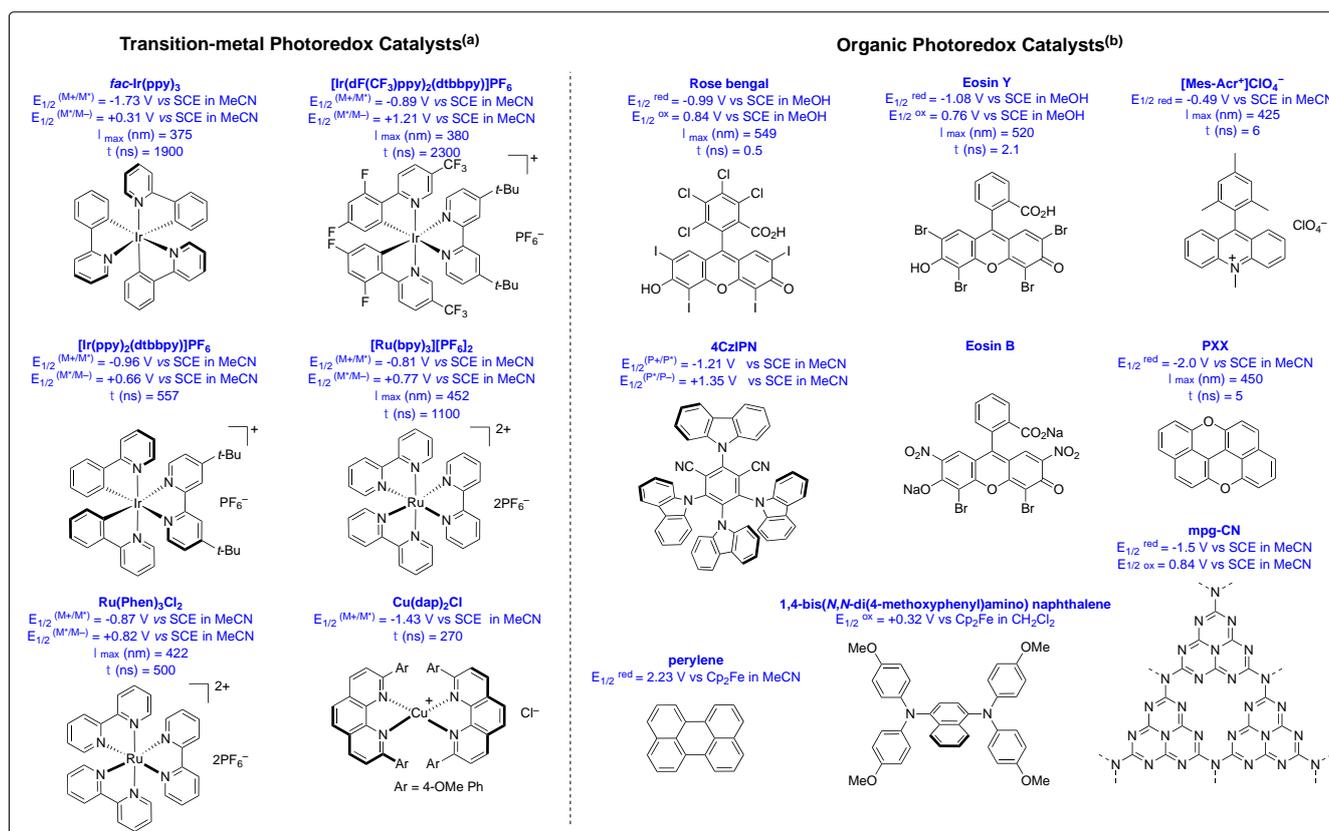
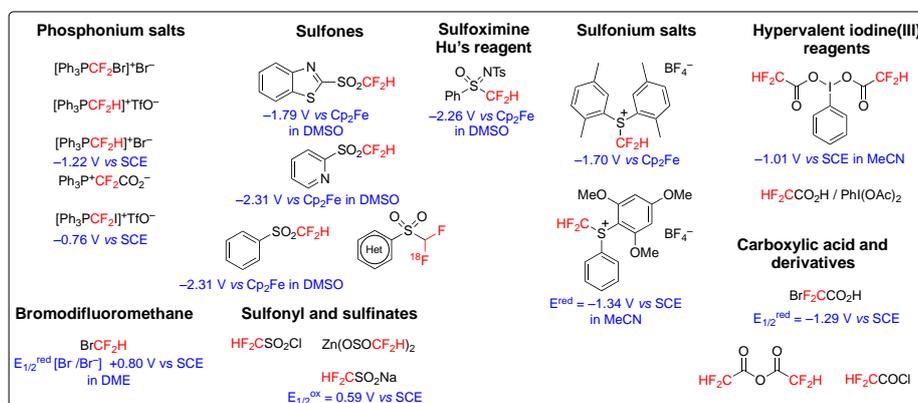
decades, outstanding progress in difluoromethylation has been made using direct and indirect approaches through electrophilic, nucleophilic, or radical processes.³ Seminal works on direct radical difluoromethylation of alkenes was reported using HCF_2I as the difluoromethylating agent as early as 1975 by Tedder's group and by Chen's group in 1994.⁴ To date, radical-based difluoromethylation remains an advantageous synthetic method for the preparation of CF_2H -containing organic molecules. In the presence of a light-absorbing metal complex or a metal-free organic dye (Figure 1), visible-light serves as an ideal external photonic energy source that is converted into chemical energy to generate highly reactive intermediate species in a predictable way under extremely mild conditions and leaving no waste.⁵ Upon photonic activation, the light-absorbing catalyst either donate or abstract an electron to an organic substrate in a single electron transfer (SET) event to form a highly reactive radical species. The photoredox approach adheres to the principles of green chemistry and environmental remediation and have attracted a great deal of attention in chemical and pharmaceutical industries.⁶ This burgeoning technology has been utilised in numerous SET reactions that include considerable efforts devoted to the visible-light-mediated fluoroalkylation. Methods developed for the trifluoromethylation often require adjustments when extended to difluoromethylation.

^a China International Science and Technology Cooperation Base of Food Nutrition/Safety and Medicinal Chemistry College of Biotechnology, Tianjin University of Science & Technology, Tianjin 300457 (P.R. China)
E-mail: lukui@tust.edu.cn

^b Department of Chemistry, College of Sciences, Tianjin University of Science & Technology, Tianjin 300457 (P.R. China)

^c CNRS, UMR 6014 COBRA, Normandie Université, 76821 Mont Saint Aignan (France)
E-mail: dominique.cahard@univ-rouen.fr

Indeed, a simple change of the number of fluorine atoms from CF_3 to CF_2H causes modified electronic properties and redox performance

Figure 1 Chemical structures of photocatalysts featured in this review.^{a)} References^{5b, 7}; ^{b)} References^{5c, 8}**Figure 2** Sources of difluoromethyl radicals. Values of redox potentials are available in references.^{3r, 9}

with the use of CF₂H radical sources requiring a stronger reductant compared with CF₃ radical sources. In this review, we showcase the application of different difluoromethylating agents under visible-light photochemical catalysis for the construction of complex organofluorine compounds. Further to the publication of two review articles on photocatalytic difluoromethylation reactions dated 2019, this vibrant field has grown considerably as evidenced by circa 45% of new articles that appeared since then.¹⁰ In addition,

general reviews on difluoroalkylation appeared in the literature but none of them specifically deal with the photocatalysed direct difluoromethylation.^{3q, 6c, 11} Therefore, this review is timely to update this rapidly growing field and is intended to provide the readers with an overview of photocatalysed direct difluoromethylation reactions that include applications and mechanistic details. The development of direct difluoromethylation reactions was made possible thanks to the availability of a variety of CF₂H donor sources

(Figure 2); the synthesis of these difluoromethylating reagents is out of the scope of this review. Indirect multi-step procedures that require introduction of a CF_2R group ($\text{R}=\text{CO}_2\text{R}'$, $\text{PO}(\text{OR}')_2$, $\text{SO}_2\text{R}'$, SiR'_3) and further cleavage for conversion into CF_2H are also not documented hereafter. This review is organized by type of substrates and sub-divided further by source of difluoromethyl radical:

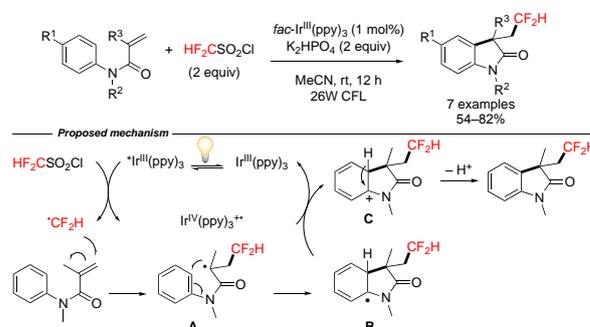
1. Introduction
2. Difluoromethylation of alkenes
 - 2.1. By means of $\text{HF}_2\text{CSO}_2\text{Cl}$
 - 2.2. By means of $[\text{Ph}_3\text{PCF}_2\text{X}]^+\text{Br}^-$ ($\text{X} = \text{Br}, \text{H}$) or $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$
 - 2.3. By means of $(\text{Het})\text{ArSO}_2\text{CF}_2\text{H}$
 - 2.4. By means of *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (Hu's reagent)
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9. ^{18}F Radiodifluoromethylation
10. Conclusion

2. Difluoromethylation of alkenes

2.1 By means of $\text{HF}_2\text{CSO}_2\text{Cl}$

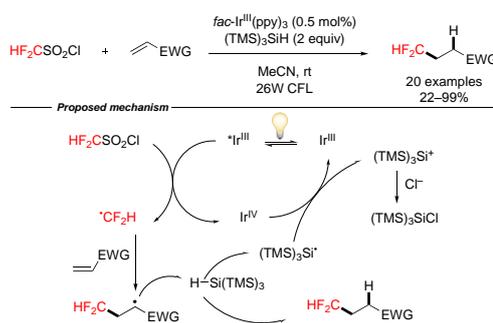
In 2014, Dolbier and co-workers reported the visible-light-catalysed difluoromethylation of *N*-arylacrylamides toward the synthesis of CF_2H -containing 3,3-disubstituted 2-oxindoles in moderate to good yields (Scheme 1).¹² In this radical reaction, $\text{HF}_2\text{CSO}_2\text{Cl}$ was effectively exploited as difluoromethyl radical source in the presence of the well-defined iridium cyclometalated complex *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ as photocatalyst and a compact fluorescent lamp (CFL) 26W, 1600 lumens. A radical addition / cyclisation mechanism was proposed in which the photochemically generated CF_2H radical reacted at the $\text{C}=\text{C}$ bond to form the intermediate radical **A** that spontaneously cyclised into **B** followed by oxidation to give carbocation **C** and the subsequent rearomatisation gave the oxindole (Scheme 1). Worthy of note, other fluorinated 3,3-disubstituted 2-oxindole systems could be synthesised through this methodology in the presence of various

fluorinated sulfonyl chlorides $\text{R}_f\text{SO}_2\text{Cl}$ provided $\text{Ru}^{\text{II}}(\text{phen})_3\text{Cl}_2$ ($E_{1/2}^{\text{III}/\text{II}} = -0.87 \text{ V vs SCE in MeCN}$) is used in place of *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ ($E_{1/2}^{\text{IV}/\text{III}} = -1.73 \text{ V vs SCE in MeCN}$). This is attributable to the fact that the reduction potential of $\text{HF}_2\text{CSO}_2\text{Cl}$ is more negative than that of perfluoro $\text{R}_f\text{SO}_2\text{Cl}$.



Scheme 1 Photoredox-catalysed radical difluoromethylation / cyclisation of *N*-arylacrylamides. Note: In all Schemes, new bonds formed are shown in bold.

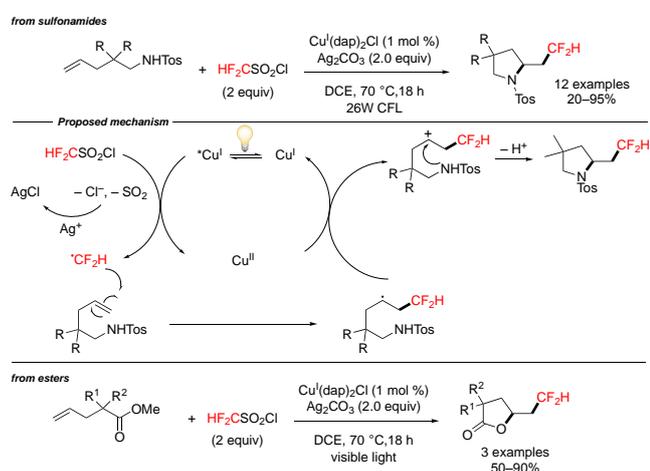
The same CF_2H radical precursor and the same photocatalyst were used for the direct photoredox-catalysed hydrodifluoromethylation of electron-deficient alkenes under neutral conditions, providing an efficient strategy for the introduction of the difluoromethyl group at sites β to electron-withdrawing groups *e.g.* amide, ketone, ester, sulfone and phosphonate (Scheme 2).¹³ Experimental and DFT computational data gave evidence that CF_2H radical is nucleophilic in nature and well suited to react with electron-deficient alkenes. In this reaction, tris(trimethylsilyl)silane acted both as hydrogen atom donor and electron donor in the radical process.



Scheme 2 Photoredox-catalysed reductive difluoromethylation of electron-deficient alkenes.

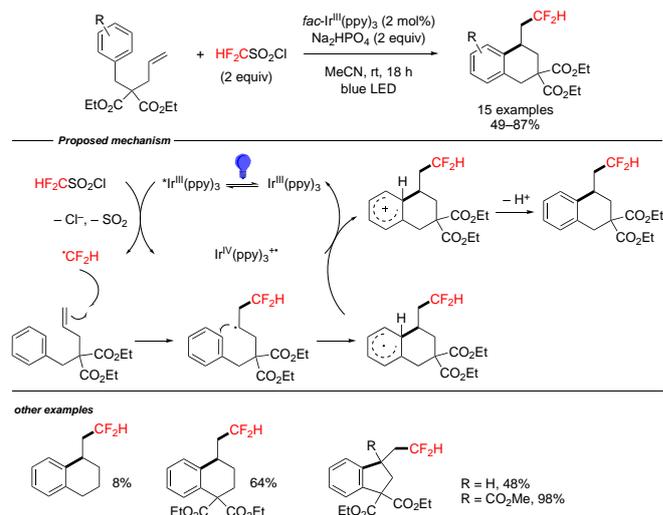
Later, Dolbier's group described photoredox-catalysed intramolecular amino- and oxy-difluoromethylation reactions with sulfonamides and esters, respectively,

featuring a remote unactivated olefin moiety. Here, $\text{Cu}^{\text{I}}(\text{dap})_2\text{Cl}$ ($E_{1/2}^{\text{II}*/\text{I}} = -1.43 \text{ V vs SCE in MeCN}$) was selected as catalyst; upon photoexcitation, $\text{Cu}^{\text{I}}(\text{dap})_2^+$ generates a long-lived excited species $^*\text{Cu}^{\text{I}}(\text{dap})_2^+$ ($\tau = 270 \text{ ns}$). This strong reductant, yet weaker than *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$, donates an electron to $\text{HF}_2\text{CSO}_2\text{Cl}$ to afford the required CF_2H radical. The overall process is a cascade addition / oxidation / cyclisation either with the nitrogen nucleophile to end up with CF_2H -containing pyrrolidines or with the oxygen nucleophile to give lactones in moderate to good yields with great functional group compatibility (Scheme 3).¹⁴ Note that when both sulfonamide and ester moieties are present in the reactant, the lactone was obtained as unique product. Mechanistic investigations demonstrated that copper catalyst and silver carbonate are essential for this cyclisation reaction in order to suppress the formation of chlorodifluoromethylated byproducts.



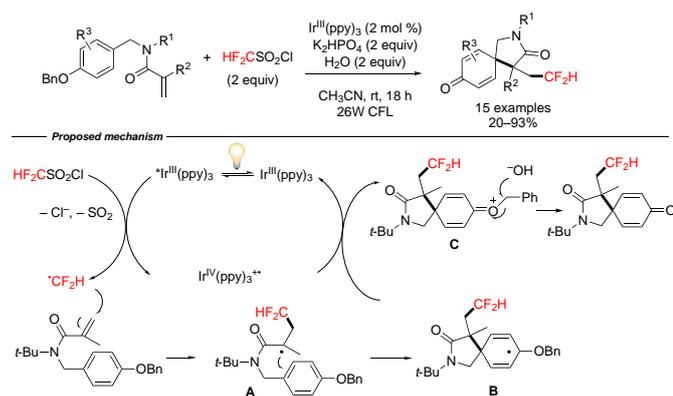
Scheme 3 Photoredox-catalysed intramolecular difluoromethylation / cyclisation of sulfonamides and esters.

Another example of photoredox-catalysed intramolecular difluoromethylation employed unactivated alkenes that feature a remote aromatic group. This mild method provided a new strategy for the construction of carbocycle rings, essentially CF_2H -substituted tetralin derivatives through a 6-exo radical cyclisation (Scheme 4).¹⁵ Crucial to get good to excellent yields was the use of a monochromatic blue LED and the presence of the *gem*-diester motif responsible for the Thorpe-Ingold effect (yield was only 8% without this motif). Two examples of indan-cored derivatives were also presented by varying the number of methylene spacers in substrates.



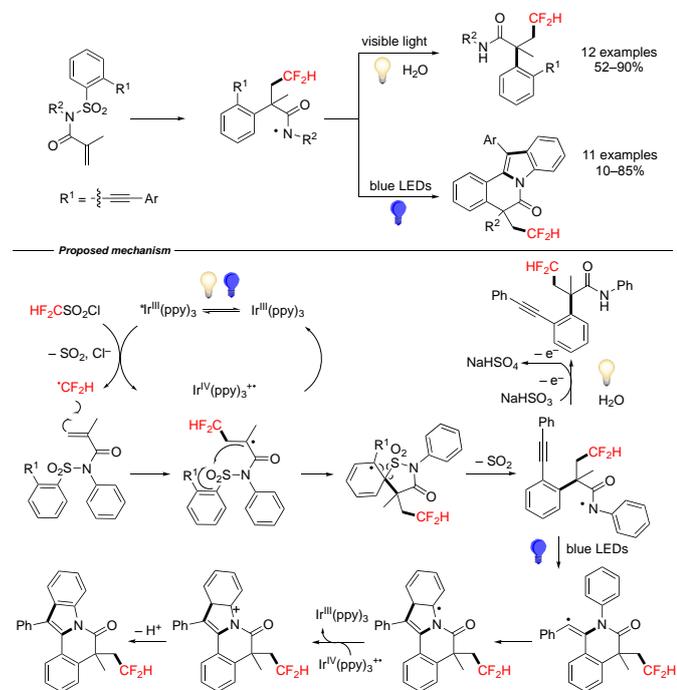
Scheme 4 Photoredox-catalysed intramolecular difluoromethylation / cyclisation of unactivated alkenes with a remote aromatic group.

In 2016, Dolbier and co-workers extended their pioneering work to the visible-light-induced difluoromethylation of *N*-benzylacrylamides with $\text{HF}_2\text{CSO}_2\text{Cl}$ affording a broad range of difluoromethylated 2-azaspiro[4,5]deca-6,9-diene-3,8-diones through a cascade cyclisation / dearomatisation process (Scheme 5).¹⁶ As was the case with *N*-arylacrylamides, *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ was the appropriate photocatalyst for efficient generation of the difluoromethyl radical along with the formation of an oxidative Ir^{IV} species through single electron transfer. This Ir^{IV} subsequently oxidised radical species **B** regenerating the Ir^{III} catalyst. The substrate scope was large with great functional group tolerance. Difluoromethylated azaspiro ring system bearing two adjacent quaternary stereocenters were obtained in moderate to good yields under mild conditions. This piece of work is part of a larger study exploring various fluorosulfonyl chloride toward the access to various fluorinated spirocyclohexadienones. The proposed mechanism revealed that added water might stabilise carbocation **C** and thus promote the desired catalytic cycle.



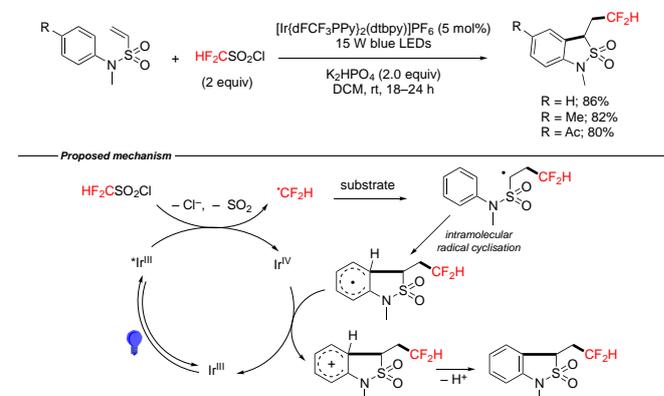
Scheme 5 Photoredox-catalysed radical difluoromethylation / cyclisation of *N*-benzylacrylamides.

Very recently, in 2022, Dolbier, Zhang, Zhou and co-workers developed a photocatalytic difluoromethylation of α , β -unsaturated arylsulfonylated amides by means of $\text{HF}_2\text{CSO}_2\text{Cl}$, affording selectively either β -difluoromethyl amides or CF_2H -containing heterocyclic compounds depending on reaction conditions. On exposure to irradiation by means of a blue light, CF_2H -containing heterocyclic products were obtained in moderate to good yields through a cascade radical addition, *ipso*-cyclisation and Smile-type rearrangement. Conversely, the chemoselectivity was changed and β -difluoromethylated amides were formed by adding H_2O and changing the light source to visible light (Scheme 6).¹⁷



Scheme 6 Photocatalytic difluoromethyl(aryl)ation of α,β -unsaturated amides.

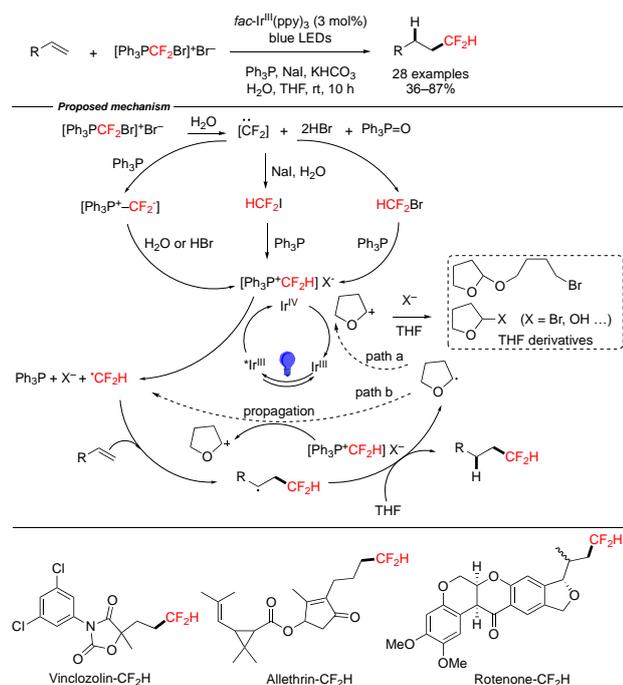
Chemists in the private industry hypothesised that the photocatalysed oxidative difluoromethylation could be extended to *N*-arylvinylsulfonamides. The reaction indeed was successfully applied to afford difluoromethylated 1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxides in good yields on three examples (Scheme 7).¹⁸



Scheme 7 Visible-light-promoted radical cyclisation of *N*-arylvinylsulfonamides.

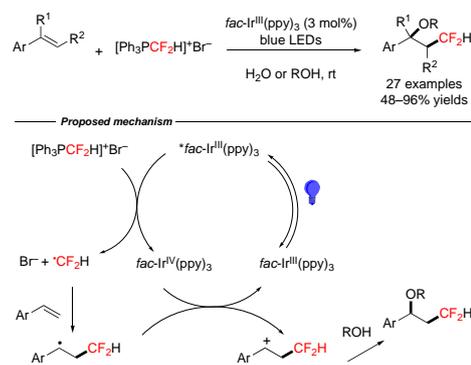
2.2. By means of $[\text{Ph}_3\text{PCF}_2\text{X}]^+\text{Br}^-$ ($\text{X} = \text{Br}, \text{H}$) or $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$

Using readily available solid bromodifluoromethyltriphenyl phosphonium bromide in place of the volatile dibromodifluoromethane motivated Qing and co-workers to generate CF_2H radical under visible-light irradiation for the direct introduction of the CF_2H group onto alkenes leading to hydrodifluoromethylated products (Scheme 8).¹⁹ The source of hydrogen was either water or THF. A wide range of sp^3 -difluoromethylated compounds were prepared that include analogues of biologically active compounds such as Allethrin, Rotenone, and Vinclozolin clearly demonstrating the potential of the method and its great functional group tolerance. Apart from one case of a *gem*-disubstituted olefin (Rotenone- CF_2H), all substrates were monosubstituted olefins. Mechanistic investigation indicated that deconstruction of the reagent $[\text{Ph}_3\text{PCF}_2\text{Br}]^+\text{Br}^-$ gave the difluorocarbene that combined with hydrogen bromide and triphenylphosphine to form the difluoromethyltriphenyl phosphonium bromide responsible of CF_2H radical transfer. Addition of sodium iodide was also beneficial to the reaction yield as it offered another path to $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ via iododifluoromethane. The oxidative quenching cycle was best performed with *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ as the catalyst and blue LEDs as light source (Scheme 8).



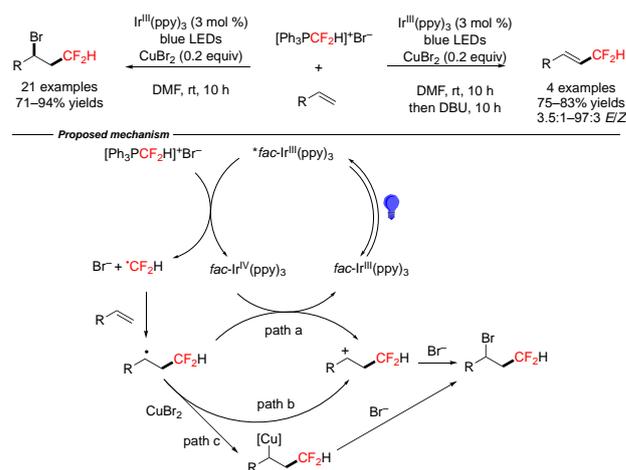
Scheme 8 Visible-light-induced hydrodifluoromethylation of alkenes.

Qing group further synthesised the putative reagent $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ for its direct application in a new visible-light-promoted oxydifluoromethylation of styrenes allowing the preparation of CF_2H -containing alcohols and ethers in moderate to good yields under mild conditions (Scheme 9).²⁰ While mono- and disubstituted olefins in styrene derivatives gave the desired products, trisubstituted ones failed to react because of greater steric hindrance. Of several photocatalysts evaluated, $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$, which is a stronger reductant than Ru- and Ir-polypyridyl complexes and the organic dye Eosin Y, was the only one to promote the oxydifluoromethylation reaction. The main points of the proposed mechanism are the reduction of $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ to deliver the CF_2H radical that adds to the styrene, a subsequent oxidation of the intermediate to give a benzylic carbocation and concomitant regeneration of the photocatalyst, finally a nucleophilic attack of carbocation by alcohols or water to afford the desired products. Importantly, no brominated product was observed albeit bromide anions are inherently present.



Scheme 9 Visible-light-promoted oxydifluoromethylation of styrenes.

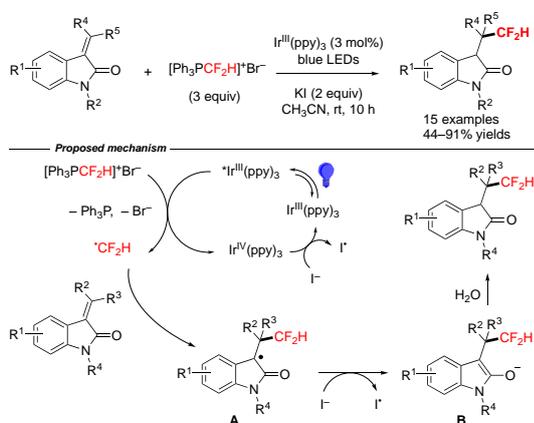
In order to develop a bromodifluoromethylation reaction under photoredox catalysis, Qing and co-workers found that the addition of a copper II salt, $\text{Cu}(\text{OAc})_2$, CuBr_2 , or $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, favored the bromide incorporation at the expense of the hydrodifluoromethylation, in particular CuBr_2 was very efficient provided that it is used catalytically (Scheme 10).²¹ Using difluoromethyltriphenyl phosphonium bromide as the CF_2H radical source, the photoredox bromodifluoromethylation was performed on a broad alkene scope in good to high yields. Additionally, bromodifluoromethyl alkenes easily underwent dehydrobromination by quenching the reaction with DBU. Mechanistic investigation revealed that CuBr_2 could promote this reaction via an alkylcopper species (path c) but the exact role of the copper salt was not clearly demonstrated.



Scheme 10 Visible-light-promoted bromodifluoromethylation of alkenes.

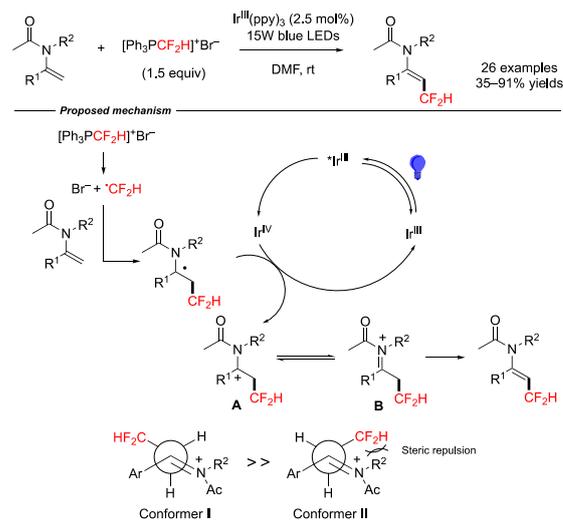
The more substituted is the olefin the more difficult is the radical difluoromethylation. Nevertheless,

tetrasubstituted alkenes such as those in 3-alkylidene indoles were successfully reacted with $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ under photoredox catalysis. This method provided a new strategy for the direct introduction of CF_2H into oxindole scaffold, which commonly exists in natural compounds, biologically active compounds and valuable synthetic intermediates (Scheme 11).²² This reaction is apparently a hydrodifluoromethylation of the $\text{C}=\text{C}$ bond but going into the details, the authors proposed that radical intermediate **A**, formed by addition of CF_2H radical, was reduced by iodide anion to form enolate **B** that was protonated by trace of water present in the reaction system. This way, novel difluoromethylated oxindoles featuring a $\text{C}-\text{CF}_2\text{H}$ quaternary center were constructed.



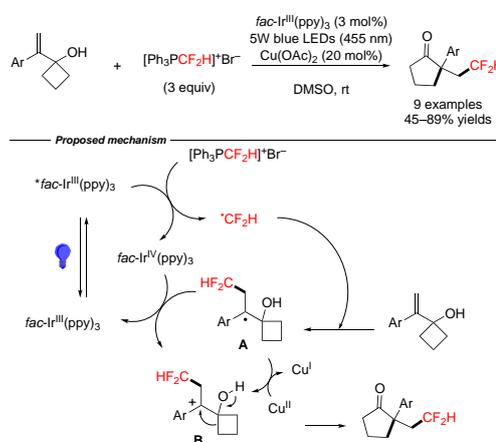
Scheme 11 Visible-light-promoted hydrodifluoromethylation of 3-vinylidene indoles.

Olefin moiety found in enamides were also subjected to studies of the photoredox-catalysed difluoromethylation. Indeed, enamides are privileged scaffolds for a large range of chemical transformations. In this context, Zhao, Loh and co-workers reported the regio- and stereoselective photoredox-catalysed difluoromethylation of enamides using difluoromethyltriphenylphosphonium bromide (Scheme 12).²³ A broad range of *E*-configured β -difluoromethylated enamides were synthesised under very mild conditions using blue LEDs and a catalytic amount of *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$. Based on literature precedence, the proposed reaction mechanism involves carbocation **A** in equilibrium with iminium **B** and a further deprotonation via the preferential conformer **I** having less steric constraints than **II** and ending up to the *E*-configured enamides. These enamides were further transformed into relevant difluoromethyl-containing isoquinolines, reduced into amines and hydrolysed to α -difluoromethylated ketone.



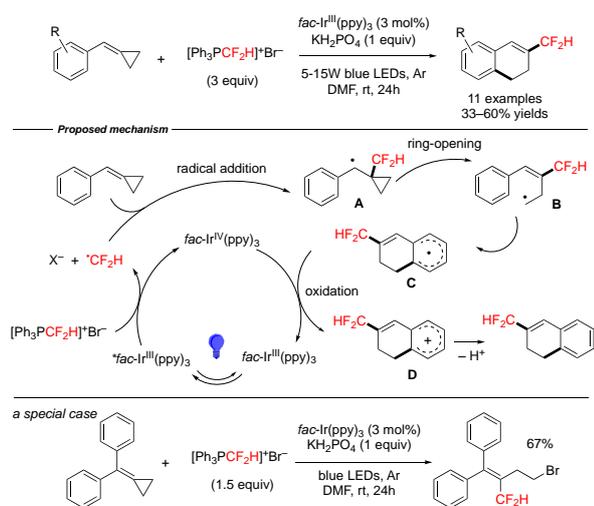
Scheme 12 Stereoselective difluoromethylation of enamides.

Kim and co-worker developed a visible-light mediated difluoromethylation of 1-(1-arylvinyl)cyclobutanol derivatives followed by a 1,2-carbon migration causing ring expansion. The optimised reaction conditions required $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$, *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ and blue LEDs in the presence of 20 mol% of copper acetate (Scheme 13).²⁴ In this example, CF_2H donors such as 2-((difluoromethyl)sulfonyl)benzo[*d*]thiazole and *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine did not deliver the expected reaction product nor the use of Ru-based and organic photocatalysts. The role of $\text{Cu}(\text{OAc})_2$ was to facilitate the oxidation of radical intermediate **A** into carbocation **B**, which is subject of ring expansion. Various 1-(1-arylvinyl)cyclobutanols bearing electron-neutral, -withdrawing and -donating aryl groups were engaged in this transformation to access a class of difluoromethyl-substituted cyclopentanone derivatives in moderate to good yields under mild conditions.



Scheme 13 Cascade photoredox difluoromethylation / ring expansion.

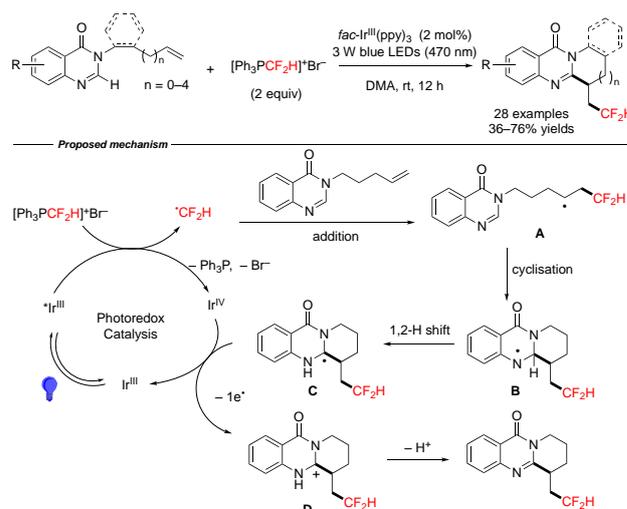
Another type of ring expansion was reported by Wu, Wang, Li and co-workers who developed a visible-light-induced radical difluoromethylation of methylenecyclopropanes to synthesise difluoromethylated 1,2-dihydronaphthalenes (Scheme 14).²⁵ In this approach, $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ served as the CF_2H source under photoredox catalysis with the aid of $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$. Several aryl substituents were tolerated except the nitro group that was not compatible under the reaction conditions. A radical mechanism was evidenced through radical trapping experiments with detection of aryl-TEMPO adducts. The blue LEDs photoexcited $\text{fac-Ir}^{\text{III}}(\text{ppy})_3^*$ allowed to generate the CF_2H radical that reacted with the substrate to form the cyclopropylcarbinyl radical **A** and further ring-opening into radical **B**. Next, **B** cyclised into **C** and **C** was oxidised by $\text{fac-Ir}^{\text{IV}}(\text{ppy})_3$ into the cationic species **D** with release of $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$. In a final step, a deprotonation afforded the difluoromethylated 1,2-dihydronaphthalene scaffold. When diphenyl methylenecyclopropane was used as substrate, the dihydronaphthalene was not observed but instead the linear product corresponding to the capture of bromide anion was produced in 67% yield (Scheme 14).



Scheme 14 Visible-light-promoted functionalisation of methylenecyclopropanes.

In 2021, Wu's group developed a cascade visible-light-mediated radical difluoromethylation / cyclisation to synthesise variously decorated quinazolinones featuring a fused six-membered ring from *N*-alkenyl starting quinazolinones and difluoromethyltriphenylphosphonium bromide (Scheme 15).²⁶ Here again, the photocatalyst $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$ proved to be superior to $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, $[\text{Mes-Acr}^+]\text{ClO}_4^-$, and eosin Y that are inefficient in this

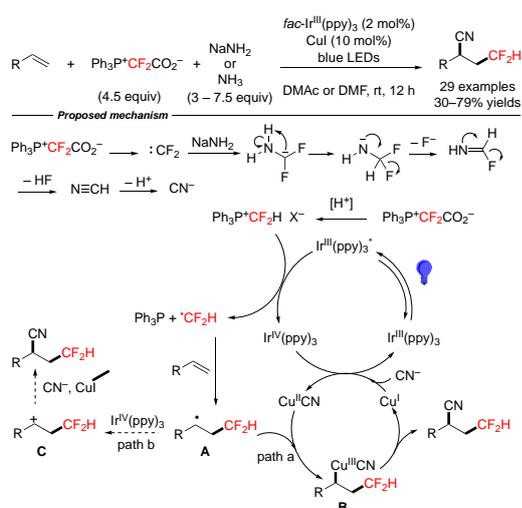
transformation. This protocol could be used in the preparation of pharmaceutically valuable difluoromethylated tricyclic quinazolinones by formation of a new five- to nine-membered fused-ring and even tetracyclic derivatives from substrates possessing an additional ortho substituted phenyl on the lateral chain. Mechanistic insights were obtained in reactions run in the presence of TEMPO and 1,1-diphenylethylene that led to considerably lower yields or absence of desired reactivity, respectively. The characterisation of radical trapping products was done by GC-MS. Moreover, On-Off experiments demonstrated that the products were formed only under visible-light irradiation. The photoexcited $\text{fac-Ir}^{\text{III}}(\text{ppy})_3^*$ reduced $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ to form the CF_2H radical together with the oxidant $\text{fac-Ir}^{\text{IV}}(\text{ppy})_3$ by single electron transfer. Next, attack of the CF_2H radical onto the terminal $\text{C}=\text{C}$ bond of the substrate gave radical **A** that cyclised into intermediate **B** and rearranged into the carbon radical **C** by 1,2-hydrogen shift. Then, oxidation of **C** by $\text{fac-Ir}^{\text{IV}}(\text{ppy})_3$ gave carbocation **D** and the final product after deprotonation.



Scheme 15 Photoredox radical difluoromethylation of unactivated alkenes / cyclisation.

Difluoromethylene phosphobetaine ($\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$, PDFA), which was previously developed for Wittig difluoroolefination could also deliver the CF_2H radical upon decarboxylation. In 2019, Xiao and co-workers reported the photocatalysed cyanodifluoromethylation of alkenes with $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$ in the presence of NaNH_2 or NH_3 (Scheme 16).²⁷ In this methodology, $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$ served not only as the CF_2H source but also as CN carbon source. As shown in Scheme 16, the cyanide anion was generated in situ under mild

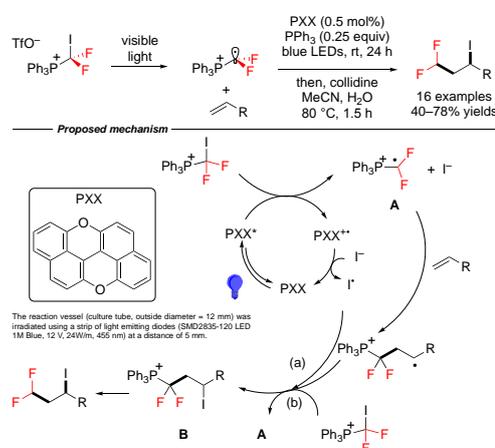
conditions, providing an eco-friendly and efficient procedure for the preparation of $\text{CF}_2\text{H}/\text{CN}$ -containing molecules. A copper source was crucial to allow the reaction to proceed and Cu(I) iodide was selected after screening various salts. It has been suggested that a Cu(II) cyanide was formed by oxidation with *fac*- $\text{Ir}^{\text{IV}}(\text{ppy})_3$ and it further reacts with radical intermediate **A** leading to the Cu(III) complex **B**. Reductive elimination offered the desired cyanodifluoromethylated product while regenerating Cu(I) . Path (a) was preferred to path (b) (Scheme 16) because no nucleophilic trapping of carbocation **C** was observed despite the presence of a good nucleophile (NaNH_2) in the reaction mixture.



Scheme 16 Photoredox radical cyanodifluoromethylation of alkenes.

In 2020, Dilman group proposed an elegant visible-light-induced iododifluoromethylation of terminal alkenes by means of iododifluoromethylphosphonium triflate. Activation of the C–I bond was accomplished by *peri*-xanthenoxanthene (PXX) under blue-light irradiation (Scheme 17).²⁸ Standard Ir- and Ru-photocatalysts gave 33% yield at the best whereas organic photocatalysts 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) and *N*-Ph-phenothiazine gave 46 and 19% yields, respectively. The reaction is large in scope as soon as the alkene is terminal and isolated from functional groups. Alkenes bearing nitrogen heterocycles and internal alkenes were ineffective in this approach under standard conditions. As showed in the proposed mechanism, the phosphonium-substituted radical **A** was formed via reductive cleavage of the C–I bond. Next, the key phosphonium **B** was generated through sequential addition on the double bond and acceptance of the

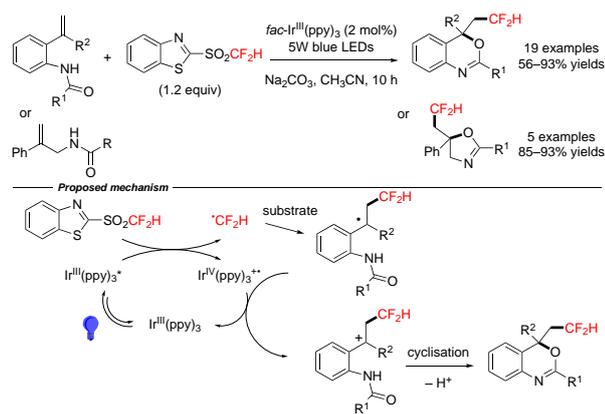
iodine radical formed concomitantly with the regeneration of PXX. Finally, the desired product was obtained under protodephosphorylative treatment of **B** with collidine and water.



Scheme 17 Visible-light-promoted iododifluoromethylation of alkenes.

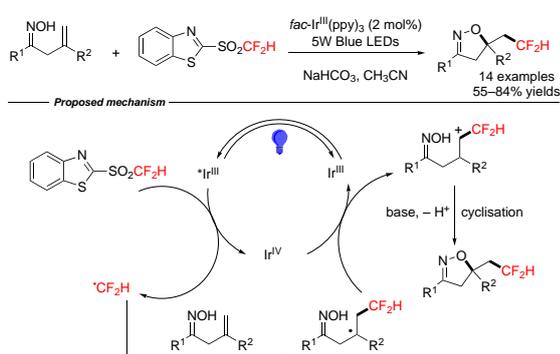
2.3. By means of (Het)ArSO₂CF₂H

Fluorinated sulfones have been developed as fluoroalkylating agents in several new constructions of highly valuable fluorine containing molecules. Although challenging, the radical difluoromethylation by $\text{HF}_2\text{C}-\text{SO}_2\text{R}$ cleavage was tamed notably under visible-light photoredox catalysis. In 2016, Fu and co-workers developed a photocatalysed radical oxydifluoromethylation of substrates bearing both an olefin and an amide function delivering a number of CF_2H -containing heterocycles, which include benzoxazines and oxazolines (Scheme 18).²⁹ By testing various CF_2H transfer reagents (e.g. difluoromethylsulfones and Hu's reagent (*N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine)), it was found that 2-[(difluoromethyl)sulfonyl]benzothiazole best performed as CF_2H radical source. The appropriate photocatalyst was here again *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ for its high reduction capacity in the excited state. Under blue LEDs irradiation, the excited state [*fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$]* was oxidised by the difluoromethyl sulfone to generate a [*fac*- $\text{Ir}^{\text{IV}}(\text{ppy})_3$]⁺ complex and the desired CF_2H radical. In this cascade radical addition and cyclisation process, the role of the sodium carbonate was to assist the final deprotonation toward difluoromethylated heterocycles (Scheme 18).



Scheme 18 Visible-light-promoted radical cascade difluoromethylation / cyclisation.

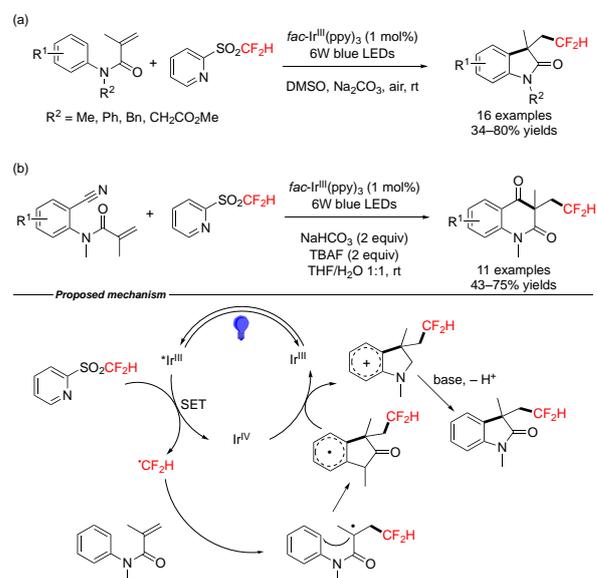
For another type of cascade difluoromethylation / cyclisation under identical conditions, Fun and co-workers in 2019 started from β , γ -unsaturated oximes and 2-[(difluoromethyl)sulfonyl]benzothiazole, which under blue LEDs irradiation furnished the corresponding isoxazoline derivatives in moderate to excellent yields (Scheme 19).³⁰ A radical mechanism was suggested based on literature precedence and authors' own observations.



Scheme 19 Visible-light-induced difluoromethylation of β , γ -unsaturated oximes.

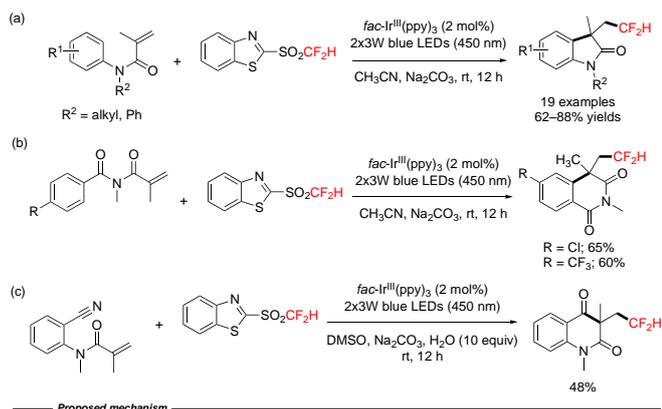
In 2019, Liu and co-workers utilised difluoromethyl 2-pyridyl sulfone as CF_2H radical source in the tandem radical addition/cyclisation of *N*-arylacrylamides (Scheme 20).³¹ With assistance of visible light, two libraries of difluoromethylated 2-oxindoles (Scheme 20a) and quinoline-2,4-diones (Scheme 20b) featuring a range of functional groups were prepared in moderate to good yields under mild conditions. In the former case the radical intermediate cyclised on the aryl ring while in the latter case the cyclisation occurred at the nitrile substituent. For quinoline-2,4-dione synthesis, water realised the final imine hydrolysis as demonstrated in an

experiment with H_2^{18}O and incorporation of ^{18}O into the final product. Sodium bicarbonate was the appropriate base and *tetra*-butyl ammonium fluoride (TBAF) was suggested to act as phase-transfer catalyst.

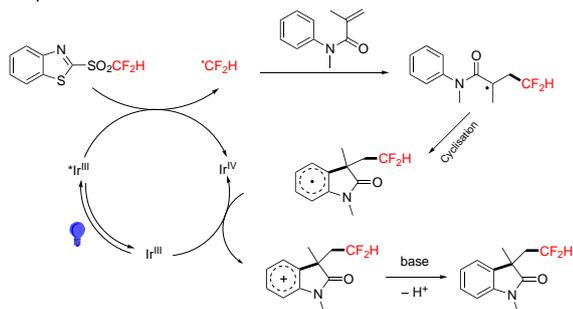


Scheme 20 Visible-light-promoted tandem radical cyclisation of *N*-arylacrylamides.

A few months later, Zhu and co-workers employed 2-[(difluoromethyl)sulfonyl]benzothiazole instead of difluoromethyl 2-pyridyl sulfone for basically the same radical difluoromethylation and cyclisation of *N*-arylacrylamides (Scheme 21).³² Under photoredox catalysis, a set of CF_2H -containing heterocycles was prepared from mainly *N*-arylacrylamides (Scheme 21a) but also from two methacryloyl benzamides (Scheme 21b) and one *ortho*-cyano arylacrylamide (Scheme 21c).

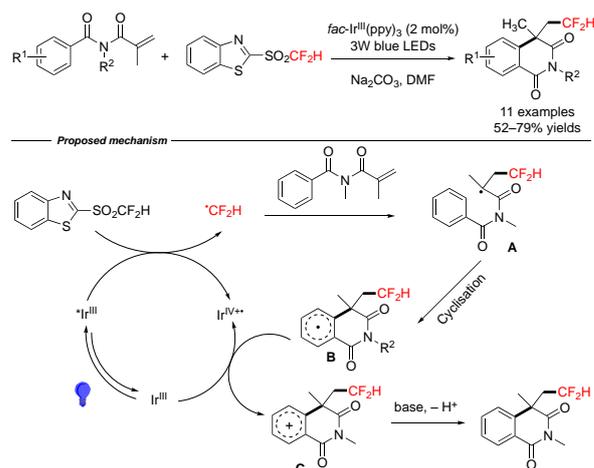


Proposed mechanism



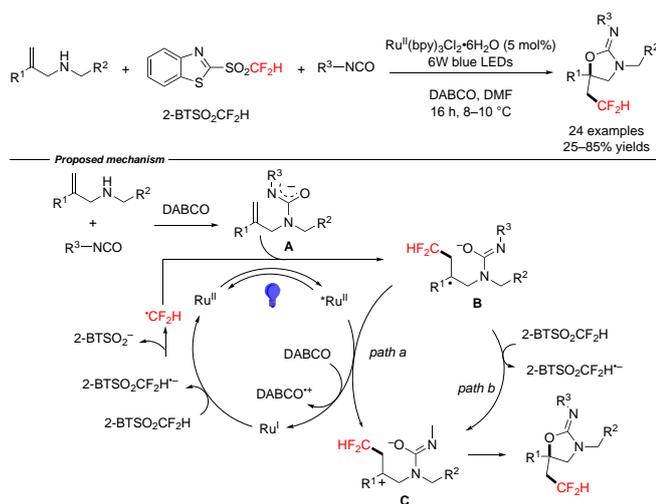
Scheme 21 Synthesis of CF₂H-containing heterocycles starting from *N*-arylacrylamides.

In fact, the reaction of *N*-methacryloyl benzamides was introduced earlier in 2017 by Zou group. A visible-light-promoted difluoromethylation / cyclisation was developed to access CF₂H-containing isoquinoline-1,3(2*H*,4*H*)-diones through a mild radical process (Scheme 22).³³ Optimisation of the reaction conditions led to the selection of 2-[(difluoromethyl)sulfonyl]benzothiazole as CF₂H radical precursor and *fac*-Ir^{III}(ppy)₃ as photocatalyst. The reaction accommodated both electron-withdrawing and electron-donating substituents regardless of their position on the phenyl ring. However, an unprotected methacryloyl benzamide was not suitable in this synthetic approach. In the proposed mechanism, the intermediate **B** was generated through intramolecular cyclisation on the aromatic ring of intermediate **A**. Then, **B** was oxidised by [*fac*-Ir^{IV}(ppy)₃]⁺ to afford the key cyclohexadienyl cation **C** and regenerating the photocatalyst. Finally, the heterocyclic product was formed through deprotonation of cation **C** with the assistance of sodium carbonate.



Scheme 22 Synthesis of CF₂H-containing isoquinolinediones.

In 2020, Sheng group described an interesting general three-component tandem reaction from aryl allylamines, 2-[(difluoromethyl)sulfonyl] benzothiazole and isocyanates affording various difluoromethylated oxazolidin-2-imines under mild conditions (Scheme 23).³⁴ The oxazolidin-2-imine skeleton exists in biologically active compounds as well as in several useful synthetic intermediates. It is noteworthy that Ru^{II}(bpy)₃Cl₂·6H₂O was superior to *fac*-Ir^{III}(ppy)₃ for which a 28% lower yield was measured. With regard to the base, DABCO in DMF gave better yields. A radical reaction mechanism was proposed; it was argued by experiments and quantum chemical calculations. The photo excited Ru^{II*} was reduced by DABCO into Ru^I that triggered 2-[(difluoromethyl)sulfonyl] benzothiazole to deliver CF₂H radical. In parallel, the condensation of allylamine with isocyanate gave intermediate **A**, which reacted with the CF₂H radical to give radical **B**. **B** is further oxidised by Ru^{II*} (path a) and/or react with 2-[(difluoromethyl)sulfonyl] benzothiazole through a single electron transfer reaction to generate the carbocation **C** (path b). Finally, the cyclisation of **C** ended up with the desired difluoromethylated oxazolidin-2-imines (Scheme 23).

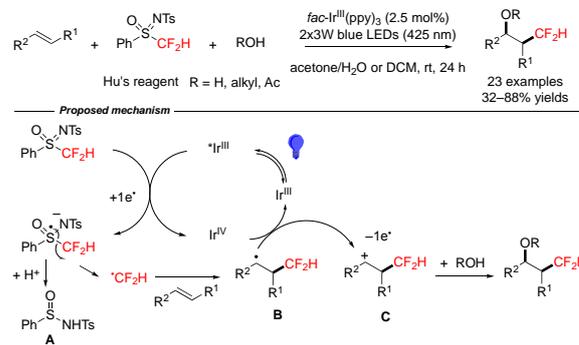


Scheme 23 Visible-light-promoted three-component tandem reaction.

2.4. By means of *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (Hu's reagent)

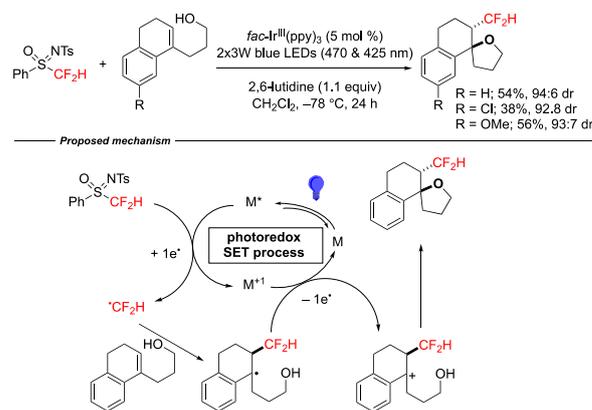
N-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (Hu's reagent) was initially developed as a useful source of difluorocarbene for the difluoromethylation of diverse nucleophiles. Akita, Koike and co-workers employed Hu's reagent as CF₂H radical precursor under visible-light conditions in the regioselective oxydifluoromethylation of alkenes in order to access various CF₂H-substituted alcohols, ethers and esters (Scheme 24).³⁵ The optimised protocol exhibited great functional group compatibility in the presence of photocatalyst *fac*-Ir^{III}(ppy)₃. Other photocatalysts such as [Ru^{II}(bpy)₃][PF₆]₂ and [Ir^{III}(ppy)₂(dtbbpy)][PF₆] failed to produce the desired CF₂H radical. The reaction did not work in the dark nor in the absence of photocatalyst. The reactions were carried out in acetone and water to provide CF₂H-substituted alcohols and in DCM / alcohol or AcOH to end up with CF₂H-substituted ethers or esters, respectively. Mechanistic insights were obtained allowing to propose a reaction mechanism (Scheme 24). First, the photocatalyst *fac*-Ir^{III}(ppy)₃ was excited by the blue LEDs to give the excited species [*fac*-Ir^{III}(ppy)₃]* that served as strong one-electron reductant to undergo single-electron transfer to Hu's reagent concomitantly to the generation of the oxidised species [*fac*-Ir^{IV}(ppy)_{3]⁺. Reduced Hu's reagent fragmented into the CF₂H radical and sulfinamide **A**. Then, CF₂H radical reacted with the alkene substrate in a regioselective fashion to give the stabilised radical intermediate **B**, which was then oxidised by [*fac*-Ir^{IV}(ppy)₃]⁺ to generate the CF₂H carbocationic intermediate **C** together with regeneration of the ground}

state photocatalyst. In a final operation, the carbocationic intermediate **C** underwent solvolysis by ROH to afford oxydifluoromethylated products.



Scheme 24 Synthesis of CF₂H-containing alcohols, ethers and esters.

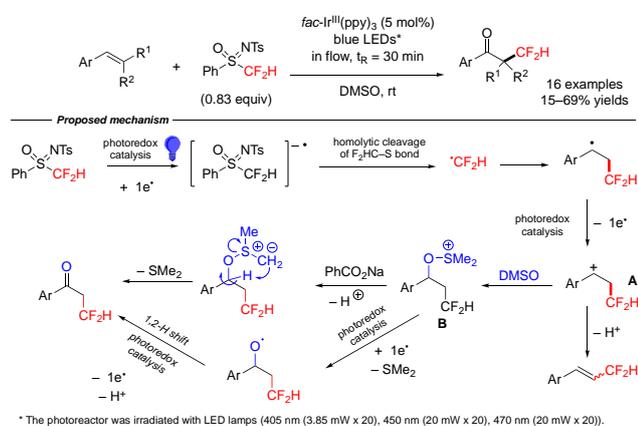
The same year, the same group reported a photoredox catalysed difluoromethylation of aryl-fused cycloalkenylalkanols allowing highly diastereoselective access to *anti*-CF₂H-containing spiroethers using Hu's reagent as CF₂H radical source (Scheme 25).³⁶ As showed in the plausible reaction mechanism, an *anti*-fashion intramolecular nucleophilic attack of the key carbocation intermediate by alcohol afforded *anti*-difluoromethylated spiroethers presumably because the nucleophilic attack is favored through the opposite side of the electronegative fluoromethyl group.



Scheme 25 Diastereoselective visible-light-promoted radical synthesis of CF₂H-substituted spiroethers.

Akita, Koike and co-workers further reported in flow blue LEDs-induced keto-difluoromethylation of readily available alkenes delivering a wide range of α -CF₂H-substituted ketones in good yields in a residence time of 30 min (Scheme 26).^{9b} A combination of Hu's reagent

(source of $\cdot\text{CF}_2\text{H}$), DMSO (source of oxygen) and *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ (source of strong oxidant $\text{Ir}^{\text{IV}}(\text{ppy})_3^{+*}$) was found optimal under blue LEDs irradiation. Base-free conditions are fine in most cases; however, added sodium benzoate improved the yields in tougher cases though a Kornblum oxidation. Electrochemical analysis, laser flash photolysis and DFT calculations demonstrated that Hu's reagent was the best difluoromethylation reagent by comparison with other sulfone-based CF_2H reagents. Mechanistic studies suggested the key alkoxysulfonium intermediate **B** was generated through nucleophilic attack of intermediate **A** by DMSO rather than a deprotonation. Then, the desired product was reached from intermediate **B** through two possible pathways: via Kornblum-type oxidation or via a second single electron transfer photoredox process (Scheme 26).



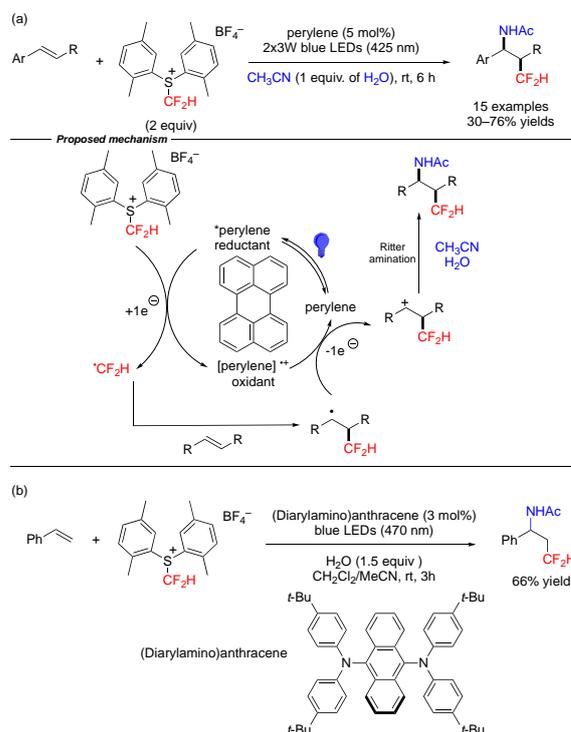
Scheme 26 Visible-light-induced keto-difluoromethylation of alkenes.

2.5. By means of diaryl(difluoromethyl)sulfonium salts

In 2017, Akita, Koike and co-workers designed the novel *S*-(difluoromethyl)-*S*-di(*p*-xylyl)sulfonium reagent that was engaged in a visible-light-mediated metal-free amino-difluoromethylation of styrenic alkenes. With this objective in mind, perylene as organic photocatalyst was explored under blue LEDs irradiation. In the studied reaction, perylene exhibited high efficiency owing to its high excited state energies while noble metal Ir catalyst gave only 29% yield. In this approach, *S*-difluoromethyl-*S*-di(*p*-xylyl)sulfonium tetrafluoroborate, as CF_2H radical source, was perfectly compatible with the perylene photocatalysis. A Ritter amination by means of acetonitrile afforded a variety of β - CF_2H substituted amines with excellent regioselectivity under mild conditions (Scheme 27a).³⁷

Conversely, CF_2H -containing alkenes were generated when α -substituted styrenes were used as substrates. Styrenic substrates, regardless of electron-withdrawing, -neutral, -donating groups in the aromatic rings, are good substrates as well as an estrone derivative albeit giving a lower yield.

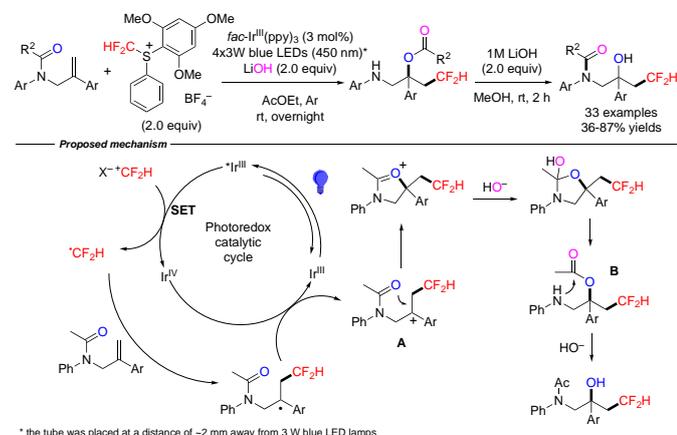
A year after, the same group gave one example using 9,10-bis(di-*p*-*tert*-butylphenyl)aminoanthracene as a photocatalyst for the amino-difluoromethylation of styrene (Scheme 27b).³⁸ This newly designed photocatalyst features high reducing power and efficient absorption capability of visible light, giving an expand dimension of photocatalyst design and exploration in many reactions.



Scheme 27 Perylene-catalysed amino-difluoromethylation of alkenes.

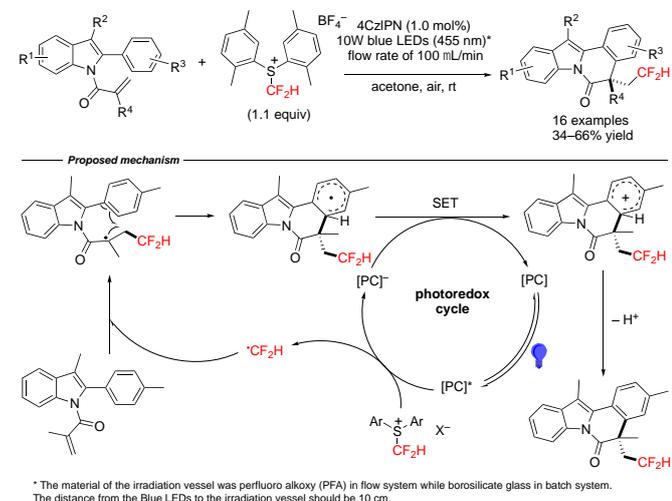
In 2021, Liu and co-workers described the oxydifluoromethylation of *N*-allyl amides with *S*-(difluoromethyl)sulfonium salt under photoredox catalysis with the aid of 3 mol% of *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ (Scheme 28).³⁹ Under the optimum conditions, a variety of CF_2H - β -amino alcohols were obtained in good to excellent yields. Mechanistic investigations demonstrated that a sequential process of difluoromethyl radical addition, oxidation, intramolecular carbocation trapping and rearrangement reaction was involved. The carbocation species **A** underwent cascade intramolecular trapping by the

carbonyl group, addition reaction of hydroxide ion and ring-opening rearrangement to afford intermediate **B**. Finally, the desired product was formed through intramolecular transesterification process (Scheme 28).



Scheme 28 Oxydifluoromethylation of *N*-allylamides.

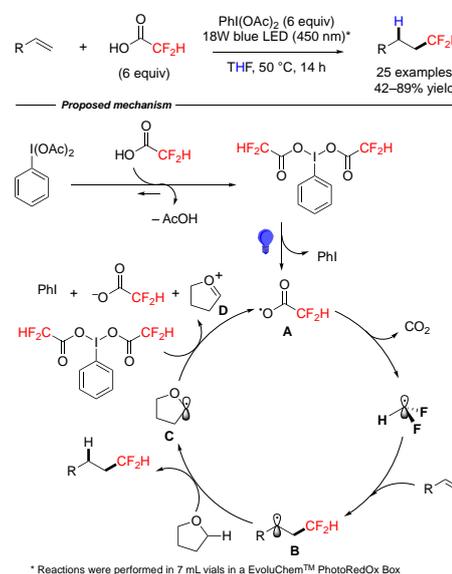
In 2021, Guo, Qiu and co-workers developed the visible-light-triggered difluoromethylation cyclisation of indole derivatives for the construction of various decorated CF₂H-containing indole[2,1-*a*]isoquinoline derivatives. The reaction was conducted in continuous flow under blue LEDs irradiation in the presence of the organic photocatalyst (4*s*,6*s*)-2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN). All other conditions being equal, *fac*-Ir^{III}(ppy)₃ provided lower yields. As CF₂H radical precursor, Akita's *S*-difluoromethyl-*S*-di(*p*-xylyl)sulfonium salt was employed. This metal-free photocatalysis in continuous flow has shown great functional group compatibility and is amenable for scale-up reactions (Scheme 29).⁴⁰



Scheme 29 Organo-photocatalysed carbodifluoromethylation of α,β -unsaturated amides.

2.6. By means of PhI(OCOCHF₂)₂

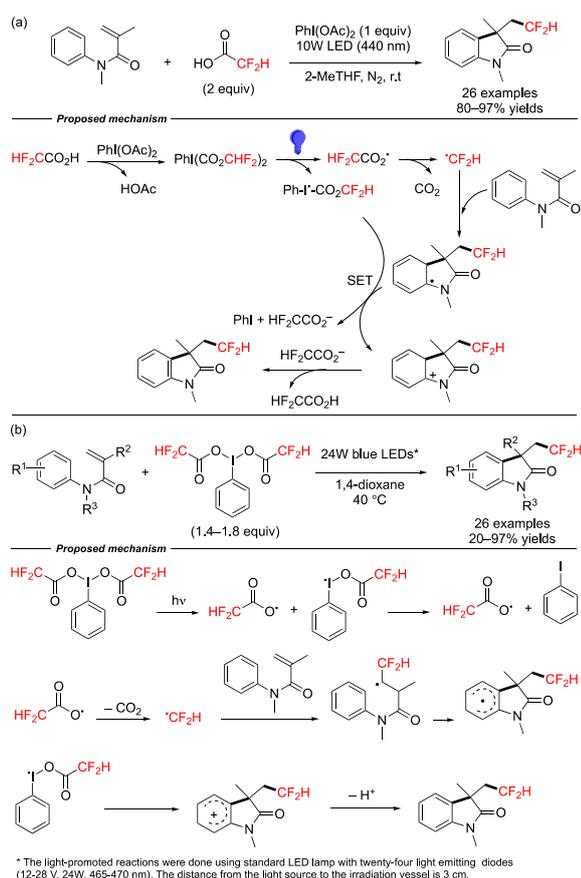
Encouraged by pioneering Maruoka's efficient photolytically induced difluoromethylation of heteroarenes by means of hypervalent iodine(III) reagents (see Scheme 38), Gouverneur and co-workers further described the visible-light-induced hydrodifluoromethylation of alkenes by difluoroacetic acid in the presence of phenyliodine(III) diacetate (PIDA) (Scheme 30).⁴¹ A major feature is that this reaction proceeds without photocatalyst. Mechanistic investigations suggested a radical-based reaction. The reaction starts with an exchange of acetate groups on PIDA with difluoroacetic acid. Then, exposure to the blue LEDs releases PhI and radical **A** that move towards the CF₂H radical through decarboxylation. The radical adds regioselectively to the alkene substrate to generate radical **B** intermediate, which abstracts a hydrogen atom from THF to afford the hydrodifluoromethylated product. Then, THF radical **C** possibly undergoes SET with [bis(difluoroacetoxy)iodo]benzene with release of radical **A**, for further alkene functionalisation, and side-products PhI, oxonium ion **D** and difluoroacetate (Scheme 30).



Scheme 30 Photocatalyst-free visible-light-induced hydrodifluoromethylation of alkenes.

Following the same procedure, He and co-workers synthesised a set of difluoromethylated oxindoles from *N*-arylacrylamides (Scheme 31a).⁴² The authors

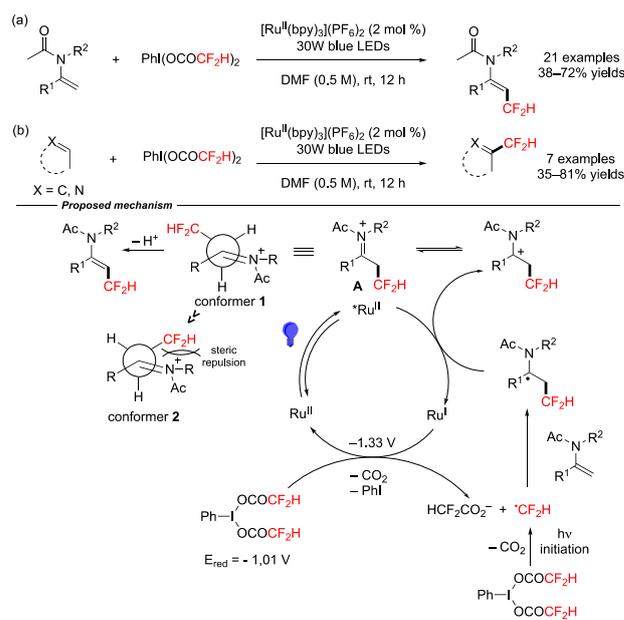
succeeded in using just a stoichiometric amount of PIDA and difluoroacetic acid. This eco-friendly procedure was promoted under very mild conditions by visible light in the absence of any additive, base, metal or external photosensitiser. A radical mechanism was established after control experiments with radical scavengers (TEMPO and BHT) have been carried out. On-Off experiments demonstrated that the products were formed only under light irradiation. Here, the solvent 2-MeTHF did not seem to participate in a SET operation, the radical intermediate **B** being oxidised by the iodine radical **A** (Scheme 31). Simultaneously to this work, the group of Lu presented an approach directly using [bis(difluoroacetoxy)iodo]benzene instead of the combination of the two components that are PIDA and difluoroacetic acid. A thorough study of the light source and solvent resulted in the choice of 24W blue LEDs in 1,4-dioxane. Under these conditions, a wide range of difluoromethyl substituted oxindoles was prepared (Scheme 31b).⁴³



Scheme 31 Photocatalyst-free visible-light-induced synthesis of difluoromethylated oxindoles.

The same year, in 2021, Wu and co-workers reported a photoredox-induced direct difluoromethylation of

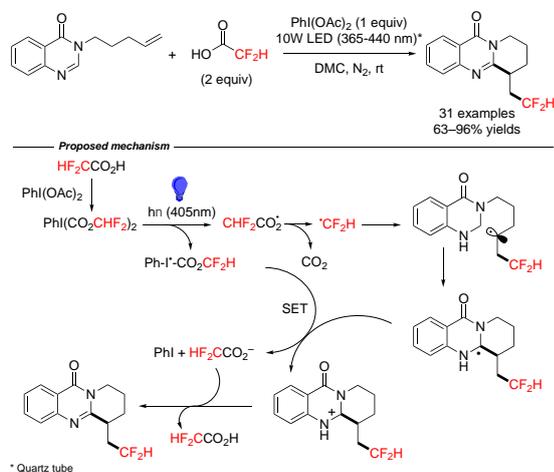
enamides and heterocycles by means of [bis(difluoroacetoxy)iodo]benzene as the CF_2H source and $[\text{Ru}(\text{bpy})_3][\text{PF}_6]_2$ as the optimum photocatalyst. Unlike previous examples, with these substrate types the reaction failed in absence of photocatalyst or in the dark. With enamides, the reaction was regio- and stereoselective leading to a number of (*E*)- β -difluoromethylated enamides in moderate to excellent yields (Scheme 32a).⁴⁴ This convenient and practical radical difluoromethylation protocol was extended to some heterocycles (Scheme 32b) and was applied for the gram-scale synthesis of a precursor of the non-steroidal anti-inflammatory drug piroxicam. The author speculated that the stereoselectivity of this transformation could be explained by the conformational analysis of the key iminium ion intermediate **A**. Product *E*-isomer was the preferential one because conformer **1** was more favorable in contrast to conformer **2** in view of steric repulsion. A reductive quenching cycle was proposed in which the Ru^{II} [$E_{1/2}(\text{Ru}^{\text{II}}/\text{Ru}^{\text{I}}) = -1.33 \text{ V vs SCE}$ in MeCN] was re-oxidised by $\text{PhI}(\text{O}_2\text{CCF}_2\text{H})_2$ (-1.01 V vs SCE in MeCN).



Scheme 32 Visible-light-induced difluoromethylation of enamides and heterocycles.

Very recently, in 2022, He and co-workers presented a visible-light-induced cascade difluoromethylation and cyclisation reaction of alkenyl-substituted quinazolinones for the preparation of a set of CF_2H -containing ring-fused quinazolinones, a scaffold widely present in biologically and pharmaceutically active molecules. Using difluoroacetic acid combined with PIDA as the CF_2H radical precursor, this eco-friendly

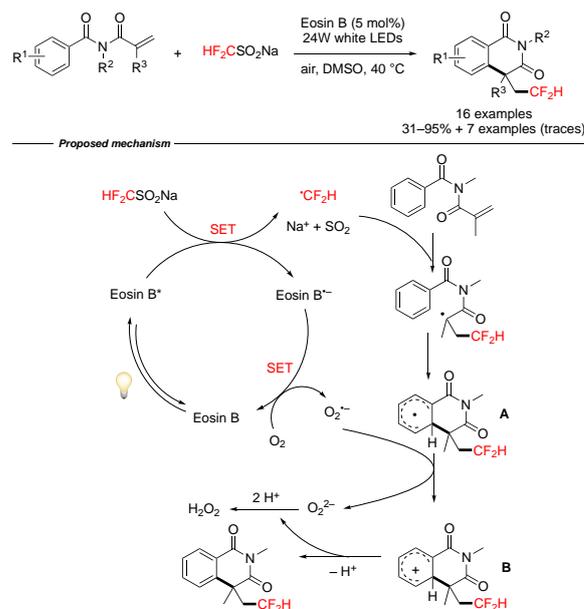
approach carried out in dimethyl carbonate (DMC) as the sole solvent exhibited great functional group tolerance under mild conditions without external photosensitiser (Scheme 33).⁴⁵



Scheme 33 Photoredox synthesis of CF_2H -substituted ring-fused quinazolinones.

2.7. By means of $\text{HF}_2\text{CSO}_2\text{Na}$

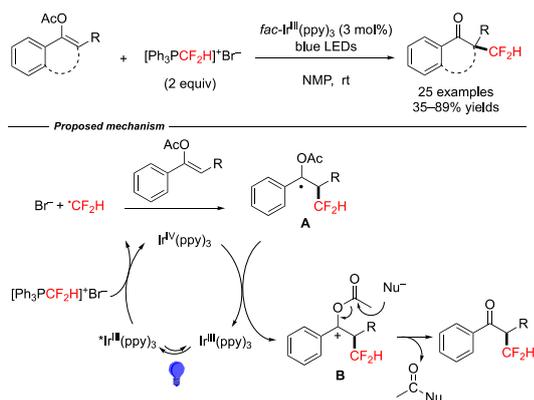
Sodium difluoromethanesulfinate was synthesised for the first time in 2015. In 2021, Deng and co-workers reported a visible-light-induced radical difluoromethylation / cyclisation reaction of *N*-benzamides using now commercially available $\text{HF}_2\text{CSO}_2\text{Na}$ as difluoromethylation reagent (Scheme 34).⁴⁶ Several CF_2H -containing isoquinoline-1,3-diones were prepared and limitations of the method were provided from seven substrates that failed to give significant amounts of the desired products. It is a metal-free air-promoted process in which Eosin B plays the role of photocatalyst. When the reaction was catalysed by Eosin Y or *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$, lower isolated yields of product were observed. **In this reaction, the electron-rich $\text{HF}_2\text{CSO}_2\text{Na}$ is the $\text{HF}_2\text{C}\cdot$ donor and allows an oxidative quenching cycle of Eosin B.** Mechanistic studies provided information on the role of air as oxidant in the reaction system. The reduced Eosin $\text{B}^{\cdot-}$ was oxidised by O_2 into Eosin B allowing the photocatalytic cycle while $\text{O}_2^{\cdot-}$ served to convert radical intermediate **A** into the carbocation **B**, which after deprotonation released the product. The oxidation of **A** resulted in the formation of O_2^{2-} and finally H_2O_2 after proton capture.



Scheme 34 Visible-light-induced difluoromethylation / cyclisation of *N*-benzamides.

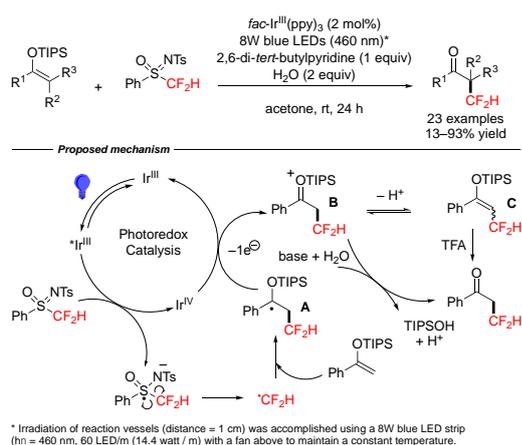
3. Difluoromethylation of enol acetates and silyl enol ethers

The $\text{C}=\text{C}$ double bond in enol derivatives has a distinctive reactivity in radical additions and it allows to target α -substituted carbonyl compounds. Based on the application of difluoromethyltriphenyl phosphonium bromide as a radical precursor, Wang's group reported in 2021 a novel visible-light-induced radical difluoromethylation reaction of aromatic enol acetates using *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ photocatalyst (Scheme 35).⁴⁷ Various α - CF_2H -substituted ketones were obtained in moderate to high yields under mild conditions. As shown earlier in the text (section 2.2), excited *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3^*$ is able to reduce $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$ to a CF_2H radical with formation of radical **A** and *fac*- $\text{Ir}^{\text{IV}}(\text{ppy})_3$. **A** was then oxidised into carbocation **B** with regeneration of *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$. The desired products were obtained through a nucleophilic attack of key intermediate **B** by nucleophilic species.



Scheme 35 Photoredox radical difluoromethylation of enol acetates.

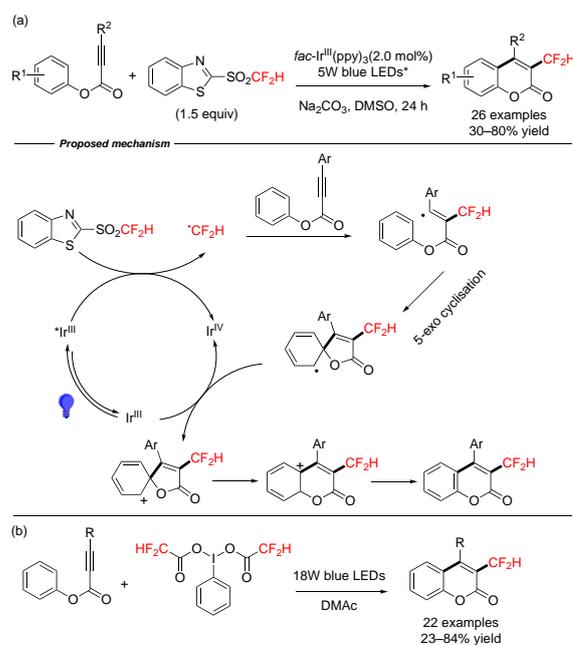
The same year, Arseniyadis and co-workers applied the visible-light-catalysed difluoromethylation on easily available silyl enol ethers using Hu's reagent as CF_2H radical precursor and $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$ photocatalyst (Scheme 36).⁴⁸ The protocol is practical and readily scalable under continuous flow conditions; it offers various $\alpha\text{-CF}_2\text{H}$ substituted arylketones in good to excellent yields. Alas, extension to alkyl ketones could not be applied. Mechanistic investigations done with radical scavengers, fluorescence quenching experiments and DFT calculations led the authors to propose the mechanism detailed in Scheme 36. In particular, the ketyl radical **A** was oxidised by $\text{Ir}^{\text{IV}}(\text{ppy})_3$ to give the silyloxonium **B**, which was converted into the desired ketone either through desilylation assisted by the base as proton acceptor or via α -deprotonation of the silyloxonium species **B** giving silyl enol ether **C**, which was observed and quenched with TFA.



Scheme 36 Photoredox radical difluoromethylation of silyl enol ethers.

4. Difluoromethylation of alkynes

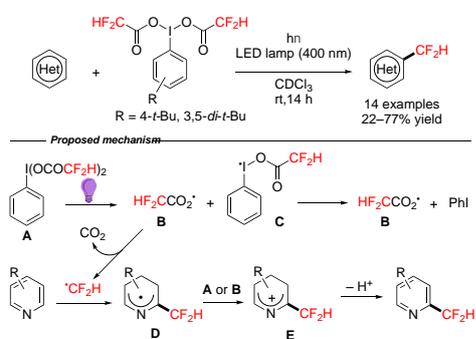
In the last decade, much efforts have been devoted to the direct difluoromethylation of alkenes under photocatalysis to afford an array of novel CF_2H -containing compounds. However, the direct introduction of CF_2H group into alkynes remains scarce. In 2017, Zhu and co-workers developed an efficient visible-light-induced direct difluoromethylation of alkynoates, giving 3-difluoromethylated coumarins in moderate to excellent yields (Scheme 37a).⁴⁹ The method employs difluoromethyl sulfone as easily accessible CF_2H radical precursor in a photoredox catalytic system. One more time $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$ photocatalyst proved to be superior to Ru-based ones. The overall process is a three-step cascade difluoromethylation / 5-exo cyclisation / ester migration ending up with the difluoromethylated heterocyclic scaffold. Coumarins are pivotal structural motifs widely present in biologically active and natural products. In 2021, Lu and co-workers reported an alternative synthesis of difluoromethylated coumarins from alkynoates under visible light irradiation without photocatalyst thanks to the use of [bis(difluoroacetoxy)iodo]benzene as source of spontaneously formed CF_2H radical (see also section 2.6) (Scheme 37b).⁵⁰ This approach is an eco-friendly alternative for the generation of fluorine-containing coumarins under mild and catalyst-free conditions. Apart the generation of CF_2H radical that is different, the subsequent steps of the mechanism are identical to the one outlined by Zhu (Scheme 37a).



Scheme 37 Visible-light-mediated difluoromethylation of alkynoates.

5. Difluoromethylation of (het)arenes

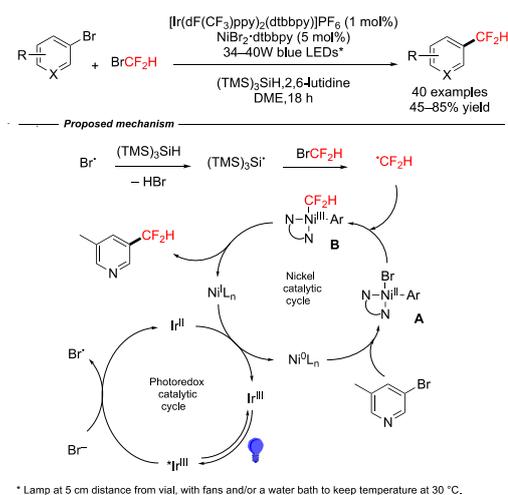
The pioneering work by Baran group in 2012 described the first direct radical difluoromethylation of nitrogen-containing heteroarenes employing zinc bis(difluoromethanesulfinate) and oxidising agent *tert*-butyl hydroperoxide.⁵¹ It is only in 2017 that a photocatalytic difluoromethylation of heteroarenes was developed by Maruoka and co-workers by means of the hypervalent iodine(III) reagent [bis(difluoroacetoxy)iodo]benzene under visible-light irradiation without any additional catalyst. The method was successfully applied to get difluoromethylated pyrimidines, pyridazines, pyrazines, triazines, and pyrazoles in moderate to good yields (Scheme 38).⁵² In this radical process, CF₂H radical was generated from the photodecomposition of hypervalent iodine(III) reagent featuring difluoroacetoxy ligands in the absence of additional reagent via radical **B** and iodanyl radical **C** followed by decarboxylation. The difluoromethyl radical subsequently reacted with heteroarenes to generate a radical intermediate **D**. The oxidation of **D** by **A** or iodanyl radical **C** gave the carbocation intermediate **E**, which furnished the desired product after proton elimination.



Scheme 38 Catalyst-free visible-light-promoted difluoromethylation of heteroarenes.

MacMillan and co-workers were the first to report on a metallaphotoredox difluoromethylation of aryl and heteroaryl bromides giving the respective difluoromethylated products. The method is characterised by moderate to high yields with a great functional group compatibility (Scheme 39).^{9a} Of particular interest, the late stage difluoromethylation of four pharmaceutical agents was reported. The metallaphotoredox process consisted of two catalytic

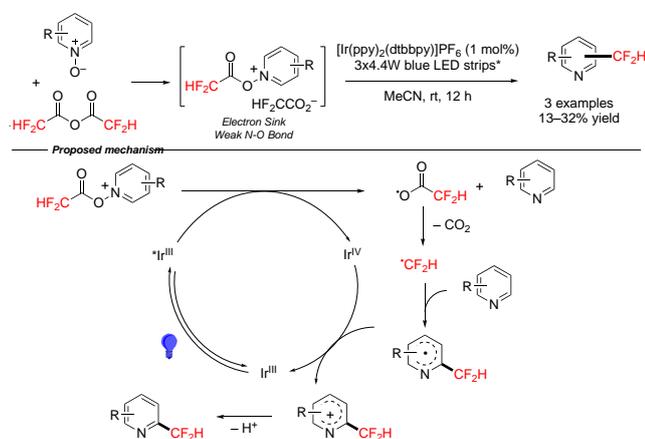
cycles in a dual nickel / photoredox-catalysed coupling procedure. Visible-light excitation of [Ir(dF(CF₃)ppy)₂(dtbbpy)][PF₆] photocatalyst generated the excited-state *Ir^{III} complex, which readily oxidised bromide anion into bromine radical. Then, Br[•] abstracted a hydrogen atom on (TMS)₃SiH to yield the nucleophilic silyl radical responsible for bromine abstraction from bromodifluoromethane with concomitant formation of the key difluoromethyl radical. At the same time, insertion of Ni⁰ catalyst in the C–Br bond of the aryl bromide substrate gave Ni^{II}–aryl intermediate **A**, which trapped the difluoromethyl radical and generated the corresponding aryl–Ni^{III}–CF₂H complex **B**. A further reductive elimination afforded the expected difluoromethyl heteroarene product and Ni^I species. Finally, a single electron transfer between the Ni^I species and reduced photocatalyst Ir^{II} regenerated Ni⁰ catalyst and ground-state Ir^{III} photocatalyst. Later in 2021, Zhang and co-workers corroborated the mechanism of this dual catalysis process through density functional theory-based computational study. The reductive quenching cycle (Ir^{III}/*Ir^{III}/Ir^{II}/Ir^{III}) and the Ni⁰-initiated catalytic cycle were confirmed.⁵³



Scheme 39 Metallaphotoredox difluoromethylation of aryl bromides.

Electron-deficient heterocyclic *N*-oxides as redox auxiliaries could activate carboxylic acid derivatives such as anhydrides or acyl chlorides by inducing reductive decarboxylation and radical formation. This approach was applied in 2018 by Stephenson and co-workers with commercially available difluoroacetic anhydride for the visible-light-promoted intramolecular fragment-coupling decarboxylative difluoromethylation of biologically relevant heterocyclic scaffolds (Scheme 40).⁵⁴ Depending on the substitution patterns of the

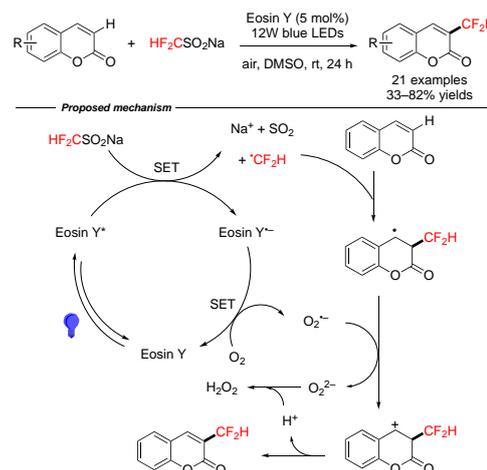
heterocycle, 2- or 4-CF₂H regioisomers were obtained. Although applied to only three examples of difluoromethylated products, this approach was primarily developed as a general alkylation method taking advantage of readily available carboxylic acid derivatives as alkylating agents.



* The light apparatuses used to irradiate the reactions were constructed from test tube racks and wrapped with three 4.4W blue LED strips. Reaction distances from the light source (~2.5 cm). At this distance the temperature of the reactions did not exceed 35 °C.

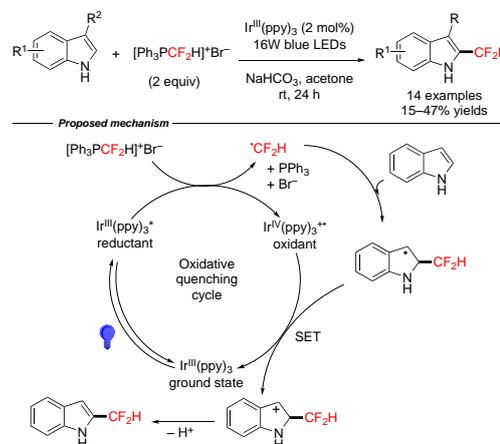
Scheme 40 Visible-light-induced decarboxylative fragment-coupling difluoromethylation of heterocyclic *N*-oxides.

Coumarin and its derivatives are naturally occurring molecules used in medicine, in laser dyes and in the perfume industry. Their structural modification with fluorine moieties was reported. With respect to difluoromethylation, Deng, Zhang and co-workers carried out Csp²-H radical difluoromethylation of coumarins with sodium difluoromethanesulfinate HF₂CSO₂Na promoted by visible-light and 5 mol % of Eosin Y (Scheme 41).⁵⁵ Under the optimised reaction conditions, a broad range of 3-difluoromethylcoumarins were obtained in good yields with great functional group compatibility. Mechanistic studies indicated that O₂, serving as oxidant, was essential for this reaction to proceed. Promising antifungal activity was identified for one representative example.



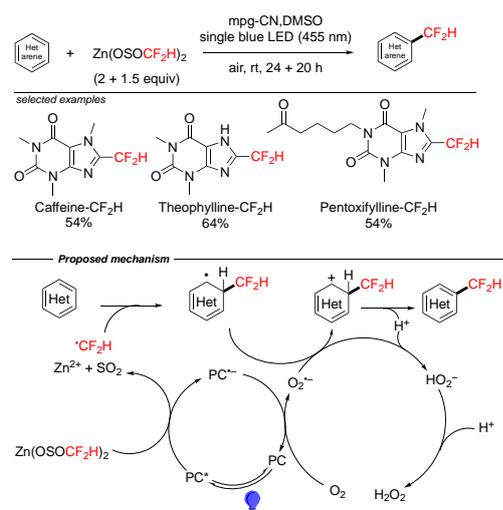
Scheme 41 Visible-light- and oxygen-promoted difluoromethylation of coumarins.

Indoles are important heterocycles commonly encountered in bioactive natural products and pharmaceuticals. The regioselective functionalisation of indoles by fluorinated motifs is of great interest. In 2019, Dolbier and co-workers developed an efficient visible-light-promoted difluoromethylation of 3- and 3,5-substituted indoles affording regioselectively various 2-difluoromethyl indoles in low to moderate yields (Scheme 42).⁵⁶ In this protocol, easily accessed [Ph₃PCF₂H]⁺Br⁻ was employed as CF₂H radical precursor under mild conditions. Experimental studies revealed that photocatalyst and visible light were essential in this radical process. Of several Ir-, Ru- and Cu-based photocatalysts *fac*-Ir^{III}(ppy)₃ was determined to give the better reaction yields. With respect to the CF₂H radical donor, HF₂CSO₂Cl and difluoromethyl sulfonyl benzothiazole gave lower yield or trace amount of product, respectively.



Scheme 42 Photoredox catalysed synthesis of 2-difluoromethyl indoles.

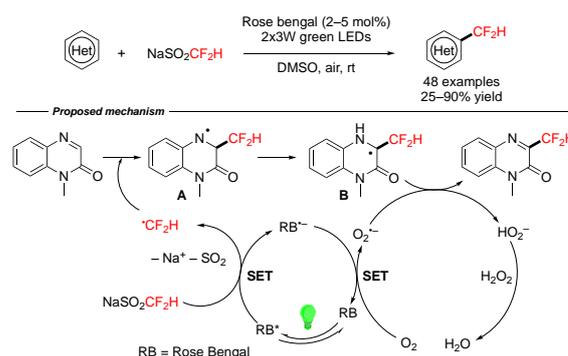
König, Antonietti and co-workers accomplished the photocatalytic difluoromethylation of heteroarenes using zinc bis(difluoromethanesulfinate) as CF_2H radical precursor in 2019 (Scheme 43).⁵⁷ In this reaction, an organic semiconductor mesoporous graphitic carbon nitride (mpg-CN) acted as efficient heterogeneous photoredox catalyst, which could be easily recovered from reaction mixture with retained activity. Exclusion of light, oxygen, or mpg-CN resulted in much lower yields. The related CF_2H -containing caffeine, theophylline, pentoxifylline derivatives were obtained through this method in moderate yields.



Scheme 43 Organic semiconductor photocatalyst in the difluoromethylation of heteroarenes.

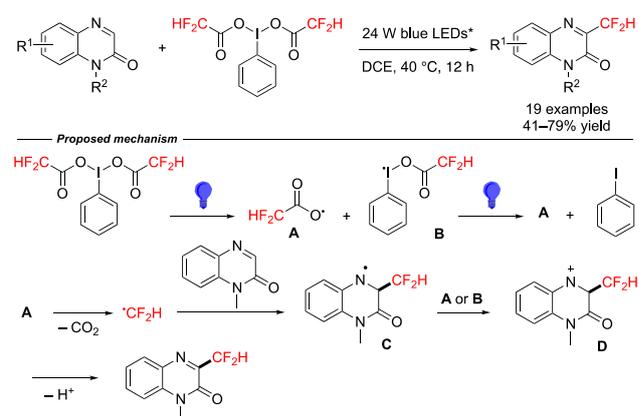
In 2020, Li, Meng and co-workers described the direct C–H difluoromethylation of a wide range of heterocycles under organic photoredox catalysis (Scheme 44).⁵⁸ In this method, Rose Bengal outperformed light-absorbing metal complexes and other organic photocatalysts such as Eosin Y and acridinium salts. Sodium difluoromethanesulfinate was chosen as CF_2H source and O_2 as a green oxidant. This approach provides an efficient alternative strategy to access nitrogen-containing biologically active molecules. Note that the reaction of 1-methyl quinoxalin-2-one with $\text{HF}_2\text{CSO}_2\text{Na}$ can also be conducted under sunlight instead of green LEDs. Light On / light Off experiment ruled out a radical chain propagation mechanism. Upon photoexcitation of Rose Bengal, one electron was transferred from sodium difluoromethanesulfinate to form the radical anion $\text{RB}^{\cdot-}$ and the CF_2H radical, which reacted with the substrate and afforded intermediate **A**. Then, molecular oxygen oxidised $\text{RB}^{\cdot-}$ to complete the photoredox cycle releasing RB and $\text{O}_2^{\cdot-}$. Nitrogen radical **A** underwent a 1,2-hydrogen shift to form

carbon radical intermediate **B** that eliminated a hydrogen atom to afford the desired product.



Scheme 44 Organic photocatalyst in difluoromethylation of heteroarenes.

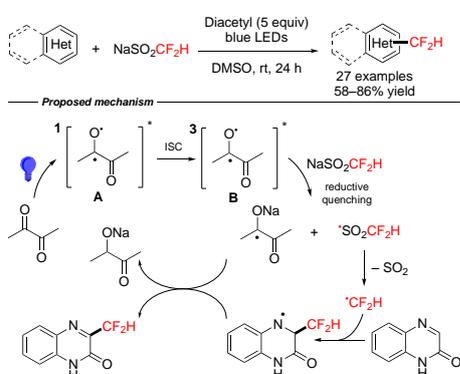
In 2021, Lu and co-workers also reported the visible-light-promoted difluoromethylation of quinoxalin-2(1*H*)-ones affording a set of C3-difluoromethylated quinoxaline-2(1*H*)-ones in moderate to good yields. The reactions were carried out with [bis(difluoroacetoxy)iodo]benzene under catalysis-free conditions (Scheme 45).⁵⁹ The eco-friendly reaction conditions and the excellent functional group tolerance make this route a practical strategy in the formation of CF_2H -containing heterocycles. The reaction starts with the photolysis of [bis(difluoroacetoxy)iodo]benzene to generate difluoromethyl carboxyl radical **A** and iodonium radical **B**, which liberates **A** and iodobenzene. Next, **A** eliminates CO_2 to release the difluoromethyl radical, that reacts with the substrate to give nitrogen-centered radical intermediate **C**. This intermediate **C** was oxidised by **A** or **B** to give nitrogen cation **D** and the desired product after deprotonation.



* The light-promoted reactions were done using standard LED lamp with 24 light emitting diodes (12–28 V, 24W, 465–470 nm). The distance from the light source to the irradiation vessel is 3 cm.

Scheme 45 Visible-light-induced catalyst-free difluoromethylation of quinoxaline-2(1*H*)-ones.

Different reaction conditions for transition metal- and oxidant-free visible light-photoinduced difluoromethylation were presented very recently in 2022 by Zhang, Gu and co-workers by means of sodium difluoromethanesulfinate (Scheme 46).⁶⁰ In this photosensitised electron transfer process, diacetyl was used in excess as simple photoredox catalyst and oxidant. This difluoromethylation approach was applied to quinoxalin-2(1*H*)-ones, quinolinones, coumarins, quinolines, isoquinolines, uracil and caffeine as substrates. From a mechanistic point of view, photoexcitation of diacetyl gave singlet ground diradical **A** and then the excited triplet by light-induced $n \rightarrow \pi^*$ transition through intersystem crossing (ISC). The reductive quenching of **B** by sodium difluoromethanesulfinate offers the CF_2H radical to be involved in the next reaction steps (Scheme 46).

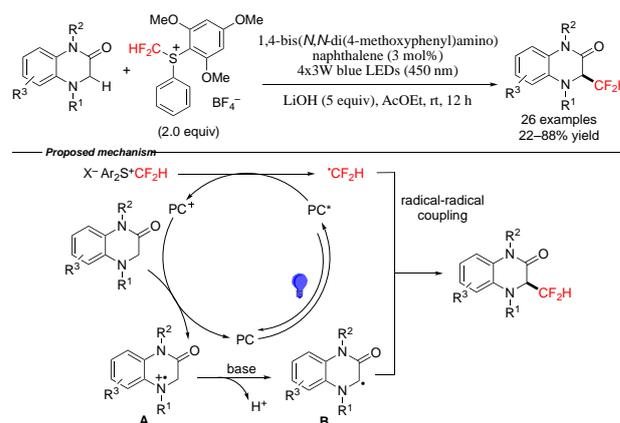


Scheme 46 Direct difluoromethylation of heterocycles with diacetyl photoredox catalyst.

6. Difluoromethylation at $\text{C}(\text{sp}^3)\text{-H}$

In the above-mentioned sections, the difluoromethylation reactions were achieved at $\text{C}(\text{sp}^2)$ and $\text{C}(\text{sp})$ centers. It is only very recently in 2022 that the group of Liu (see also Scheme 28) addressed the cross-coupling direct $\text{C}(\text{sp}^3)\text{-H}$ difluoromethylation under visible-light photoredox catalysis. They used a *S*-(difluoromethyl)sulfonium salt as CF_2H radical source in the presence of a catalytic amount of organic photocatalyst, *tetra*-anisylarylenediamines and in particular 1,4-bis(*N,N*-di(4-methoxyphenyl)amino) naphthalene. A variety of 1,4-dihydroquinoxalin-2-ones were subjected to these conditions to afford the desired products under blue LEDs irradiation (Scheme 47).⁶¹ The mechanism was elucidated giving evidence of a radical-radical cross-coupling process. The CF_2H radical was formed by single electron transfer reduction by the excited photocatalyst PC^* ; the resulting PC^+ species then wrested an electron to the substrate to give the cationic nitrogen radical **A**, which via deprotonation

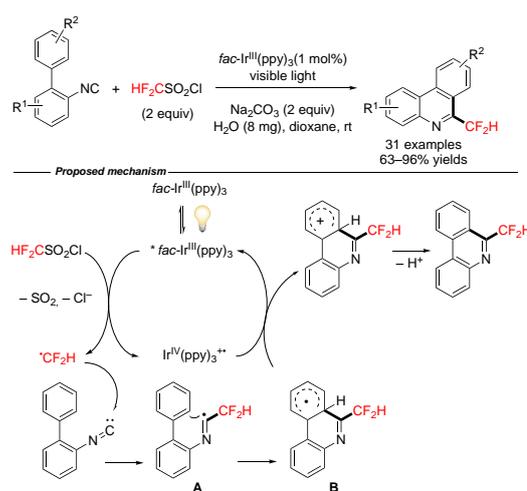
by lithium hydroxide render the $\text{C}(\text{sp}^3)$ radical **B**. Finally, the radical-radical coupling provided the 3-difluoromethyl-1,4-dihydroquinoxalin-2-ones.



Scheme 47 Direct $\text{C}(\text{sp}^3)\text{-H}$ difluoromethylation of 1,4-dihydroquinoxalin-2-ones.

7. Difluoromethylation of isocyanides

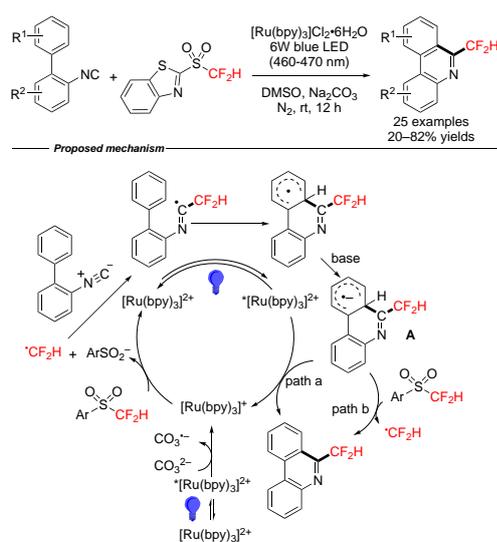
Isocyanides (or isonitriles) are employed as building blocks in multi-component reactions (Ugi and Passerini reactions) and they often participate in cycloaddition reactions for the construction of new heterocyclic architectures. With this in mind, Dolbier and co-workers reported in 2015 the photoredox-catalysed direct difluoromethylation of biphenyl isocyanides for the preparation of an array of 6-(difluoromethyl)phenanthridines in moderate to excellent yields through a cascade addition/cyclisation/oxidation process (Scheme 48).⁶²



Scheme 48 Photoredox-catalysed cascade insertion/cyclisation reactions.

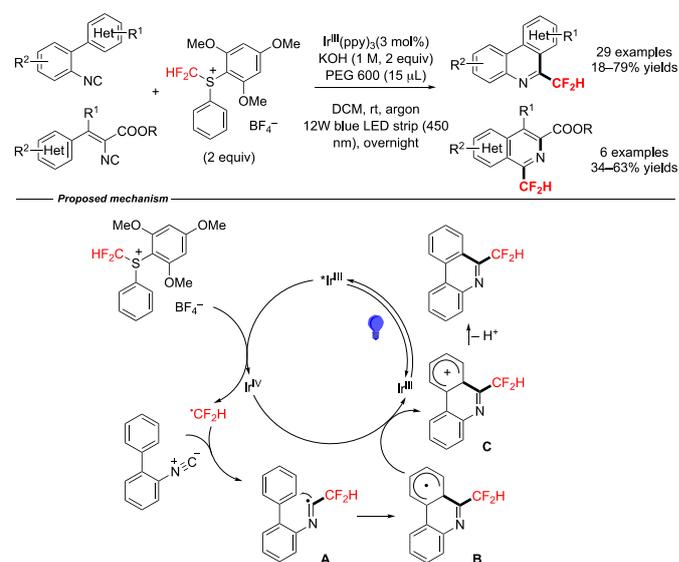
In this protocol, difluoromethylsulfonyl chloride was used as CF_2H radical precursor, which shows excellent reactivity toward isocyanides. As shown in the proposed mechanism, the CF_2H radical addition to isocyanide generated imidoyl radical **A**, which underwent intramolecular cyclisation to afford cyclohexadienyl radical **B**. Finally, the desired product was obtained through oxidation by the high-valent catalyst and deprotonation. Interestingly, the two new carbon carbon bond creations take place at the carbon atom of the isocyanide motif.

A year after, using difluoromethyl sulfones as CF_2H radical source, Hu and co-workers also developed the difluoromethylation of isocyanides under visible-light photoredox catalysis (Scheme 49).⁶³ The radical reactivity of four difluoromethyl sulfones was investigated by cyclic voltammetry and 2-[(difluoromethyl)sulfonyl]benzothiazole was selected as optimised radical precursor because of its highest reduction potential. The methodology provided an efficient strategy for the incorporation of the difluoromethylated moiety into structural complex organic molecules. The process probably starts with the oxidation of carbonate ion CO_3^{2-} into $\text{CO}_3^{\cdot-}$ by the photoexcited $^*[\text{Ru}(\text{bpy})_3]^{2+}$ and then $[\text{Ru}(\text{bpy})_3]^+$ donates an electron to the difluoromethylsulfonyl reagent for the generation of CF_2H radical and subsequent addition to the isocyanide, intramolecular cyclisation, deprotonation by the base to provide radical anion **A**. Intermediate **A** could be oxidised by $^*[\text{Ru}(\text{bpy})_3]^{2+}$ into the final product (path a) or it could react with difluoromethylsulfone to generate the product and $\cdot\text{CF}_2\text{H}$ (path b).



Scheme 49 Visible light photocatalysed difluoromethylation of isocyanides.

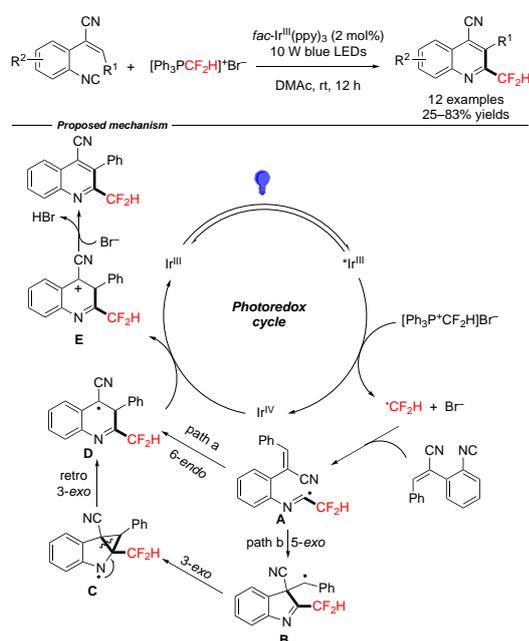
More recently, other difluoromethylating agents have been successfully applied in the visible-light-induced difluoromethylation of isocyanides; thus, in 2020, Liu and co-workers reported the difluoromethylation of isocyanides by means of *S*-(difluoromethyl)diarylsulfonium salt. A broad range of CF_2H -containing phenanthridines and isoquinolines were obtained in moderate to good yields, the former derived from biphenyl isocyanides, the latter derived from 2-isocyanoacrylates (Scheme 50).⁶⁴ Isocyanide substrates bearing electron-withdrawing groups show decreased reactivity in this transformation. The practicability of this radical difluoromethylation was illustrated in the synthesis of the pharmaceutically relevant 6-(difluoromethyl)trispiperidine, a potent DNA intercalator. Mechanistically speaking, photoexcited $[\text{Ir}^{\text{III}}(\text{ppy})_3]^*$ species reduces *S*-(difluoromethyl)diarylsulfonium salt to form the CF_2H radical, followed by its addition to the isocyanide group to afford imidoyl radical **A**, which subsequently cyclises to give cyclohexadienyl radical **B**. Next, radical **B** is oxidised by the high-valent $\text{Ir}^{\text{IV}}(\text{ppy})_3$ to afford the cyclohexadienyl cation **C** with concomitant regeneration of the catalyst. A final rearomatisation step via deprotonation ends up to the desired product.



Scheme 50 Synthesis of difluoromethylated phenanthridines and isoquinolines.

In 2020, Li, Wang and co-workers developed the photocatalysed difluoromethylation of *o*-alkenyl aromatic isocyanides by using difluoromethyltriphenylphosphonium bromide under blue LEDs irradiation. The procedure afforded CF_2H -containing quinolines in moderate to good yields. Two

pathways were suggested for the reaction mechanism. Once the CF_2H radical is photochemically generated, it selectively attacks the isonitrile leading to the corresponding imidoyl radical **A**. At this stage, there are two possibilities to reach the hydroquinoline alkyl radical **D**: (1) radical intermediate **A** undergoes direct 6-endo-trig cycloaddition to C2 position of *o*-vinyl group in aromatic isocyanides; (2) radical **A** participates to a 5-exo-trig addition to generate radical **B**, which undergoes a 3-exo-trig to intermediate **C** and a retro-3-exo-trig process to end up with hydroquinoline alkyl radical **D**. Then, a further SET process gives carbocation intermediate **E** and finally the desired quinoline after deprotonation (Scheme 51).⁶⁵

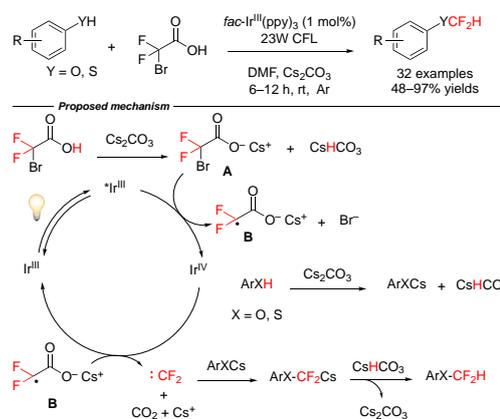


Scheme 51 Synthesis of difluoromethylated quinolines.

8. Difluoromethylation of (thio)phenols

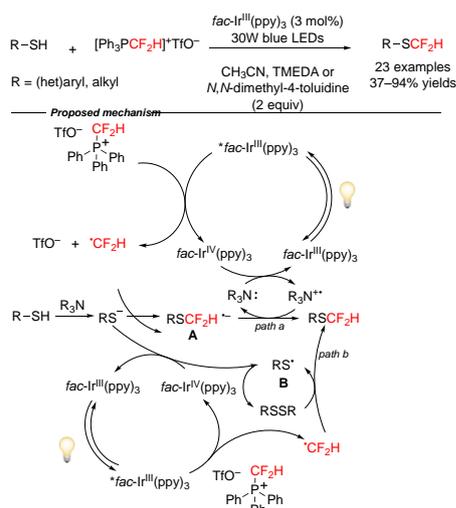
Apart from the difluoromethylation at carbon centers, rare examples *O*- and *S*-difluoromethylations under photocatalysis are available in the literature. It is fascinating to note that PhOCF_2H and PhSCF_2H have hydrogen bond acidities similar to thiophenol and aniline as it was quantified by the [A] parameter.^{2f} Two articles appeared in 2017. Fu and co-workers reported the visible-light photoredox difluoromethylation of phenols and thiophenols affording various *O*- and *S*-difluoromethylated products with great functional group tolerance (Scheme 52).⁶⁶ In this process, commercially available difluorobromoacetic acid was used as efficient difluoromethylating reagent under mild conditions using

a 23W CFL. Ru- and Ir-based photocatalysts were evaluated and *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ was selected. This method provides a simple and efficient strategy for the formation of aryl difluoromethyl (thio)ethers, which are widely present in medicinally important compounds. Mechanistic studies demonstrated the efficiency of photocatalyst *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ as a strong electron donor in order to reduce carboxylate **A** forming the carbon-centered radical **B**. The key difluorocarbene was obtained by SET of **B** to Ir^{IV} with concomitant regeneration of the Ir^{III} photocatalyst. Then, the difluorocarbene reacts with cesium (thio)phenolate ArXC_s and subsequent protonation with CsHCO_3 produces the desired products.



Scheme 52 Photoredox difluoromethylation of phenols and thiophenols.

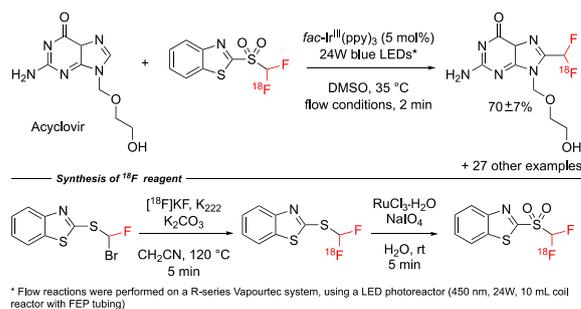
Simultaneously, Qing and co-workers described the radical difluoromethylation of thiols with the aid of difluoromethyltriphenylphosphonium triflate under photoredox catalysis. Here again, *fac*- $\text{Ir}^{\text{III}}(\text{ppy})_3$ was selected to afford a broad range of difluoromethyl thioethers with great chemoselectivity under mild conditions (Scheme 53).⁶⁷ In addition to the above study, both (het)aryl and alkyl thiols were difluoromethylated, albeit alkyl thiols gave only moderate yields up to 42%. Two mechanistic pathways were proposed. Once the CF_2H radical is photocatalytically generated, it could react with the thiolate affording the corresponding radical anion intermediate **A**, which undergoes a SET with the amine base to give the final difluoromethyl thioether (path a). Otherwise, thiolate might be oxidised by *fac*- $\text{Ir}^{\text{IV}}(\text{ppy})_3$ to sulfur radical **B** or the corresponding disulfide and its reaction with CF_2H gives the difluoromethyl thioether (path b). The authors gave more credit to path b as the result of the high chemoselective thiol versus aryl difluoromethylation.



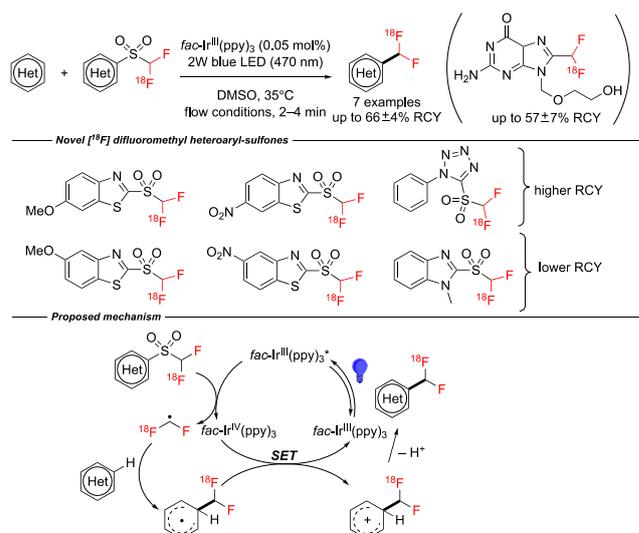
Scheme 53 Photoredox difluoromethylation of thiols.

9. ¹⁸F Radiodifluoromethylation

Photo-mediated radiofluorination has received a great deal of attention for the installation of fluorine-18 radioisotope in radiopharmaceuticals for positron emission tomography. Of the synthetic methodologies nowadays employed, photocatalysis is a much appreciated green method for monofluorination as well as for difluoromethylation.⁶⁸ In 2019, Genicot, Luxen and co-workers described a late-stage efficient photoredox flow ¹⁸F-difluoromethylation reaction of *N*-heteroaromatics affording a variety of C¹⁸FFH radiolabeled molecules in a flow system. The automation includes the synthesis of the ¹⁸F-2-[(difluoromethyl)sulfonyl] benzothiazole in a two-step sequence via Halex reaction and subsequent oxidation; it was obtained with a 13.4±0.4% radiochemical yield (RCY) for 45 minutes after HPLC purification and a specific activity of 81.4±11.1 GBq μmol⁻¹. A total of 28 *N*-heteroaromatic compounds including simple *N*-heteroaromatics but also caffeine derivatives, nucleosides, nucleic bases and drugs were subjected to the [¹⁸F]difluoromethylation in the presence of Ir^{III}(ppy)₃ as photocatalyst under irradiation of blue LEDs at 35 °C in a flow reactor. The overall radiosynthesis time was 95 minutes. To illustrate the method, the difluoromethylation of the antiviral Acyclovir is depicted in Scheme 54.⁶⁹ After optimisation the authors published a fully automated process in which Ir^{III}(ppy)₃ was replaced by the organic photocatalyst 4CzIPN that appeared to be more efficient, cheaper, easier to remove and less toxic than metal-photocatalysts.⁷⁰

Scheme 54 Photoredox flow reaction for ¹⁸F-difluoromethylation of *N*-heteroaromatics.

Encouraged by the efficiency of ¹⁸F-2-[(difluoromethyl)sulfonyl] benzothiazole, Genicot, Luxen, Lemos and co-workers explored the influence of six new structurally related ¹⁸F-difluoromethyl heteroarylsulfones featuring electron-donating or electron-withdrawing groups on the benzothiazolyl cycle or featuring a distinct heteroaryl ring. Their ¹⁸F radiosynthesis was described and, based on the radiochemical yields, three of these difluoromethylating reagents were found suitable to be engaged in the photocatalysed ¹⁸F-difluoromethylation under continuous flow conditions of *N*-heteroaromatics with emphasis for Acyclovir (Scheme 55).⁷¹ The reaction is characterised by a low amount of photocatalyst Ir^{III}(ppy)₃ and short residence times in the flow system. Radical-trapping experiments indicated that radical intermediates were generated in this process. The C¹⁸FFH radical is generated upon a photoredox oxidative quenching cycle via the photoexcited *fac*-Ir^{III}(ppy)₃* catalyst.

Scheme 55 The ¹⁸F-difluoromethylation of heteroarenes by visible light photoredox catalysis.

Conclusions

Assuredly, the CF₂H motif participates to the ever-growing interest in organofluorine chemistry thanks to its sought-after chemical and biological properties. Over the past recent years, visible light photocatalysis in the service of direct difluoromethylation has continuously delivered novel approaches to forge C–CF₂H bond. As illustrated in this review, photoredox catalysis has received widespread adoption for the construction of CF₂H-containing complex and value-added products under extremely mild reaction conditions. Taking benefit from a wide panoply of easily accessible difluoromethylating reagents and a large choice of light-absorbing catalysts, transition-metal or organic catalysts, the appealing direct difluoromethylation is nowadays at least partially tamed. Yet, this review allows to pinpoint several challenges still remaining in this area that require further research and development. For example, the majority of reported difluoromethylation reactions rely on iridium-mediated photocatalysis albeit Ir is one of the least abundant transition-metals, so the use of more available and less expensive metal catalysts and catalyst-free photochemical processes remain underexplored and highly desirable. In addition, the design of *de novo* organic photoredox catalysts holds great promise in the discovery of new difluoromethylation methodologies. As regards chirality, the field of asymmetric radical difluoromethylation under photocatalysis is still virgin yet very challenging.⁷² Overall, the recent progress in photochemical difluoromethylation contributes to the revival of radical chemistry and nicely complements polar (ionic) difluoromethylation reactions. We believe this review will be a source of inspiration for practionners of organofluorine chemistry and beyond for future fruitful developments.

Author contributions

Jiaxu Feng : resources; original draft preparation (equal). Xiaodong Jia: resources; original draft preparation (equal). Shuyue Zhang: resources; original draft preparation (equal). Kui Lu : original draft preparation (lead); writing – review and editing (equal). Dominique Cahard: original draft preparation (equal); writing – review and editing (equal).

ORCIDiS

Dr Dominique Cahard: 0000-0002-8510-1315

Pr Kui Lu : 0000-0002-9685-2691

Jiaxu Feng : 0000-0002-3338-2098

Biographies



Jiaxu Feng was born in 1993 in Shanxi, China. She received her PhD degree from Nankai University in 2020 under the guidance of Pr. You Huang. She joined Tianjin University of Science & Technology in 2020. Her research interests focus on organic small-molecular catalysis and organofluorine chemistry.



Xiaodong Jia was born in Sichuan in 1996. He received his bachelor's degree from Sichuan University of Arts and Sciences in 2019, and then pursued his master's degree at Tianjin University of Science & Technology under the supervision of Pr. Kui Lu. His main research interest is photo-catalysed difluoromethylation.



Shuyue Zhang was born in Tianjin in 1997. She received her bachelor's degree from Tianjin University of Science & Technology in 2019, and then pursued her master's degree at the same University under the supervision of Pr. Kui Lu. Her main research interest is photo-catalysed difluoromethylation.



Kui Lu was born in Jiangxi Province, China, in 1981. He received his BS degree from China Agricultural University in 2002, and then a Ph.D. degree in organic chemistry from Peking University in 2007 under the supervision of Pr. Zhen Yang. After the postdoctoral research in the laboratory of Professor Ohyun Kwon at the University of California, Los Angeles, USA, he

worked as group leader of medicinal chemistry in Bioduro Co., Ltd in China. In 2011, he started his independent career as an associate Professor at Tianjin University of Science & Technology and was promoted to full professor in 2020. His research involved total synthesis of natural product, organosulfur chemistry and organofluorine chemistry.



Dominique Cahard was born in 1968 in Normandy, France. His career started in 1994 with a PhD from the University of Rouen under the supervision of Pr. Jean-Marie Poirier and Pr. Pierre Duhamel. He enjoyed two postdoctoral positions with Pr. Chris McGuigan in Southampton (UK) and then in Cardiff (Wales), and with Pr. Tadashi Nakata at RIKEN, Tokyo (Japan). In 1996, he joined the CNRS as an associate researcher, completed his Habilitation in 2001, and was promoted to CNRS Research Director in 2007. Dominique Cahard is heading a research group that has interest in innovative methodologies for synthesis of fluorinated molecules with emphasis for chirality control.

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Conflicts of interest

There are no conflicts to declare.

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