Progress in Difluoroalkylation of Organic Substrates by Visible Light Photoredox Catalysis

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Abstract: The selective incorporation of fluorinated motifs, in particular CF_2FG (FG = a functional group) and CF_2H groups, into organic compounds has attrracted increasing attention since organofluorine molecules are of the utmost importance in the areas of nuclear imaging, pharmaceutical, agrochemical, and material sciences. A variety of synthetic approaches has been employed in late-stage difluoroalkylation reactions. Visible light photoredox catalysis for the production of CF_2FG and CF_2H radicals has provided a more sustainable alternative to other conventional radical-triggered reactions from the viewpoint of safety, cost, availability, and "green" chemistry. A wide range of difluoroalkylating reagents has been successfully implemented in these organic transformations in the presence of transition metal complexes or organic photocatalysts. In most cases, upon excitation *via* visible light irradiation with fluorescent light bulbs or blue light-emitting diode (LED) lamps, these photocatalysts can act as both reductive and oxidative quenchers, thus enabling the application of electron-donor or electron-acceptor difluoroalkylating reagents for the generation of CF_2FG and CF_2H radicals. Subsequent radical addition to substrates and additional organic transformations afford the corresponding difluoroalkylated derivatives. The present review describes the distinct strategies for the transition metal- and organic-photocatalyzed difluoroalkylation of a broad range of organic substrates by visible light irradiation reported in the literature since 2014.

Keywords: C−H functionalization; difluoroalkylation; late-stage fluorination; organophotocatalysis; transition metal photocatalysis; visible light

1 General Introduction

Organic compounds containing fluorine substituents or fluoroalkyl moieties are abundant and have attracted considerable attention because of their wide applications in agrochemical,[1] pharmaceutical,[2,3] and material science[4] industries, and nuclear imaging.[5,6] In pharmaceutical research and drug development, the incorporation of fluoroalkyl motifs, in particular the difluoromethyl (CF_2H) group, has gained great interest for use in isostere-based drug design. As a lipophilic hydrogen-bond donor,[7] the CF_2H substitution offers a viable alternative to conventional hydrogen-bond donors [e.g., hydroxy (OH), amino (NH_2), thiol

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(SH), carbinol (CH_2OH), amide ($CONH_2$), and hydroxamic acid (CONHOH) groups] in terms of lipophilicity, cell membrane permeability, and metabolic stability, thus improving the biological activity.[8,9] Given the relevance of difluoroalkyl substituents in life sciences, the implementation of efficient approaches for the preparation of CF_2-containing organic molecules has become a major research area in the field of organofluorine chemistry. Apart from the huge progress in the development of strategies for C–H functionalization involving fluorination and trifluoromethylaton reactions,[10–18] significant research efforts have been directed toward the late-stage introduction of CF_2FG (FG = a functional group) and CF_2H moieties in organic skeletons *via* nucleophilic, electrophilic, and radical approaches.[19–22] Among the mentioned approaches for the difluoroalkylation process, the radical-triggered reactions *via* visible light photoredox catalysis have been the subject of intensive research by the chemical community, owing to

their unique advantages such as the use of "green" and environmentally benign reaction conditions, excellent functional group versatility, and high reactivity.[23–30] In fact, the use of photoredox catalysis has provided a powerful and versatile tool to afford a large variety of fluorinated radicals under very mild conditions, compared with conventional radical reactions that usually demand the use of high-energy ultraviolet (UV) light equipment or the employment of highly toxic radical initiators. In general, these visible light-induced chemical transformations rely on the ability of photocatalysts, such as transition metal complexes,[31–33] organic dyes[34,35] or heterogeneous semiconductors[36,37] to promote single-electron transfer (SET) processes with organic molecules upon excitation with visible light. Remarkably, the lack of visible light absorbance of many organic molecules enables the application of these photocatalysts in these reactions, minimizing the occurence of unwanted side reactions resulting from the photoexcitation and the de-
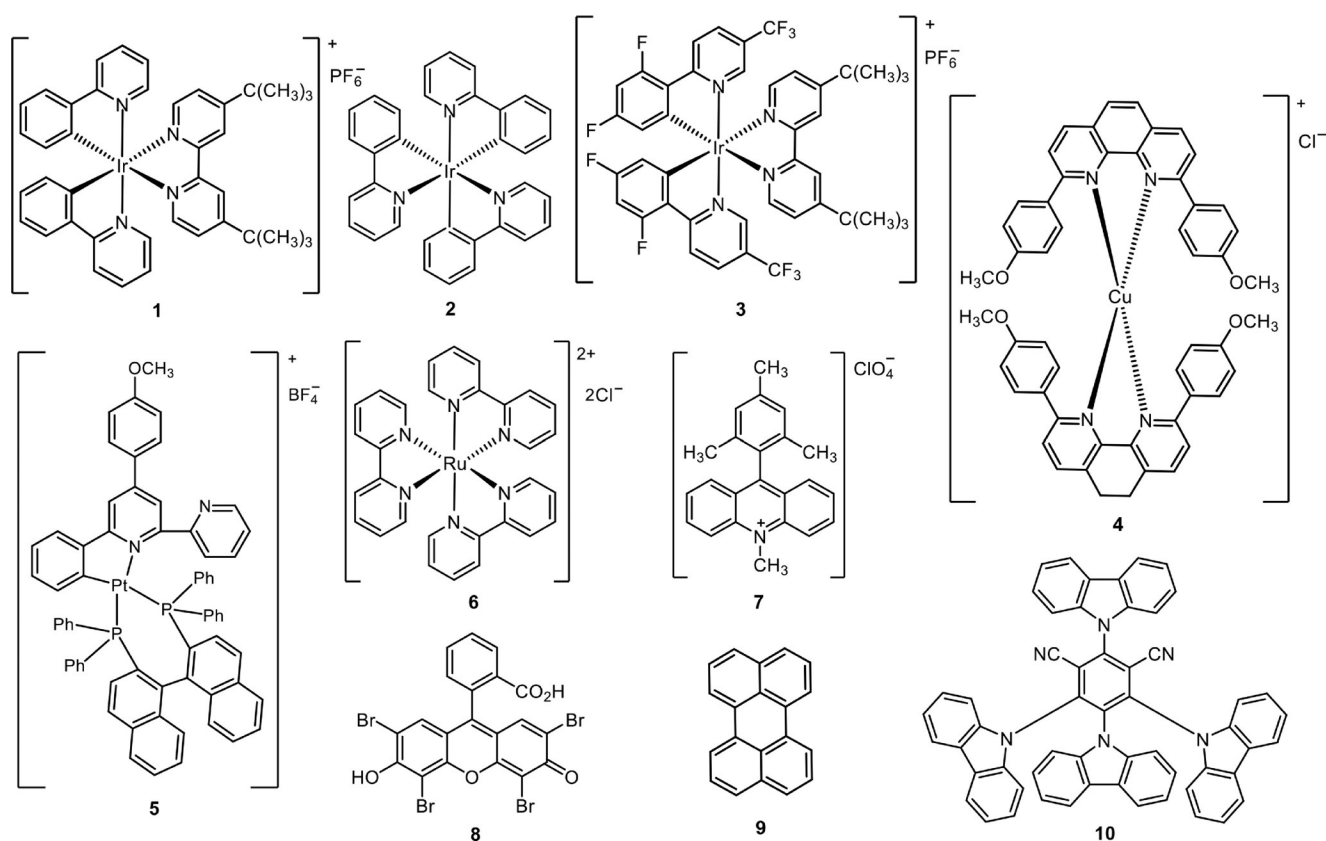
Figure 1. Transition metal (**1–6**) and organic photocatalysts (**7–10**) employed in difluoroalkylation reactions. **1** – [Ir(dtbb-py)(ppy)$_2$]PF$_6$; **2** – *fac*-Ir(III)(ppy)$_3$; **3** – [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$; **4** – [Cu(dap)$_2$]Cl; **5** – Pt(II)[R(C^N^P^P)] (R = 4-CH$_3$OC$_6$H$_4$); **6** – [Ru(bpy)$_3$]Cl$_2$; **7** – *N*-methyl-9-mesitylacridinium perchlorate ([Mes-Acr]ClO$_4$); **8** – eosin Y; **9** – perylene; **10**-1,2,3,5-tetrakis(carbazolyl)-4,6-dicyanobenzene (4CzIPN).

composition of reaction products. Visible light irradiation is often carried out using inexpensive light sources such as blue light-emitting diode (LED) lamps and fluorescent light bulbs. A variety of transition metal photocatalysts, such as iridium {[Ir(dtbbpy)-(ppy)$_2$]PF$_6$ (**1**, Figure 1), *fac*-Ir(III)(ppy)$_3$ (**2**, Figure 1), and [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**3**, Figure 1)}, copper {[Cu(dap)$_2$]Cl (**4**, Figure 1)}, platinum {Pt(II)[R(C^N^P^P)] (R = 4-CH$_3$OC$_6$H$_4$) (**5**, Figure 1)}, and ruthenium {[Ru(bpy)$_3$]Cl$_2$ (**6**, Figure 1)} complexes, and organic photocatalysts, including *N*-methyl-9-mesitylacridinium perchlorate ([Mes-Acr]ClO$_4$) (**7**, Figure 1), eosin Y (**8**, Figure 1), perylene (**9**, Figure 1), and 1,2,3,5-tetrakis(carbazol-yl)-4,6-dicyanobenzene (4CzIPN) (**10**, Figure 1) have been implemented in photochemistry for the difluoroalkylation of organic substrates. These photocatalysts are capable of absorbing light at a certain wavelength in the visible region, resulting in the generation of photoexcited species that possess the unique property of being both more oxidizing and more reducing than the species in the ground state. The standard reduction potentials are used to quantify the redox properties of a photocatalyst in the excited state under specific standard conditions (Table 1), and describe the

electrochemical potential associated with a half-reaction (E$_{1/2}$) of reduction. The reduction potential determines the propensity of a chemical species to be reduced. In fact, the more positive the potential values, the greater is the tendency of a molecule to be reduced. For example, *fac*-Ir(III)(ppy)$_3$* is a much more potent electron donor [E$_{1/2}$ (PC$^+$/PC*) = −1.73 V *vs.* SCE] than the *fac*-Ir(III)(ppy)$_3$ in the ground state [E$_{1/2}$ (PC$^+$/PC) = +0.77 V *vs.* SCE]. Reduction potentials of difluoroalkylating reagents (**11–34**, Figure 2) are also highlighted in this review. Depending on the reduction potentials of the photocatalysts in the excited state and the difluoroalkylating reagents, the excited photocatalysts can act as SET reductants or oxidative quenchers (oxidative quenching cycle, OQC) and SET oxidants or reductive quenchers (reductive quenching cycle, RQC), allowing the formation of CF$_2$H and CF$_2$FG radicals. The resulting oxidized or reduced species will then undergo a second SET reduction or oxidation, respectively, returning the photocatalyst to its initial low-energy state. The redox potentials of both difluoroalkylating reagents and photocatalysts must be taken into consideration in order to select the most appropriate partners for the design of a photocatalytic difluoroalkylation reaction.[38,39] Sub-

Table 1. Redox potentials and photophysical properties of transition metal (**1–6**) and organic photocatalysts (**7–10**) utilized in difluoroalkylation reactions.[a] (PC = a photocatalyst).

| PC	$E_{1/2}$ (PC$^+$/PC*)	$E_{1/2}$ (PC*/PC$^-$)	$E_{1/2}$ (PC$^+$/PC)	$E_{1/2}$ (PC/PC$^-$)	Excited-state lifetime τ [ns]	Excitation λ_{max} [nm]	Emission λ_{max} [nm]	Refs.
1	−0.96	+0.66	+1.21	−1.51	557	410	581	[54,55]
2	−1.73	+0.31	+0.77	−2.19	1900	375	494[b]	[50]
3	−0.89	+1.21	+1.69	−1.37	2300	380	470	[55]
4	−1.43		+0.62		270	400–600	670[c]	[62]
5	−1.90[d]	+0.82[d]	+0.61[d]	−1.69[d]	93[d]	350[d]	543[d]	[81]
6	−0.81	+0.77	+1.29	−1.33	1100	452	615	[79,80]
7		+2.06		−0.57	6.4	430	570	[134–137]
8	−1.11[e]	+0.83[e]	+0.78[e]	−1.06[e]	24000[e]	539[e]		[127]
9	−2.23	+0.72	+0.61	−2.12	8.2	407, 434	670	[133]
10	−1.04	+1.35	+1.52	−1.21	5100	435	535	[140–142]

[a] All potentials are given in volts *versus* the saturated calomel electrode (SCE). Measurements were performed in MeCN at room temperature unless otherwise noted.
[b] Determined in 1:1 EtOH/MeOH at 77 K.
[c] Determined in DCM.
[d] Potentials are given in volts *versus* the ferrocene (Cp$_2$Fe).
[e] Determined in 1:1 MeCN/H$_2$O.
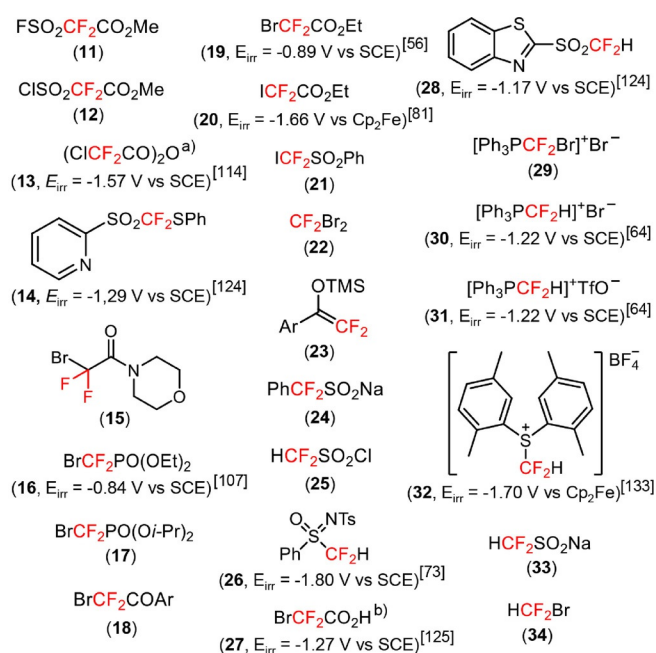
Figure 2. List of CF$_2$FG (**11–24**) and CF$_2$H reagents (**25–34**) employed in visible light-mediated difluoroalkylation reactions and their potentials given in volts *versus* the saturated calomel electrode (SCE) or ferrocene (Cp$_2$Fe).
a) Potential of **13** in combination with pyridine *N*-oxide.
b) Potential of the intermediate BrCF$_2$CO$_2$Cs.

sequent addition of CF$_2$FG and CF$_2$H radicals in sp^2-hybridized (C=C, C=N) and sp-hybridized (C≡C, C≡N) carbon atoms of organic substrates and further chemical transformations would afford the corresponding CF$_2$FG- and CF$_2$H-containing products. Alternatively, the CF$_2$FG moiety of difluoroalkylated derivatives can be converted into other CF$_2$-contain-

ing functional groups, including CF$_2$H, under certain reaction conditions. Interestingly, the radical difluoroalkylation of key organic molecules can provide useful intermediates for the formation of structurally complex and functionalized heterocycles of pharmaceutical and medical interest. Pioneering works in fluoroalkylation chemistry *via* visible light photoredox catalysis have been reported by MacMillan, Cho, and Sanford. In 2009, MacMillan's group achieved the enantioselective α-trifluoromethylation and α-perfluoromethylation of aldehydes with trifluoroiodomethane (CF$_3$I) using the readily available [Ir(dtbbpy)-(ppy)$_2$]PF$_6$ and an imidazolinone catalyst.[40] Later, in 2011, the same group developed photoredox-based protocols for the α-trifluoromethylation of enol silanes, silylketene acetals and *N*,*O*-acetals derived from ketones, esters, and amides using CF$_3$I[41] and for the trifluoromethylation of arenes as well as five-, and six-membered heteroarenes with trifluoromethanesulfonyl chloride (CF$_3$SO$_2$Cl), in the presence of [Ru(bpy)$_3$]Cl$_2$ and [Ru(phen)$_3$]Cl$_2$, respectively.[42] In 2012, Cho and collaborators described a procedure for the trifluoromethylation of electron-rich heterocycles *via* [Ru(bpy)$_3$]Cl$_2$ photocatalysis.[43] In the same year, Sanford's group reported the trifluoromethylation and perfluoroalkylation of arylboronic acids by merging photoredox and copper catalysis.[44] Since then, photoinduced fluoroalkylation reactions have mostly relied on the incorporation of trifluoromethyl (CF$_3$) groups in organic substrates. Seminal works in visible light-induced difluoroalkylation chemistry were reported in 2014 and, to date, a myriad of difluoroalkylating reagents (**11–34**, Figure 2) has been successfully implemented for structurally diverse organic molecules. Remarkably, one of the most critical

challenges of late-stage difluoroalkylation compared to trifluoromethylation is that the replacement of one electronegative fluorine atom in CF₃-containing reagents by a hydrogen atom or by other functional groups may induce a signficant diminution of the reduction potentials. For instance, the generation of CF₂H radicals from electrophilic CF₂H precursors requires the use of more strongly reducing catalysts when compared with the case of CF₃ radicals.

Numerous reviews in fluoroalkylation chemistry have emphasized the various synthetic approaches for visible light-mediated trifluoromethylation and other perfluoroalkylation reactions.[38,39,45,46,47] Although some of these reviews have covered the area of difluoroalkylation chemistry in part,[46,47] a review focusing exclusively on the incorporation of CF₂H and CF₂FG groups under visible light photoredox conditons will be convenient due to the increasing interest in the formed difluoroalkylated products in life sciences. In addition, major breakthroughs have been accomplished in this research field since the first reported works in 2014. Herein, the present review highlights the distinct synthetic strategies for transition metal- and organic-photocatalyzed difluoroalkylation of a broad range of organic substrates by visible light irradiation that have been reported in the literature since 2014. Owing to the attractive characteristics of visible light photoredox catalysis and the late-stage introduction of difluoroalkyl groups, we expect that the present review will inspire organic chemists to explore additional synthetic routes for installation of these moieties.

2 Transition Metal Photocatalyzed Difluoroalkylation Reactions

The importance of transition metal complexes as effective SET reductants and oxidants, upon excitation *via* irradiation with visible light, has been demonstrated by the considerable number of research works that were reported recently, involving the incorporation of CF₂FG and CF₂H moieties in a variety of substrates bearing unsaturated bonds, including C=C and C=N, and the concomitant formation of new C–C bonds. In most cases, iridium transition metal complexes have proven to be priviliged photocatalysts in the difluoroalkylation of unactivated alkenes, styrenes, enol derivatives, allylic alcohols, and α,β-unsaturated carboxylic acids, arenes, and heteroarenes.

2.1 Difluoroalkylation of *sp*² Carbon Atoms in Unactivated Alkenes and Styrenes

The commercially available and easy-to-handle methyl 2,2-difluoro-2-(fluorosulfonyl)acetate
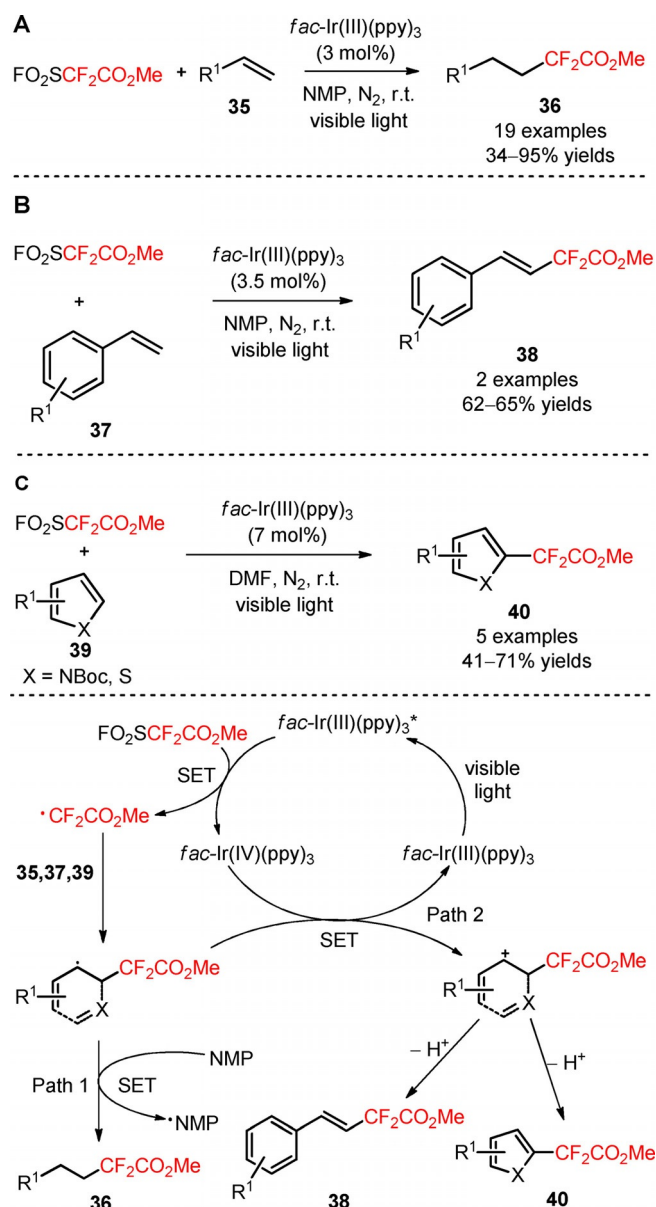
Scheme 1. Methoxycarbonyldifluoromethylation of alkenes (**35**), styrenes (**37**), and heteroarenes (**39**) by visible light photoredox catalysis and the suggested mechanism.

(FSO₂CF₂CO₂Me, Chen's reagent, CAS number: 680-15-9) has been exclusively employed for the preparation of trifluoromethylated derivatives.[48,49] Qing and collaborators disclosed the application of FSO₂CF₂CO₂Me for the installation of CF₂CO₂Me substituents in alkenes (**36**, Scheme 1A: 19 examples, 34–95% yields), styrenes (**38**, Scheme 1B: 2 examples, 62–65% yields), and heteroarenes (**40**, Scheme 1C: 5 examples, 41–71% yields) under visible light photoredox conditions, in the presence of *fac*-Ir(III)(ppy)₃.[50] A plausible reaction mechanism involved the formation of CF₂CO₂Me radicals from the reduction of FO₂SCF₂CO₂Me *via* oxidative quenching of *fac*-Ir(III)(ppy)₃* and the loss of SO₂ and F⁻. The entrap-

ment of these radicals by alkenes (**35**), styrenes (**37**), and heteroarenes (**39**) afforded the corresponding difluoroalkylated intermediates. The resulting radical intermediates can undergo two distinct pathways depending on the substrates. For alkenes (**35**), hydrogen abstraction of the radical intermediate from NMP gave the hydro-difluoroalkylated alkanes (**36**). For styrenes (**37**) and heteroarenes (**39**), the oxidation of the radical intermediate and subsequent deprotonation provided the methoxycarbonyldifluoromethylated products (**38** and **40**).[51]

The difluoroalkylating reagent ethyl 2-bromo-2,2-difluoroacetate (BrCF$_2$CO$_2$Et, CAS number: 565-53-7) was also implemented by Cho's group for the difluoroalkylation of unactivated alkenes (**41**).[52] Interestingly, the authors found that the selection of the bases and solvents was critical for guiding the chemoselective synthesis of difluoroalkylated alkanes and alkenes. In fact, difluoroalkylated alkanes were preferentially obtained using a mixture of bases DBU/TMEDA in DCM (**42**, Scheme 2: 9 examples, 65–90%
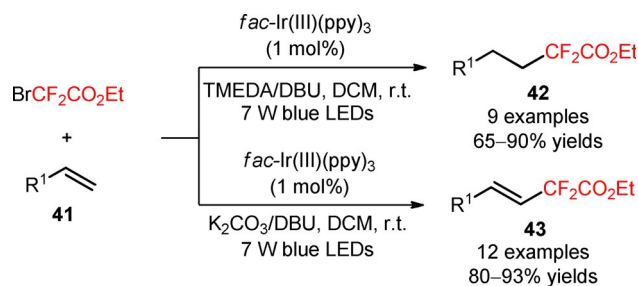
Scheme 2. Hydro-difluoroalkylation and alkenyl-difluoroalkylation of unactivated alkenes (**41**) under visible light photoredox conditions in the presence of *fac*-Ir(III)(ppy)$_3$.

yields). On the other hand, the formation of difluoroalkyl-containing alkenes with high levels of regio- and *E/Z* stereoselectivity (90–97%) was achieved by complete conversion of the aliphatic alkenes and styrenes to the bromodifluoroalkylated products using the base K$_2$CO$_3$ and subsequent dehydrobromination with DBU in DMF (**43**, Scheme 2: 12 examples, 80–93% yields).

Partially hydrogenated naphthalenes and quinolines containing difluoroalkyl moieties (**45**) were efficiently prepared *via* radical difluoroalkylation of α-cyclopropylstyrenes and α-cyclopropylpyridines (**44**) with BrCF$_2$CO$_2$Et, respectively, opening of cyclopropyl ring, and consecutive annulation reaction.[53] In the presence of [Ir(dtbbpy)(ppy)$_2$]PF$_6$,[54,55] a wide range of α-cyclopropyl olefins bearing electron-donating and electron-withdrawing groups regioselectively afforded the corresponding products with moderate yields (**45**, Scheme 3: 15 examples, 47–68% yields). The developed methodology can be extended to other brominated compounds including bromodifluoro-
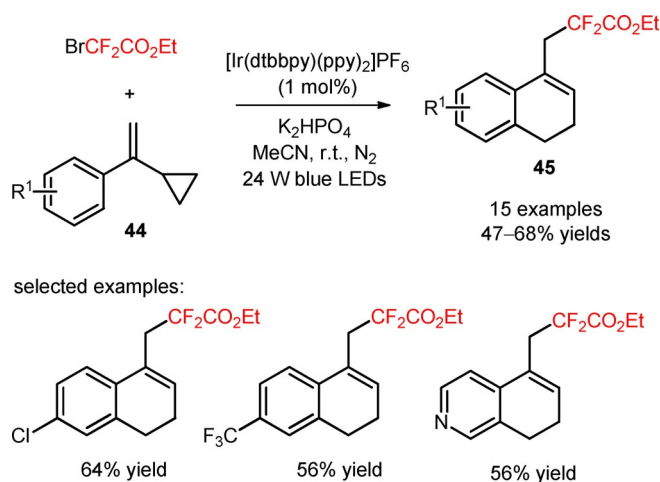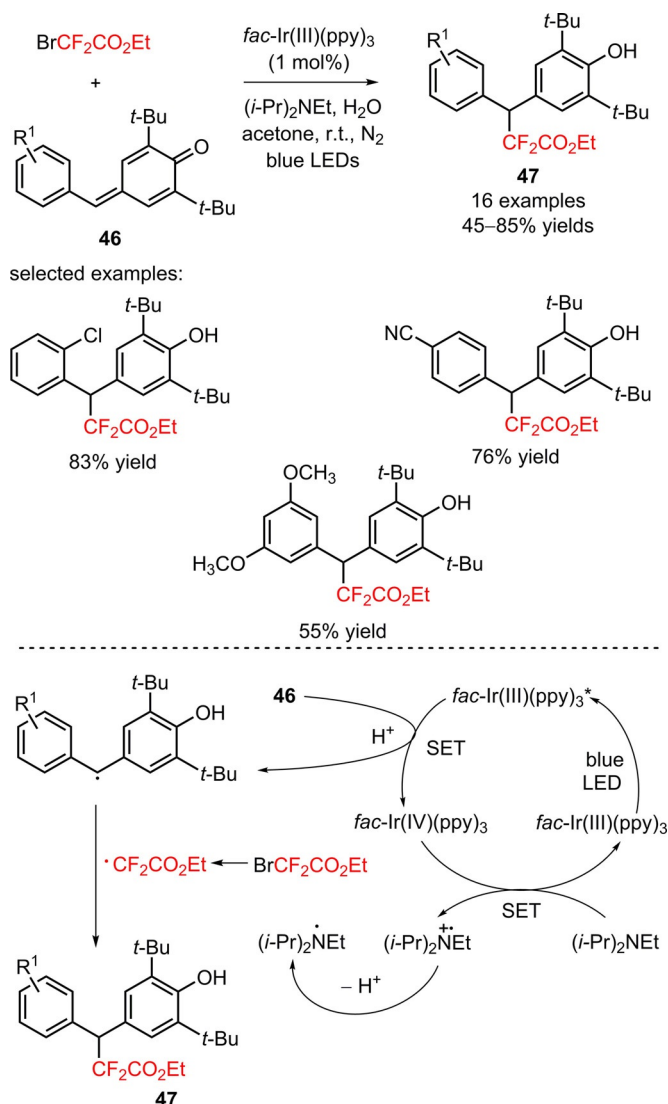

Scheme 3. Photoinduced difluoroalkylation of α-cyclopropylstyrenes and α-cyclopropylpyridines (**44**).

acetamides, ethyl 2-bromo-2-fluoroacetate (BrCHFCO$_2$Et), 2-bromoacetonitrile, and diethyl 2-bromomalonate.

Xu and collaborators reported a new approach to access difluoroalkylated diarylmethanes (**47**) from *para*-quinone methides (**46**) and BrCF$_2$CO$_2$Et *via* radical-radical cross-coupling, under irradiation with blue LEDs.[56] In the presence of *fac*-Ir(III)(ppy)$_3$, the inclusion of H$_2$O and the reductant (*i*-Pr)$_2$NEt in the reaction system was beneficial for the difluoroalkylation process. *para*-Quinone methides bearing electron-withdrawing and electron-donating groups on the aromatic ring provided the corresponding products with moderate to excellent yields. Disubstitution with chloro and methoxy groups was also well tolerated (**47**, Scheme 4: 16 examples, 45–85% yields). Remarkably, the developed strategy can be implemented using other difluoroalkylating reagents with acylamino, carbonyl, esteryl, and heteroaryl substituents. Stern–Volmer fluorescence quenching studies and radical-trapping experiments suggested the formation of diarylmethyl radicals *via* oxidative quenching of *fac*-Ir(III)(ppy)$_3$* species and the CF$_2$CO$_2$Et radicals *via* oxidation of the (*i*-Pr)$_2$NEt radical intermediate. Cross-coupling between diarylmethyl and CF$_2$CO$_2$Et radicals afforded the difluoroalkylated diarylmethanes (**47**).
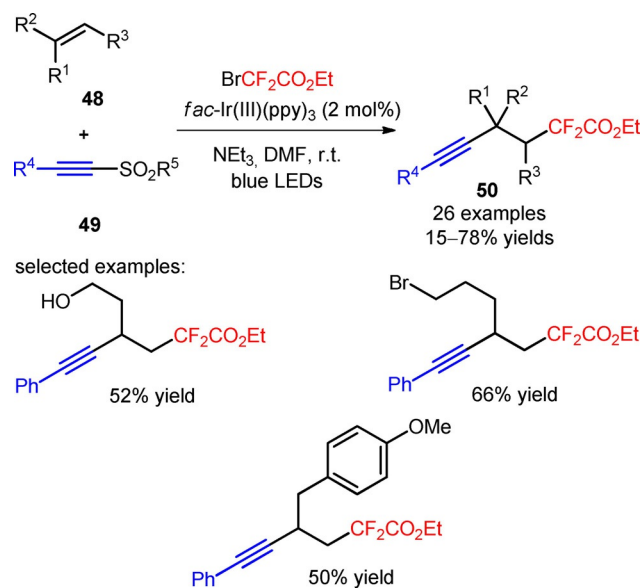
Recently, Zhu and co-workers described a novel tactic for the intermolecular alkynyl-difluoroalkylation of unactivated alkenes (**48**) *via* a three-component condensation with BrCF$_2$CO$_2$Et and alkynyl sulfones (**49**), under visible light photoredox conditions.[57] The combined use of *fac*-Ir(III)(ppy)$_3$ with the DMF and the base NEt$_3$ was critical for the selective formation of β-difluoroalkylated alkynes (**50**), minimizing the unwanted bromine addition and direct difluoroalkylation of the alkynyl sulfones (**49**). Terminal and internal alkenes with a variety of functional

Scheme 4. Visible light-induced radical-radical cross-coupling difluoroalkylation of *para*-quinone methides (**46**).

Scheme 5. Visible light-induced three-component alkynyl-difluoroalkylation of unactivated alkenes (**48**), BrCF$_2$CO$_2$Et, and alkynyl sulfones (**49**).

groups (**48**), and alkynyl sulfones bearing aryl and heteroaryl substituents (**49**) were all suitable substrates for the alkynyl-difluoroalkylation process (**50**, Scheme 5: 26 examples, 15–78% yields). Bromodifluoroacetamides can also provide the corresponding β-fluoroalkylated alkynes under the developed methodology.

Diethyl (bromodifluoromethyl)phosphonate [(BrCF$_2$PO(OEt)$_2$, CAS number: 65094-22-6] was implemented by Li and co-workers in the hydro-phosphonodifluoromethylation of alkenes (**51**) using the Hantzsch ester Et-HE as a hydrogen source and the thiyl radical precursor HSAcOMe, under irradiation with blue LEDs.[58] The authors found that combining the thiyl radical-catalyzed hydrogen atom transfer ability of the HE with RQC may avoid the use of strongly basic conditions and block the undesirable halogen atom transfer addition pathway *via* OQC. In

the presence of *fac*-Ir(III)(ppy)$_3$, mono- and disubstituted alkenes bearing electron-rich and electron-deficient aromatic groups as well as heterocyclic and aliphatic groups (**51**) were compatible substrates with the hydro-difluoroalkylation process (**52**, Scheme 6: 28 examples, 25–100% yields). This procedure was applied to the single-step synthesis of the intermediate of a purine nucleoside phosphorylase (PNP) inhibitor. Mechanistic studies with radical scavengers and alternative reductants suggested a reductive quenching of *fac*-Ir(III)(ppy)$_3$*, and consecutive generation of CF$_2$PO(OEt)$_2$ radicals *via* reduction of BrCF$_2$PO(OEt)$_2$. Radical difluoroalkylation of the alkenes (**51**) followed by hydrogen atom transfer between HSAcOMe and the difluoroalkylated radical intermediate afforded the corresponding products (**52**).
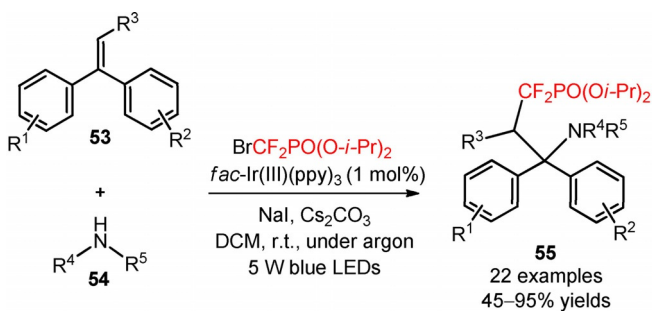
The synthesis of α,α-difluoro-γ-aminophosphonates (**55**) was described by Qiang and collaborators through intramolecular amino-phosphonodifluoromethylation of diarylalkenes (**53**) with diisopropyl (bromodifluoromethyl)phosphonate [BrCF$_2$PO(O-*i*-Pr)$_2$, CAS number: 65094-24-8] under irradiation with 5 W blue LEDs.[59] A palette of electron-rich and electron-deficient diarylalkenes (**53**), and arylamines (**54**) can be effectively converted into the difluoroalkylated products (Scheme 7, **55**, 22 examples, 45–95% yields). Interestingly, this procedure was applied to the synthesis of phosphonodifluoromethylated chiral binaphthylamines using (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine [(*R*)-BINAM] and (*R*)-(+)-2′-amino-1,1′-binaphthalen-2-ol [(*R*)-NOBIN] as the substrates, and of the α,α-difluoro-γ-aminophosphoric acid. Radical-trapping and light on/off experiments suggested the inter-
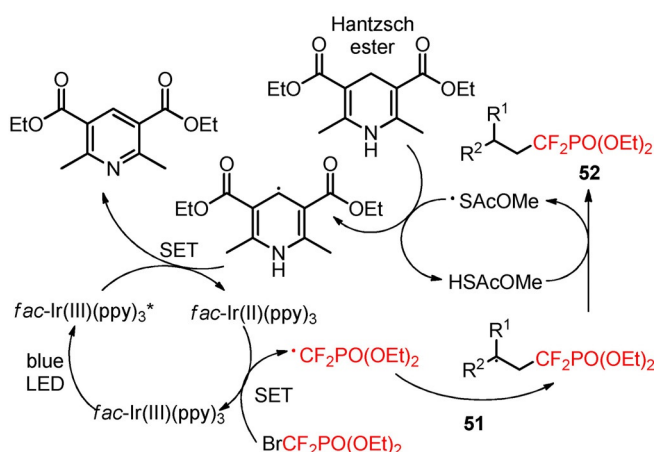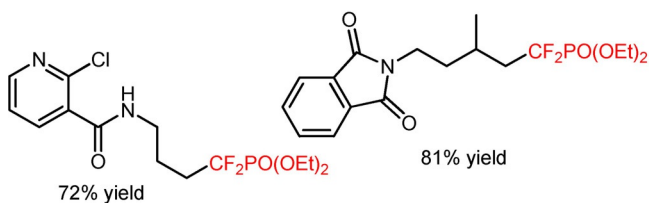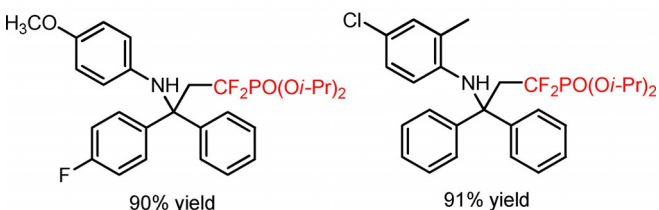
**Scheme 6.** Hydro-phosphonodifluoromethylation of alkenes (**51**) *via* thiyl radical/photoredox catalysis.


Scheme 7. Photocatalyzed intermolecular amino-phosphono-difluoromethylation of alkenes (**53**).

mediacy of CF$_2$PO(O-*i*-Pr)$_2$ radicals *via* oxidative quenching of *fac*-Ir(III)(ppy)$_3$*.

Dolbier's group developed a novel strategy for the hydro-difluoromethylation of alkenes (**56**) bearing a large variety of electron-withdrawing groups with the reagent difluoromethanesulfonyl chloride (HCF$_2$SO$_2$Cl, CAS number: 1512-30-7) as the source of CF$_2$H radicals, under irradiation with 26 W compact fluorescent lamp (CFL) (**57**, Scheme 8: 20 exam-
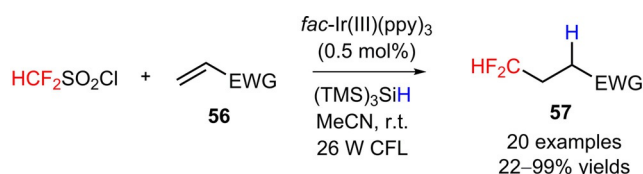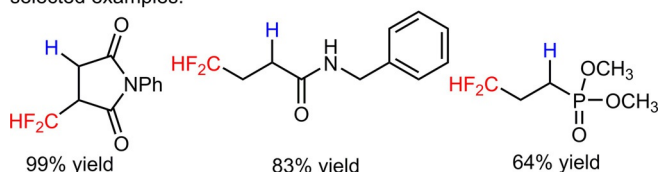
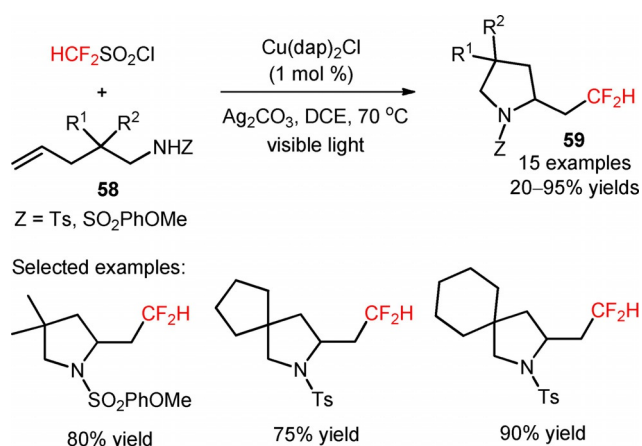
Scheme 8. Visible light-catalyzed hydro-difluoromethylation of electron-deficient alkenes (**56**) with HCF$_2$SO$_2$Cl.

ples, 22–99% yields).[60] In addition to the photocatalyst *fac*-Ir(III)(ppy)$_3$, the introduction of tris(trimethylsilyl)silane [(TMS)$_3$SiH] with hydrogen atom donor properties was pivotal for the direct hydro-difluoromethylation of alkenes, circumventing the formation of chloro-difluoromethylated products. Other difluoroalkylating compounds, including (bromodifluoromethyl)benzene (PhCF$_2$Br), 1,1-difluoroethane-1-sulfonyl chloride (CH$_3$CF$_2$SO$_2$Cl), and 2-azido-1,1-difluoroethane-1-sulfonyl chloride (N$_3$CH$_2$CF$_2$SO$_2$Cl) can be implemented in the hydro-difluoroalkylation of the substrates under the described reaction conditions.

The reagent HCF$_2$SO$_2$Cl was also efficiently employed in the preparation of difluoromethylated pyrrolidines and lactones through installation of difluoromethyl groups in sulfonamides and esters (**58**), respectively, and subsequent radical cyclization by visible light photoredox catalysis (**59**, Scheme 9: 15 examples, 20–95% yields).[61] The implementation of [Cu(dap)$_2$]Cl[62] as photocatalyst and the base Ag$_2$CO$_3$ was crucial for supression of the chloro-difluoromethylation process.

Alkenes containing *gem*-dialkoxycarbonyl substituents (**60**) were employed as substrates for photoinduced intramolecular difluoromethylation using the reagent HCF$_2$SO$_2$Cl, in the presence of *fac*-Ir(III)-(ppy)$_3$.[63] A spectrum of difluoromethylated tetralin derivatives possessing electron-donating and electron-withdrawing groups in the aromatic ring and alkyl substituents at the β-position was efficiently obtained in moderate to good yields (**61**, Scheme 10: 13 exam-

Scheme 9. Visible light-induced difluoromethylation of sulfonamides and esters (**58**) and subsequent radical cyclization in the presence of [Cu(dap)$_2$]Cl.
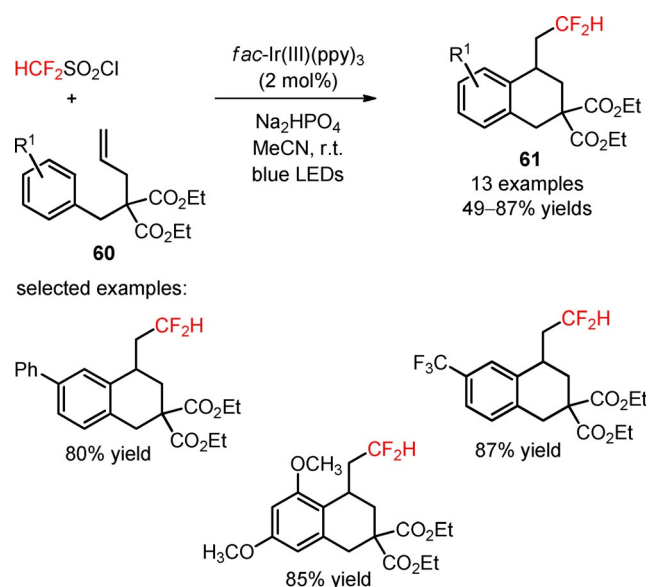
Scheme 10. Visible light-catalyzed difluoromethylation/6-*exo* cyclization of unactivated alkenes (**60**) with HCF$_2$SO$_2$Cl.

ples, 49–87% yields). Alternative difluoroalkyl R$_f$X radical precursors [R$_f$ = CF$_2$CH$_3$, CF$_2$CO$_2$Et, CF$_2$CONHPh, CF$_2$CON(CH$_2$CH$_2$)$_2$O; X = SO$_2$Cl, Br] were also compatible with the developed synthetic methodology.

Qing and co-workers developed a methodology for visible light-driven hydro-difluoromethylation of alkenes (**62**) with the easy-to-handle (bromodifluoromethyl)triphenylphosphonium bromide [(Ph$_3$PCF$_2$Br)$^+$Br$^-$] for the insertion of CF$_2$H groups, in the presence of H$_2$O and THF.[64] The reagent (Ph$_3$PCF$_2$Br)$^+$Br$^-$ was recognized exclusively as a difluorocarbene precursor.[65–69] Nevertheless, the authors found that (Ph$_3$PCF$_2$Br)$^+$Br$^-$ can be implemented as a CF$_2$Br donor, under visible light irradiation.

The additional formation of hydro-difluoromethylated derivatives was solely observed in the presence of the photocatalyst *fac*-Ir(III)(ppy)$_3$. The authors suggested the formation of (difluoromethyl)triphenylphosphonium bromide [(Ph$_3$PCF$_2$H)$^+$Br$^-$] resulting from the reaction between (Ph$_3$PCF$_2$Br)$^+$Br$^-$ and H$_2$O to explain the unexpected hydro-difluoromethylation. Interestingly, the presence of H$_2$O, PPh$_3$, NaI, and KHCO$_3$ in the reaction medium was critical for selective synthesis of hydro-difluoromethylated alkanes (**63**). Terminal and internal alkenes bearing various functional groups (**62**) were compatible with the desired organic transformation, affording the hydro-difluoromethylated products in moderate to high yields (**63**, Scheme 11: 28 examples, 36–87% yields). In addition, this synthetic approach can be extended to more structurally complex substrates such as analogues of 4-methyl-umbelliferone (**64**, Figure 3), phthalimide (**65**, Figure 3), L-phenylalanine (**66**, Figure 3), and estrone (**67**, Figure 3), as well as to biologically active
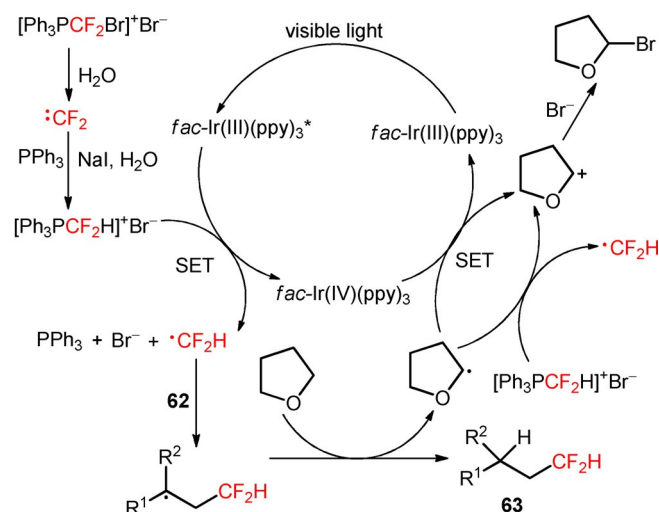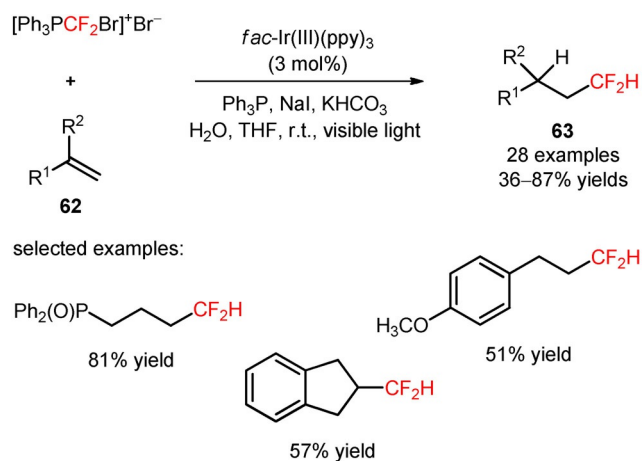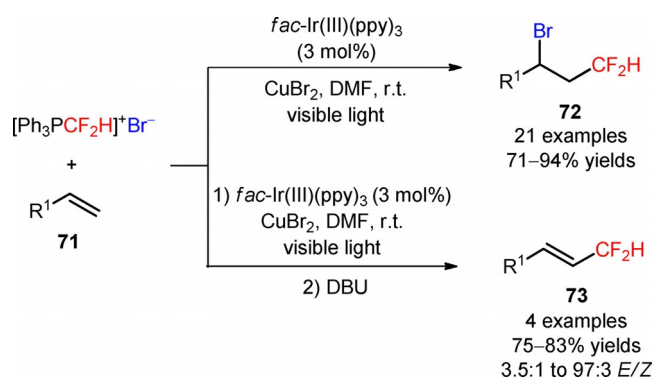
Scheme 11. Hydro-difluoromethylation of unactivated alkenes (**62**) with [Ph$_3$PCF$_2$Br]$^+$Br$^-$ under visible light photoredox conditions.
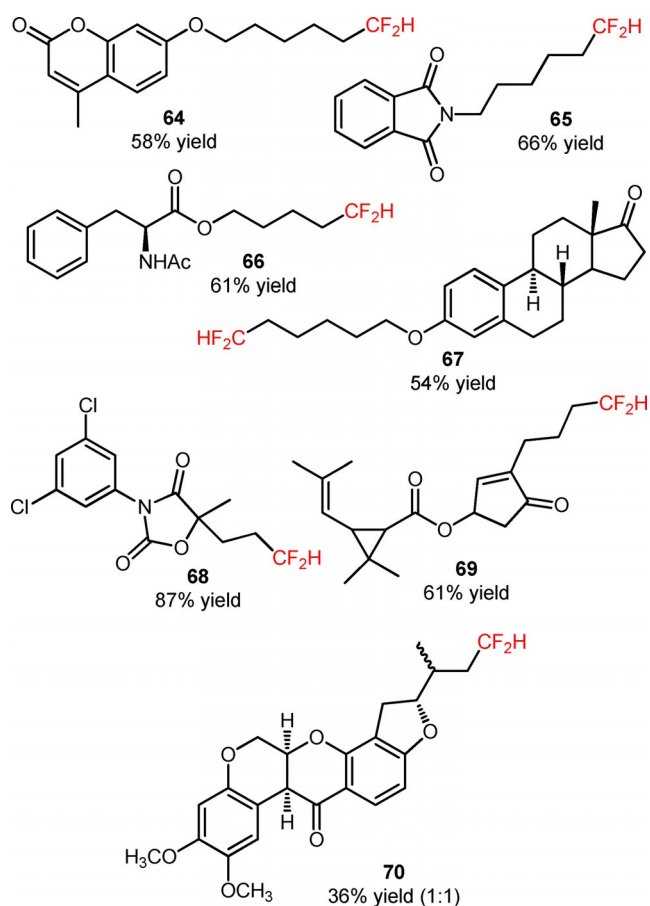
Figure 3. Chemical structures of hydro-difluoromethylated analogues of 4-methylumbelliferone (**64**), phthalimide (**65**), L-phenylalanine (**66**), and estrone (**67**), vinclozolin (**68**), allethrin (**69**), and rotenone (**70**).

Scheme 12. Visible light-induced photocatalytic bromo-difluoromethylation and direct difluoromethylation of alkenes (**71**) with $[Ph_3PCF_2H]^+Br^-$.

compounds, including the fungicide vinclozolin (**68**, Figure 3) and the two insecticides allethrin (**69**, Figure 3) and rotenone (**70**, Figure 3). Isotopic mechanistic experiments involving D_2O and THF-d_8 demonstrated that both H_2O and THF were the sources of hydrogen atoms for the hydro-difluoromethylation process. The authors proposed a mechanism of oxidative quenching of *fac*-Ir(III)(ppy)$_3$* and concomitant reduction of $(Ph_3PCF_2H)^+Br^-$ to CF_2H radicals. Electrophilic addition of CF_2H radicals to the alkenes (**62**) and subsequent abstraction of a hydrogen atom from THF afforded the respective hydro-difluoromethylated derivatives (**63**).

Later, the same group described the application of $(Ph_3PCF_2H)^+Br^-$ in the bromo-difluoromethylation of alkenes (**71**) under visible light photoredox conditions.[70] The use of catalytic amounts of *fac*-Ir(III)-(ppy)$_3$ and CuBr$_2$ allowed the selective preparation of bromo-difluoromethylated alkanes (**71**), suppressing the unwanted hydro-difluoromethylation of the substrates (**72**, Scheme 12: 21 examples, 71–94% yields). The protocol was also applied to the direct bromo-di-

fluoromethylation of more complex and biologically active molecules, including the fungicide vinclozolin (**74**, Figure 4) and the insecticides allethrin (**75**, Figure 4) and rotenone (**76**, Figure 4). Difluoromethylated alkenes were achieved *via* a one-pot bromo-difluoromethylation/dehydro-bromination process (**73**, Scheme 12: 4 examples, 75–83% yields).
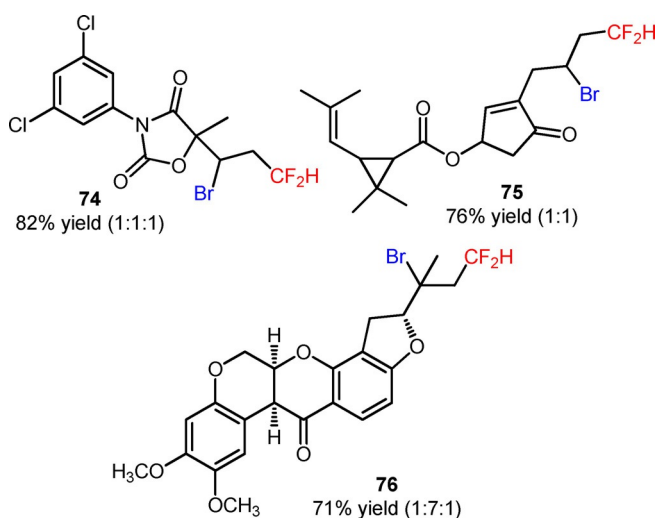
Figure 4. Chemical structures of bromo-difluoromethylated vinclozolin (**74**), allethrin (**75**), and rotenone (**76**).

Difluoromethylated ethers and alcohols were efficiently obtained *via* visible light-mediated oxy-difluoromethylation of styrenes (**77**, **79**) with the difluoromethylating reagent $[Ph_3PCF_2H]^+Br^-$ using alcohol derivatives and water, respectively, as nucleophiles (**78**, Scheme 13A: 21 examples, 48–96% yields; **80**, Scheme 13B: 6 examples, 81–91% yields).[71] The protocol was applicable to the late-stage oxy-difluoromethylation of vinyl-*N*-benzoyl-L-tyrosine ethyl ester (**81**, Figure 5) and vinylestrine (**82**, Figure 5).

A

selected examples:

B

selected examples:
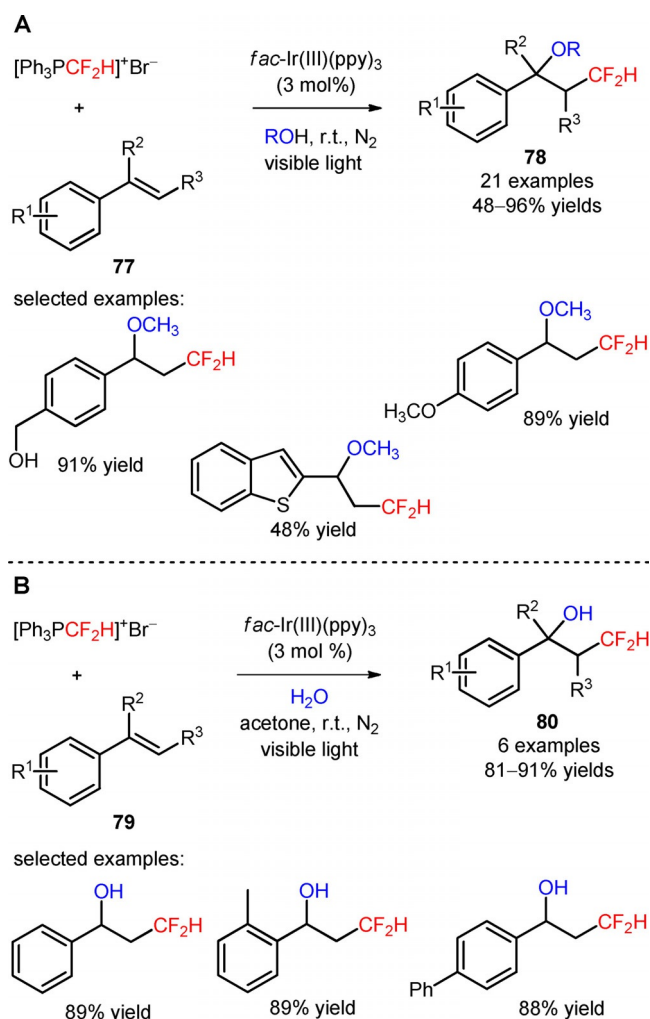
Scheme 13. Visible light-induced oxy-difluoromethylation of styrenes with [Ph$_3$PCF$_2$H]$^+$Br$^-$ using alcohol derivatives (**A**) and water (**B**).
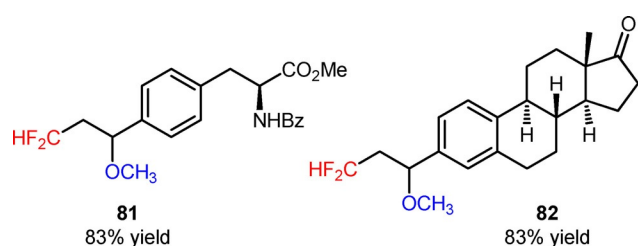

Figure 5. Chemical structures of the products of oxy-difluoromethylation of vinyl-*N*-benzoyl-L-tyrosine ethyl ester (**81**) and vinylestrine (**82**).

The shelf-stable and easy-to-handle *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (CAS number: 1097192-99-8, so-called Hu's reagent), with the electron-withdrawing sulfoximine group was initially conceived as a difluorocarbene source for the introduc-

tion of CF$_2$H groups to C-, N-, and S-nucleophiles.[72] Recently, it has been found that this reagent can also be implemented as a precursor of CF$_2$H radicals under photoredox conditions. In fact, Akita and co-workers reported an efficient protocol to achieve the oxy-difluoromethylation of alkenes and styrenes (**83**) using *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine and the nucleophile H$_2$O under irradiation with blue LEDs.[73] In the presence of *fac*-Ir(III)(ppy)$_3$, a broad range of difluoromethylated alcohols containing electron-donating and electron-withdrawing groups was sucessfully synthesized (**84**, Scheme 14: 20 examples,

selected examples:
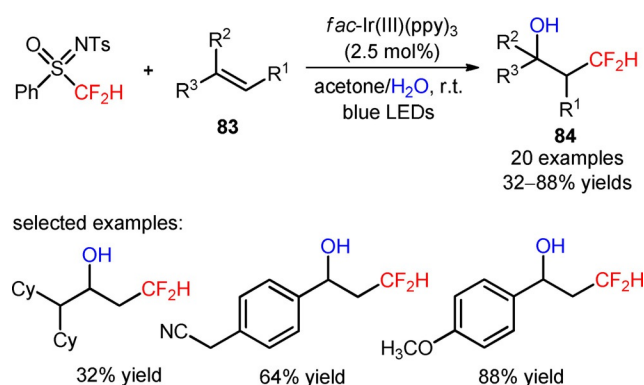
Scheme 14. Oxy-difluoromethylation of alkenes (**83**) using *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine and H$_2$O in the presence of *fac*-Ir(III)(ppy)$_3$.

32–88% yields). Moreover, structurally complex alkenes, such as vinylestrone (**85**, Figure 6) and vinyl-*N*-benzoyl-L-tyrosine ethyl ester (**86**, Figure 6), as well as other oxygen nucleophiles, such as alcohols and carboxylic acids, were also compatible with the described oxy-difluoromethylation strategy. Mechanistic experiments with the radical scavenger 2,2,6,6-tetra-methylpiperidine *N*-oxide (TEMPO) suggested the intermediacy of CF$_2$H radicals *via* oxidative quenching of *fac*-Ir(IV)(ppy)$_3$*.
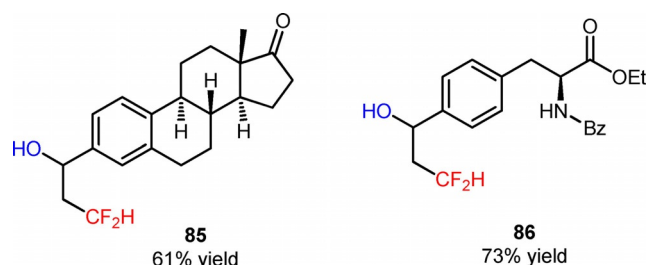
Figure 6. Chemical structures of the products of oxy-difluoromethylation of vinylestrone (**85**) and vinyl-*N*-benzoyl-L-tyrosine ethyl ester (**86**).

2.2 Difluoroalkylation of sp^2 Carbon Atoms in Enol Derivatives, α,β-Unsaturated Carboxylic Acids, and Allylic Alcohols

Dolbier and collaborators described a methodology for the visible light-mediated insertion of methoxycarbonyldifluoromethyl groups in enol acetates (**87**) with methyl 2,2-difluoro-2-(chlorosulfonyl)acetate (ClSO$_2$CF$_2$CO$_2$Me, CAS number: 18225-68-8).[74] A wide array of 2,2-difluoro-γ-keto esters was efficiently prepared in moderate to very good yields (**88**, Scheme 15: 7 examples, 50–83% yields) using the catalyst Ir{[dF(CF$_3$)ppy]$_2$(dtbbpy)}PF$_6$[55] and the additive LiBF$_4$ to enable removal of the acetyl groups.
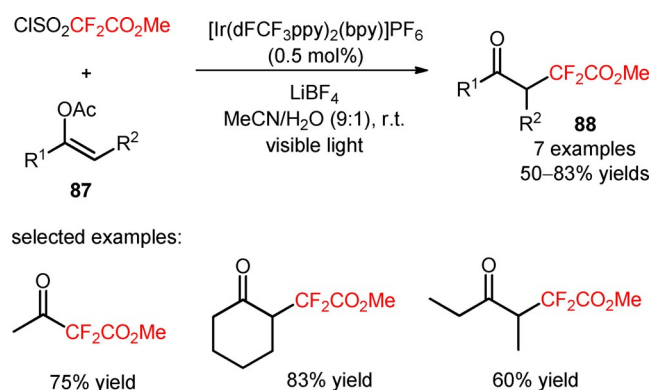
Scheme 15. Methoxycarbonyldifluoromethylation of enol acetates (**87**) by visible light photoredox catalysis.

Difluoroalkylated polycyclic lactones (**90**) were synthesized by radical difluoroalkylation of 2-oxo-2,3-dihydrofuran derivatives (**89**) with α-bromo-α,α-difluoroacetophenones and a consecutive annulation reaction, under irradiation with 33 W fluorescent light bulbs.[75] The strategy of cascade difluoroalkylation/annulation was efficiently performed in the presence of *fac*-Ir(III)(ppy)$_3$, the base 2,6-lutidine, and using a solvent mixture of DMA and DCE in a ratio of 1:1 (Scheme 16). Alkyl-substituted enol lactones (**89**), and α-bromo-α,α-difluoroacetophenones bearing electron-rich and electron-withdrawing groups on the aromatic ring provided a wide range of annulated difluoroalkyl-containing products with an excellent diastereoselectivity (only *cis* products were generated) in moderate to excellent yields (**90**, 17 examples, 31–94% yields).
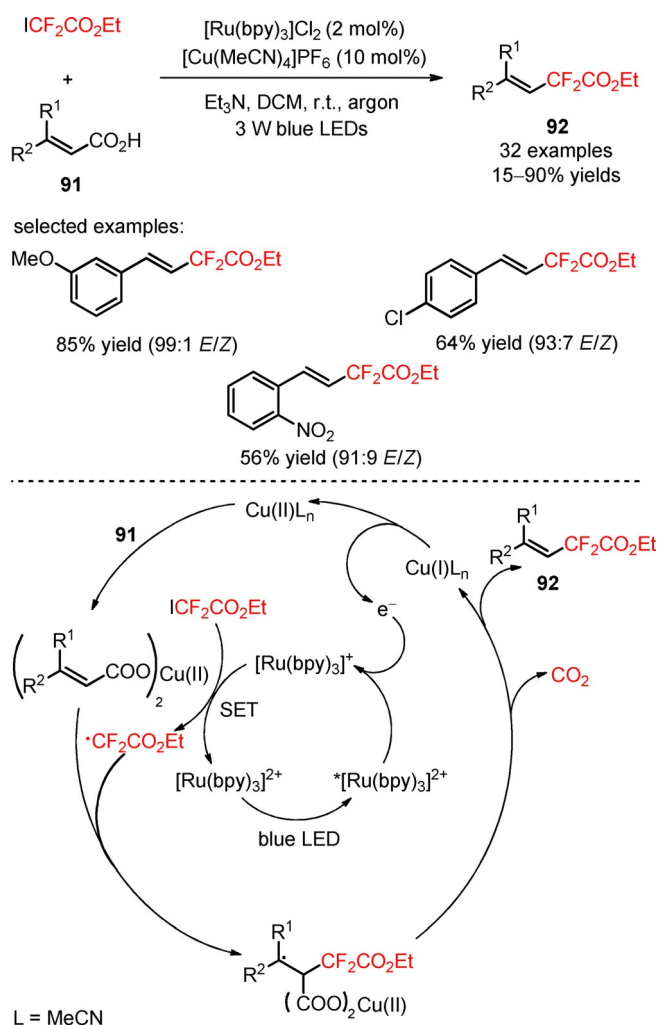
α,β-Unsaturated carboxylic acids have been used as substrates for decarboxylative difluoroalkylation under transition metal catalysis.[76,77] Visible light-driven methodologies using these substrates have been described by several groups. In 2016, Liu and co-workers have developed a methodology for the decarboxylative functionalization of α,β-unsaturated carboxylic acids (**91**) with the difluoroalkylating reagent
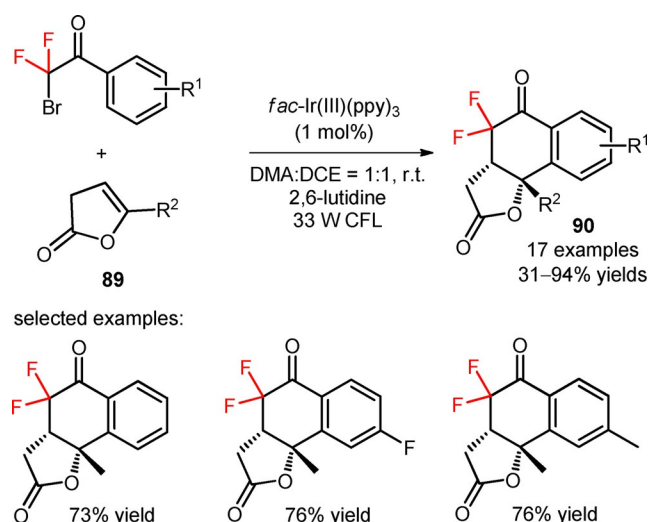
Scheme 16. Visible light-mediated photocatalytic difluoroalkylation of 2-oxo-2,3-dihydrofuran derivatives (**89**) with α-bromo-α,α-difluoroacetophenones. CFL = compact fluorescent lamp.

ethyl 2,2-difluoro-2-iodoacetate (ICF$_2$CO$_2$Et, CAS number: 7648-30-8) by using a dual-catalytic system merging photocatalysis and copper catalysis.[78] The photocatalyst [Ru(bpy)$_3$]Cl$_2$,[79,80] the copper catalyst [Cu(MeCN)$_4$]PF$_6$, and the solvent DCM constituted the selected conditions for the difluoroalkylation reaction (Scheme 17). A wide array of α,β-unsaturated carboxylic acids possessing electron-rich and electron-deficient (hetero)aromatic groups gave the corresponding difluoroalkylated styrenes with high E/Z selectivity in moderate to excellent yields (**92**, 32 examples, 15–90% yields). The authors hypothesized a mechanism involving a reductive quenching of *[Ru(bpy)$_3$]$^{2+}$ *via* [Cu(MeCN)$_4$]$^+$. Subsequent reduction of ICF$_2$CO$_2$Et to CF$_2$CO$_2$Et radicals led to the regeneration of the photocatalyst in its ground state. Electrophilic radical addition to the α-position of the double bond in the substrates followed by elimination of CO$_2$ and [Cu(MeCN)$_4$]$^+$ afforded the difluoroalkylated styrenes (**92**).

The application of the platinum photocatalyst Pt(II)[R(C^N^P^P)] (R = 4-CH$_3$OC$_6$H$_4$) was described as an alternative approach for the construction of E-difluoroalkylstyrenes from reaction between α,β-unsaturated carboxylic acids (**93**) and ICF$_2$CO$_2$Et, under irradiation with blue LEDs (**94**, Scheme 18A: 27 examples, 30–92% yields).[81] A mechanism for the difluoroalkylation mediated by oxidation of the Pt(II) complex and formation of CF$_2$CO$_2$Et radicals was proposed along with an initial deprotonation of the α,β-unsaturated carboxylic acids (**93**) by NaHCO$_3$. The developed methodology for the difluoroalkylation of α,β-unsaturated carboxylic acids (**95**) can also be performed using the reagent BrCF$_2$CO$_2$Et (**96**, Scheme 18B: 6 examples, 35–60% yields). In the pres-

Scheme 17. Photoredox- and copper-catalyzed decarboxylative difluoroalkylation of α,β-unsaturated carboxylic acids (**91**) with ICF_2CO_2Et and the proposed mechanism.

Scheme 18. Platinum-catalyzed difluoroalkylation of α,β-unsaturated carboxylic acids (**93**, **95**) with the reagents ICF_2CO_2Et (**A**) and $BrCF_2CO_2Et$ (**B**).

ence of *N,N*-diisopropylethylamine (DIPEA), the reagent ICF_2CO_2Et can also be used for the synthesis of difluoroalkyl-containing alkenyl iodides and *Z*-difluoroalkylstyrenes *via* photoinduced difluoroalkylation of terminal arylalkynes.

As an alternative to ICF_2CO_2Et, Noël and co-workers employed the reagent $BrCF_2CO_2Et$ for the decarboxylative difluoroalkylation of α,β-unsaturated carboxylic acids (**97**) in the presence of *fac*-Ir(III)-(ppy)₃.[82] The developed strategy required no higher temperatures, no metal co-catalysts, or hypervalent iodine reagents to facilitate the decarboxylation process. A spectrum of *meta*- and *para*-substituted α,β-unsaturated carboxylic acids bearing electron-neutral, electron-donating, and electron-withdrawing substituents on the aromatic ring and heterocyclic substituents (pyridine and thiophene) (**97**) afforded the respective difluoroalkylated styrenes with a good to excellent *E*-stereoselectivity (**98**, Scheme 19: 18 exam-

ples, 33–81% yields). In contrast, the decarboxylative difluoroalkylation of *ortho*-substituted α,β-unsaturated carboxylic acids (**99**) provided the corresponding *Z*-products (**100**) under batch conditions. A switch in the stereoselectivity was observed when the decarboxylative functionalization of the substrates was performed under continuous-flow conditions (**100**, Scheme 20: 12 examples, batch: 55–87% yields, continuous flow: 39–67% yields). Interestingly, this methodology can be successfully applied to *ortho*-, *meta*-, *para*-substituted arylpropiolic acids (**101**) for the syn-
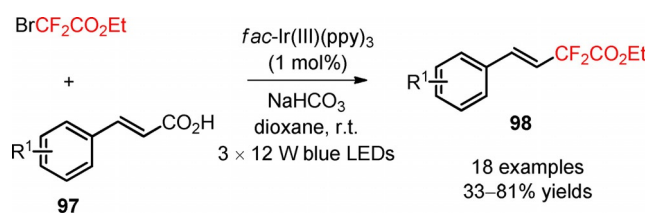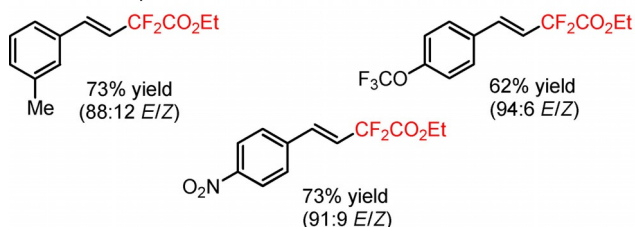
Scheme 19. Visible light-promoted photocatalytic decarboxylative difluoroalkylation of *meta*- and *para*-substituted α,β-unsaturated carboxylic acids (**97**).
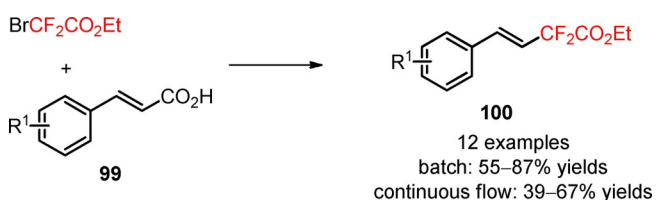
batch conditions: *fac*-Ir(III)(ppy)₃, NaHCO₃/H₂O, dioxane, r.t., under argon, 3 × 12 W blue LEDs, 24 h
continuous flow conditions: *fac*-Ir(III)(ppy)₃, 2,6-lutidine, dioxane/EtOH, r.t., under argon, 3 × 12 W blue LEDs, residence time: 15 min

selected examples:

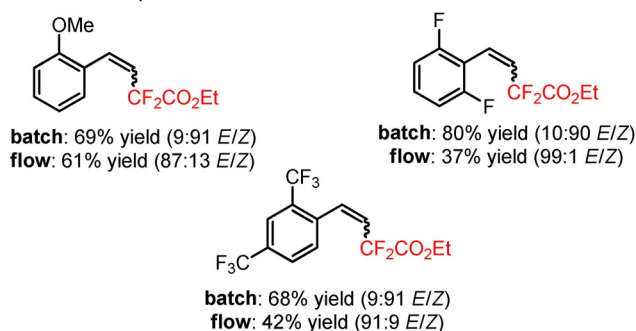**Scheme 20.** Visible light-promoted photocatalytic decarboxylative difluoroalkylation of *ortho*-substituted α,β-unsaturated carboxylic acids (**99**) under batch and continuous flow conditions.

thesis of difluoroalkylated phenylacetylenes (**102**, Scheme 21: 12 examples, 17–62% yields).

The synthesis of carbodifluoroalkylated ketones by visible light-promoted difunctionalization of allylic alcohols through a sequential difluoroalkylation and functional group migration process has been reported in the literature. Zhu and co-workers disclosed an efficient methodology for the carbodifluoroalkylation of α,α-diarylallylic alcohols with electron-donating and
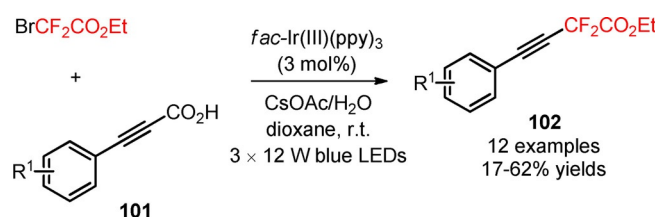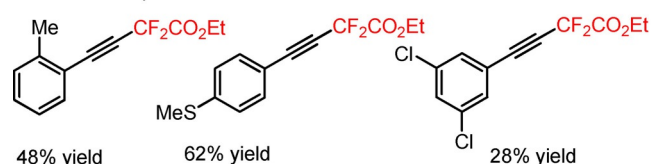
Scheme 21. Visible light-promoted photocatalytic decarboxylative difluoroalkylation of arylpropiolic acids (**101**).

electron-withdrawing substituents (**103**) attached to the aromatic rings and a subsequent 1,2-aryl migration process, in the presence of *fac*-Ir(III)(ppy)₃, the base KOAc, and BrCF₂CO₂Et (**104**, Scheme 22: 20 examples, 33–83% yields).[83] The difluoroalkylation/functional group migration process was also achievable using bromodifluoroacetamides.
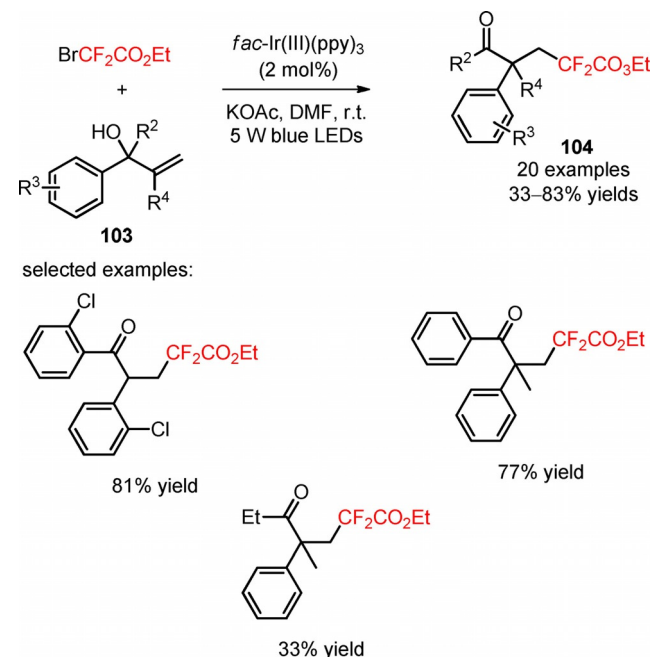
Scheme 22. Photoinduced carbo-difluoroalkylation of α,α-diarylallylic alcohols (**103**).

Recently, Noël's group reported a similar synthetic strategy for the difluoroalkylation of heteroaryl-containing allylic alcohols (**106**) and concomitant 1,2-heteroaryl migration with BrCF₂CO₂Et.[84] Heteroaryl-containing allylic alcohols were synthesized *via* reactions between heteroaryl ketones (**105**) and vinylmag-

nesium bromide, under continuous-flow conditions (**106**, Scheme 23A: 15 examples, 33–92% yields). A higher efficiency for the difluoroalkylation/1,2-heteroaryl migration process was achieved when *fac-*

A

105

106
15 examples
33–92% yields
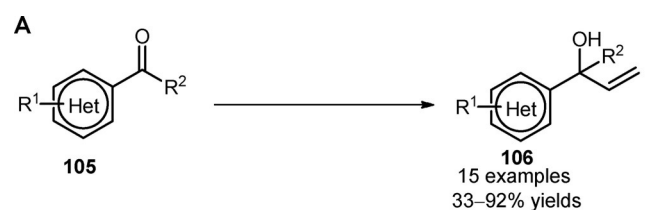
continuous-flow conditions: (i) CH$_2$CHMgBr, THF, 0 °C, residence time: 5 min; (ii) NH$_4$Cl quench

B

BrCF$_2$CO$_2$Et

107

108
12 examples
batch: 45–89% yields
flow: 61–98% yields
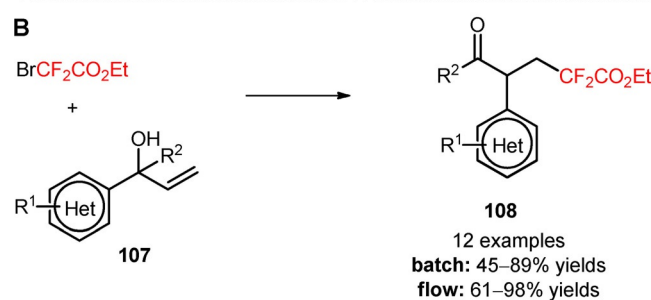
batch conditions: *fac-*Ir(III)(ppy)$_3$ (1 mol%), imidazole, DCM, r.t., 12 W blue LEDs, 6 h.
continuous flow conditions: *fac-*Ir(III)(ppy)$_3$ (1 mol%), imidazole, DCM, r.t., 12 W blue LEDs, residence time: 10 min.

selected examples:

batch: 82% yield
flow: 98% yield

batch: 87% yield
flow: 93% yield

batch: 60% yield
flow: 84% yield

Scheme 23. Photocatalytic difluoroalkylation-induced 1,2-heteroaryl migration of allylic alcohols (**106**).

Ir(III)(ppy)$_3$ and imidazole were chosen as photocatalyst and base, respectively. Under the optimized photochemical conditions, the 4-pyridyl, 3-pyridyl, 2-pyridyl, pyrazyl, and benzothiophenyl groups exhibi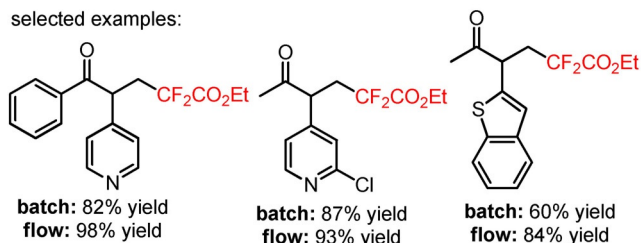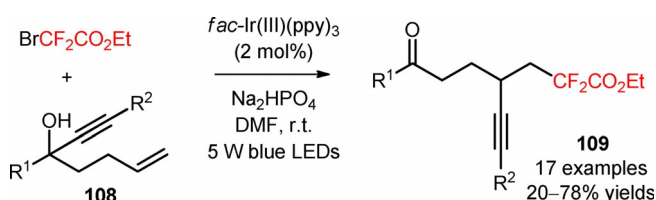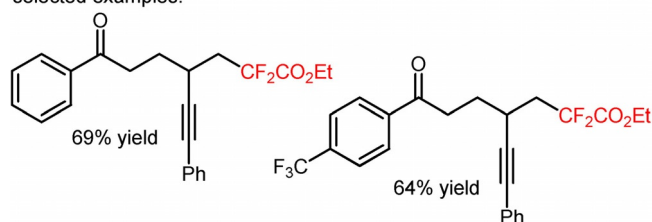ted a migratory aptitude induced by incorporation of CF$_2$CO$_2$Et groups, affording the final products in good yields under batch conditions (**107**, Scheme 23B: 12 examples, batch: 45–89% yields). A switch to continuous-flow conditions enabled a reduction of the reaction time with a concomitant increase of the reaction yields (batch: 45–89% yields *vs.* continuous-flow: 61–98% yields). The radical addition of two CF$_2$CO$_2$Et groups was observed with benzofuranyl- and thiophenyl-containing substrates, yielding the respective bis-functionalized derivatives. Other difluoro-

alkyl precursors including BrCF$_2$PO(OEt)$_2$ and bromodifluoroacetamide derivatives efficiently promoted the heteroaryl migration. Mechanistic experiments with the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) corroborated the involvement of a radical-mediated difluoroalkylation.

Alkynyl-substituted difluoroalkyl ketones were achieved by photoinduced difluoroalkylation of unactivated alkenes (**108**) with BrCF$_2$CO$_2$Et and subsequent migration of the alkynyl groups (**109**, Scheme 24: 17 examples, 20–78% yields).[85] A series of aromatic alkynyl motifs bearing electron-donating and electron-withdrawing groups exhibited this migratory aptitude. The developed methodology can be extended to different difluoroalkyl reagents such as bromodifluoroacetamides and 2-bromo-2,2-difluoro-1-morpholinoethan-1-one.

BrCF$_2$CO$_2$Et

*fac-*Ir(III)(ppy)$_3$
(2 mol%)

Na$_2$HPO$_4$
DMF, r.t.
5 W blue LEDs

108

109
17 examples
20–78% yields

selected examples:

69% yield

64% yield

Scheme 24. Photoinduced difluoroalkylation of unactivated alkenes (**108**) in the presence of *fac-*Ir(III)(ppy)$_3$.

The strategy of distal functional group migration was also implemented by Zhu and collaborators for the carbodifluoroalkylation of unactivated alkenes (**110**, **112**, **114**, **116**) in combination with visible light photocatalysis.[86] For the carbodifluoroalkylation process, intramolecular migration was observed for products bearing a series of functional groups including heteroaryl (**111**, Scheme 25A: 18 examples, 53–95% yields), imino (**113**, Scheme 25B: 3 examples, 74–91% yields), formyl (**115**, Scheme 25C: 12 examples, 60–83% yields), and alkynyl groups (**117**, Scheme 25D: 18 examples, 41–70% yields), in the presence of *fac-*Ir(III)(ppy)$_3$ and BrCF$_2$CO$_2$Et. The authors suggested a mechanism involving electrophilic addition of CF$_2$CO$_2$Et radicals to the alkene moiety and subsequent cyclization with the radical acceptor groups (heteroaryl, imino, formyl, and alkynyl groups). Ring-opening homolysis followed by oxidation *via fac-*

Kim and collaborators using the difluoroalkyl precursors BrCF₂CO₂Et[87] and [Ph₃PCF₂H]⁺Br⁻.[88] A wide range of 1-(1-arylvinyl)cyclobutanols bearing electron-donating, electron-neutral, and electron-withdrawing groups furnished the difluoroalkyl-substituted cyclic ketones with moderate to good yields (**119**, Scheme 26A: 8 examples, 29–73% yields; **121**, Scheme 26B: 9 examples, 45–89% yields).

Scheme 25. Visible light-induced heteroaryl- (**110**), imino- (**112**), formyl- (**114**), and alkynyl-difluoroalkylation of unactivated alkenes (**116**) based on distal functional group migration and the proposed mechanism.
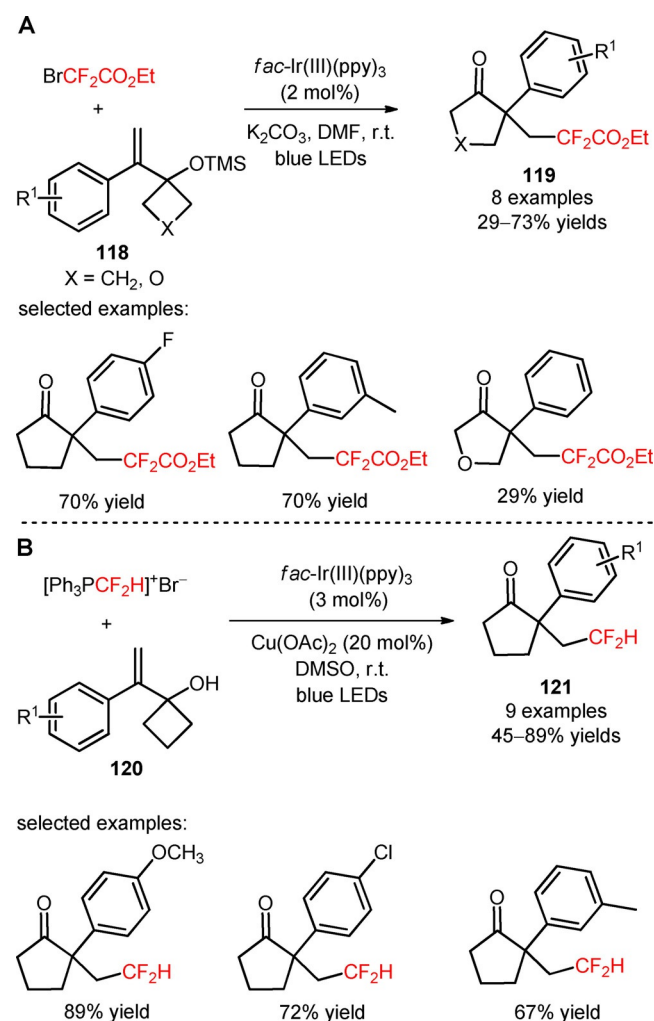
Scheme 26. Visible light-induced photocatalytic difluoroalkylation/1,2-carbon migration of 1-(1-arylvinyl)cyclobutanol derivatives (**118**, **120**) with BrCF₂CO₂Et (**A**) and [Ph₃PCF₂H]⁺Br⁻ (**B**).

Ir(IV)(ppy)₃ and base-mediated deprotonation gave the respective difluoroalkylated ketones (**111**, **113**, **115**, **117**).

Visible light-mediated difluoroalkylation of 1-(1-arylvinyl)cyclobutanol derivatives (**118**, **120**) and ring expansion *via* 1,2 carbon migration was described by

The difluoromethyl precursor *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine was effectively implemented in the diastereoselective synthesis of *anti*-difluoromethyl-substituted spiroethers through visible light-mediated oxy-difluoromethylation of aryl-fused cycloalkenyl alcohol derivatives (**122**) in the presence of *fac*-Ir(III)(ppy)₃ (**123**, Scheme 27: 3 examples, 38–56% yields).[89]
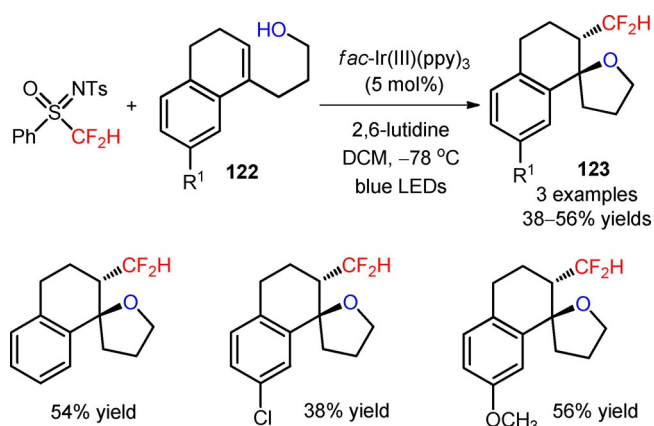
Scheme 27. Oxy-difluoromethylation of aryl-fused cycloal-kenylalkanols (**122**) with *N*-tosyl-*S*-difluoromethyl-*S*-phenyl-sulfoximine under visible light photoredox conditions.

Scheme 28. Visible light-mediated tandem difluoromethyla-tion/cyclization of *N*-arylacrylamides (**124**) with HCF₂SO₂Cl.

2.3 Difluoroalkylation of *sp²* Carbon Atoms in Unsaturated Amides, Hydrazones, and Allylamines

The radical difluoroalkylation of a series of unsaturated amides has been employed as an efficient strategy of producing synthetic precursors to access more complex and functionalized heterocyclic derivatives. In 2014, Dolbier and collaborators disclosed a methodology for tandem difluoromethylation of *N*-arylacryl-amides (**124**) with HCF₂SO₂Cl and consecutive cyclization, under irradiation with visible light.[90] The authors found that the *fac*-Ir(III)(ppy)₃ was the most effective catalyst for the reduction of HCF₂SO₂Cl and generation of CF₂H radicals under mild conditions. The introduction of electron-donating and electron-withdrawing groups in the aromatic ring of *N*-arylacrylamides (**124**) was well tolerated with the desired organic transformation affording the respective difluoromethylated 3,3-disubstituted 2-oxindoles in moderate to good yields (**125**, Scheme 28: 7 examples, 54–82% yields).

Other difluoroalkylating reagents, including BrCF₂CO₂Et and BrCF₂PO(OEt)₂, have been implemented in the preparation of difluoroalkylated oxindoles from *N*-arylacrylamides (**126**, **128**), in the presence of *fac*-Ir(III)(ppy)₃ and the base Na₂HPO₄ (**127**, Scheme 29A: 18 examples, 68–91% yields; **129**, Scheme 29B: 17 examples, 65–92% yields).[91,92] In 2017, Sun and co-workers developed a methodology for the photoinduced difluoroalkylation with BrCF₂CO₂Et and BrCF₂PO(OEt)₂ of *N*-arylacryla-mides (**130**) and consecutive intramolecular radical addition to the cyano groups and homolytic aromatic substitution.[93] A variety of *N*-arylacrylamides bearing electron-donating and electron-withdrawing groups on the aromatic ring furnished the difluoroalkylated phenanthridines (**131**, Scheme 29C: 16 examples, 63–82% yields). Alternative approaches for the synthesis
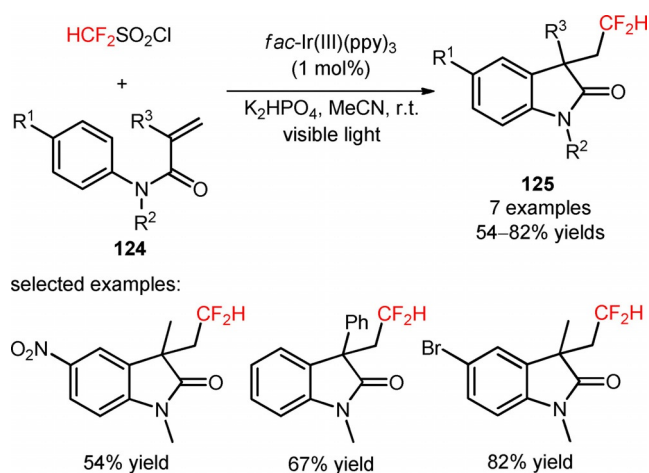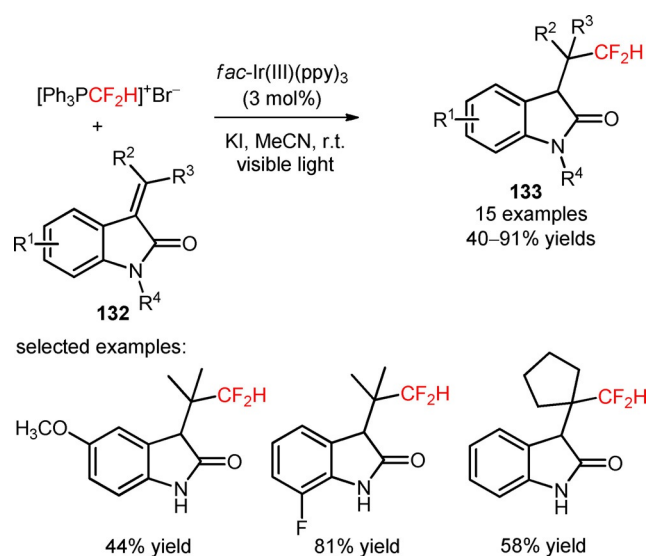
of functionalized phenanthridines from biphenyl iso-cyanides will be discussed in Section 2.5.

An alternative methodology for the synthesis of di-fluoromethylated oxindoles was developed by Qing and co-workers through the photoinduced hydro-di-fluoromethylation of oxindole-derived alkenes (**132**) using the difluoromethylating reagent [Ph₃PCF₂H]⁺Br⁻.[94] In the presence of *fac*-Ir(III)-(ppy)₃, a wide range of oxindole-derived alkenes bearing electron-donating and electron-withdrawing substituents on their aromatic ring and polysubstituted oxindole derived-alkenes afforded the hydro-difluoro-methylated derivatives in moderate to high yields (**133**, Scheme 30: 15 examples, 40–91% yields).

Difluoromethylated 2-azaspiro[4.5]deca-6,9-diene-3,8-diones (**135**) were prepared by Dolbier and collaborators *via* the photoinduced difluoromethylation of *N*-benzylacrylamides (**134**) with HCF₂SO₂Cl and subsequent 5-*exo*-cyclization.[95] Apart from the relevance of *fac*-Ir(III)(ppy)₃ and the base K₂HPO₄ in the di-fluoromethylation/5-*exo*-cyclization process, the addition of water to the reaction system influenced significantly its efficiency. A wide scope of *N*-benzylacryl-amides containing *N*-substituents such as cyclohexyl, isopropyl, *n*-butyl, and *tert*-butyl, and electron-rich and electron-deficient aromatic substituents furnished the desired products (**135**, Scheme 31: 16 examples, 20–93% yields). The authors found that the steric properties of the *N*-substituents may influence the efficiency of the spirocyclization process. This synthetic approach can be extended to other fluoroalkyl radical sources, in particular BrCF₂CO₂Et.

Later, Wang's group used 2-[(difluoromethyl)sulfo-nyl]benzo[*d*]thiazole (2-BTSO₂CF₂H, CAS number: 186204-66-0) for the radical difluoromethylation of *N*-methacryloylbenzamides (**136**) and consecutive intra-molecular cyclization, under visible light photoredox conditions.[96] A palette of difluoromethylated isoqui-

A

127
18 examples
68–91% yields

selected examples:

88% yield

91% yield

78% yield

B

129
17 examples
65–92% yields

selected examples:

85% yield

92% yield

79% yield

C

131
16 examples
63–82% yields

R³ = CO₂Et, PO(OEt)₂

selected examples:

75% yield

76% yield

Scheme 29. Visible light-driven difluoroalkylation of *N*-aryl-acrylamides with BrCF₂CO₂Et (**A**), BrCF₂PO(OEt)₂ (**B**) and both reagents (**C**).

133
15 examples
40–91% yields

selected examples:

44% yield

81% yield

58% yield

Scheme 30. Photoinduced difluoromethylation of oxindole-derived alkenes (**132**).

135
16 examples
20–93% yields

selected examples:

82% yield

76% yield

78% yield
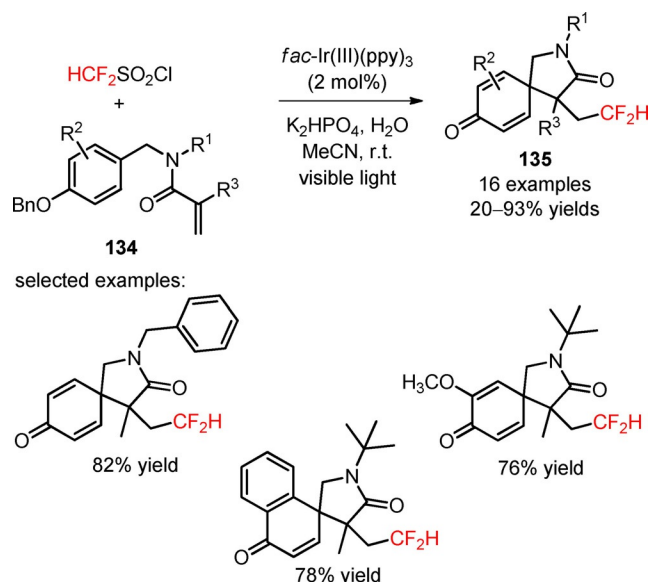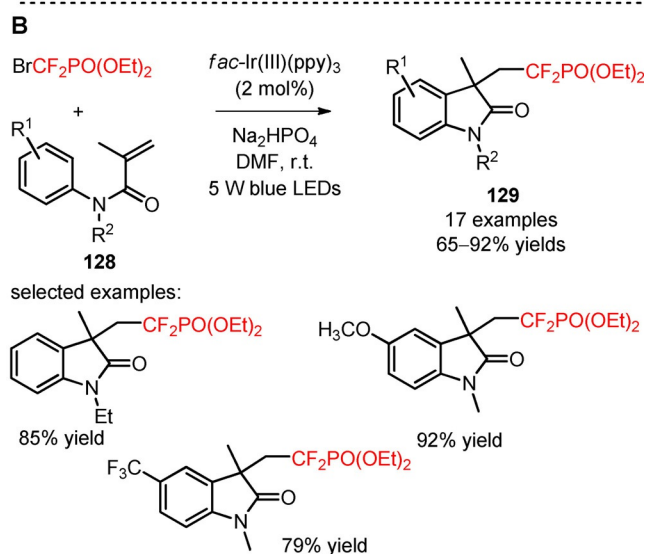
Scheme 31. Photoinduced difluoromethylation/5-*exo* radical cyclization of *N*-benzylacrylamides (**134**).

noline-1,3(2*H*,4*H*)-diones bearing *N*-alkyl substituents, electron-rich, and electron-deficient aromatic substituents on the benzamide moiety was successfully obtained in moderate to good yields (**137**, Scheme 32: 11 examples, 52–79% yields). The authors suggested a mechanism involving oxidative quenching of *fac*-Ir(III)(ppy)₃* and reduction of 2-BTSO₂CF₂H to CF₂H radicals for the preparation of the difluoro-methylated products (**137**).

N-Phenylcinnamamides were applied as substrates for the visible light-catalyzed difluoroalkylation using the reagent BrCF₂CO₂Et.[97] In the presence of *fac*-Ir(III)(ppy)₃, a broad scope of *N*-phenylcinnamamides
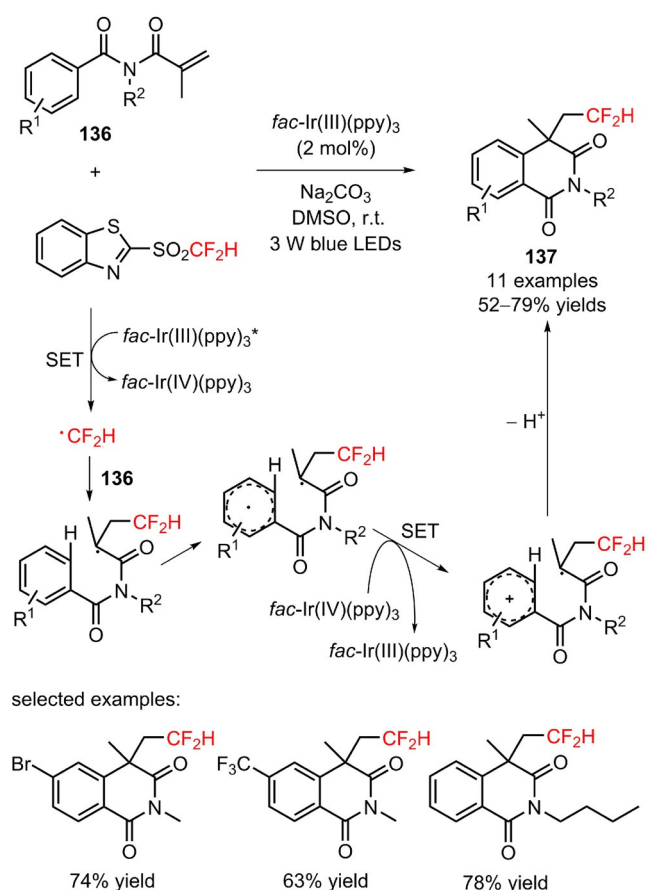
Scheme 32. Visible light-driven difluoromethylation of *N*-methacryloylbenzamides (**136**) with 2-[(difluoromethyl)sulfonyl]benzo[*d*]thiazole (2-BTSO$_2$CF$_2$H).

possessing bulky groups at the *N*-position and electron-withdrawing groups attached to the aromatic rings (**138**) proved to be compatible substrates for the synthesis of difluoroalkylated quinoline-2-ones after intramolecular 6-*endo* cyclization (**139**, Scheme 33A: 14 examples, 43–79% yields). A different pattern of cyclization was found when methoxy or hydroxy groups were attached to the aromatic amide moiety in the *para* position of the aromatic rings (**140**). The unexpected 5-*exo* cyclization/dearomatization process afforded the respective difluoroalkylated spiro[4.5]decanes under the defined reaction conditions (**141**, Scheme 33B: 5 examples, 36–69%).

Difluoroalkylated tetracycles embedded with indole and dihydroisoquinolinone scaffolds (**143**) were effectively constructed by the photoinduced difluoroalkylation/cyclization of 1,8-enynes (**142**) with the reagent BrCF$_2$CO$_2$Et, in the presence of [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$.[98] Under irradiation with 3 W blue LEDs, the combination of the selected photocatalyst with the base Na$_2$HPO$_4$ provided the best reaction conditions for the respective difluoroalkylation process (**143**, Scheme 34: 22 examples, 51–
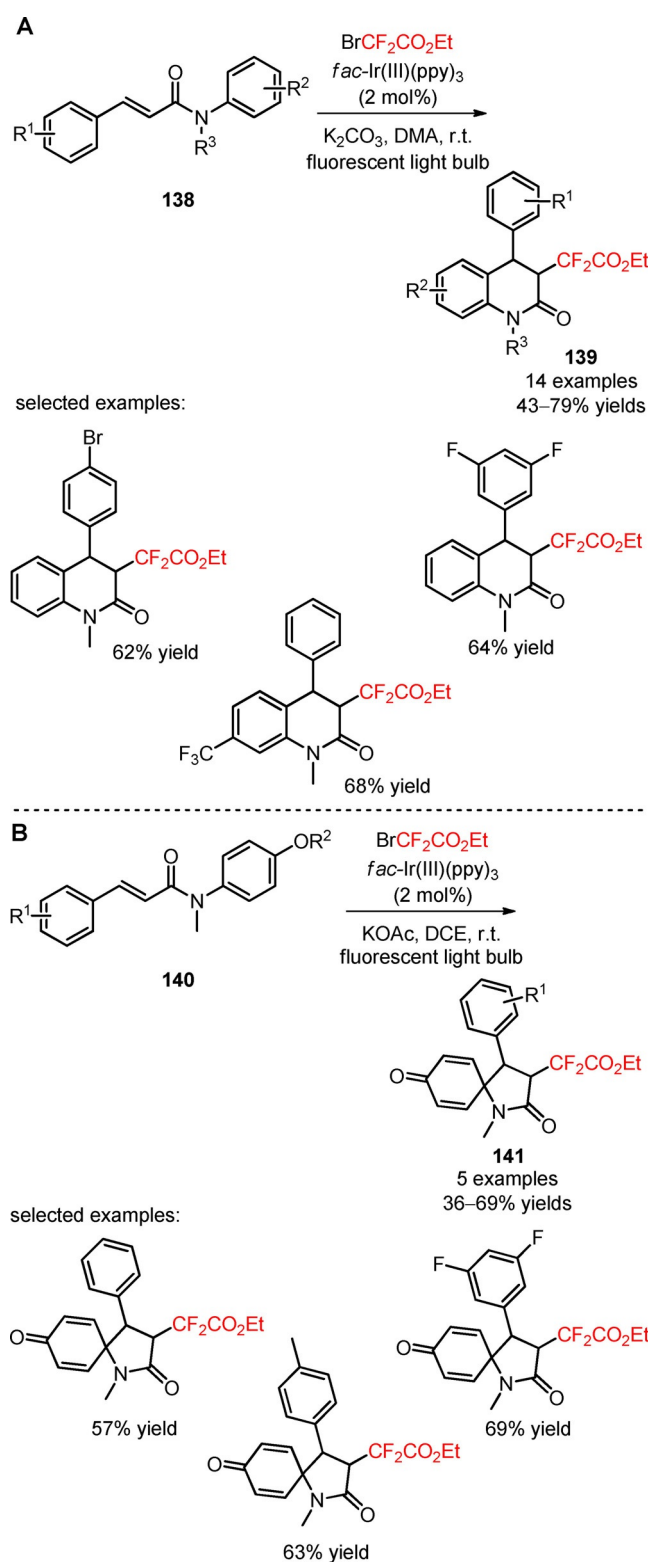
Scheme 33. Photoinduced difluoroalkylation of *N*-phenylcinnamamides (**138**, **140**) for the regioselective synthesis of difluoroalkylated quinoline-2-ones (6-*endo* cyclization) (**139**) and 1-azaspiro[4.5]decanes (5-*exo* cyclization/dearomatization) (**141**).
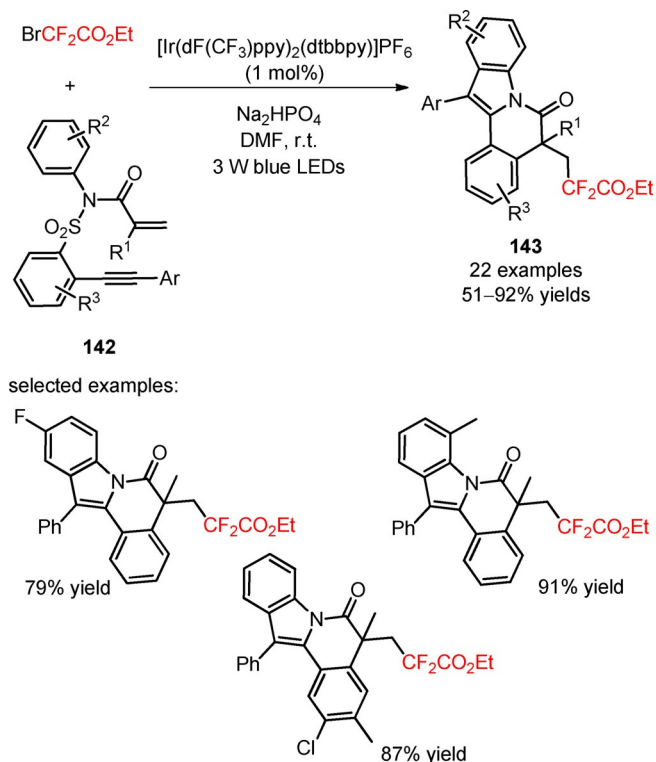
Scheme 34. Visible light-mediated radical difluoroalkylation/cyclization of 1,8-enynes (**142**).

Scheme 35. Photoinduced difluoroalkylation/cyclization reaction of *N*-(but-2-enoyl)indoles (**144**).

92% yields). The difluoroalkyl group of the corresponding products can undergo postfunctionalization steps and be converted into difluoroalkylated alcohol, amide or carboxylic acid derivatives.

Recently, Li and co-workers applied the difluoroalkylating reagent BrCF$_2$CO$_2$Et for the preparation of difluoroalkylated pyrrolo[1,2-*a*]indoles (**145**) from *N*-(but-2-enoyl)indoles (**144**), under irradiation with 3 W blue LEDs.[99] The introduction of electron-donat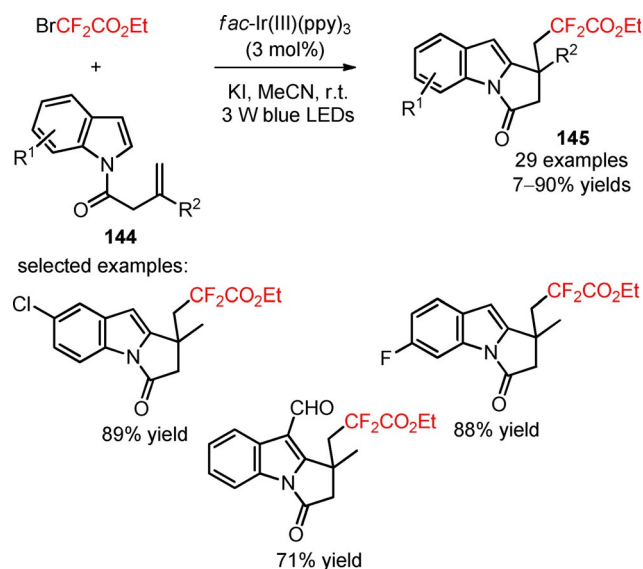ing and electron-withdrawing groups on the aromatic ring and of structurally distinct functional groups on the heteroarene ring of the indole moiety (e.g., cyano, ester, formyl, phenyl, and methyl substituents) was compatible with the desired organic transformation (**145**, Scheme 35: 29 examples, 7–90% yields). Remarkably, difluoroalkylation with alternative reagents derived from difluoroalkyl bromides, including bromoacetates, bromodifluoromethyl ketones, bromodifluoroacetamides, and BrCF$_2$PO(OEt)$_2$ proceeded smoothly with the described methodology.
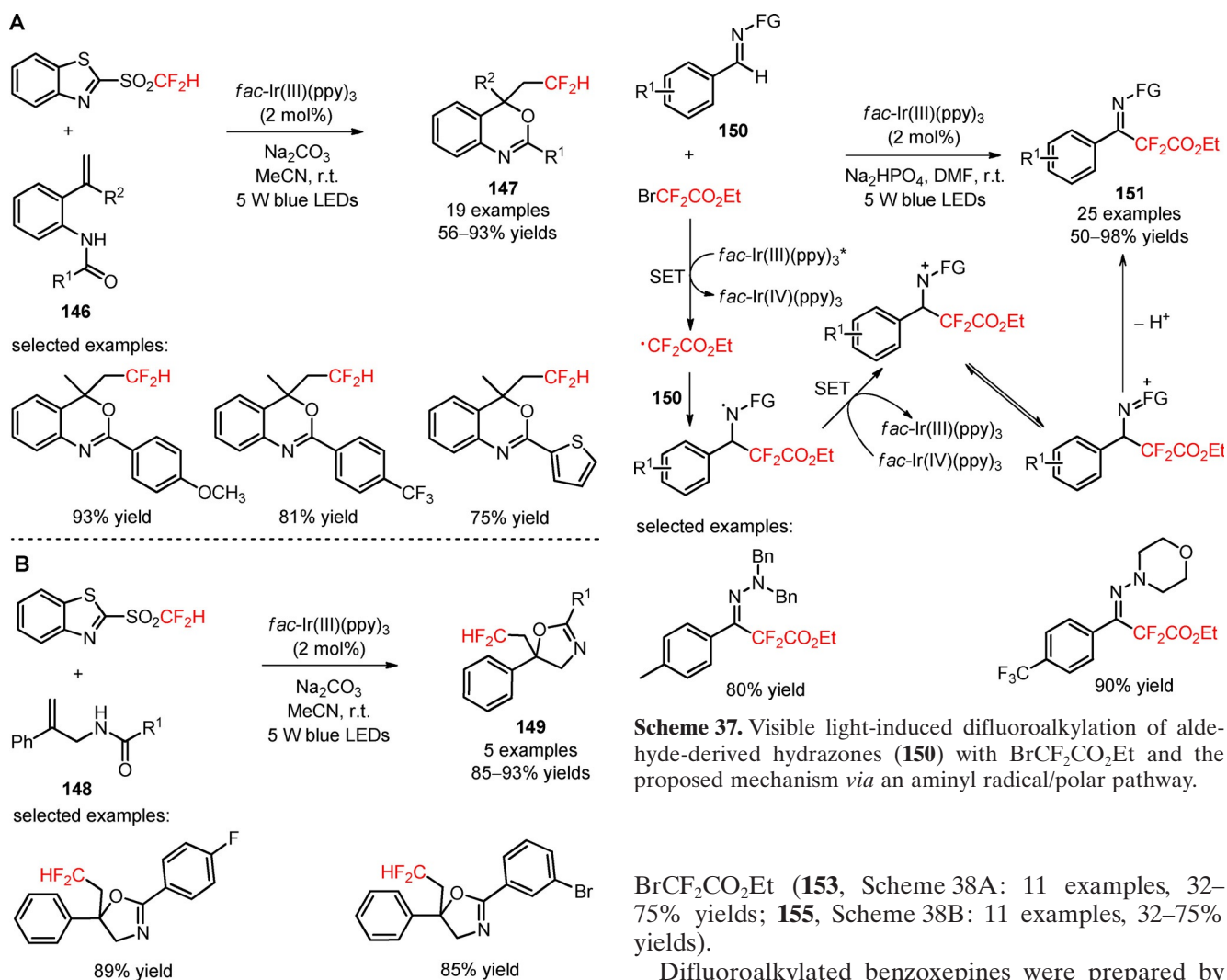
An efficient methodology involving the visible light-induced incorporation of CF$_2$H groups in benzamides (**146**) with 2-BTSO$_2$CF$_2$H and concomitant cyclization to a benzoxazine ring has been reported.[100] A variety of benzamides possessing electron-neutral, electron-donating, and electron-withdrawing groups onto the aromatic rings, heterocyclic, and aliphatic groups (**146**) was efficiently converted into the difluoromethylated benzoxazines (**147**, Scheme 36A: 19

examples, 56–93% yields). Mechanistic experiments with radical scavengers suggested the occurrence of radical-mediated difluoromethylation process and reduction of 2-BTSO$_2$CF$_2$H to CF$_2$H radicals *via* oxidative quenching of *fac*-Ir(III)(ppy)$_3$*. This protocol was expanded to the difluoromethylation of *N*-allylamides (**148**) in excellent yields (**149**, Scheme 36B: 5 examples, 85–93% yields).

Radical difluoroalkylation of the sp^2-hybridized carbon atom of C=N bonds in aldehyde-derived hydrazones (**150**) with BrCF$_2$CO$_2$Et was reported by Zhu and co-workers.[101] The selection of the photocatalyst *fac*-Ir(III)(ppy)$_3$, the base Na$_2$HPO$_4$, and the use of 5 W LEDs as light source resulted in an enhanced efficiency of the difluoroalkylation process (Scheme 37). The introduction of an *N,N*-dialkyl structural motif was critical for the reactivity of *N*-substituted aldehyde-derived hydrazones. Interestingly, a large diversity of *N,N*-dialkyl aldehyde-derived hydrazones bearing electron-rich and electron-deficient aromatic groups, heteroaryl, and aliphatic groups (**150**) furnished the difluoroalkylated hydrazones with moderate to excellent yields (**151**, 25 examples, 50–98% yields). Other difluoroalkyl motifs, including bromodifluoroacetamides and phenylalanine-derived bromodifluoroamide, were also compatible with the developed difluoroalkylation procedure. Two possible reaction pathways were proposed for the formation of difluoroalkyl-containing hydrazones (**151**): an aminyl radical/polar process and a carbon radical/polar process. Computational calculation of Gibbs free-energy profiles for both reaction pathways excluded the occurrence of a carbon radical/polar process. Therefore, the authors proposed a mechanism involving the addition of CF$_2$CO$_2$Et radicals to

A

147
19 examples
56–93% yields

selected examples:

93% yield   81% yield   75% yield

B

149
5 examples
85–93% yields

selected examples:

89% yield   85% yield

Scheme 36. Visible light-mediated radical oxy-difluoromethylation of benzamides (**146**) and *N*-allylamides (**148**) and with 2-BTSO$_2$CF$_2$H.

151
25 examples
50–98% yields

selected examples:

80% yield   90% yield

Scheme 37. Visible light-induced difluoroalkylation of aldehyde-derived hydrazones (**150**) with BrCF$_2$CO$_2$Et and the proposed mechanism *via* an aminyl radical/polar pathway.

the C=N bond of the substrates (**150**) and generation of an aminyl radical intermediate. Concurrently, the aminyl radical was oxidized *via fac*-Ir(IV)(ppy)$_3$ to an aminyl cation (aminyl radical/polar cross-over step). Further tautomerization and deprotonation then furnished the corresponding difluoroalkylated products (**151**).

Apart from unsaturated amides and hydrazones, the difluoroalkylation of allylamine derivatives such as *ortho*-hydroxyaryl enaminones has also been regarded as a promising approach to access more complex heterocyclic scaffolds of biological relevance. In 2017, two independent works reported by the Zhang[102] and Yang[103] groups have described the synthesis of functionalized chromones by the visible light-mediated difluoroalkylation of *ortho*-hydroxyaryl enaminones bearing electron-donating and electron-withdrawing groups (**152**, **154**) using the reagent

BrCF$_2$CO$_2$Et (**153**, Scheme 38A: 11 examples, 32–75% yields; **155**, Scheme 38B: 11 examples, 32–75% yields).

Difluoroalkylated benzoxepines were prepared by the introduction of CF$_2$CO$_2$Et groups into (*E*)-1-[2-(allyloxy)phenyl]-3-(substituted amino)prop-2-en-1-ones (**156**) under visible light photoredox conditions.[104] Yang's group envisioned that the design of a range of substrates bearing an enaminone moiety and an olefin functionality could trigger an efficient installation of difluoroalkyl moieties and simultaneous intramolecular annulation to afford seven-membered rings. The combined use of the photocatalyst [Ir(dtbbpy)(ppy)$_2$]PF$_6$ with BrCF$_2$CO$_2$Et, the base NaOAc, and the solvent mixture DCM/H$_2$O (10:1) proved to be the optimal conditions for the difluoroalkyl radical-triggered annulation process (Scheme 39). Unexpectedly, the authors found that *N*-disubstituted enaminones could be hydrolyzed to the corresponding benzoxepines with a 1,3-dicarbonyl moiety. Substitution at both *meta*- and *para*-positions of the aromatic ring of *N*-disubstituted enaminones gave the corresponding products in moderate to good yields (**157**, 12 examples, 33–64% yields). In addition, *N*-monosubstituted substrates bearing structurally diverse acyclic and cyclic groups provided the desired benzoxepine derivatives without the occurrence of a

A

B
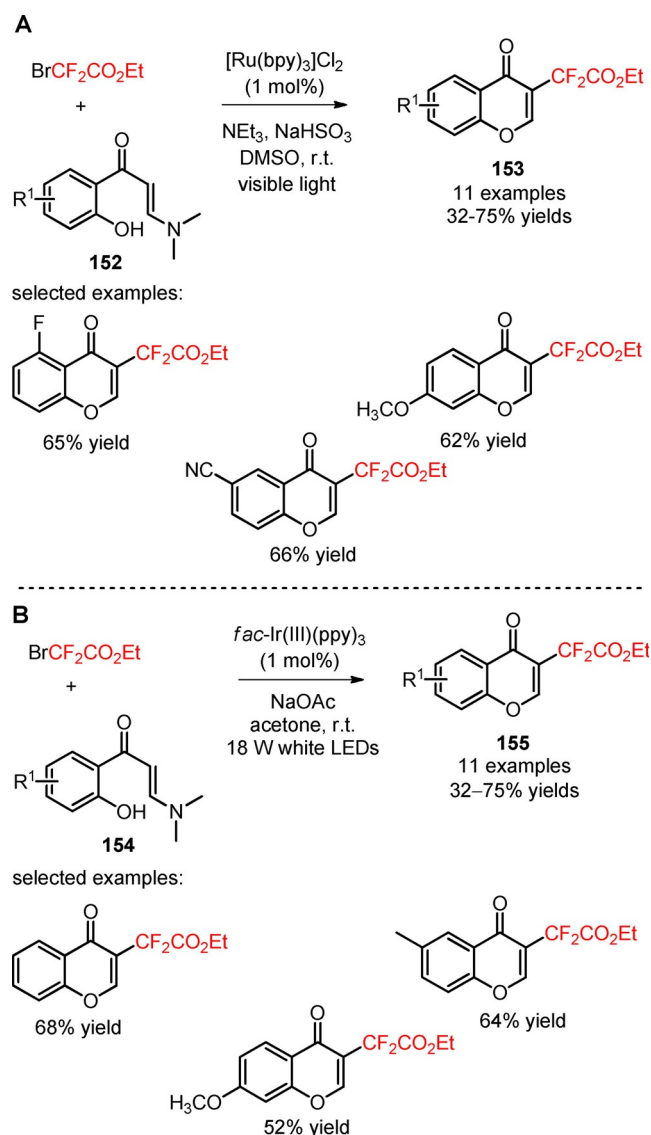
Scheme 38. Visible light-induced difluoroalkylation of *ortho*-hydroxyaryl enaminones (**152**, **154**) in the presence of [Ru(bpy)$_3$]Cl$_2$ (**A**) and *fac*-Ir(III)(ppy)$_3$ (**B**).

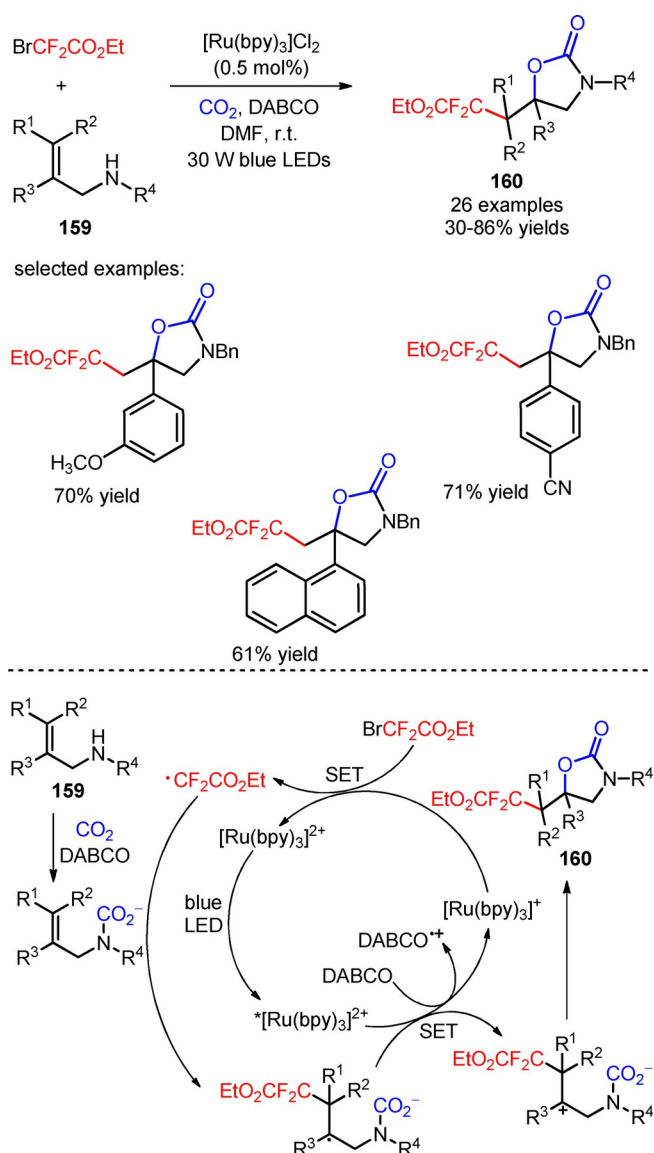**Scheme 39.** Photoinduced difluoroalkylation of *N,N*-disubstituted and *N*-monosubstituted (*E*)-1-[2-(allyloxy)phenyl]-3-(substituted amino)prop-2-en-1-ones (**156**).

BTSO$_2$CF$_2$H. The authors suggested a mechanism involving the intermediacy of CF$_2$CO$_2$Et radicals *via* reductive quenching of *[Ru(bpy)$_3$]$^{2+}$ and oxidation of DABCO for the difluoroalkylation/carboxylative cyclization process.

2.4 Difluoroalkylation of *sp*^{2} Carbon Atoms in Arenes and Heteroarenes

Transition metal photocatalysis can also be considered as a very valuable tool in organic synthesis for the introduction of difluoroalkyl substituents in arenes and heteroarenes using various difluoroalkylating reagents.

The reagent 2-bromo-2,2-difluoro-1-morpholino-ethan-1-one (CAS number: 149229-27-6) was employed by Liu and co-workers for the visible light-induced incorporation of difluoroalkyl moieties in unactivated arenes (**161**) and heteroarenes (**163**).[106] An investigation of the reaction conditions using benzene as the organic substrate showed that the corresponding difluoroalkylated derivative was obtained in higher reaction yield when using DCM and the base KOAc, in the presence of *fac*-Ir(III)(ppy)$_3$ (Scheme 41). The authors found that the difluoroalkylation procedure can be extended to a wide range of mono-, di-, and trisubstituted arenes bearing electron-donating and electron-withdrawing substituents (**162**, Scheme 41A: 14 examples, 51–95% yields) and heteroarenes (pyrazines, pyridazines, pyridines, pyrimidines, and thiophenes) (**164**, Scheme 41B: 14 examples, 48–95% yields). Alternative substrates with

deamination process (**158**, 15 examples, 37–61% yields).

Yu and collaborators developed a novel approach for the utilization of CO$_2$ and BrCF$_2$CO$_2$Et in the difluoroalkylation of allylamines (**159**) and subsequent carboxylative cyclization *via* visible light photoredox catalysis, under atmospheric conditions.[105] In the presence of [Ru(bpy)$_3$]Cl$_2$ and the base DABCO, a large variety of difluoroalkylated 2-oxazolidinones bearing electron-rich and electron-poor aromatic groups was obtained without detection of any amino-difluoroalkylated by-products (**160**, Scheme 40: 26 examples, 30–86% yields). The developed protocol was applied to the oxy-difluoroalkylation of substrates using other difluoroalkyl reagents such as BrCF$_2$PO(OEt)$_2$, bromodifluoroacetamides, and 2-

Scheme 40. Radical difluoroalkylation/carboxylative cyclization of allylamines (**159**) with CO_2 and $BrCF_2CO_2Et$ *via* visible light photoredox catalysis and the proposed mechanism.

Scheme 41. Difluoroacetamidation of unactivated arenes (**161**) and heteroarenes (**163**) with 2-bromo-2,2-difluoro-1-morpholinoethan-1-one.

more complex aromatic rings such as napropamide (**165**, Figure 7) and pentoxifylline (**166**, Figure 7) can also be successfully difluoroalkylated. In addition, diverse bromodifluoroacetamides possessing distinct amino groups on the amide moiety, including aniline, cyclooctanamine, cyclopropylmethanamine, piperazine, piperidine, were all compatible for the desired organic transformation. A radical-mediated mechanism was suggested by photoluminescence quenching, electron spin resonance (ESR), spin-trapping, and kinetic isotope effect (KIE) experiments.

The same group implemented the reagent $BrCF_2PO(OEt)_2$ for the introduction of $CF_2PO(OEt)_2$ moieties in arenes and heteroarenes (**167**) under irradiation with 3 W blue LEDs.[107] Di- and trisubstituted

Figure 7. Chemical structures of difluoroacetamidated napropamide (**165**) and pentoxyfylline (**166**).

arenes containing electron-donating and electron-withdrawing groups, and heteroarenes (benzofurans, benzothiophenes, furans, indoles, pyridines, pyrimidines, selenophenes, and thiophenes) afforded the phosphonodifluoromethylated derivatives in moderate to excellent yields (**168**, Scheme 42: 21 examples, 35–95% yields).
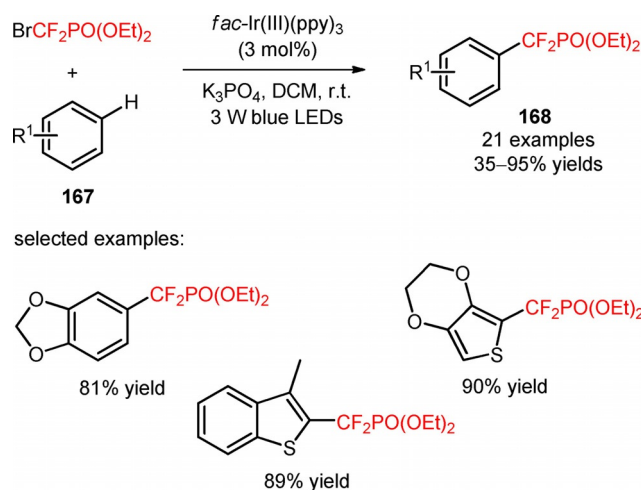

Scheme 42. Visible light-mediated phosphonodifluoromethylation of arenes and heteroarenes (**167**) with BrCF$_2$PO(OEt)$_2$.

An efficient photocatalytic method for the synthesis of difluoroalkylated arenes and heteroarenes was developed by Cho's group.[108] The visible light-promoted difluoroalkylation of unactivated electron-rich arenes (**169**) was successfully achieved using BrCF$_2$CO$_2$Et in the presence of *fac*-Ir(III)(ppy)$_3$ and the base *t*-BuOK (**170**, Scheme 43A: 10 examples, 65–91% yields). Phosphorescence quenching experiments suggested that the difluoroalkylation process was mediated by the oxidative quenching of photoexcited *fac*-Ir(III)(ppy)$_3$ and reduction of BrCF$_2$CO$_2$Et to CF$_2$CO$_2$Et radicals. Compared with electron-rich arenes, the heteroarenes (**171**) exhibited a higher reactivity, requiring a lower amount of photocatalyst and BrCF$_2$CO$_2$Et, and the weak bases TEA and K$_3$PO$_4$. Various difluoroalkylated heteroaromatics, including benzofurans, benzothiophenes, furans, indoles, pyrroles, thiophenes can be obtained using this protocol (**172**, Scheme 43B: 7 examples, 70–96% yields).

3,3-Difluoro-2-oxindoles (**174**) were successfully synthesized through *ortho*-difluoroalkylation of aniline derivatives (**173**) with BrCF$_2$CO$_2$Et and consecutive intramolecular amidation.[109] The difluoroalkylation/intramolecular amidation process exhibited an extensive substrate scope and a high functional group tolerance. In fact, the introduction of electron-neutral, electron-withdrawing, and electron-donating substituents on the aromatic ring of the aniline derivatives
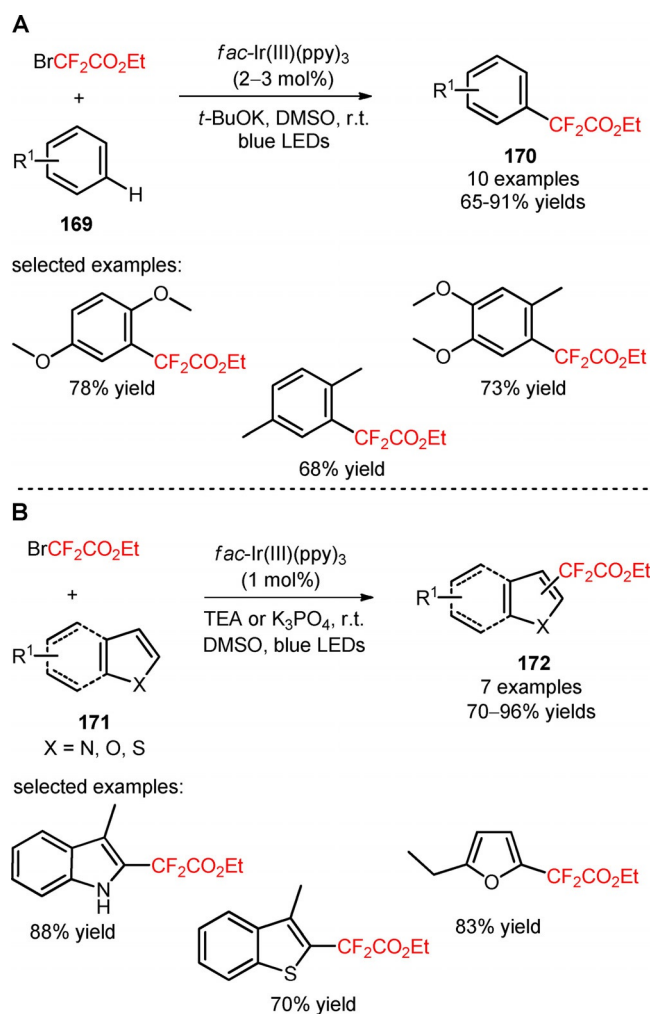
Scheme 43. Visible light-mediated difluoroalkylation of arenes (**169**) and heteroarenes (**171**) with BrCF$_2$CO$_2$Et.

was well tolerated in the desired organic transformation (**174**, Scheme 44: 23 examples, 30–79% yields). Radical-trapping experiments with TEMPO suggested the intermediacy of CF$_2$CO$_2$Et radicals *via* oxidative quenching of *fac*-Ir(III)(ppy)$_3$*.

In 2017, Fu and collaborators reported two related research works concerning a methodology for the visible light difluoroalkylation of imidazo[1,2-*a*]pyridines (**175**, **179**) using the reagents BrCF$_2$CO$_2$Et (Scheme 45A)[110] and [(difluoroiodomethyl)sulfonyl]-benzene (ICF$_2$SO$_2$Ph, CAS number: 802919-90-0) (Scheme 45C),[111] in the presence of *fac*-Ir(III)(ppy)$_3$. Electron-rich, electron-neutral, and electron-deficient 2-arylimidazo[1,2-*a*]pyridines were compatible with the difluoroalkylation process using both reagents, and gave the corresponding products in moderate to excellent yields (**176**, Scheme 45A: 17 examples, 60–94% yields; **180**, Scheme 45C: 15 examples, 62–91% yields). The functionalization of benzo[*d*]imidazo[2,1-*b*]thiazoles (**177**, **181**) was possible under the described reaction conditions (**178**, Scheme 45B: 3 ex-
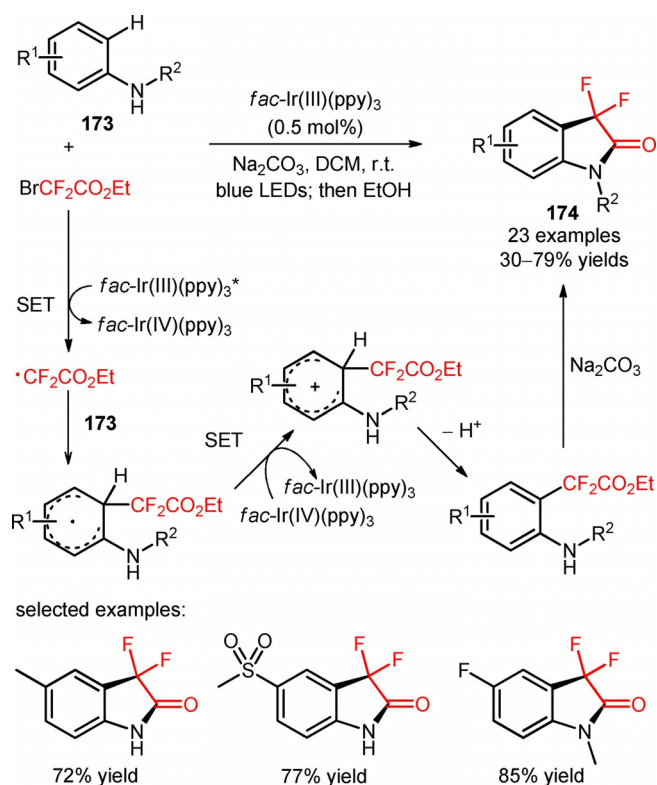
Scheme 44. Photoinduced difluoroalkylation and intramolecular amidation of anilines (**173**) with BrCF$_2$CO$_2$Et and the proposed mechanism.

amples, 89–95% yields; **182**, Scheme 45D: 2 examples, 84–87% yields).

The reagent ICF$_2$SO$_2$Ph was also efficiently applied in the difluoromethylation of N-, O-, and S-containing electron-rich heteroarenes (**183**) under irradiation with 26 W light bulbs.[112] In the presence of [Ru(bpy)$_3$]Cl$_2$, electron-rich and electron-deficient pyrroles, furans, thiophenes, indoles and other heteroarenes containing two heteroatoms furnished the respective CF$_2$SO$_2$Ph-containing heteroarenes (**184**, Scheme 46A: 39 examples, 58–96% yields). Mechanistic investigations involving radical scavengers suggested a radical-mediated difluoroalkylation process *via* oxidative quenching of *[Ru(bpy)$_3$]$^{2+}$. Removal of the –SO$_2$Ph group through reductive desulfonylation afforded the difluoromethylated derivatives (**185**, Scheme 46B: 9 examples, 71–95% yields). Interestingly, an analogue of the natural product melatonin (**186**) can be difluoromethylated in *stepwise* and *one-pot* procedures (**187**, Scheme 47: *stepwise*: 56% yield; *one-pot*: 51% yield).

Difluoroalkylation of arenediazonium tetrafluoroborates (**188**) was achieved using α-aryl-β,β-difluoroenol silyl ethers as the difluoroalkyl precursors under irradiation of visible light.[113] The selection of the photocatalyst [Ru(bpy)$_3$]Cl$_2$ and the base Cs$_2$CO$_3$ was critical for preferential difluoroalkylation on the aro-
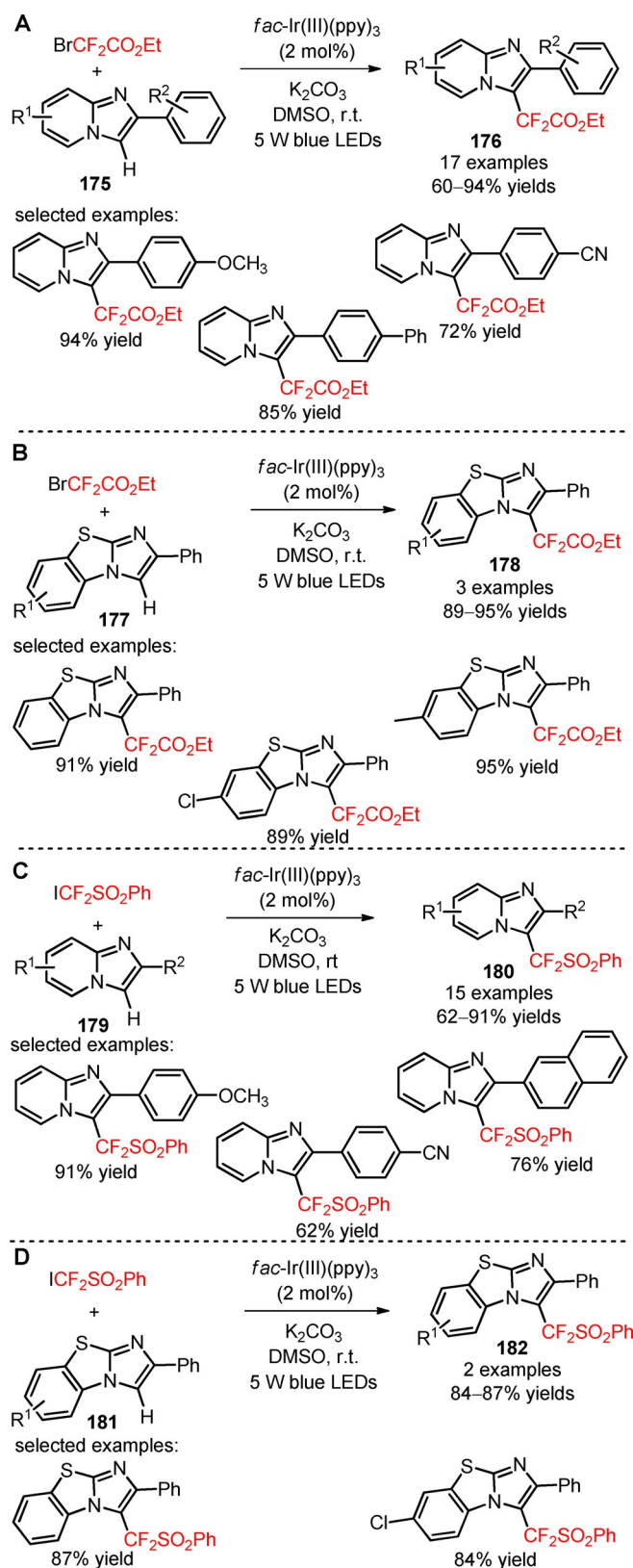
Scheme 45. Visible light-mediated difluoroalkylation of imidazo[1,2-*a*]pyridines (**175**, **179**) and benzo[*d*]-imidazo[2,1-*b*]thiazoles (**177**, **181**) with BrCF$_2$CO$_2$Et and ICF$_2$SO$_2$Ph.
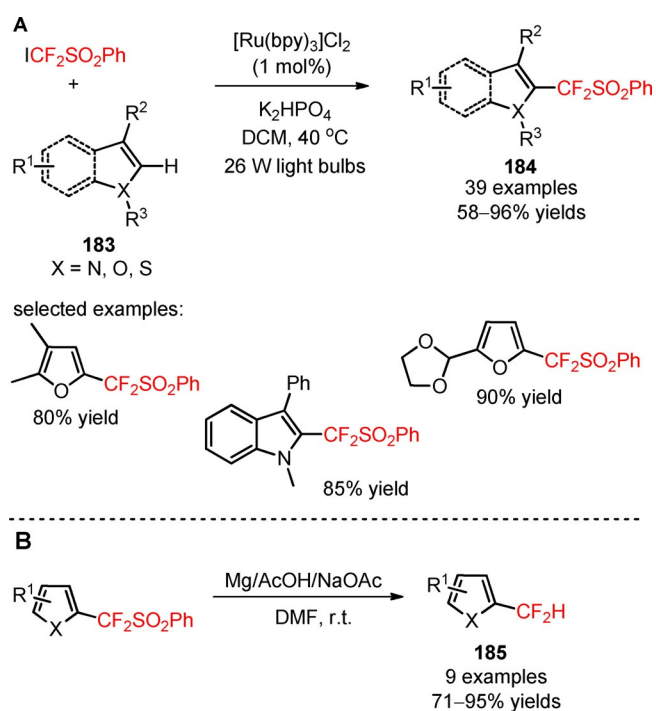
Scheme 46. (**A**) Visible light-driven difluoroalkylation of N-, O-, and S-containing heteroarenes (**183**) with ICF₂SO₂Ph. (**B**) Reductive desulfonylation of CF₂SO₂Ph-containing heteroarenes.
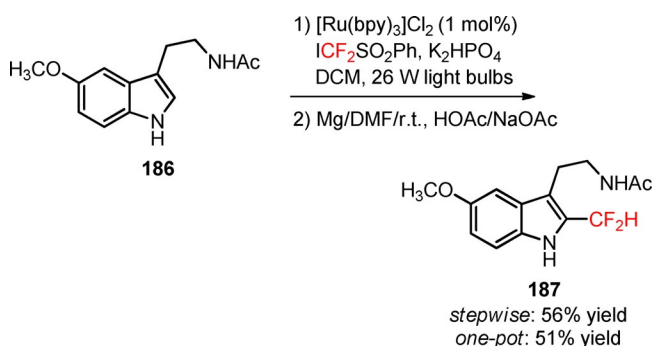
Scheme 47. Difluoromethylation of an analogue of melatonin (**186**) in *stepwise* and *one-pot* procedures.

matic ring of the substrates and elimination of the unwanted difluoroalkylation of N≡N bonds (Scheme 48). A wide range of arenediazonium tetrafluoroborates bearing electron-neutral and electron-withdrawing groups furnished the corresponding α-aryl-α,α-difluoro ketones in moderate to high yields (**189**, 25 examples, 20–90% yields). Quantum mechanical density functional theory calculations suggested a preferential mechanism involving the *in situ* generation of aryl radicals from arenediazonium tetrafluoroborates (**188**) *via* *[Ru(bpy)₃]²⁺ species. Radical difluoroalkylation of aryl radicals, SET oxidation from another substrate, and abstraction of the trimethylsilyl

group gave the respective α-aryl-α,α-difluoro ketones (**189**).

Stephenson's group achieved the radical chloro-difluoromethylation of arenes and heteroarenes (**190**) by *in situ* formation of a redox-active complex resulting from the combination of heter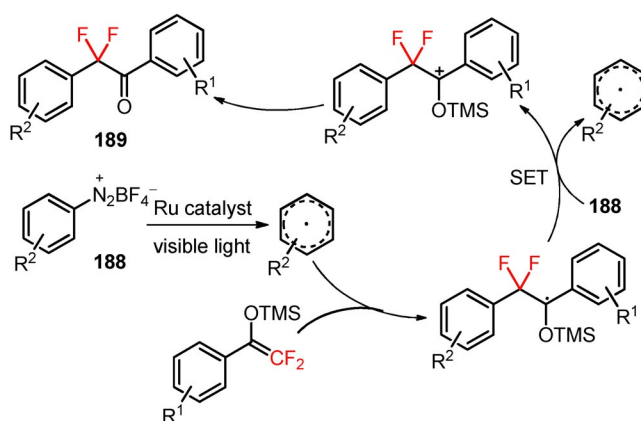ocyclic N-oxides (pyridine N-oxide and 4-phenylpyridine N-oxide) with the commercially available chlorodifluoroacetic anhydride [(ClCF₂CO)₂O, CAS number: 2834-23-3], in the presence of [Ru(bpy)₃]Cl₂.[114] Electron-rich heteroarenes and other pharmaceutically valuable agents with diverse functional groups were competent substrates for the desired organic transformation under both batch and flow conditions (**191**, Scheme 49: 19 examples, 25–84% yields). Interestingly, the chlorodifluoromethyl group-containing compounds (**191**) can be used as synthetic percursors to access electron-rich difluoromethylated arenes and heteroarenes.

Scheme 48. Difluoroalkylation of arenediazonium tetrafluoroborates (**188**) under visible light photoredox conditions and the proposed mechanism.
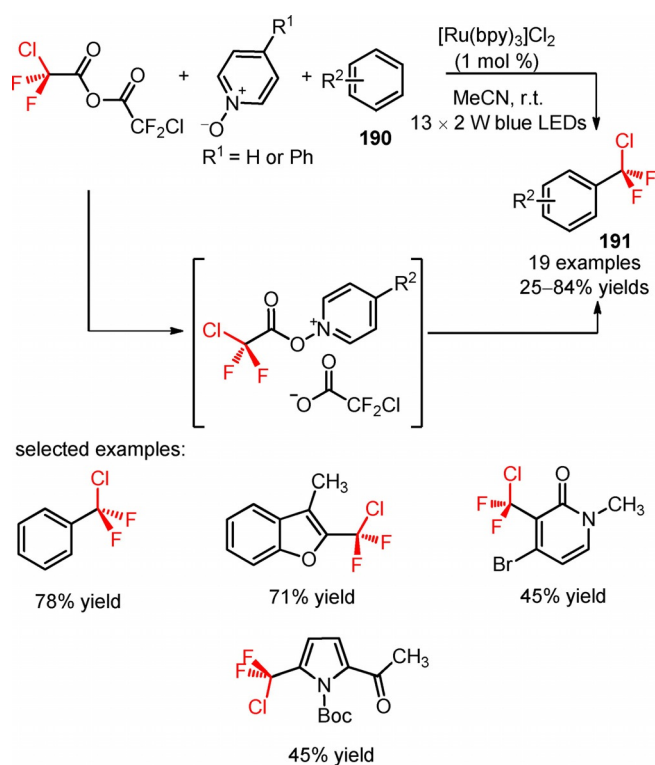
Scheme 49. Chlorodifluoromethylation of arenes and heteroarenes (**190**) under visible light photoredox conditions.

Recently, MacMillan's group reported a convenient approach for the direct difluoromethylation of aryl (**192**) and heteroaryl bromides (**194**) by combining nickel catalysis (NiBr$_2$·dtbbpy) with iridium photocatalysis {[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$}.[115] Bromodifluoromethane (HCF$_2$Br, CAS number: 1511-62-2) was employed as a direct source of CF$_2$H radicals *via* a (TMS)$_3$Si radical-mediated halogen abstraction pathway. The authors suggested a mechanism of reductive quenching of [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$* and simultaneous oxidation of the bromide anion. The resulting bromine radical can then induce the formation of (TMS)$_3$Si radicals that, in turn, can promote the bromine elimination from HCF$_2$Br to afford the CF$_2$H radicals. Concomitantly, an oxidative addition of the nickel catalyst to (hetero)aryl bromides and subsequent trapping of the CF$_2$H radicals afforded a CF$_2$H-Ni(II)-(hetero)aryl intermediate. Reductive elimination gave the respective difluoromethylated arenes (**193**) and heteroarenes (**195**). Under irradiation with blue LEDs, a variety of aryl bromides bearing electron-withdrawing, electron-neutral, and electron-donating groups was compatible with the desired organic transformation (**193**, Scheme 50A: 18 examples, 55–85% yields). The developed strategy was extended to the late-stage difluoromethylation of heteroaryl bromides (**194**), including bromo-1*H*-benzoimidazoles, bromo-1*H*-indazoles, bromopyrazines, bromopyrazoles, bromopyridines, bromopyrimidines, bro-
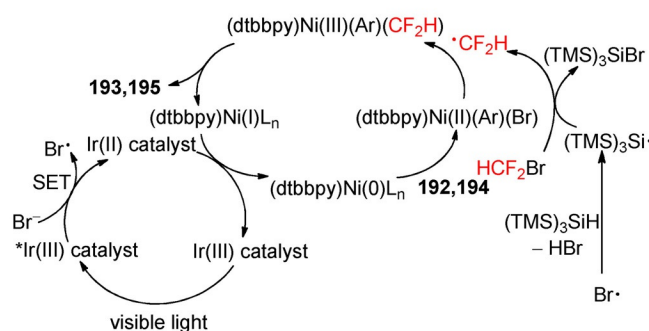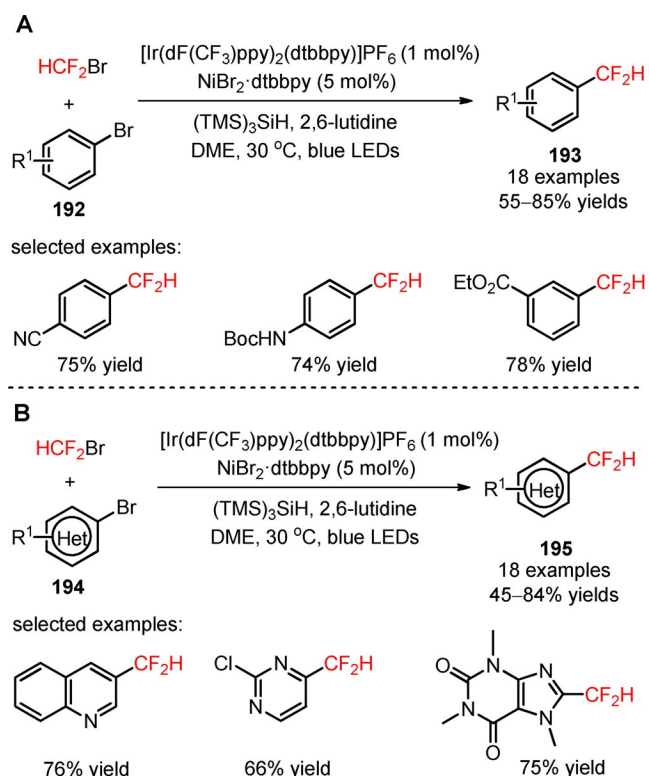
Scheme 50. Metallaphotoredox difluoromethylation of aryl (**192**) and heteroaryl bromides (**194**) with HCF$_2$Br.

moquinolines, and bromoquinoxalines (**195**, Scheme 50B: 18 examples, 45–84% yields) and analogues of sulfadimethoxine (**196**, Figure 8), celecoxib (**197**, Figure 8), indomethacin (**198**, Figure 8), and pomalidomide (**199**, Figure 8).

2.5 Difluoroalkylation of *sp* Carbon Atoms in Alkynes and Biphenyl Isocyanides

Apart from the huge progress in visible light photocatalytic difluoroalkylation of *sp²*-hybridized carbon atoms in organic substrates, determined efforts have been also devoted to the exploration of efficient methodologies for the introduction of difluoroalkyl groups to *sp*-hybridized carbon atoms, including C≡C
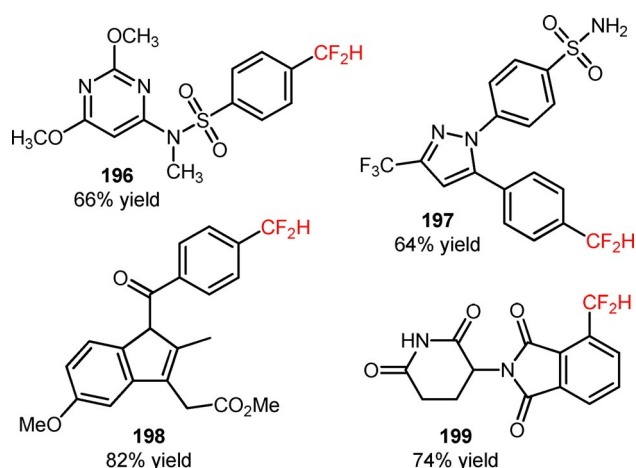
Figure 8. Chemical structures of difluoromethylated analogues of sulfadimethoxine (**196**), celecoxib (**197**), indomethacin (**198**), and pomalidomide (**199**).

bonds of alkynes and C≡N bonds of biphenyl isocyanides. Direct difluoroalkylation of these substrates has been demonstrated to afford synthetically useful precursors for the construction of functionalized heterocyclic molecules, such as difluoroalkylated coumarins, quinolines, and phenanthridines, under visible light irradiation.

In 2015, Ji and collaborators described a protocol for the visible light-mediated difluoroalkylation of aryl 3-phenylpropiolates (**200**) with BrCF₂CO₂Et and subsequent construction of a coumarin ring.[116] In the presence of *fac*-Ir(III)(ppy)₃, the radical difluoroalkylation/intramolecular annulation of a broad scope of aryl 3-phenylpropiolates bearing electron-donating and electron-withdrawing substituents in the aromatic rings gave the corresponding 3-difluoroalkylated coumarins (**201**, Scheme 51A: 21 examples, up to 87% yields). A mechanism of oxidative quenching of *fac*-Ir(III)(ppy)₃* and subsequent CF₂CO₂Et radical-mediated difluoroalkylation of C≡C bonds of the substrates (**200**) was proposed. Difluoromethyl-containing coumarins were also achieved *via* the photoinduced installation of CF₂H groups in aryl 3-phenylpropiolates (**202**) using 2-BTSO₂CF₂H (**203**, Scheme 51B: 24 examples, 30–80% yields).[117]

Recently, Sun and co-workers described a methodology for the visible light-induced radical difluoroalkylation of *N*-propargyl aromatic amines (**204**) with the reagent BrCF₂CO₂Et and consecutive cyclization to form a quinoline ring.[118] A large diversity of 3-difluoroalkylated quinolines bearing electron-withdrawing and electron-donating substituents on the aniline and benzene rings was effectively obtained in moderate to high yields (**205**, Scheme 52: 24 examples, 35–91% yields).

In 2014, Yu and co-workers developed a *stepwise* procedure for the preparation of difluoromethylated phenanthridine derivatives (**207**) involving the
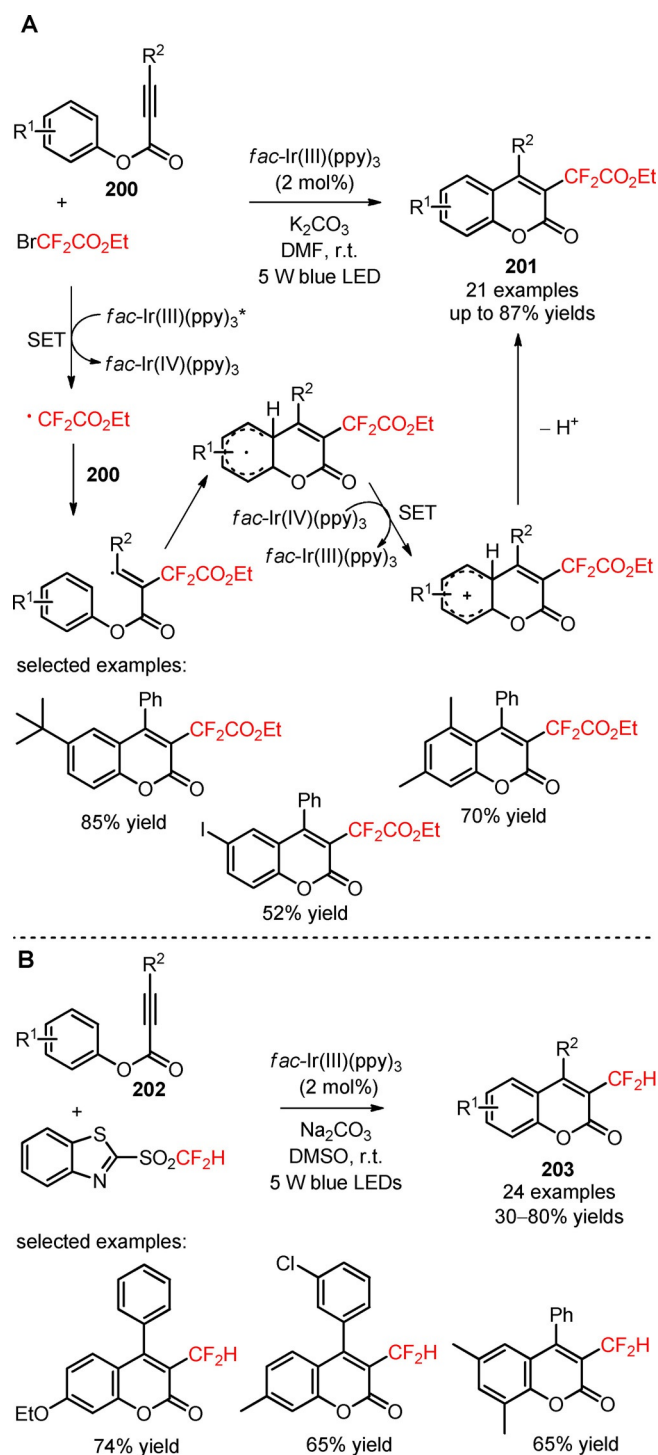
Scheme 51. Visible light-mediated radical difluoroalkylation/intramolecular annulation of aryl 3-phenylpropiolates (**200**, **202**) with BrCF₂CO₂Et (**A**) and 2-BTSO₂CF₂H (**B**).

difluoroalkylation/radical cyclization of biphenyl isocyanides (**206**) with BrCF₂CO₂Et and subsequent decarboxylation under basic conditions.[119] The difluoromethylation of the substrates took place upon visible light irradiation in the presence of *fac*-Ir(III)ppy₃, together with KHPO₄ in DMF at room temperature.
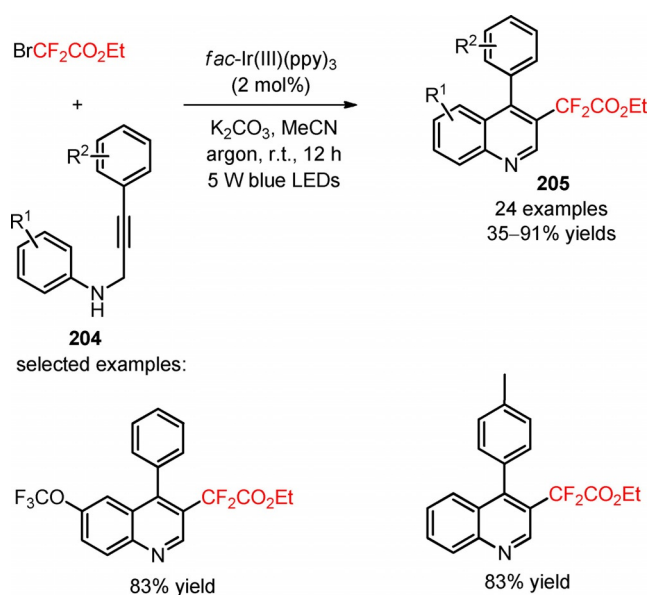
Scheme 52. Photoinduced cascade difluoroalkylation/cyclization of *N*-propargyl aromatic amines (**204**).

After the radical-induced difluoroalkylation, the ester functionality was removed *via* saponication and subsequent acid-mediated decarboxylation. The authors investigated the influence of a *one-pot* procedure on the overall efficiency of difluoromethylation of biphenyl isocyanides (**206**). They found that a *one-pot* procedure could afford a range of electron-deficient and electron-rich phenanthridine derivatives (**207**, Scheme 53A: 15 examples; *one-pot*: up to 94%; *stepwise*: up to 89%) with reaction yields comparable to those of the *stepwise* methodology, and could be easily scaled up.

Later, two independent papers published by the Liu[120] and Wang[121] groups have shown the successful utilization of BrCF$_2$PO(OEt)$_2$ in the phosphono-difluoromethylation of biphenyl isocyanides (**208**, **210**) under visible light photoredox conditions. A variety of biphenyl isocyanides bearing electron-donating and electron-withdrawing substituents attached to the aromatic rings was efficiently converted into the respective phosphonodifluoromethylated phenanthridines (**209**, Scheme 53B: 16 examples, 51–96% yields; **211**, Scheme 53C: 16 examples, 51–78% yields).

The visible light-mediated installation of CF$_2$H groups into biphenyl isocyanides (**212**) was reported for the first time by Dolbier and collaborators using the reagent HCF$_2$SO$_2$Cl.[122] This method enabled the synthesis of difluoromethylated phenanthridines (**213**), excluding the need of a *stepwise* procedure involving the conversion of other *gem*-difluoroalkyl groups into a difluoromethyl group. An improved reactivity for difluoromethylation of the substrates was accomplished using wet dioxane and K$_2$HPO$_4$, in the presence of *fac*-Ir(III)(ppy)$_3$ (Scheme 54). Substrates
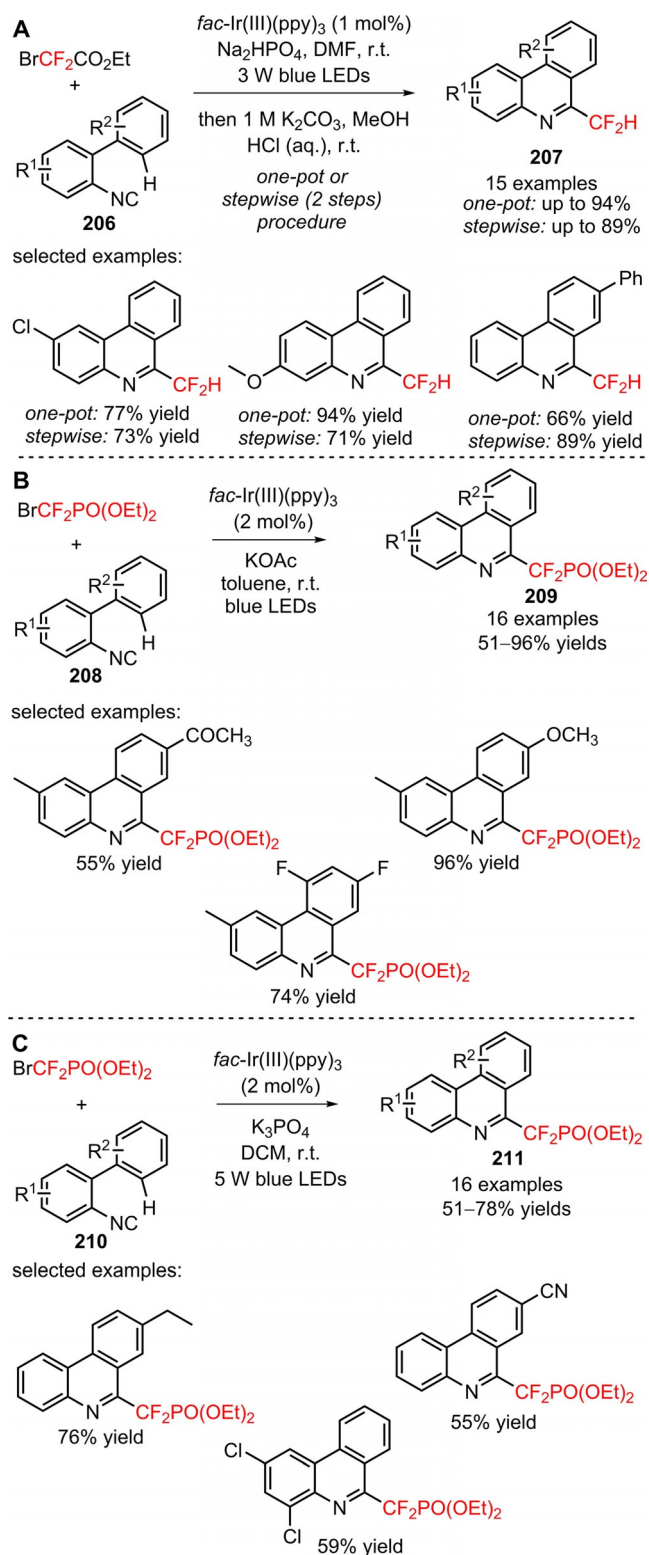
Scheme 53. Visible light-mediated difluoroalkylation of biphenyl isocyanides (**206**, **208**, **210**) reported by Yu (**A**), Liu (**B**), and Wang (**C**) groups.

with electron-donating and electron-withdrawing substituents in both aromatic rings were efficiently con-
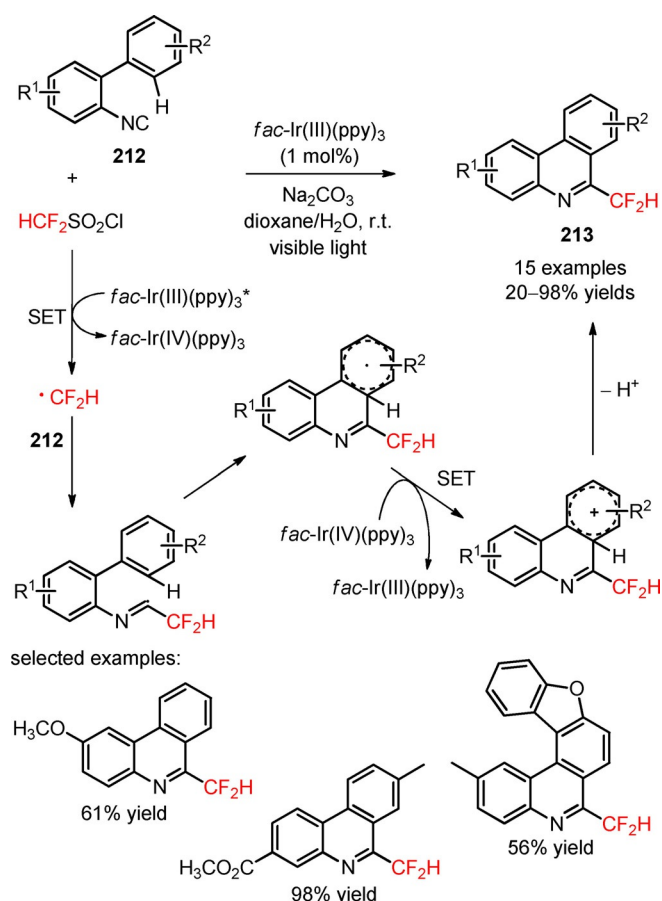
Scheme 54. Photoinduced difluoromethylation of biphenyl isocyanides (**212**) and the suggested mechanism.

verted into the respective difluoromethylated phenanthridines (**213**, 15 examples, 20–98% yields). Other radical fluoroalkyl precursors, in particular PhCF$_2$Br and CH$_3$CF$_2$SO$_2$Cl, were compatible with the developed methodology. The authors suggested a mechanism for the formation of phenanthridine scaffold involving the generation of CF$_2$H radicals *via* oxidative quenching of *fac*-Ir(III)(ppy)$_3$* and radical addition to the C≡N bond of biphenyl isocyanides (**212**). Subsequent cyclization onto the aromatic ring, oxidation *via fac*-Ir(IV)(ppy)$_3$, and base-assisted deprotonation gave the final products (**213**). Similar mechanistic pathways have been proposed to the difluoroalkylation reactions described in the Scheme 53.

Difluoroalkyl sulfones, including 2-BTSO$_2$CF$_2$H[123] and 2-PySO$_2$CF$_2$SPh,[124] have also been implemented in the synthesis of difluoromethylated (**215**) and arylthio-difluoromethylated phenanthridines (**217**), respectively, from biphenyl isocyanides (**214**, **216**), under irradiation with 6 W blue LEDs. Optimal conditions for the difluoromethylation and arylthiodifluoromethylation were achieved by combining the photocatalyst [Ru(bpy)$_3$]Cl$_2$ with the base Na$_2$CO$_3$ and DMSO. Biphenyl isocyanides bearing electron-

donating and electron-withdrawing substituents on the aromatic rings were suitable substrates for the desired transformation (**215**, Scheme 55A: 26 examples, 20–82% yields; **217**, Scheme 55B: 13 examples, 30–93% yields). The developed methodology was also extended to other fluoroalkyl sulfones containing 1,1-di-
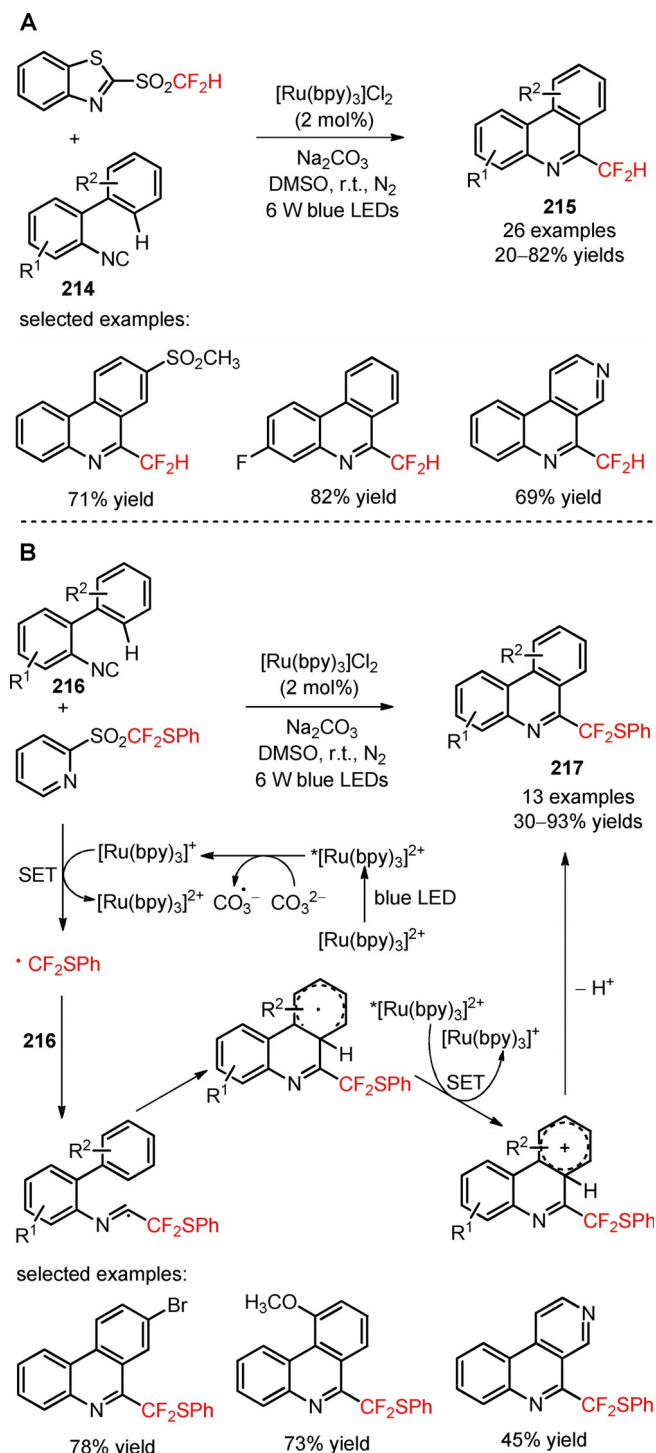
Scheme 55. Visible light-promoted difluoromethylation of biphenyl isocyanides (**214**, **216**) with 2-BTSO$_2$CF$_2$H (**A**) and 2-PySO$_2$CF$_2$SPh (**B**).

fluoroethyl ($-CF_2CH_3$), (phenyl)difluoromethyl ($-CF_2Ph$), (benzoyl)difluoromethyl ($-CF_2COPh$), and arylthiodifluoromethyl ($-CF_2SAr$) moieties. Luminescence quenching experiments suggested a mechanism of difluoroalkylaytion mediated by reductive quenching of $*[Ru(bpy)_3]^{2+}$ *via* oxidation of CO_3^{2-}.

2.6 Difluoroalkylation of SH- and OH-Containing Substrates

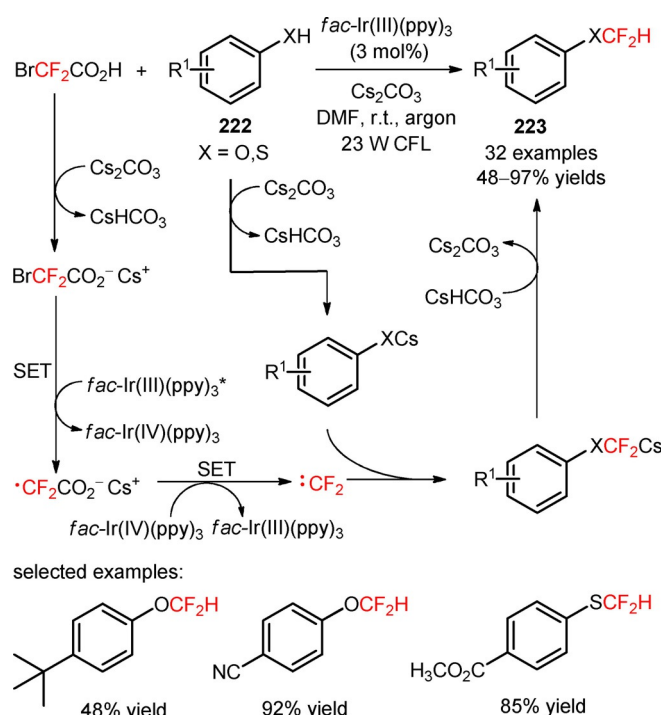Transition metal-photoinduced difluoroalkylation of sp^2- and sp-hybridized carbon atoms has been widely described under the scope of this review. On the other hand, the difluoroalkylation of other groups, in particular SH and OH groups, by visible light photoredox catalysis has been underdeveloped. The resulting $-SCF_2H$ and $-OCF_2H$ substituents have emerged as important functional groups in bioactive molecules, including the pyriprole (**218**, Figure 9), flomoxef sodium (**219**, Figure 9), pantoprazole (**220**, Figure 9), and roflumilast (**221**, Figure 9). Just recently in 2017, the Fu and Qing groups reported on the use of fluoroalkylating agents for the synthesis of difluoroalkyl (thio)ether derivatives under photoredox conditions.

The commercially available bromodifluoroacetic acid ($BrCF_2CO_2H$, CAS number: 354-08-5) was employed in the difluoromethylation of phenols and thiophenols (**222**) under visible light with a 23 W CFL.[125] Screening of photocatalysts, bases, and solvents showed that the combination of *fac*-Ir(III)-(ppy)$_3$, Cs_2CO_3, and DMF, respectively, was appropriate for the efficiency of difluoromethylation process (Scheme 56). Phenols and thiophenols possessing electron-donating and electron-withdrawing groups gave the corresponding difluoromethylated (thio)eth-
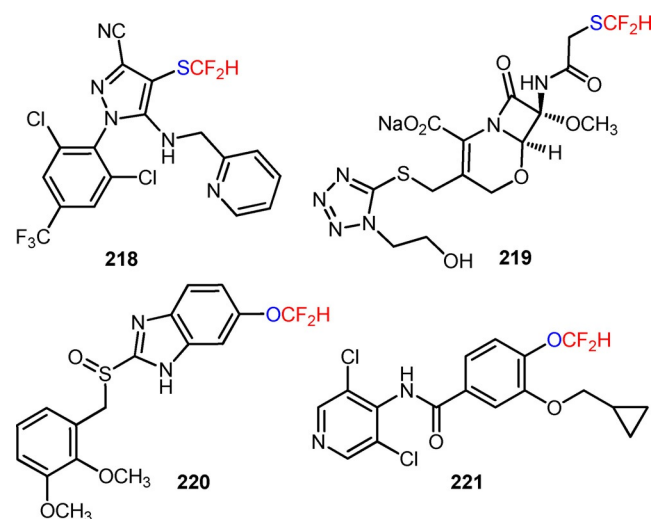
Scheme 56. Photoinduced difluoromethylation of phenols and thiophenols (**222**) with $BrCF_2CO_2H$ in the presence of *fac*-Ir(III)(ppy)$_3$ and the proposed mechanism.

ers (**223**, 32 examples, 48–97% yield). The protocol was also applied to other substrates, such as heteroaryl alcohols and heteroaryl thiols. The authors hypothesized a mechanism for the difluoromethylation involving the generation of a difluorocarbene ($:CF_2$) intermediate *via* oxidation of a radical carbanion intermediate resulting from the reaction between $BrCF_2CO_2H$ and Cs_2CO_3, and subsequent reduction. Concurrently, reaction of the phenol and thiophenol derivatives (**222**) with Cs_2CO_3 provided ArXCs (X = O, S) and $CsHCO_3$. The reaction of ArXCs with $:CF_2$ and subsequent treatment with $CsHCO_3$ provided the difluoromethylated (thio)ether derivatives (**223**).

In addition, the reagent (difluoromethyl)triphenylphosphonium triflate ([Ph_3PCF_2H]$^+$TfO$^-$) was applied in the radical difluoromethylation of thiols (**224**, **226**) under irradiation with visible light.[126] Apart from [Ph_3PCF_2H]$^+$TfO$^-$, the selection of photocatalyst *fac*-Ir(III)(ppy)$_3$ and TMEDA as the base was critical for the success of the difluoroalkylation reactions (Scheme 57). A large variety of thiophenols possessing electron-neutral, electron-donating, and electron-withdrawing substituents and heteroaryl thiols including benzo[*d*]thiazole-2-thiols, 2-thiopyridines, 4-thiopyridines, and 2-thiopyrimidines yielded the corresponding difluoromethylated thioethers (**225**, Scheme 57A: 12 examples, 71–93% yields; **227**, Scheme 57B: 9 examples, 65–94% yields). Interestingly, an excellent S/X (X = O, N) chemoselectivity of
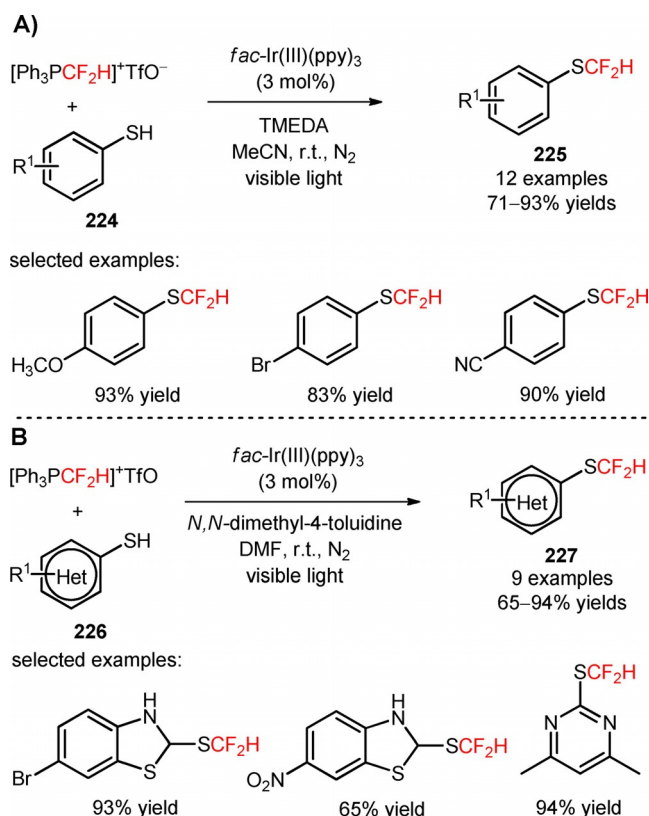

Figure 9. Chemical structures of SCF$_2$H- [pyriprole (**218**) and flomoxef sodium (**219**)] and OCF$_2$H-containing bioactive molecules [pantoprazole (**220**) and roflumilast (**221**)].

A)

B

Scheme 57. Visible light-induced photocatalytic difluorome-thylation of thiophenols (**224**) and heteroaryl thiols (**226**) using the reagent $[Ph_3PCF_2H]^+TfO^-$.

the difluoromethylation process was observed. Two plausible pathways were proposed for the radical di-fluoromethylation of thiols (Scheme 58). Electrophilic addition of CF_2H radicals to the thiolates and subsequent oxidation afforded the corresponding products (Path 1). Alternatively, the thiolate can be oxidized by *fac*-Ir(IV)(ppy)$_3$ to a sulfur radical and then converted into the disulfide derivative. Difluoromethylated thioethers (**225**, **227**) were obtained from the reaction between the CF_2H radicals and the disulfide (Path 2). The latter mechanism was considered the more likely pathway due to the observed chemoselective S-difluoromethylation.

3 Organic Photocatalyzed Difluoroalkylation Reactions

Over the last years, we have seen promising advances in the application of transition metal photocatalysts in the late-stage difluoroalkylation of organic substrates. Nevertheless, metal-catalyzed processes usually present a number of drawbacks, including the use of expensive metal catalysts, their potential toxicity, and in a few cases problems related to the elimination of the

Path 1

Path 2
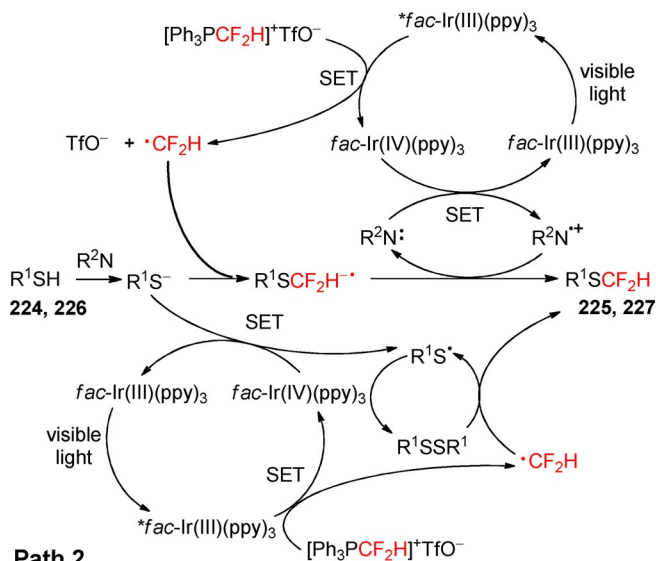
Scheme 58. Proposed mechanistic pathways for the photoinduced difluoromethylation of thiophenols (**224**) and heteroaryl thiols (**226**).

metal catalyst at the end of a reaction.[35,127,128] The development of synthetic approaches using organic dyes and other metal-free organic compounds has been regarded as an attractive alternative to transition metal complexes in photoredox catalysis. These organic photocatalysts are typically less expensive, less toxic, and easy to handle.[129,130] The development of metal-free catalyzed protocols is highly desirable in the pharmaceutical industries in order to restrict the maximal amount of transition metal impurities used in the production of pharmaceuticals. A survey of difluoro-alkylation reactions that make use of organic photo-catalysts is presented in this section.

A photoinduced hydro-bromodifluoromethylation of alkenes (**228**) was reported by Qing and co-work-ers[131] using dibromodifluoromethane (CF_2Br_2, CAS number: 75-61-6) as difluoroalkylating reagent and eosin Y as photocatalyst.[127] Under irradiation with visible light, the combined use of THF as hydrogen atom donor with the additive $KHCO_3$ was appropriate to achieve selectivity of the hydro-bromodifluoro-methylation process and to minimize the competitive bromine trapping after the bromodifluoromethylation process (Scheme 59). Mono- and disubstituted alkenes possessing a wide range of functional groups, including aldehydes, alkyl and allylic alcohols, amides, carboxylic acids, esters, ethers, halides, ketones, nitriles, nitro groups, phosphine oxides, sulfones, can be converted into the corresponding hydro-bromodifluoro-methylated products (**229**, 25 examples, 41–90% yields). Remarkably, the developed protocol for hydro-bromodifluoromethylation can be extended to more complex alkenes, including an L-phenylalanine
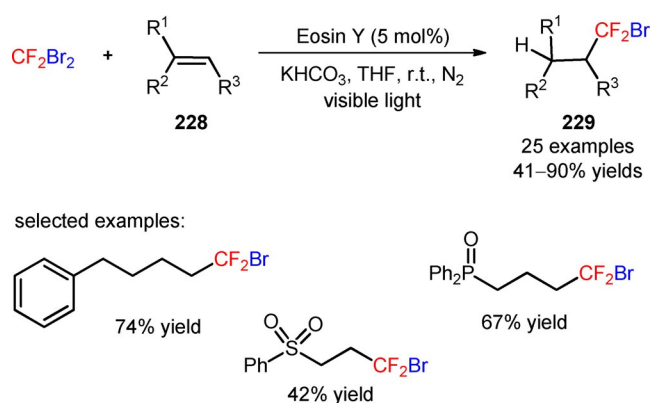
Scheme 59. Photoinduced hydro-bromodifluoromethylation of alkenes (**228**) with CF$_2$Br$_2$.

derivative (**230**, Figure 10), vinclozolin (**231**, Figure 10), and rotenone (**232**, Figure 10), as well as alkynes **233** (**234**, Scheme 60: 4 examples, 53–55% examples). Mechanistic studies suggested the involvement of photoexcited eosin Y in the reduction of CF$_2$Br$_2$ with concomitant generation of bromodifluoromethyl (CF$_2$Br) radicals. Subsequent radical addition to the alkenes (**228**) and hydrogen

abstraction from THF afforded the hydro-bromodifluoromethylated products (**229**). Labelling experiments with THF-d_8 corroborated the suggested mechanism of hydrogen abstraction.

Eosin Y was also effectively employed as a metal-free photocatalytic system for the decarboxylative difluoroalkylation of α,β-unsaturated carboxylic acids (**235**) with BrCF$_2$CO$_2$Et under mild conditions.[132] The use of the hypervalent iodine reagent 1-hydroxy-3-oxobenziodoxole (BI-OH) enabled the decarboxylative difluoromethylation of the substrates *via* activation of the carboxylic acid group. Under irradiation with a 15 W household bulb, an improved reaction efficiency was accomplished using the solvent mixture DCE/H$_2$O and the reducing agent (*i*-Pr)$_2$NEt (Scheme 61). A wide range of (*E*)-difluoroalkylated styrenes possessing both electron-donating and electron-withdrawing groups at *meta*- and *para*-positions on the aromatic ring was successfully synthesized in good yields (**236**, 24 examples, 46–87% yields). The authors suggested a reaction mechanism involving reductive quenching of the photoexcited eosin Y *via* SET oxidation of (*i*-Pr)$_2$NEt with concomitant formation of CF$_2$CO$_2$Et radicals. The hypervalent iodine reagent BI-OH is incorporated into the carboxylic acid moiety of the substrates to generate a benziodoxole vinyl carboxylic acid complex. Radical difluoroalkyla-

Figure 10. Chemical structures of hydro-bromodifluoromethylated L-phenylalanine derivative (**230**), vinclozolin (**231**), and rotenone (**232**).
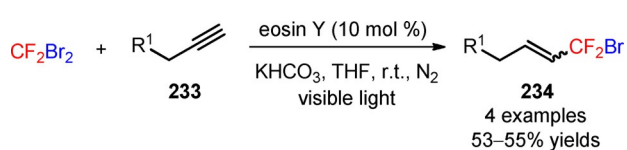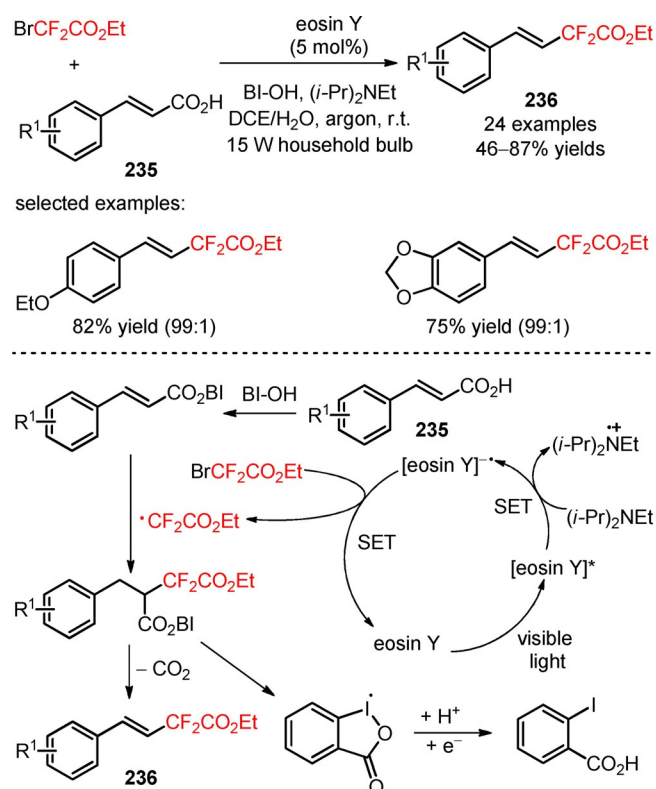

Scheme 60. Photoinduced hydro-bromodifluoromethylation of alkynes (**233**) with CF$_2$Br$_2$.

Scheme 61. Visible light-mediated decarboxylative difluoromethylation of α,β-unsaturated carboxylic acids (**235**) and the proposed mechanism.

tion to the α-carbon atoms of the benziodoxole vinyl carboxylic acid and subsequent elimination of CO_2 and benziodoxole radical provided the desired (*E*)-difluoroalkylated styrenes (**236**).

In 2017, Akita and collaborators described the visible light-induced amino-difluoromethylation of styrenes, using the shelf-stable and easy-to-handle difluoromethylating reagent *S*-difluoromethyl-*S*-di(*para*-xylyl)sulfonium tetrafluoroborate (CAS number: 2133476-50-1) and the photocatalyst perylene in the presence of MeCN and H_2O.[133] The presence of the two methyl groups of the *para*-xylyl unit in the proximity of the sulfur atom of *S*-difluoromethyl-*S*-di(*para*-xylyl)sulfonium tetrafluoroborate confers easy-handling and stability to this reagent. The amino-difluoromethylation process exhibited a good functional group tolerance (electron-donating and electron-deficient groups) and afforded a variety of amino-difluoromethylated products in moderate to good yields (**238**, Scheme 62: 14 examples, 30–76% yields). Perylene also promoted the amino- and chloro-trifluoromethylation of styrenes using the Yagupolskii–Umemoto reagent and CF_3SO_2Cl, respectively. A plausible mechanism for the amino-difluoromethylation of styrenes (**237**) involved the formation

of CF_2H radicals *via* oxidative quenching of photoexcited perylene and reductive cleavage of the C−S bond of the reagent. Radical addition to styrenes, oxidation, and subsequent Ritter amination with MeCN/H_2O gave the corresponding products (**238**).

Liu and co-workers described a successful application of the organic photocatalyst [Mes-Acr]ClO$_4$[134–137] to the visible light-mediated insertion of CF_2H and CF_2Ph radicals into biphenyl isocyanides (**239**) using sodium difluoromethanesulfinate (HCF$_2$SO$_2$Na, CAS number: 275818-95-6) (**240**, 6 examples, 45–52% yields) and sodium difluoro(phenyl)methanesulfinate (PhCF$_2$SO$_2$Na, CAS number: 268730-04-7) (**241**, 9 examples, 57–70% yields), in the presence of the oxidant $K_2S_2O_8$ and the base Na_2CO_3 (Scheme 63A).[138] The authors suggested a reductive quenching of photoexcited [Mes-Acr]$^+$ and oxidation of HCF$_2$SO$_2$Na

Scheme 62. Perylene-catalyzed amino-difluoromethylation of styrenes (**237**) with *S*-difluoromethyl-*S*-di(*para*-xylyl)sulfonium tetrafluoroborate and the proposed mechanism.
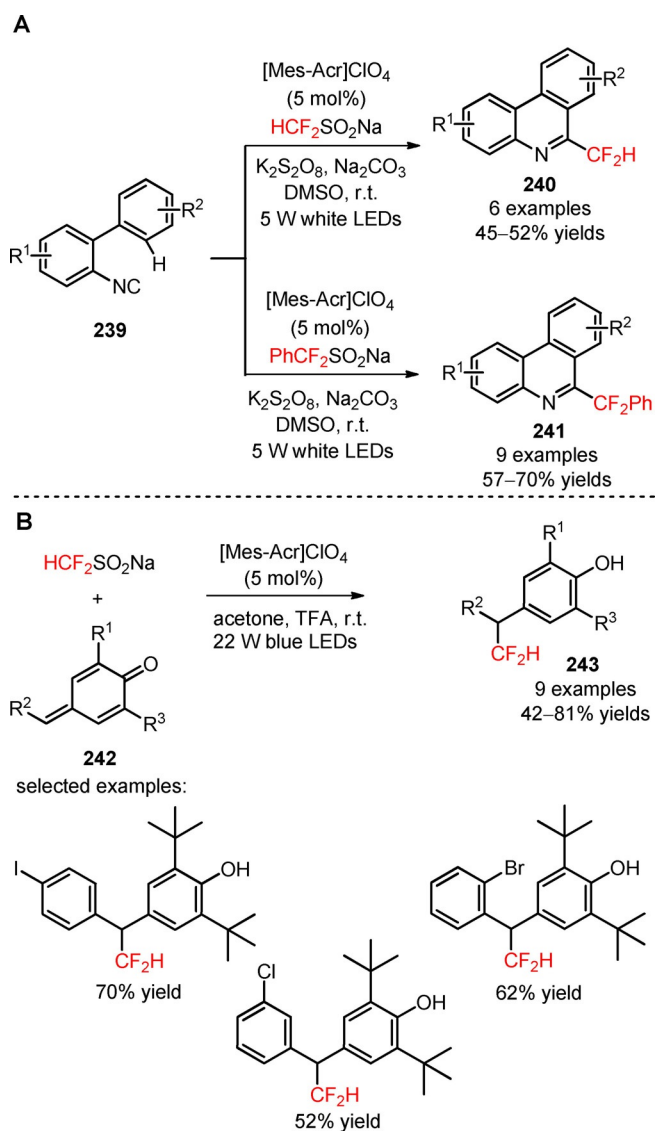
Scheme 63. Visible light-induced difluoroalkylation of biphenyl isocyanides (**239**) and *para*-quinone methides (**242**).

and PhCF$_2$SO$_2$Na *via* photoexcited [Mes-Acr] or by K$_2$S$_2$O$_8$ to produce the CF$_2$H and CF$_2$Ph radicals, respectively. *para*-Quinone methides (**242**) were also difluoromethylated using the reagent HCF$_2$SO$_2$Na and the photocatalyst [Mes-Acr]ClO$_4$, in the presence of TFA (Scheme 63B).[139] Under irradiation with 9 W white LEDs, a range of difluoromethylated derivatives could be obtained in moderate to good yields (**243**, 9 examples, 42–81% yields) and no competitive nucleophilic addition of the double bond of the substrates (**242**) to the sulfonate group of the reagent was observed.

Wang and co-workers employed the photocatalyst 4CzIPN[140–142] in the difluoroalkylation of aldehyde-derived hydrazones *via* a three-component coupling of aldehydes (**244**), hydrazines (**245**) and BrCF$_2$CO$_2$Et, under irradiation with 8 W blue LEDs.[143] An investigation of the substrate scope for the difluoroalkylation process demonstrated that aldehydes bearing electron-donating and electron-withdrawing substituents at *ortho*-, *meta*-, and *para*-positions on the aromatic ring, as well as heterocyclic and aliphatic groups were compatible substrates, providing the corresponding products in moderate to excellent yields (**246**, Scheme 64: 22 examples, 41–93% yields). This methodology can also be applied to different hydrazines and other reagents such as bromodifluoro-acetamides and 2-(bromodifluoromethyl)benzoxazole. Radical trapping and fluorescence quenching experiments suggested a mechanism involving the *in situ* coupling between aldehydes (**244**) and hydrazines (**245**), the reductive quenching of [4CzIPN]*, and the intermediacy of CF$_2$CO$_2$Et radicals in the difluoroalkylation process.
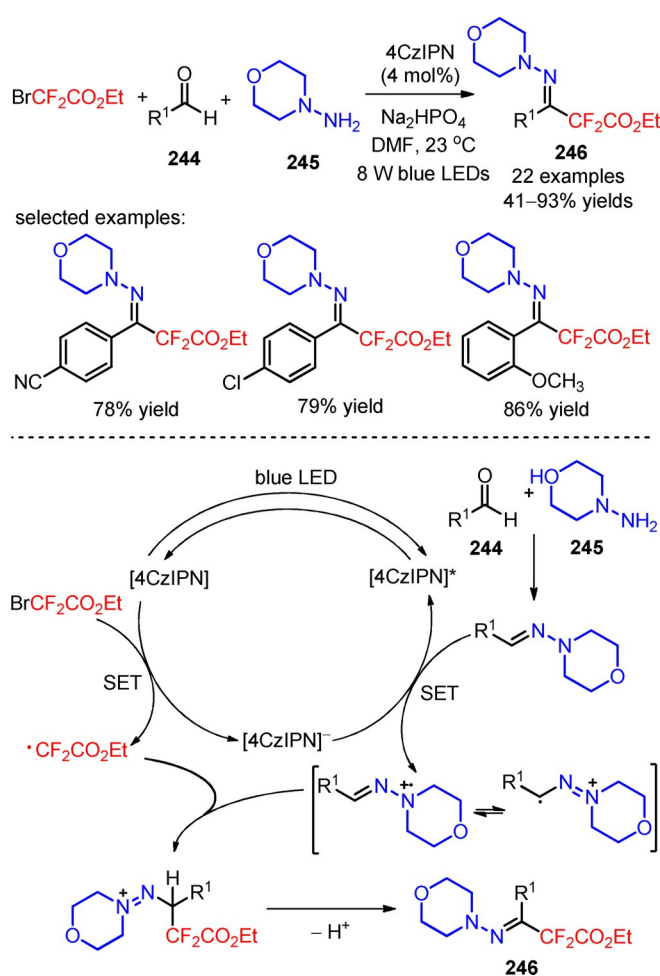
Scheme 64. Organic dye-catalyzed three-component coupling of aldehydes (**244**), hydrazines (**245**) and BrCF$_2$CO$_2$Et, under visible light photoredox conditions.

4 Concluding Remarks

The present review provides a general survey of visible light photoredox methodologies for the late-stage installation of CF$_2$FG and CF$_2$H substituents into diverse families of organic substrates in the presence of distinct transition metal complexes and organic photocatalysts. In recent years, visible light photoredox catalysis has been an extensively exploited tool for promoting radical-involved transformations, including the activation of organic substrates and further construction of the corresponding difluoroalkylated products. Most of the reported photoinduced reactions are operationally simple, are efficiently performed under mild conditions, and require minimal amounts of transition metal (0.05–7 mol%) and organic photocatalyst (4–10 mol%).

Diverse difluoroalkylating reagents have been successfully employed in the incorporation of difluoroalkyl moieties, including CF$_2$CO$_2$Me, CF$_2$CO$_2$Et, CF$_2$CON(CH$_2$CH$_2$)$_2$O, CF$_2$COPh, CF$_2$PO(OEt)$_2$, CF$_2$PO(O-*i*-Pr)$_2$, CF$_2$SPh, CF$_2$Cl, CF$_2$Br moieties, and some of them can undergo further chemical modifications into other CF$_2$-containing functional groups, including CF$_2$H. Alternative difluoroalkyl percursors have enabled the direct introduction of CF$_2$H substituents without the need of a post-functionalization step. Interestingly, we have seen a major progress in the development of photoinduced difluoroalkylation reactions involving the use of transition metal complexes as photocatalysts, in particular by *fac*-Ir(III)(p-py)$_3$. In spite of the recent works regarding transition metal-free difluoroalkylation reactions with organic photocatalysts, further research work in this field is still needed. In fact, the organophotocatalysis is a particular concern in the area of pharmaceutical industry, in order to minimize the utilization of transition metals.

The mechanistic pathway for most of the photoredox-catalyzed difluoroalkylation reactions is initiated by visible light irradiation of the transition metal or organic photosensitizer at a certain wavelength and

consecutive stimulation to an excited state. Excited photosensitizers may undergo an oxidative or reductive quenching, depending on the redox potential of the difluoroalkylating reagents, thus enabling the application of electron-donor or electron-acceptor difluoroalkylating reagents for the generation of CF_2FG and CF_2H radicals. The majority of the photoinduced difluoroalkylations reported in this review involves a mechanism of oxidative quenching of the photocatalysts and reduction of the difluoroalkylating reagents. The radical addition into carbon atoms of C=C, C=N, C≡C, C≡N bonds and further chemical transformations (e.g., oxidation, halogen addition, cyclization) results in the formation the corresponding CF_2-containing products. A variety of skeletons including alkenes, arenes, heteroarenes, α,β-unsaturated carboxylic acids, allylic alcohols, allylic amines, unsaturated amides, alkynes, biphenyl isocyanides, and thiols have proven to be suitable for the preparation of the corresponding difluoroalkylated compounds. Furthermore, the difluoroalkylation of structurally simple starting materials provides valuable intermediates for the synthesis of highly complex and functionalized heterocycles of potential biological interest, including benzoxazines, chromones, coumarins, oxindoles, phenanthridines, polycyclic lactones, and tetralins, in a single-step operation. Overall, the attractive characteristics of visible light photoredox reactions including environmentally benign conditions, excellent functional group versatility, and cost effectiveness will enable the application of these approaches by organic chemists in the exploration of novel methodologies for the introduction of difluoroalkyl substituents.

Acknowledgements

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