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Direct C–H difluoromethylation of heteroaromatic compounds: emerging methods and developments through 2025

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Heteroarenes bearing a difluoromethyl (CF_2H) group have emerged as important structural motifs in pharmaceuticals, agrochemicals, and materials science, as the CF_2H unit can fine-tune lipophilicity, strengthen biological interactions, and enhance metabolic stability. Among the available synthetic approaches, direct C–H difluoromethylation of heteroaromatic frameworks stands out as an efficient, step-economical, and atom-economical strategy. In this review, we highlight the most significant advances and developments in the direct C–H difluoromethylation of heteroaromatic compounds reported up to the end of 2025. Catalyst-free reactions are discussed first, followed by metal-catalyzed/mediated and photoredox-catalyzed transformations. Finally, electrocatalytic approaches are covered at the end of the review.

1. Introduction

Owing to its electronic characteristics and its ability to function as a weak hydrogen bond donor (A = 0.035–0.165), the difluoromethyl (CF_2H) group is regarded as a metabolically stable and more lipophilic bioisostere of OH, SH, and NH groups.[1] This unique combination of properties has drawn considerable attention in medicinal chemistry, as the CF_2H motif can enhance the pharmacokinetic and pharmacodynamic profiles of bioactive molecules.[2] Among the 340 fluorine-containing drugs approved by the FDA up to 2020, seventeen (around 5%) feature a CF_2H (or a functionalized difluoromethyl) group within their molecular structure.[3] Between 2021 and 2024, three of the 37 newly approved fluorinated drugs also featured a CF_2H group, making it the second most frequently employed fluorinated functional group in drug design after CF_3, which appears in over ten approved drugs.[4] Unlike the CF_3 which primarily serves as a hydrophobic group and H-bond acceptor, as mentioned, the CF_2H group acts as a weak hydrogen bond donor while retaining hydrophobic character. This dual functionality often leads to improved solubility and enhanced metabolic stability. Heterocycles, on the other hand, are highly valued in pharmaceutical chemistry as ubiquitous scaffolds, with more than 85% of FDA-approved small-molecule drugs containing at least one heterocyclic moiety.[5] The strategic integration of difluoromethyl groups into heterocyclic cores is exemplified by bioactive compounds such as inavolisib, bixafen, and pyrapropoyne (Fig. 1). Consequently, the development of efficient and selective methodologies for the direct difluoromethylation of heterocyclic substrates has become a topic of significant and growing interest.[6]

Direct C–H functionalization has emerged as a highly attractive synthetic strategy for forming C–C and C–X (X = heteroatom) bonds, as it enables the direct transformation of ubiquitous yet inert C–H bonds without the need for pre-functionalized starting materials; compared with conventional methods that rely on halogenated or otherwise activated substrates, this approach offers enhanced step economy, improved atom efficiency, and a substantial reduction in chemical waste.[7] Among the various methods developed for the synthesis of CF_2H-substituted compounds, direct C–H difluoromethylation has attracted increasing attention in recent years.[6,8] In particular, the direct difluoromethylation of heteroaromatic C–H bonds has experienced rapid growth over the past few years due to its efficiency and broad applicability (Scheme 1). Although several excellent reviews on difluoromethylation have appeared,[9] a comprehensive summary focused specifically on the direct C–H difluoromethylation of heteroaromatic

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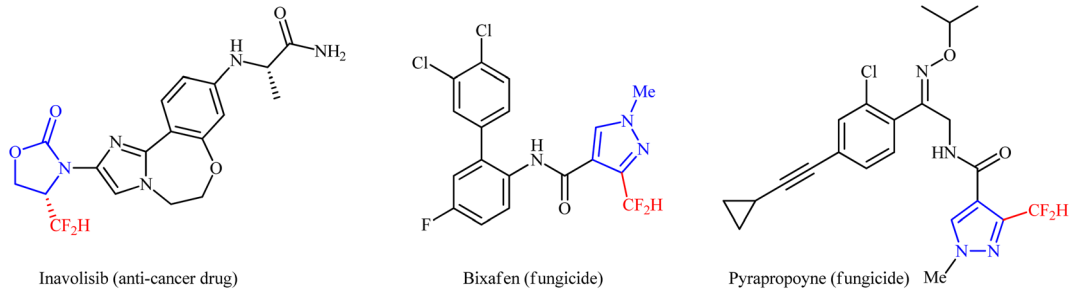


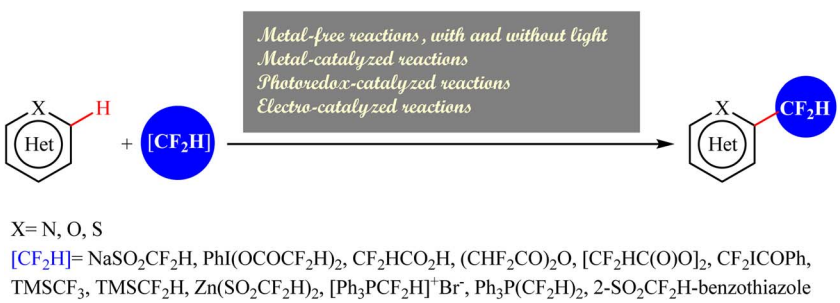
Fig. 1 Selected examples of bioactive CF_2H-substituted heterocyclic compounds.

compounds has not yet been reported. This review aims to provide a detailed overview of the most significant advances and developments in this area, covering literature reported up to the end of 2025. It should be noted that the discussion does not include the incorporation of functionalized difluoromethyl groups into C–H bonds.[10]

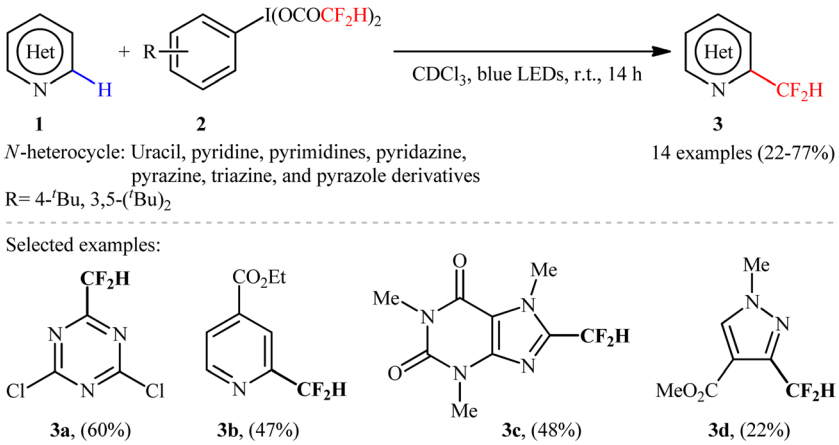
2. Metal-free reactions, with and without light

One of the earliest reports on the direct difluoromethylation of heteroaromatic C–H bonds under catalyst-free conditions was published by Maruoka and co-workers in 2017.[11] They demonstrated that treatment of various five- and six-membered N-heteroarenes **1** with hypervalent iodine(III) reagents **2** under visible-light irradiation, in the absence of any catalyst or additive, afforded the corresponding difluoromethylated heteroarenes **3** in low to relatively good yields (Scheme 2). The reaction generally proceeded with high regioselectivity, installing a single difluoromethyl group at the position adjacent to the nitrogen atom, unless that site was blocked. Notably, minor amounts of bis-difluoromethylated products were occasionally detected as side products. Interestingly, a one-pot variant of this transformation, employing *in situ* generation of the hypervalent iodine(III) reagent **2a**, was also explored using caffeine as the substrate under the standard conditions, delivering the desired product in satisfactory yield. On the basis of a series of control experiments, the authors proposed a plausible mechanism for this transformation (Scheme 3). The process is initiated by visible-light-induced homolysis of the iodine(III) reagent **2** to generate a carboxyl radical **A** and an iodanyl radical **B**. Subsequent decarboxylation of radical **A** produces a difluoromethyl radical ($^{\bullet}CHF_2$), while iodanyl radical **B** decomposes to release iodoarene along with an additional equivalent of carboxyl radical **A**. The resulting $^{\bullet}CHF_2$ radical then adds to heteroarene **1** to form radical intermediate **C**, which is subsequently oxidized by either reagent **2** or radical **A** to give cationic intermediate **D**. Final deprotonation of this cationic species affords the expected difluoromethylated heteroarenes **3**. Four years later, Lu and co-workers developed a related method for the direct C–H difluoromethylation of quinoxalin-2(1*H*)-one derivatives using [bis(difluoroacetoxy)iodo]benzene as the difluoromethylating reagent.[12]

Inspired by these works, Zhang and colleagues reported a catalyst- and light-free protocol for the C3-selective difluoromethylation of coumarins **4** using stable and environmentally benign sodium difluoromethanesulfinate ($NaSO_2CF_2H$) as the difluoromethyl source and potassium persulfate ($K_2S_2O_8$) as the oxidant in DMSO at 90 °C (Scheme 4a).[13] The transformation proceeds efficiently under purely thermal conditions, as $K_2S_2O_8$ is readily activated upon heating to generate sulfate radical anions. Notably, the protocol exhibited a broad substrate scope and was applicable not only to coumarins but also to diverse N-heteroarenes, including quinolinones, quinoxalinones, isoquinolines, uracil, and caffeine. On the basis of mechanistic considerations, the authors proposed a reaction pathway analogous to that previously reported by Maruoka and co-workers for difluoromethylation using hypervalent iodine(III) reagents. Shortly thereafter, the same research group developed an alternative set of reaction conditions for the direct C(sp^2)–H difluoromethylation of heteroarenes with $NaSO_2CF_2H$ under catalyst- and oxidant-free



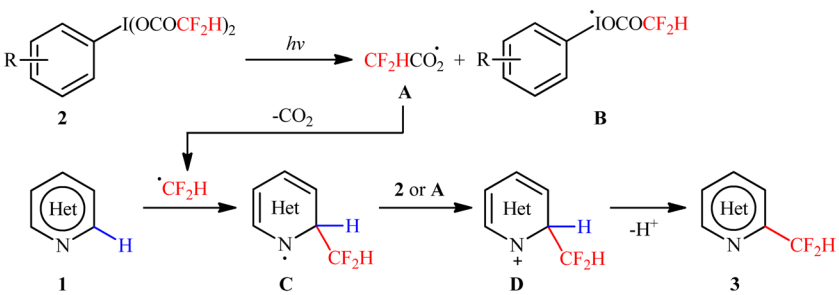
Scheme 1 Direct C–H difluoromethylation of heteroaromatic compounds.



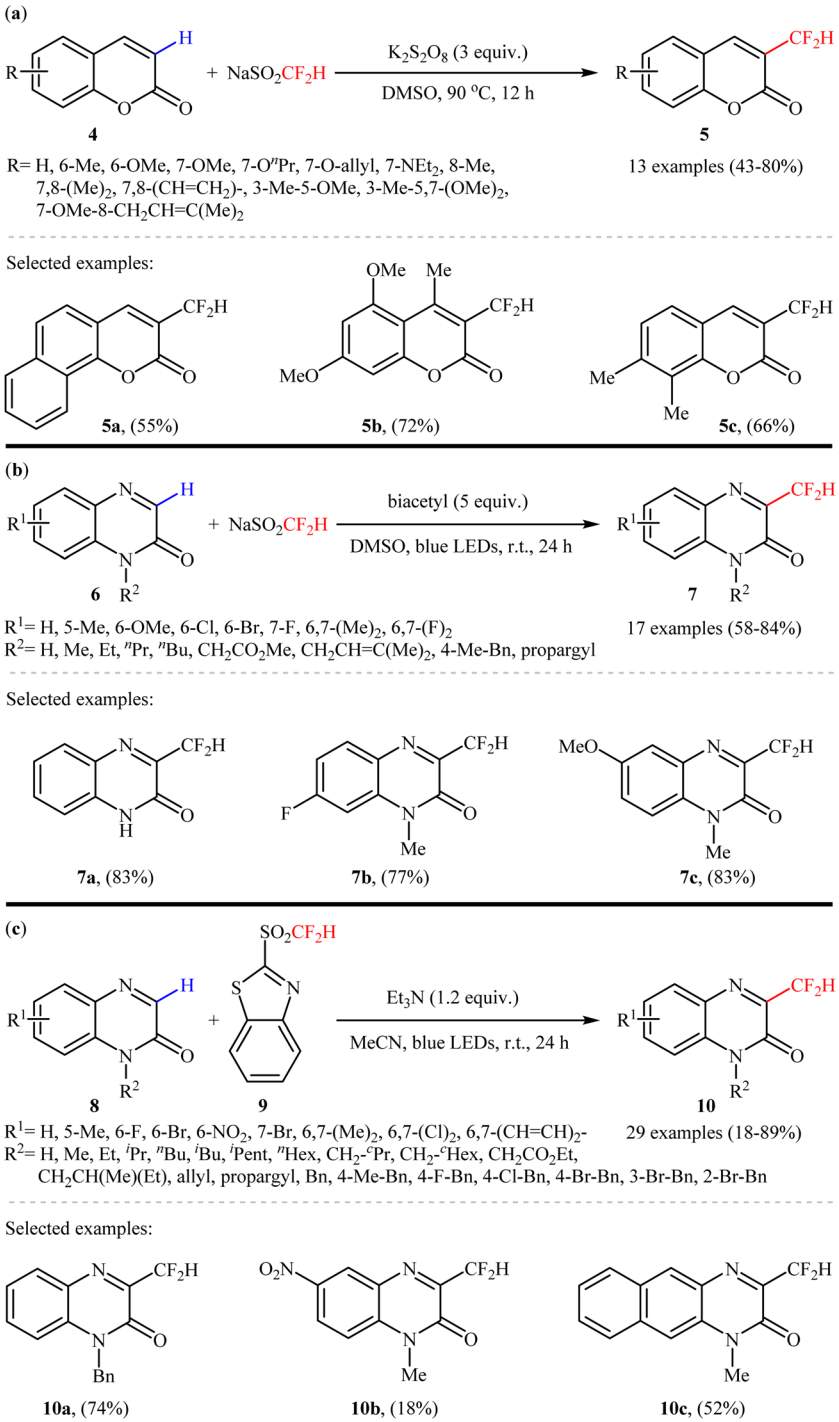
Scheme 2 Visible-light-induced catalyst-free difluoromethylation N-heteroarenes **1** with hypervalent iodine(III) reagents **2**.

conditions, employing an excess of biacetyl as an energy-transfer mediator under visible-light irradiation at room temperature.[14] Under these conditions, a range of NH-free and *N*-substituted quinoxalin-2(1*H*)-one derivatives **6** underwent selective C3-difluoromethylation to give the corresponding difluoromethylated products **7** in modest to high yields (Scheme 4b). Mechanistically, it was proposed that upon photoexcitation, biacetyl oxidizes the sulfinate salt to generate, after desulfonylation, a difluoromethyl radical, which then adds to the starting heteroarene. Very recently, Mei's research team reported a related strategy for the direct difluoromethylation of quinoxalin-2(1*H*)-ones **8** using 2-((difluoromethyl)sulfonyl) benzo[*d*]thiazole **9** as a commercially available difluoromethylating reagent.[15] The reaction was conducted in the presence of 1.2 equivalents of Et_3N in MeCN under blue LED irradiation, without the need for an external photocatalyst or oxidant, and delivered C3-difluoromethylated quinoxalin-2(1*H*)-ones **10** in yields ranging from 18% to 89% (Scheme 4c). It is noteworthy that all three reactions summarized in Scheme 4 most likely proceed *via* radical pathways, involving the generation of a difluoromethyl radical intermediate, analogous to that depicted in Scheme 3.

In a complementary study, Lu and co-workers achieved the synthesis of nineteen C3-difluoromethylated quinoxalin-2(1*H*)-one derivatives **12** from the corresponding quinoxalin-2(1*H*)-ones **11** in fair to good yields by employing difluoroacetic anhydride as a difluoromethyl radical precursor in combination with pyridine *N*-oxide under visible-light irradiation (Scheme 5).[16] The protocol exhibited good tolerance toward a variety of sensitive functional groups, including fluoro, chloro, bromo, ketone, ether, and ester functionalities, as well as alkene and alkyne substitutions. Additionally, the method was successfully applied to the difluoromethylation of structurally complex drug-derived quinoxalinones such as ibuprofen and naproxen. Moreover, beyond quinoxalin-2(1*H*)-ones, pyrazin-2(1*H*)-one and pyrido[2,3-*b*]pyrazin-3(4*H*)-one were also found to be suitable substrates under identical conditions. Compared with the three previously reported strategies, this method affords yields comparable to Mei's protocol, though in some cases lower than those reported by Zhang and Maruoka, particularly for NH-free substrates. Nevertheless, the use of significantly more cost-effective difluoromethylating agents constitutes a clear practical advantage over earlier approaches. Based on a series of control experiments and the previous literature report, the authors proposed two possible pathways for this transformation as depicted in Scheme 6. In pathway a, pyridine *N*-oxide reacts with $(CHF_2CO)_2O$ to generate the acylated pyridine *N*-oxide salt **A**, which after reaction with quinoxalin-2(1*H*)-one **11** forms EDA complex **B**. Subsequently, photoexcitation of this complex leads to the formation of key intermediates **C** and **D** through an intermolecular single-electron transfer (SET) process. Intermediate **D** then decomposes to give the CHF_2



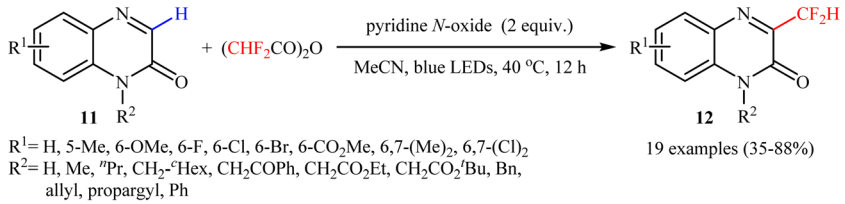
Scheme 3 Plausible mechanistic pathway for the formation of difluoromethylated heteroarenes **3**.



Scheme 4 (a) Zhang's synthesis of 3-difluoromethylcoumarins **5**; (b) Zhang's synthesis of C3-difluoromethylated quinoxalin-2(1*H*)-ones **7**; (c) Mei's synthesis of C3-difluoromethylated quinoxalin-2(1*H*)-ones **10**.

radical *via* the difluoromethyl carboxyl radical **E**. Finally, the CHF_2 radical adds to intermediate **C** to form intermediate **F**, which upon deprotonation furnishes the final product **12**. In pathway **B**, quinoxalin-2(1*H*)-one **11** is directly excited under blue light to its excited state **11′**, which after a photoinduced electron transfer (PET) process with **A** affords the same key intermediates **C** and **D**. The reaction then proceeds analogously to pathway **A**, ultimately furnishing the final product **12**.

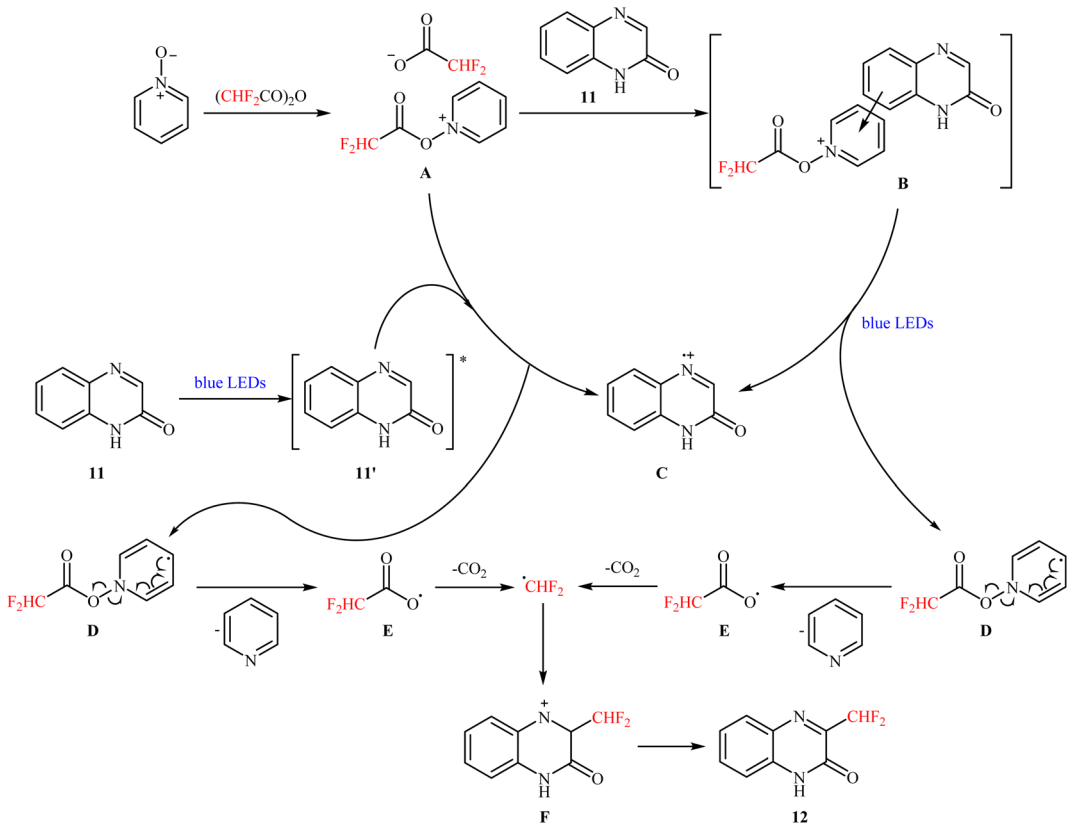
In a notable contribution to this field, Grygorenko and co-workers reported that treatment of *N*-substituted imidazoles **13** with trifluoromethyltrimethylsilane ($TMSCF_3$) and tetrabutylammonium difluorotriphenylsilicate (TBAT) in THF under catalyst-free conditions furnished the corresponding C2-



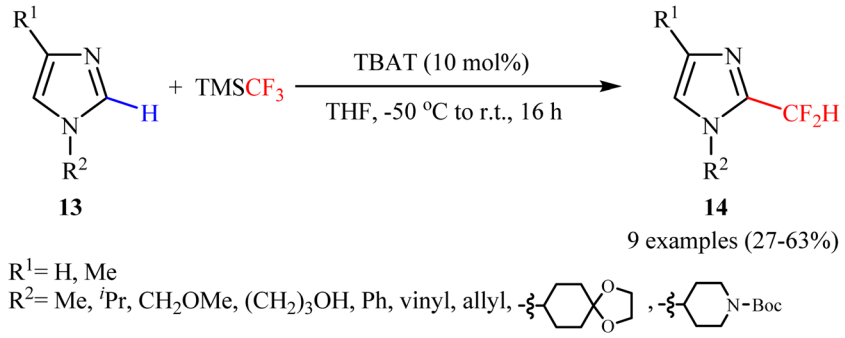
Scheme 5 Lu's synthesis of C3-difluoromethylated quinoxalin-2(1*H*)-ones **12**.

difluoromethylated imidazoles **14** with excellent regioselectivity and yields ranging from low to good (Scheme 7).[17] However, the generality of this transformation was limited, as it was effective only for simple *N*-substituted imidazoles without additional ring substitution. Notably, attempts to extend the protocol to other azole systems, including pyrazoles, oxazoles, thiazoles, benzoxazoles, benzothiazoles, and even benzimidazoles, were unsuccessful, with exclusive recovery of the starting materials. The authors elucidated a plausible reaction mechanism on the basis of combined NMR spectroscopic investigations and DFT calculations (Scheme 8). Initially, free difluorocarbene ($:CF_2$) is generated through fluoride dissociation from a transient CF_3 anionoid formed upon interaction of $TMSCF_3$ with TBAT. The resulting CF_3^- species then deprotonates imidazole **13** to give imidazolyl anion **A**, which subsequently traps the difluorocarbene to form intermediate **B**. Finally, protonation of intermediate **B** by CF_3H delivers the desired imidazole **14**.

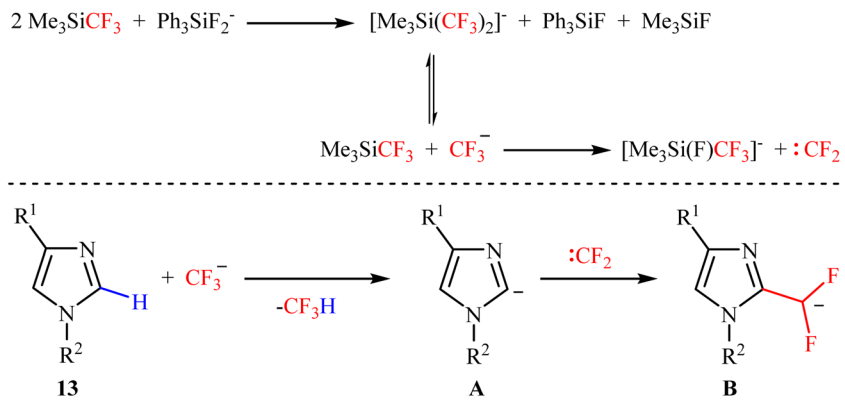
In this context, Studer and co-workers recently developed two complementary approaches for site-selective *meta*- and *para*-difluoromethylation of pyridines.[18] For *meta*-selective difluoromethylation, pyridines **15** were first converted into oxazino pyridine intermediates **A**, which were then treated with 2,2-difluoro-2-iodo-1-phenylethan-1-one (CF_2ICOPh) in the presence of HOAc and 2,2,6,6-tetramethylpiperidine (TMP) under visible-light irradiation. Subsequent basic hydrolysis of the 2,2-difluoro-1-phenyl-2-(pyridin-3-yl)ethanone intermediate **B** afforded the *meta*-difluoromethylated products **16** (Scheme 9). *Para*-selective difluoromethylation was accomplished *via* a two-step sequence starting from the same oxazino intermediates **A**. Treatment with (±)-camphorsulfonic acid ((±)-CSA) in dry acetone, followed by reaction with excess bis(difluoroacetyl) peroxide [$CF_2HC(O)OOC(CO)CF_2H$] for 4 hours and acidic hydrolysis, furnished the corresponding *para*-difluoromethylated pyridines **17**. Concurrently, Hong and co-



Scheme 6 Mechanistic proposal for the formation of C3-difluoromethylated quinoxalin-2(1*H*)-ones **12**.



Scheme 7 Grygorenko's synthesis of difluoromethylated imidazoles **14**.



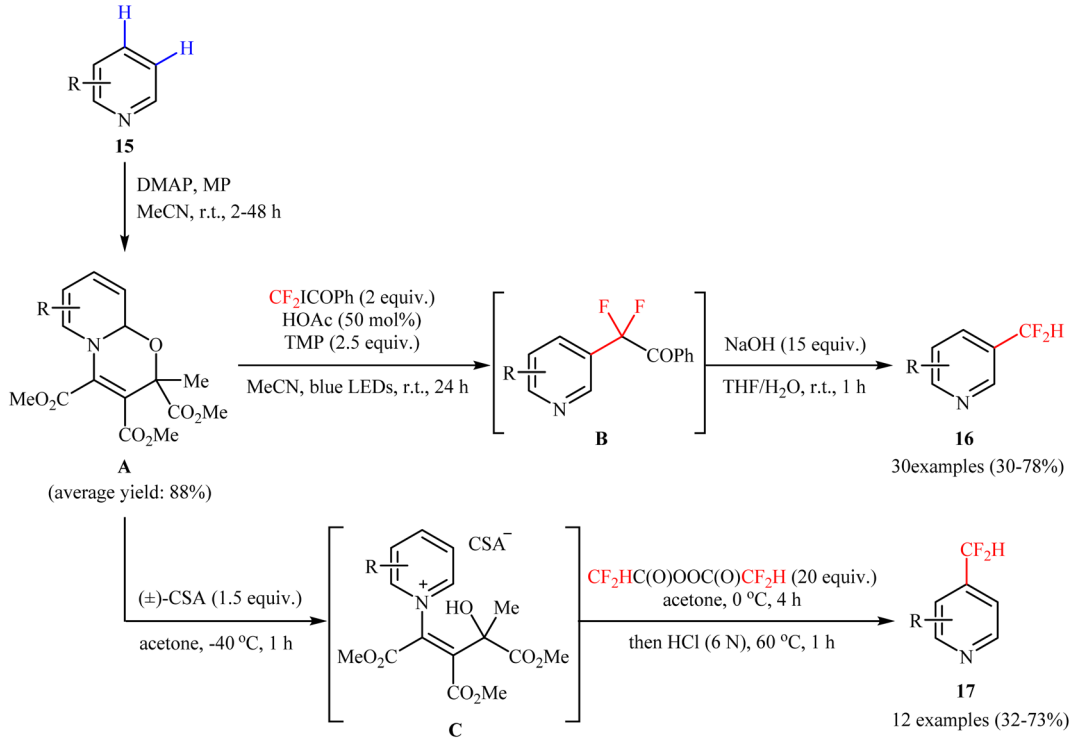
Scheme 8 Plausible mechanism for the formation of difluoromethylated imidazoles **14**.

workers developed an efficient strategy for site-selective *para*-difluoromethylation of pyridines involving initial conversion of pyridines into 1-(*N*,4-dimethylphenylsulfonamido)pyridin-1-ium tetrafluoroborate salts, followed by treatment with $NaSO_2CF_2H$ in DMSO under blue LED irradiation at room temperature, without the need for any catalyst or additive.[19]

3. Metal-catalyzed/mediated reactions

On the basis of the pioneering work of Baran and co-workers, who disclosed the direct C–H difluoromethylation of heteroarene substrates by using zinc difluoromethanesulfinate ($Zn(SO_2CF_2H)_2$, DFMS),[20,21] the group of Nielsen developed the first metal-catalyzed protocol for the direct C–H difluoromethylation of heteroarenes employing readily available difluoroacetic acid (CF_2HCO_2H) as the difluoromethylating reagent.[22] To evaluate the reaction parameters, methyl isonicotinate was chosen as the model substrate. Screening of various silver salts (AgF, AgOTf, $AgNO_3$, AgDFA, and $AgClO_4$) identified $AgNO_3$ the optimal catalyst, while $K_2S_2O_8$ proved to be a more effective oxidant than H_2O_2, ^tBuOOH, $(NH_4)_2S_2O_8$. To further enhance the reaction efficiency, H_2SO_4 was introduced as an additive to facilitate protonation. Under the optimized conditions, a broad range of six-membered N-heteroaromatic substrates **18** including pyridine, pyrimidine, pyrazine, quinoline, and quinoxaline derivatives reacted efficiently with CF_2HCO_2H to give the corresponding mono-difluoromethylated products **19** in 32–89% yields with excellent site-selectivity (Scheme 10). In all cases, difluoromethylation occurred preferentially at the position adjacent to the nitrogen atom, and this selectivity was retained even in substrates containing multiple potentially reactive C–H sites. The synthetic utility of the method was further highlighted by a gram-scale preparation of methyl 2-(difluoromethyl)isonicotinate using reduced loadings of $AgNO_3$ (20 mol%) and $K_2S_2O_8$ (2.5 equiv.), affording the desired product in 60% yield on a 1 g scale. Despite these successes, the method exhibits certain limitations. Substrates such as indole, caffeine, and 1-methylisoquinoline were unreactive under the standard conditions, indicating that the scope of the reaction may be restricted to specific six-membered N-heteroaromatic systems. Mechanistic studies indicate that the reaction proceeds *via* formation of a difluoromethyl radical generated through Ag-catalyzed oxidative decarboxylation of CF_2HCO_2H by persulfate, followed by radical addition to the heteroaromatic ring (Scheme 11).

Subsequently, Zhu *et al.* demonstrated that oxazoles **20** can undergo selective C2-difluoromethylation using commercially available (difluoromethyl)trimethylsilane ($TMSCF_2H$) as the difluoromethyl source. The reaction was carried out at room temperature in *N*-methylpyrrolidone (NMP) using a CuCN/9,10-phenanthrenequinone (PQ)/^{t}BuOK catalytic system (Scheme

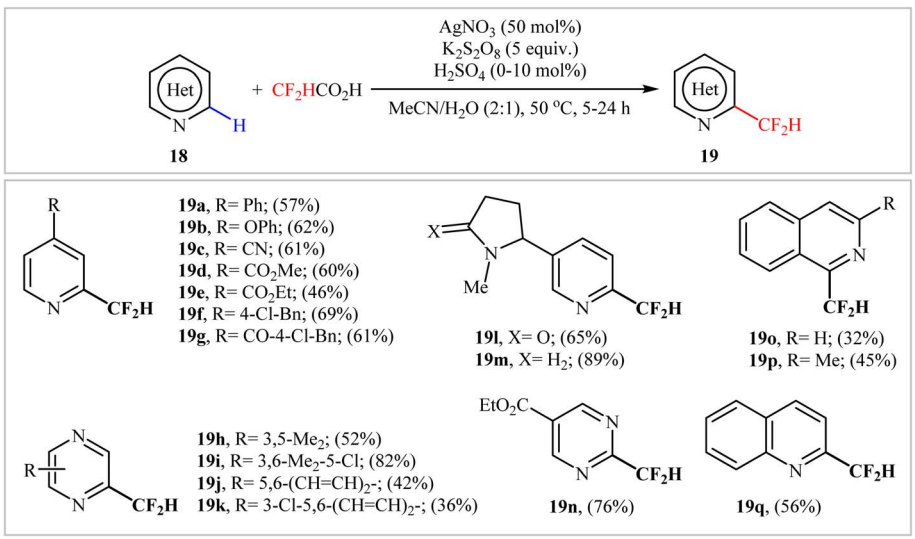


Scheme 9 Site-selective *meta*- and *para*-difluoromethylation of pyridines **15**, developed by Studer and co-workers.

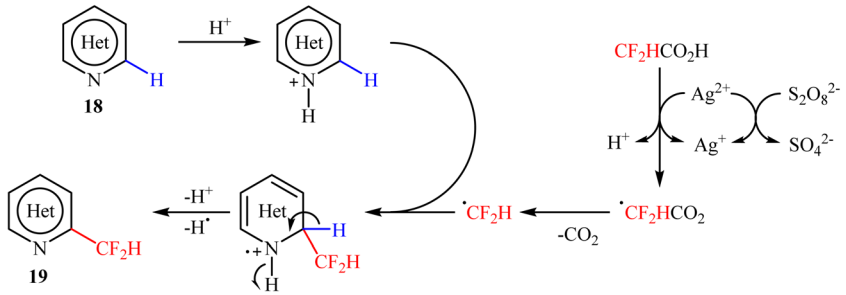
12a).[23] Under these conditions, seventeen difluoromethylated oxazoles **21** were obtained in moderate to high yields. In addition, the authors reported ten examples of direct C–H difluoromethylation of other heteroarenes, including thiazole, imidazole, 1,3,4-oxadiazole, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*b*]thiophene, pyridine, and thiophene derivatives, under the same reaction conditions, highlighting the broader applicability of the method. According to the authors (Scheme 12b), a plausible reaction mechanism involves the initial generation of $CuCF_2H$ and $Cu(CF_2H)_2^-$ species through the reaction of $TMSCF_2H$ with ^{t}BuOK and CuCN. Subsequent deprotonation of oxazole **20** by ^{t}BuOK, followed by transmetalation, furnishes intermediate **A**. Oxidation of this intermediate by PQ, and subsequent reductive elimination, then delivers the difluoromethylated product **21**.

4. Photoredox-catalyzed reactions

In 2020, Meng and Li, together with their co-workers, reported one of the earliest examples of visible-light photoredox-



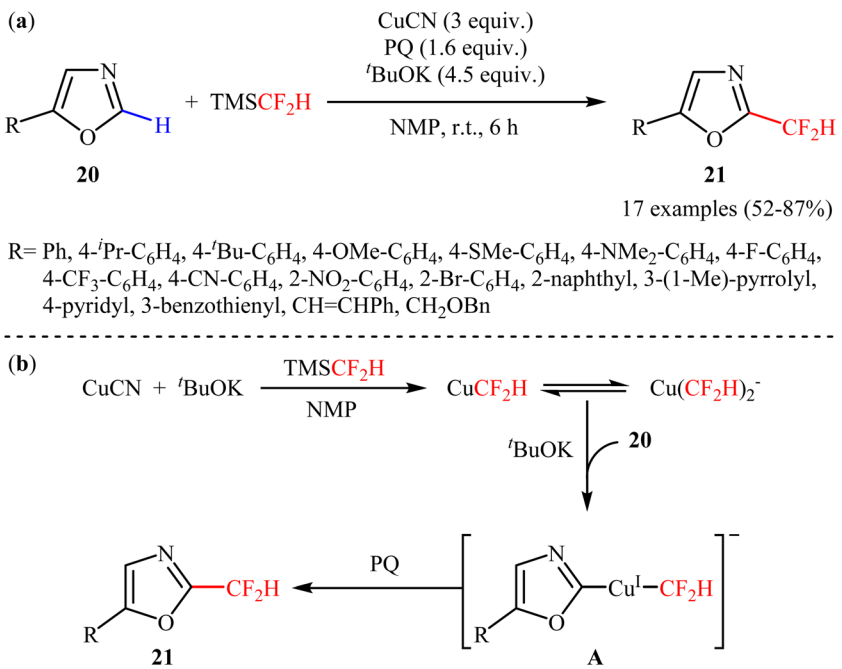
Scheme 10 Nielsen's synthesis of difluoromethylated heteroarenes **19**.



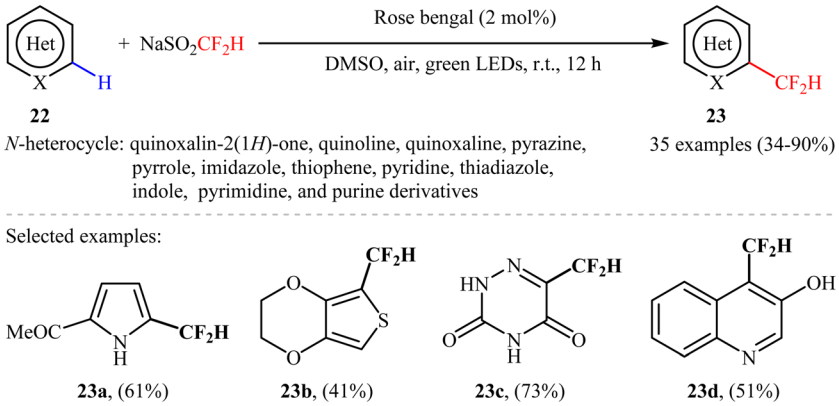
Scheme 11 Plausible mechanism for metal-catalyzed synthesis of difluoromethylated heteroarenes **19**.

catalyzed direct C–H difluoromethylation of heteroarenes using air as a green oxidant.[24] They demonstrated that, in the presence of only 2 mol% of Rose Bengal (RB) as a non-toxic organic photoredox catalyst, a variety of heteroarenes **22** underwent selective difluoromethylation at the position adjacent to the heteroatom upon green LED irradiation with $NaSO_2CF_2H$, without the need for any additives. This mild and operationally simple protocol furnished the corresponding difluoromethylated heteroarenes **23** in modest to excellent yields (Scheme 13). Importantly, the protocol was also amenable to certain arene substrates and enabled late-stage functionalization of complex nitrogen-containing bioactive molecules, such as deoxyuridine, allopurinol, voriconazole, and pentoxifylline. A plausible mechanistic pathway for this transformation is depicted in Scheme 14. The process is initiated by photoexcitation of ground-state RB under visible light to generate the excited photocatalyst RB*. Subsequent single-electron transfer from RB* to $NaSO_2CF_2H$ produces the $RB^{\bullet-}$ radical anion along with a $^{\bullet}CF_2H$ radical species. Oxidation of $RB^{\bullet-}$ by molecular oxygen regenerates the ground-state photocatalyst and generates superoxide ($O_2^{\bullet-}$). The $^{\bullet}CF_2H$ radical then adds to heteroarene **22** to form intermediate **A**, which undergoes a 1,2-hydrogen shift to yield carbon-centered radical intermediate **B**. Finally, hydrogen atom abstraction from intermediate **B** by $O_2^{\bullet-}$ furnishes the desired difluoromethylated product **23**.

Subsequently, Zhu-Wu's research team accomplished monoselective difluoromethylation of a series of O- and N-heteroarenes **24** with [bis(difluoroacetoxy)iodo]benzene [$PhI(O_2CCHF_2)_2$] as the difluoromethylation reagent employing $Ru(bpy)_2Cl_2 \cdot 6H_2O$ as the photocatalyst and blue LEDs as the light source in DMF at room temperature (Scheme 15a).[25] Notably, this chemistry was also well suited for the direct C(sp^2)–H difluoromethylation of enamides. More importantly, the practicality of this protocol was demonstrated through a gram-scale difluoromethylation of a piroxicam precursor, namely methyl 2-methyl-2*H*-benzo[*e*][1,2]thiazine-3-carboxylate



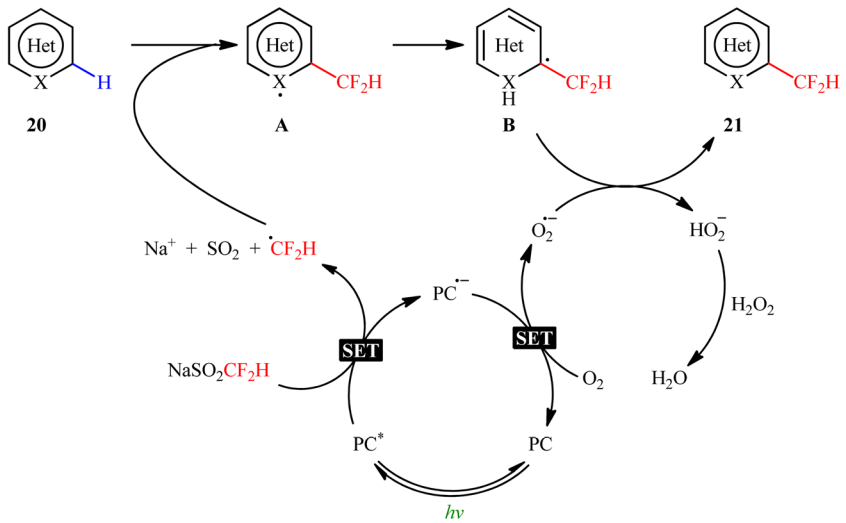
Scheme 12 (a) Cu-mediated difluoromethylation of oxazoles **20** with $TMSCF_2H$; (b) more detailed Cu-mediated difluoromethylation of oxazoles **20**.



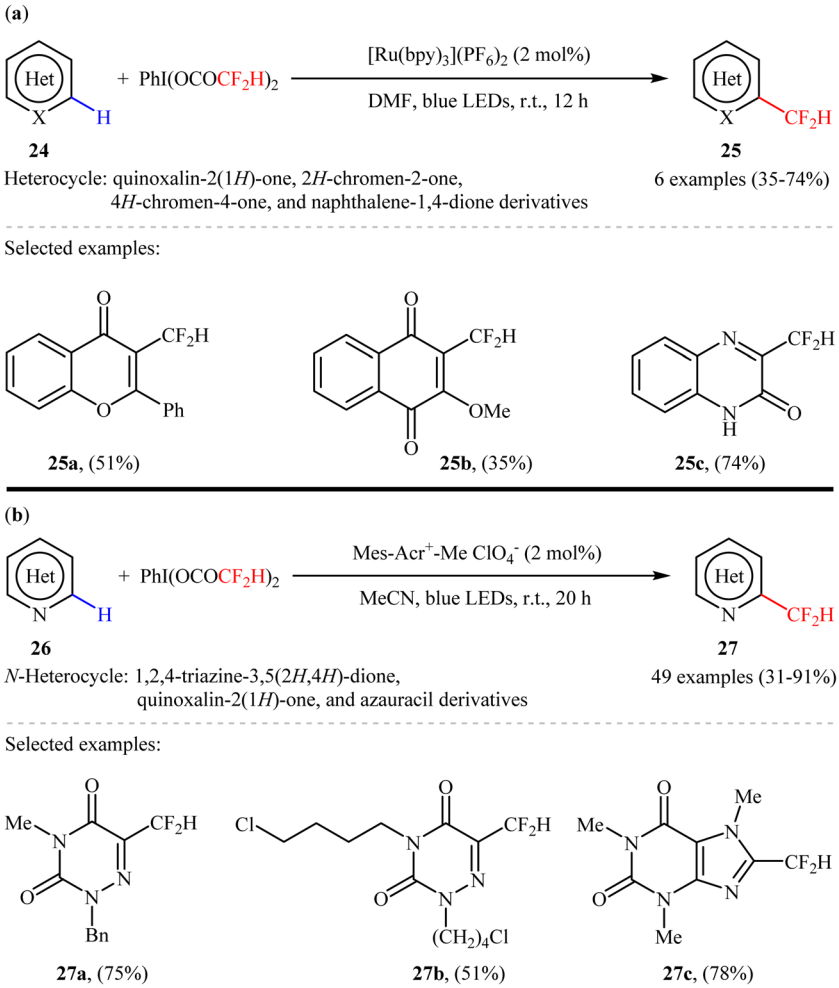
Scheme 13 RB-catalyzed direct C–H difluoromethylation of heteroarenes **22** with $NaSO_2CF_2H$.

1,1-dioxide, which proceeded effectively on a 1.52 g scale to afford the corresponding difluoromethylated product in 81% isolated yield. Quite recently, Xie and co-workers reported further examples of difluoromethylated heteroarenes **27** synthesis *via* direct C–H difluoromethylation of N-heterocycle substrates **26** with $PhI(O_2CCHF_2)_2$ using Mes-Acr^+-Me ClO_4^- as the photocatalyst under visible light irradiation (Scheme 15b).[26] This transformation displayed a broad substrate scope and excellent functional-group tolerance, accommodating a wide range of substituents, including F, Cl, Br, I, CF_3, OH, OAc, Ac, CN and NO_2. The proposed mechanism for this difluoromethylation reaction is depicted in Scheme 16. Upon irradiation, $PhI(O_2CCHF_2)_2$ undergoes homolytic cleavage to generate the difluoromethyl radical, which subsequently adds to heteroarene **26** to form intermediate **A**. The photoexcited catalyst (PC*) then oxidizes intermediate **A** *via* a single-electron transfer to produce the cationic intermediate **B**. Concurrently, the difluoromethylating reagent accepts an electron from $PC^{\bullet -}$, completing the photoredox cycle and generating $CF_2HCO_2^-$, PhI, and another difluoromethyl radical. Next, intermediate **B** undergoes electron delocalization to form cation **C**, which is finally deprotonated by $CF_2HCO_2^-$ to afford the observed product **27** along with the corresponding difluoroacetic acid.

Following these works, Yuan and co-workers reported the visible-light-mediated Ir-photoredox-catalyzed difluoromethylation of quinoxalin-2(1*H*)-one derivatives using difluoromethyltriphenylphosphonium bromide salt ($[Ph_3PCF_2H]^+Br^-$) as the CF_2H radical precursor.[27] The optimal conditions of the reaction involve the use of only 1 mol% of *fac*-$[Ir(ppy)_3]$ as the catalyst and blue LEDs as light source. Among the various common organic solvents, such as DMF, DMSO, DCM, DCE, THF, MeCN, H_2O, dioxane; MeCN proved to be the most efficient for this C–H functionalization reaction. The optimized condition tolerated both NH-free and *N*-functionalized quinoxalin-2(1*H*)-ones **28**, and provided the desired difluoromethylative quinoxalin-2(1*H*)-ones **29** in good yields with excellent regioselectivity (Scheme 17a). Unfortunately, quinolin-2(1*H*)-one was incompatible with this transformation, suggesting that the presence of the nitrogen atom at the 4-position plays a crucial role in enabling the reaction. Moreover, attempts

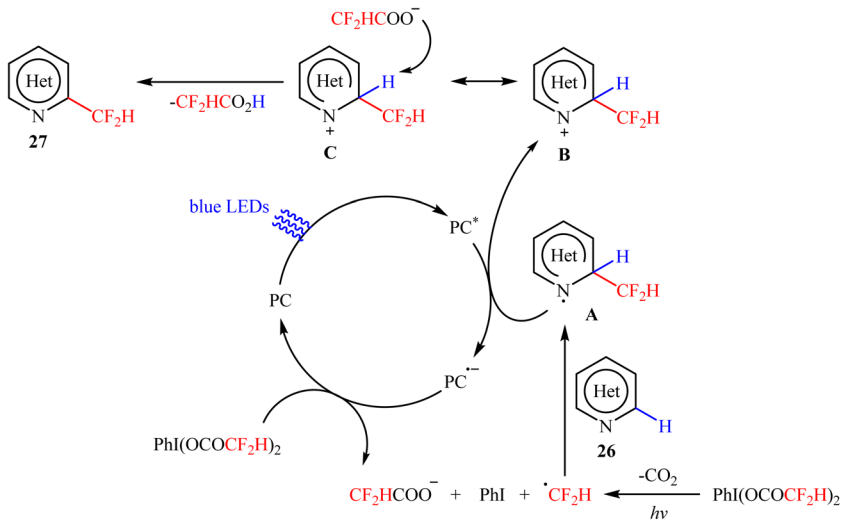


Scheme 14 Proposed mechanism for the RB-catalyzed direct C–H difluoromethylation of heteroarenes **22** with $NaSO_2CF_2H$.

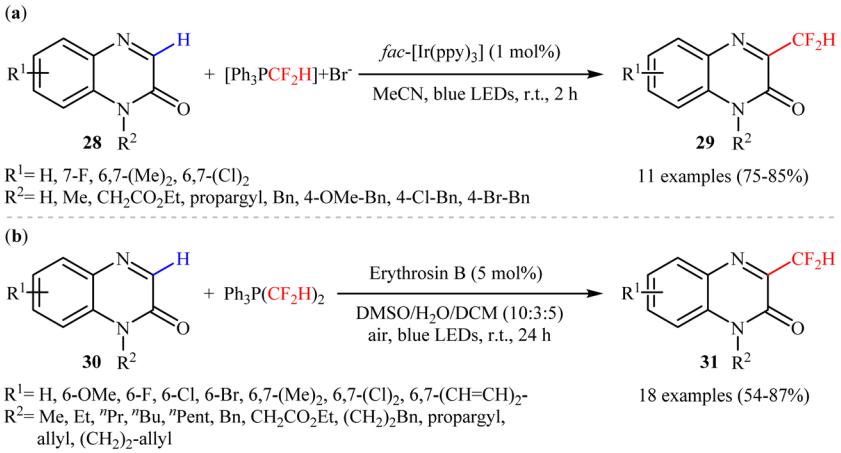


Scheme 15 (a) Zhu-Wu's synthesis of difluoromethylated heteroarenes **25**; (b) Xie's synthesis of difluoromethylated heteroarenes **27**.

to extend the substrate scope to coumarin and quinoline were unsuccessful, as no formation of the anticipated products was observed. Concurrently, Hu and co-workers reported a closely related difluoromethylation of quinoxalin-2(1*H*)-ones **30** using bis(difluoromethyl)pentacoordinate phosphorane ($PPh_3(CF_2H)_2$) as the difluoromethylation reagent.[28] This transformation

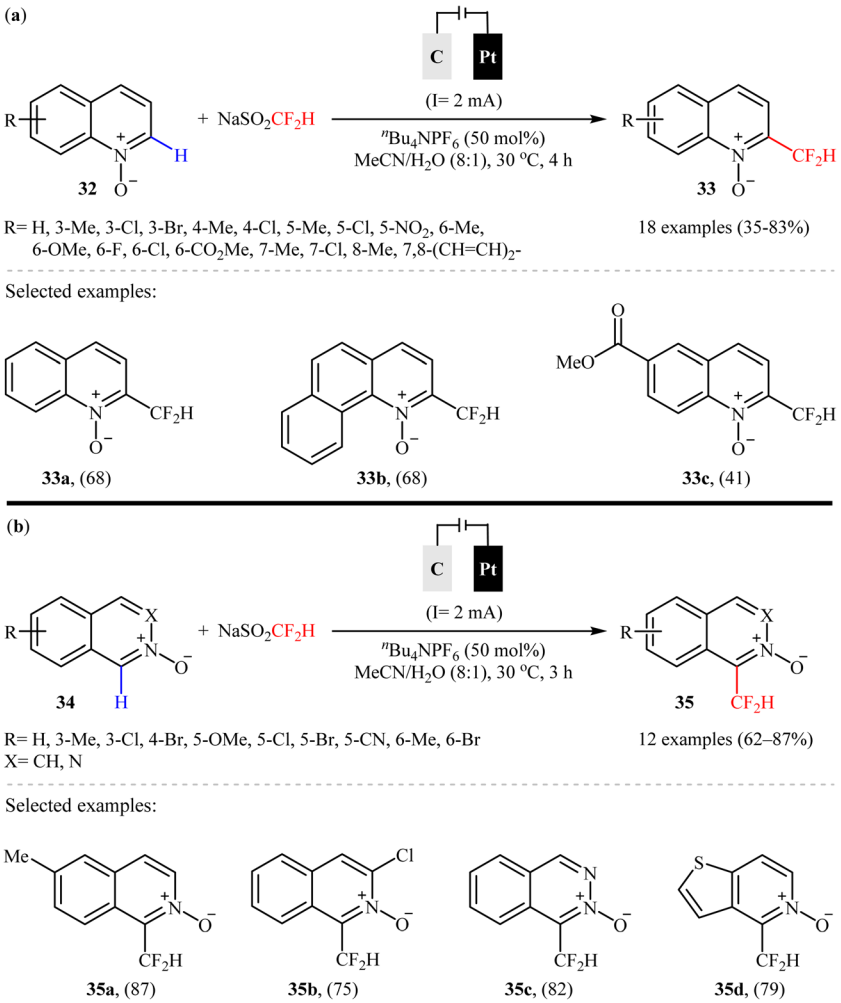


Scheme 16 Proposed mechanism for the reaction in Scheme 15b.

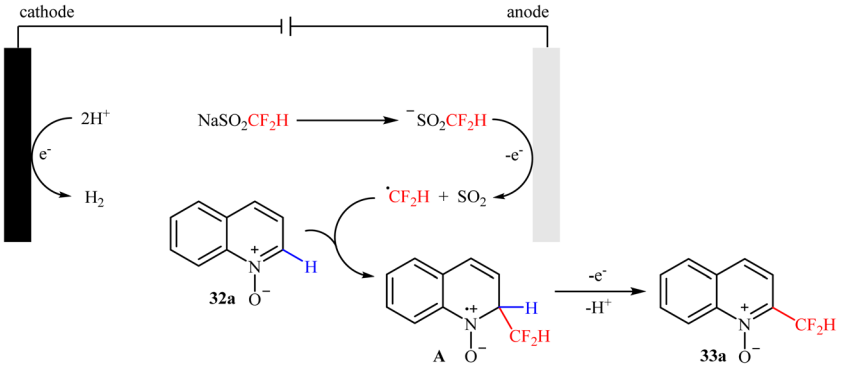


Scheme 17 (a) Yuan's difluoromethylation of quinoxalin-2(1*H*)-ones **28**; (b) Hu's synthesis of C3-difluoromethylated quinoxalin-2(1*H*)-ones **31**.

was carried out in the presence of a catalytic amount of readily available erythrosin B under visible-light irradiation in a DMSO/H_2O/DCM solvent mixture, tolerated various sensitive functional groups, and delivered the desired difluoromethylated products **31** in moderate to high yields (Scheme 17b). In addition to quinoxalin-2(1*H*)-ones, the methodology was also successfully extended to five-membered benzo-fused heterocycles as well as coumarin derivatives. Along this line, Zhao and



Scheme 18 Zhang's synthesis of (a) 2-(difluoromethyl)quinoline 1-oxides **33**; (b) 1-(difluoromethyl)isoquinoline *N*-oxides **35**.



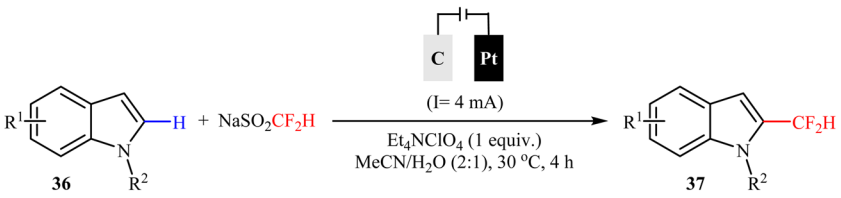
Scheme 19 Mechanism that accounts for the formation of 2-(difluoromethyl)quinoline 1-oxides **33**.

co-workers recently designed and synthesized a novel dual-active-site vinylidene-linked photocatalytic covalent organic framework (V-COF–AN–BT) by incorporating anthracene and benzothiadiazole moieties into a tristyryltriazine-based framework, and applied it as an efficient heterogeneous photocatalyst for the direct difluoromethylation of various heteroarenes with $NaSO_2CF_2H$ under visible-light irradiation.[29] In this system, the anthracene (AN) units play a key role in promoting the oxidation of $NaSO_2CF_2H$ to generate CF_2H radicals, while the benzothiadiazole (BT) units efficiently reduce molecular oxygen to superoxide ($O_2^{\bullet-}$), thereby synergistically facilitating the overall difluoromethylation process.

5. Electro-catalyzed reactions

In 2022, Zhang's research team reported the first example of electrochemical direct difluoromethylation of aromatic C–H bonds under catalyst-free conditions.[30] They demonstrated that a variety functionalized quinoline *N*-oxides **32** underwent C2-selective difluoromethylation using $NaSO_2CF_2H$ in an undivided cell equipped with a graphite anode and a platinum cathode employing $^nBu_4NPF_6$ as the supporting electrolyte. The reactions were carried out under air in an open tube under a constant current of 2 mA, tolerated a range of functional groups (*e.g.* F, Cl, Br, NO_2, CO_2Me, OMe) and furnished the corresponding 2-(difluoromethyl)quinoline 1-oxides **33** in synthetically useful yields (Scheme 18a). Notably, when isoquinoline *N*-oxides **34** were subjected to the same conditions, the corresponding 1-(difluoromethyl)isoquinoline *N*-oxides **35** were obtained with complete regioselectivity and high yields (Scheme 18b). However, the process appears to be poorly scalable, as a significant decrease in yield was observed upon scale-up (from 85% on a 0.2 mmol scale to 62% on a 4.0 mmol scale). To probe the reaction mechanism, a series of control experiments, including kinetic isotope effect (KIE) studies, radical scavenger experiments, and cyclic voltammetry (CV) analyses were performed. The results support a radical-mediated pathway and indicate that cleavage of the C–H bond is not involved in the rate-determining step of the reaction. On the basis of these experimental findings and literature precedents, the authors proposed that the reaction is initiated by dissociation of $NaSO_2CF_2H$ to generate the difluoromethanesulfinate anion ($CF_2HSO_2^-$), which undergoes anodic oxidation followed by desulfurization to form a difluoromethyl radical ($^{\bullet}CF_2H$). This radical then selectively adds to quinoline *N*-oxide **32a** to afford intermediate **A**. Subsequent single-electron transfer and proton elimination restore aromaticity, delivering the difluoromethylated product **33a**, while protons are reduced at the cathode to generate H_2 (Scheme 19).

The same authors later extended this methodology, with only minor modifications, namely, replacement of $^nBu_4NPF_6$ with Et_4NClO_4 and an increase in the constant current to 4 mA, to achieve C2-selective difluoromethylation of a series of *N*-functionalized indole derivatives **37** (Scheme 20).[31] The reaction tolerated a range of electron-donating and electron-withdrawing groups at various positions on the indole ring; however, an electron-withdrawing group on the nitrogen atom was essential for successful transformation. Although



Scheme 20 Zhang's synthesis of 2-(difluoromethyl)-indoles **36**.

Table 1 Comparison of results of direct difluoromethylation of heteroaromatic C–H bonds

Entry	CF_2H reagent	Commercial availability of CF_2H reagent	Conditions	Number of examples	Yield (%)	Ref.
1	$Ar–I(OCOCF_2H)_2$	—	$CDCl_3$, blue LEDs, r.t., 14 h	14	22–77	11
2	$PhI(OCOCF_2H)_2$	+	DCE, blue LEDs, 40 °C, 12 h	19	40–79	12
3	$NaSO_2CF_2H$	+	$K_2S_2O_8$ (3 equiv.), DMSO, 90 °C, 12 h	23	32–80	13
4	$NaSO_2CF_2H$	+	Biacetyl (5 equiv.), DMSO, blue LEDs, r.t., 24 h	27	54–86	14
5	2-SO_2CF_2H-benzothiazole	+	Et_3N (1.2 equiv.), MeCN, blue LEDs, r.t., 24 h	29	18–89	15
6	$(CHF_2CO)_2O$	+	PNO (2 equiv.), MeCN, blue LEDs, 40 °C, 12 h	23	35–88	16
7	$TMSCF_3$	+	TBAT (10 mol%), THF, −50 °C to r.t., 16 h	9	27–63	17
8	CF_2ICOPh	+	Multi-step	30	30–78	18
9	$[CF_2HC(O)O]_2$	—	Multi-step	12	32–73	18
10	$NaSO_2CF_2H$	+	DMSO, blue LEDs, r.t., 16 h	26	50–83	19
11	$Zn(SO_2CF_2H)_2$	+	^tBuOOH (3 equiv.), TFA (1 equiv.), DCM/H_2O, 23 °C, 1–24 h	20	30–90	20
12	CF_2HCO_2H	+	$AgNO_3$ (50 mol%), $K_2S_2O_8$ (5 equiv.), H_2SO_4 (0–10 mol%), MeCN/H_2O (2 : 1), 50 °C, 5–24 h	17	32–89	22
13	$TMSCF_2H$	+	CuCN (3 equiv.), PQ (1.6 equiv.), ^tBuOK (4.5 equiv.), NMP, r.t., 6 h	27	46–87	23
14	$NaSO_2CF_2H$	+	Rose bengal (2 mol%), DMSO, air, green LEDs, r.t., 12 h	48	25–90	24
15	$PhI(OCOCF_2H)_2$	+	$[Ru(bpy)_3](PF_6)_2$ (2 mol%), DMF, blue LEDs, r.t., 12 h	6	35–74	25
16	$PhI(OCOCF_2H)_2$	+	Mes-Acr^+-Me ClO_4^- (2 mol%), MeCN, blue LEDs, r.t., 20 h	49	31–91	26
17	$[Ph_3PCF_2H]^+Br^-$	+	*fac*-[Ir(ppy)$_3$] (1 mol%), MeCN, blue LEDs, r.t., 2 h	11	75–85	27
18	$Ph_3P(CF_2H)_2$	—	Erythrosin B (5 mol%), DMSO/H_2O/DCM (10 : 3 : 5), air, blue LEDs, r.t., 24 h	35	54–87	28
19	$NaSO_2CF_2H$	+	V-COF–AN–BT, DMSO, blue LEDs, r.t., 24 h	16	53–95	29
20	$NaSO_2CF_2H$	+	C anode, Pt cathode, 2 mA, $^nBu_4NPF_6$ (50 mol%), MeCN/H_2O (8 : 1), 30 °C, 3–4 h	30	35–87	30
21	$NaSO_2CF_2H$	+	C anode, Pt cathode, 4 mA, Et_4NClO_4 (1 equiv.), MeCN/H_2O (2 : 1), 30 °C, 4 h	22	38–76	31

a significant number of examples were provided in this study, no examples were reported for substrates with a blocked C2 position. Given the numerous advantages of electrochemically driven radical C–H fluoromethylation reactions,[32] further investigation and development of efficient $C_{(aryl)}$–H difluoromethylation under electrochemical conditions remains a significant research opportunity.

6. Conclusion

The relevance of difluoromethylated heteroarenes is steadily increasing in medicinal and agricultural chemistry, prompting researchers to develop innovative, concise, and efficient strategies for their synthesis. Among the various approaches developed, direct difluoromethylation of heteroaromatic C–H bonds has gained significant attention due to its high atom- and step-economy, as it eliminates the need for pre-functionalized starting materials. As highlighted in this review, the past few years have witnessed rapid growth in this field, with various catalyst-free and catalytic protocols emerging (Table 1). Importantly, many of these protocols exhibit excellent functional group tolerance and are amenable to scale-up, providing multigram quantities of products in good yields. Nevertheless, there are still many challenges to be addressed in this area. Some of these are listed below: (i) the substrate scope is largely limited to nitrogen-containing heteroarenes, highlighting the need for further protocols applicable to other heteroarenes; (ii) no general methodology has yet been developed for direct C–H difluoromethylation of arenes; thus, development of protocols which can allow the use of arenes in this chemistry would be highly desirable; (iii) examples of regio-switchable difluoromethylation remain scarce, which limits the ability to selectively functionalize different positions on the heteroarene scaffold; and (iv) the diversity of difluoromethylating reagents is still limited and requires further development.

Conflicts of interest

There are no conflicts to declare.

Data availability

This article is a review and does not report any original experimental data. Therefore, no new data were generated or analyzed, and data sharing is not applicable.

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