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# Photocatalytic fluoroalkylation by ligand-to-metal charge transfer

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Trifluoromethyl (CF<sub>3</sub>) and other fluoroalkyl groups are of great significance in the fields of pharmaceutical chemistry and agricultural chemicals. Fluoroalkyl acids, especially trifluoroacetic acid (TFA) is considered the most ideal fluoroalkylation reagent due to its low cost and easy availability. However, the extremely high oxidation potential requirement of TFA limits its wide application. In recent years, since visible-light-induced fluoroalkylation through the ligand-to-metal charge transfer (LMCT) process can overcome the above limitations, it has become an effective synthetic tool for the construction of fluorinated compounds with complex molecules and structures. In this review, according to the classification of different metal catalysts, we summarize the trifluoromethylation and fluoroalkylation of olefins, heteroaromatics, and terminal alkynes in different metal catalytic systems and their corresponding reaction mechanisms. The photocatalytic fluoroalkylation via LMCT is believed to expedite the development of fluoro-containing drugs, and more novel fluoroalkylation methodologies using this strategy will be disclosed.

## KEYWORDS

trifluoromethylation, fluoroalkylation, visible-light-induced, LMCT, iron

## 1 Introduction

The introduction of fluorine atoms into pharmaceuticals can improve their lipophilicity and membrane permeability, further affecting their metabolic stability and bioavailability (Gillis et al., 2015; Inoue et al., 2020; Han et al., 2021; Zhou et al., 2016; Purser et al., 2008; Chhetri et al., 2024). The first fluorine-containing drug was fluorocortisone, which was launched in 1954. Encouraged by the success of these drugs, the number of approved fluorine-containing drugs has steadily increased over half a century (Inoue et al., 2020). A recent estimate suggests that over 20% of all marketed drugs have been fluorine-containing drugs and fluorinated compounds also account for about 30%–40% of agricultural chemicals; obviously, the proportion of fluoride drugs is increasing day by day (Figure 1) (Inoue et al., 2020; Chhetri et al., 2024; Shaw et al., 2024). Among them, fluoroalkyl, especially trifluoromethyl, is the most commonly used functional group in drug research and development, and widely exists in drugs. For example, a long-acting HIV-1 therapeutic and preventive drug lenacapavir approved in 2022, contains multiple trifluoromethyl and trifluoromethyl groups, which could endow the drug with low hepatic clearance (Marshall et al., 2024). Perfluorohexane, a 2023 newly approved drug to treat dry eye consists of perfluoroalkyl group and alkyl group (Ma et al., 2024). Therefore,

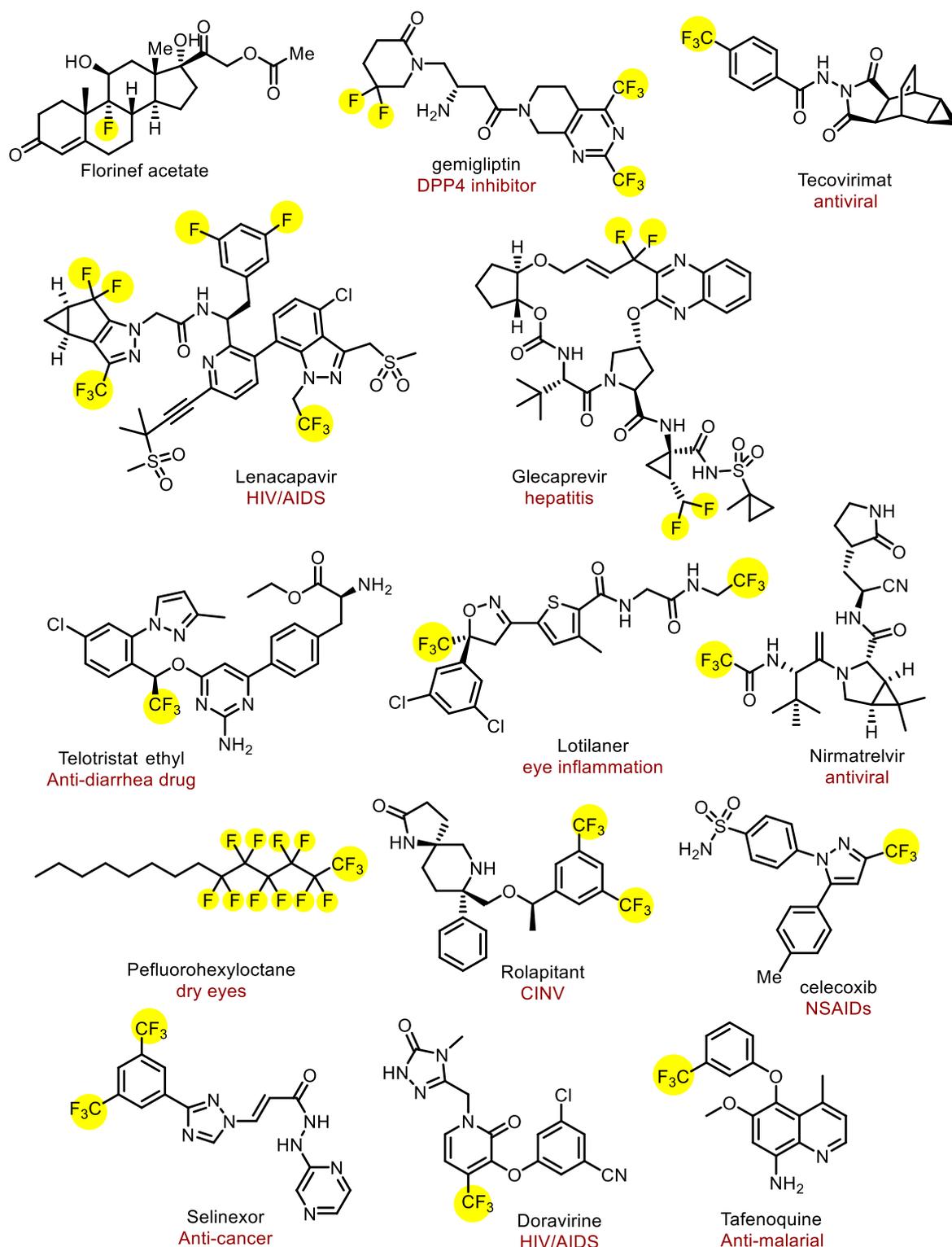


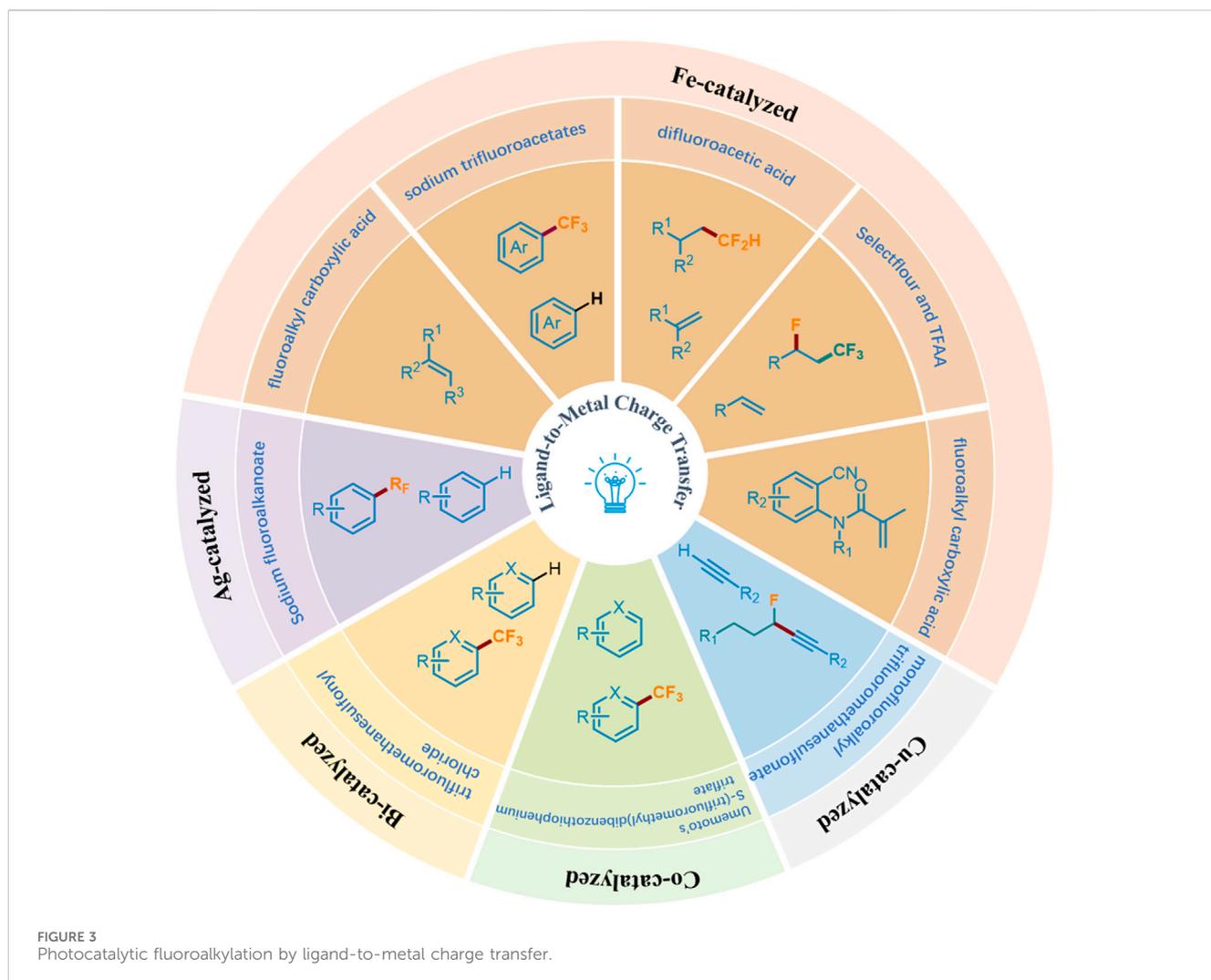
FIGURE 1  
The pharmaceuticals containing fluoroalkyl groups.

the development of efficient fluoroalkylation methods has become a vital topic in medicinal chemistry and synthetic methodology.

Many fluoroalkylation reactions have been reported (Lalloo et al., 2021; Kuehl and Taylor, 2023; Jin et al., 2024; Pan et al.,

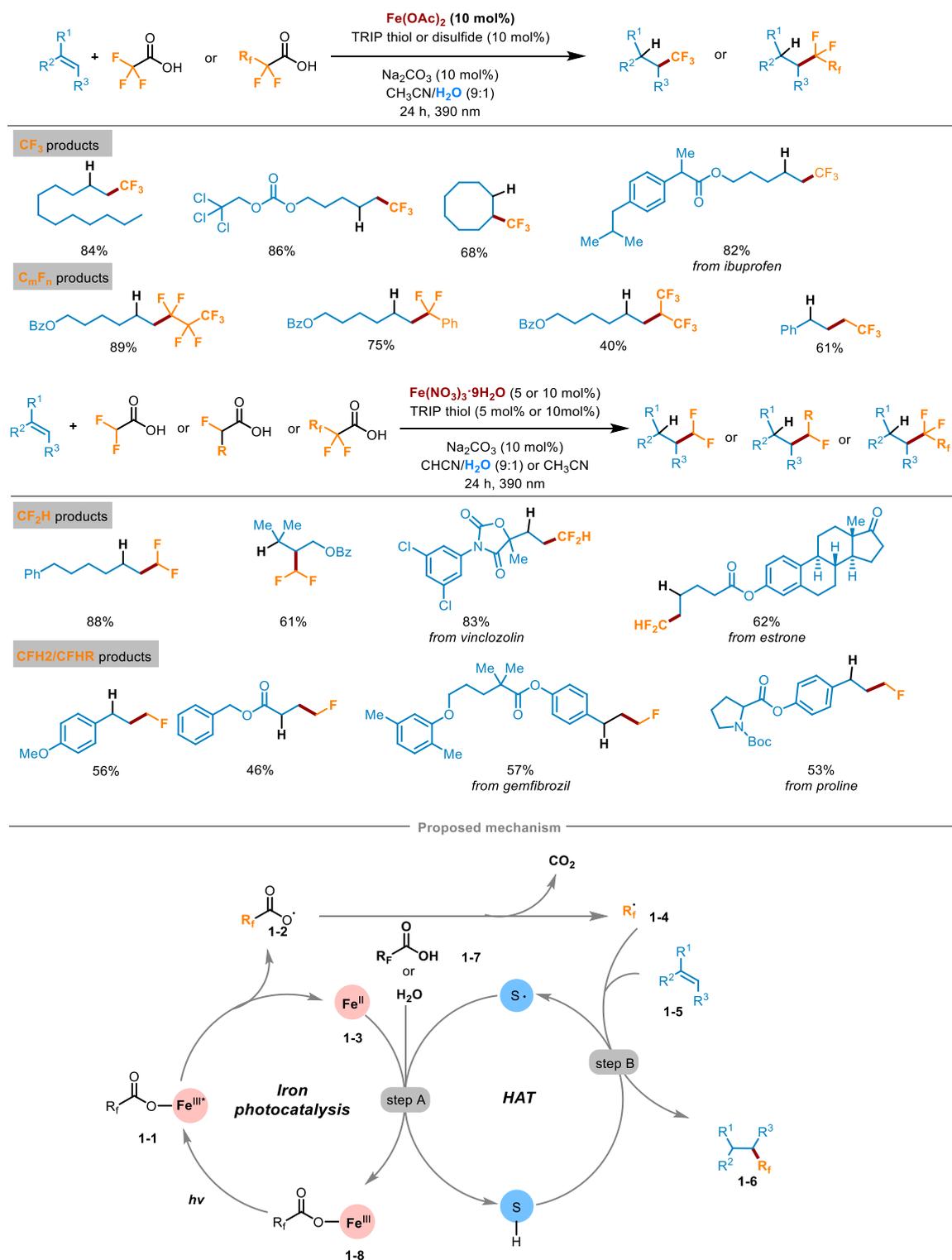
2016; Tian et al., 2024; Liang et al., 2023). The early used reagents, such as  $\text{CF}_3\text{I}$  (Kino et al., 2010),  $\text{CF}_3\text{SO}_2\text{Cl}$  (Kamigata et al., 1991), and  $\text{CF}_3\text{SO}_2\text{Na}$  (Langlois et al., 1991), have been constrained in their widespread applicability owing to excessively harsh conditions and





compounds. In 2023, West's research group at *Rice University* reported a visible-light-induced fluoroalkylation of unactivated olefins using cheap and easily available fluoroalkyl carboxylic acid as the only fluoroalkyl radical source, which realized the hydrofluoroalkylation (including trifluoro-, difluoro-, monofluoro- and perfluoroalkylation) of alkenes through the dual-catalytic synergism of iron photocatalysis and redox active thiol catalyzed hydrogen-atom-transfer (HAT) process (Scheme 1) (Bian et al., 2023). The method demonstrated high compatibility with a wide array of alkenes with different functional groups, and the corresponding products were obtained in medium to good yields. A series of natural products or drug-derived alkenes could also be successfully compatible with this transformation, demonstrating the potential effectiveness of the late-stage modification. The deuterium labeling study by replacing  $H_2O$  with  $D_2O$  showed the deuterio-trifluoromethylated product could be afforded in a high deuterium incorporation rate which confirmed that hydrogen was provided by the cosolvent  $H_2O$ . A sequence of mechanism studies were undertaken to elucidate the underlying reaction pathway of this transformation. Initially, when the radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) was introduced into the reaction system, the formation of products was completely

inhibited and almost all the alkene starting materials were recovered. What's more, the presence of TEMPO- $CF_3$  adduct indicated radical intermediates involved in the reaction. Subsequently, the authors investigated the reaction employing two distinct substrates capable of eliciting a radical clock process. The experimental results also demonstrated the involvement of radical intermediates. Finally, the parallel kinetic isotope effect (KIE) experiment pinpointed the HAT process as the rate-determining step of this transformation. Guided by these investigations, the following mechanistic pathway was proposed in Scheme 1. Firstly, the fluoroalkyl carboxylic acid chelated with Fe(II) to generate Fe(III) complex 1-1, which was excited under visible light irradiation. Then LMCT occurred in the excited iron complex to cause homolytic cleavage of the O-Fe bond, affording carboxyl radicals 1-2 and low-valent  $Fe^{II}$  species 1-3. After removing one molecule of  $CO_2$  from 1-2, the key fluorinated alkyl radical 1-4 was generated. It then was captured by alkenes 1-5, affording a transient alkyl radical intermediate. Then, a HAT process occurred between the thiol cocatalyst and alkyl radical intermediate, gaining the desired hydrofluoroalkylation product 1-6 and thiol radicals (step B). At last, the thiol radical further oxidized  $Fe^{II}$  1-3 to release high-valent  $Fe^{III}$  species 1-8, simultaneously obtaining a proton from

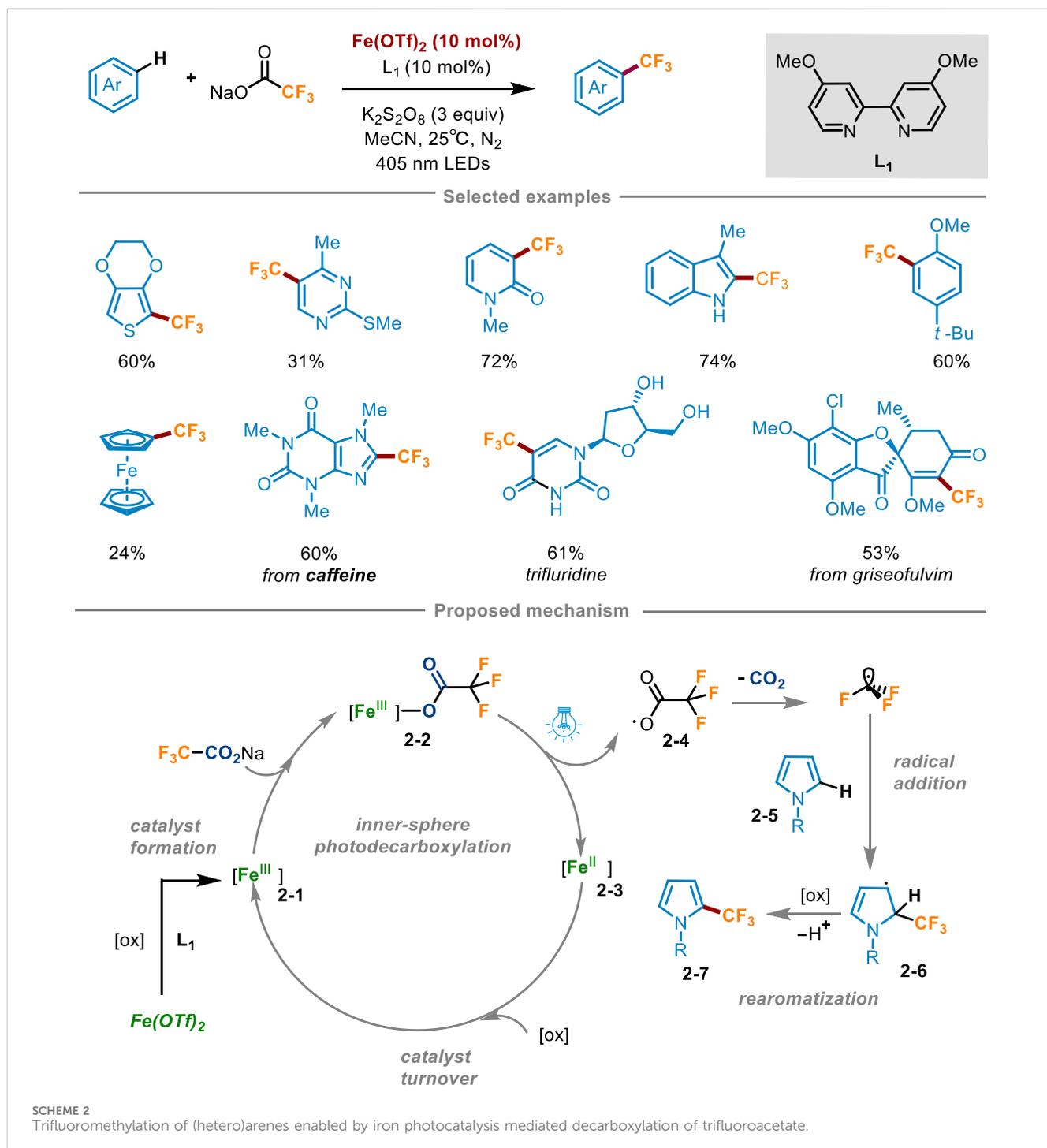


SCHEME 1  
Photocatalytic hydrofluoroalkylation of alkenes with carboxylic acids.

another carboxylic substrate 1-7 or H<sub>2</sub>O, closing both the iron photocatalysis cycle and redox active thiol catalytic cycle (step A).

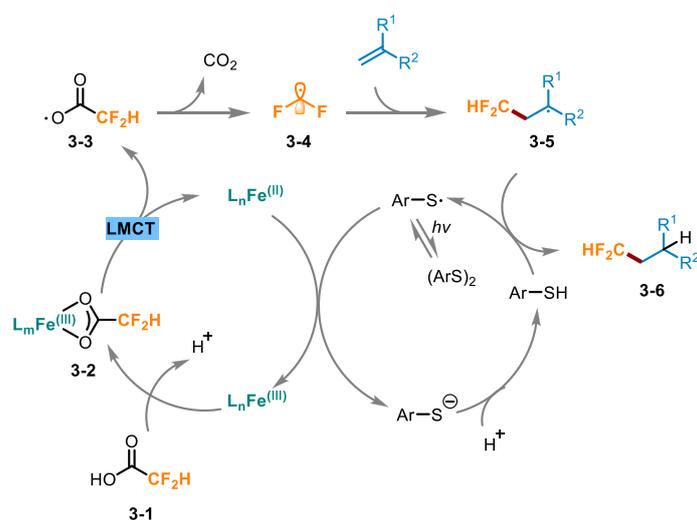
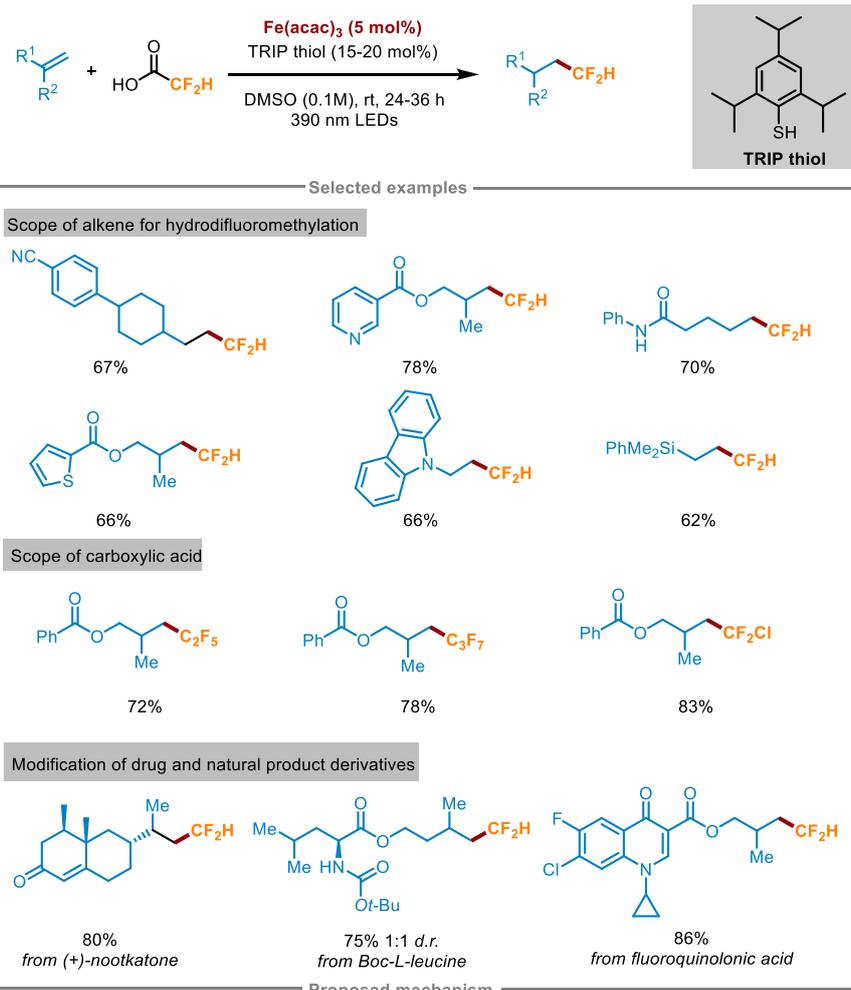
Trifluoroacetates are cheap and easily available trifluoromethyl sources, which play a crucial role in pharmaceuticals and agricultural chemicals. However, trifluoroacetate has a high

oxidation potential (+2.4 V vs. SCE in MeCN) (Depecker et al., 1999), which makes it hard to generate trifluoromethyl radical through decarboxylation reaction to participate in the subsequent reaction. In 2023, Francisco's group developed a direct C–H trifluoromethylation of various electron-rich (hetero)aromatics



through iron(II) trifluoromethanesulfonate  $\text{Fe}(\text{OTf})_2$  catalyzed photodecarboxylation of trifluoroacetates (Scheme 2) (Fernández-García et al., 2024). The optimal reaction conditions were determined as follows: (hetero)arene reacted with sodium trifluoroacetate (4–6 equiv) in the presence of  $\text{Fe}(\text{OTf})_2$  (10 mol %) and 4,4'-dimethoxy-2,2'-bipyridine ( $\text{L}_1$ , 10 mol %) as the active catalyst,  $\text{K}_2\text{S}_2\text{O}_8$  (3 equiv.) as the oxidant, acetonitrile (0.1 M) as the solvent under the irradiation of 405 nm LED. Oxidants did not involve in the decarboxylation process, but were crucial for the conversion of Fe(II) to catalytically active Fe(III) species. Substrate

scope investigation revealed that a range of pyrroles with *N*-aromatic or aliphatic substitution, thiophene, pyridine, pyrimidine, indoles, and arenes with an electron donating group could achieve direct functionalization via this reaction. It was worth noting that this scheme also allowed for direct trifluoromethylation of ferrocene, which was difficult to access by the previous methods. The utility of this protocol was highlighted by the successful last-stage trifluoromethylation of drugs, agrochemicals and natural products. For instance, caffeine, pentoxifylline, theophylline, uracil, protected pyrimidine nucleobases, antifungal griseofulvin,



**SCHEME 3**  
Photoinduced hydrodifluoromethylation of alkenes enabled by Fe-LMCT mediated decarboxylation.

muscle relaxant metaxalone, nonsteroidal anti-inflammatory indomethacin, and natural product melatonin could be converted into the corresponding trifluoromethylated products. Moreover, one of the largest-selling drugs trifluridine (Lonsurf<sup>®</sup>) could be afforded

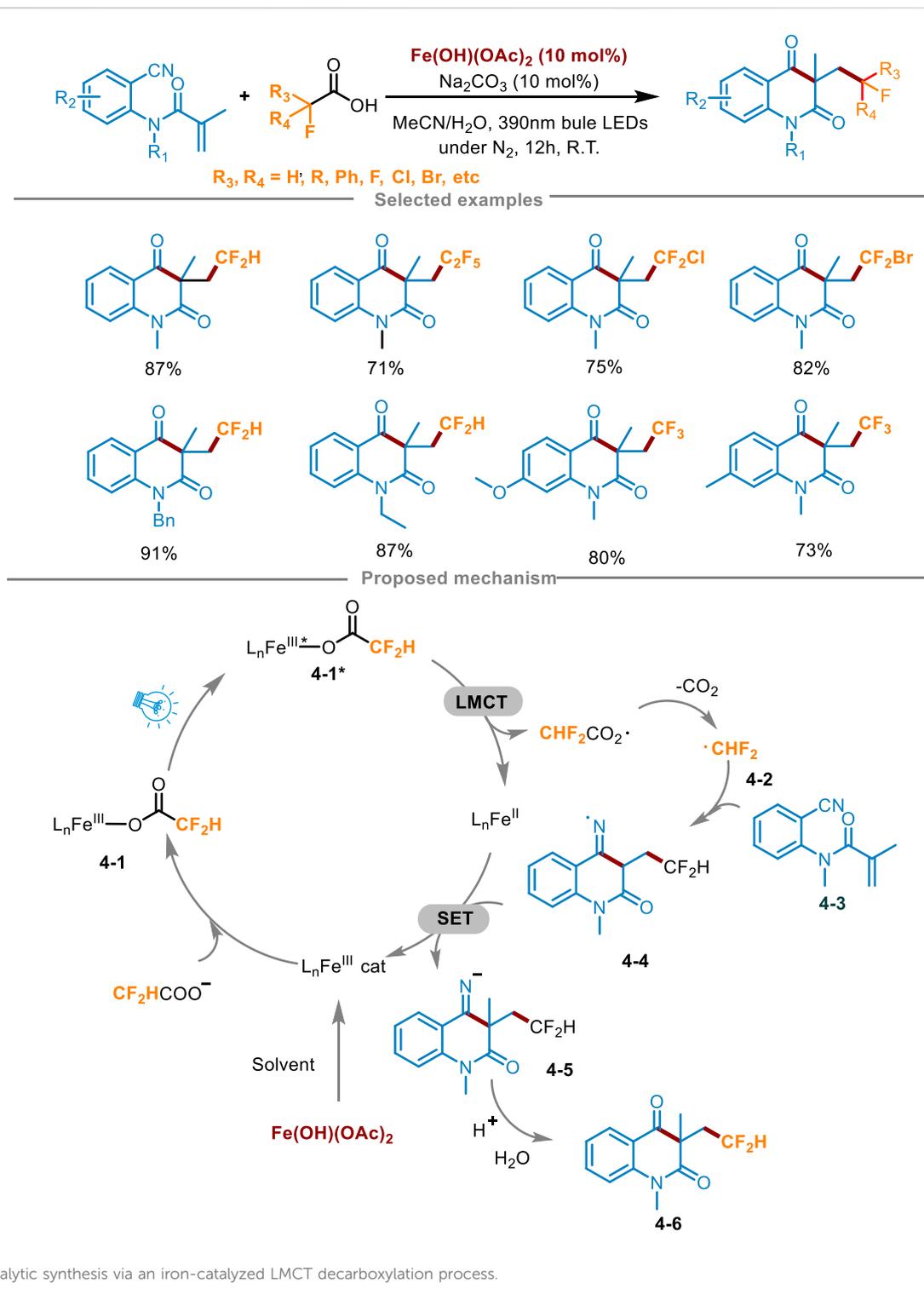
using this method from unprotected 2-deoxyuridine in a good yield. The radical trapping experiment offered definitive evidence for the mechanism of the reaction being a free radical process, whereas the UV-visible spectroscopic analysis corroborated the occurrence of a

trifluoroacetic acid-mediated photodecarboxylation reaction of **2-3**. The mechanism was depicted in **Scheme 2**: at first, *in situ* coordination of  $\text{Fe}(\text{OTf})_2$  with **LI**, followed by oxidation with  $\text{K}_2\text{S}_2\text{O}_8$  to form catalytically active  $\text{Fe}(\text{III})$  species **2-1**. Subsequently, sodium trifluoroacetate coordinated with the  $\text{Fe}(\text{III})$  substance **2-1**, resulting in the formation of  $\text{Fe}(\text{III})$  carboxylic acid complex **2-2**. Under visible light irradiation at 405 nm, LMCT occurred to trigger  $\text{Fe}-\text{O}$  homolytic cleavage, furnishing  $\text{Fe}(\text{II})$  species **2-3** and trifluoroacetic acid radical **2-4**, which then underwent decarboxylation to gain  $\text{CF}_3$  radical. Then  $\text{CF}_3$  radical was added to the substrate **2-5**, producing the radical intermediate **2-6** which was further converted into the trifluoromethylation product **2-7** after oxidation and deprotonation.  $\text{Fe}(\text{II})$  **2-3** was oxidized by  $\text{K}_2\text{S}_2\text{O}_8$  to regenerate  $\text{Fe}(\text{III})$  **2-1** and achieve the catalyst turnover.

Difluoroalkylation pathways of alkenes include halogen atom transfer (e.g.,  $\text{BrCF}_2\text{H}$ ,  $\text{ClCF}_2\text{H}$ ) (Zhang et al., 2022; Bacauanu et al., 2018) single-electron oxidation or reduction (e.g.,  $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$  or  $\text{ClSO}_2\text{CF}_2\text{H}$ ) (Fujiwara et al., 2012; Tang and Dolbier, 2015). However, most of the reported reactions also need to use expensive fluoroalkylation reagents, stoichiometric oxidants or additives, which are relatively not atomic economical. To overcome these limitations, Xia and Gou's group presented a universal synthesis method in 2024 (Scheme 3) (Qi et al., 2024), which utilized visible light to induce ligand-to-iron charge transfer, and activated difluoroacetic acid to form difluoromethyl radical without adding additional stoichiometric oxidants, thus overcoming the high redox potential of fluoroalkyl carboxylic acid raw materials. The reaction system easily facilitated the difluoromethylation of unactivated alkenes, demonstrating its compatibility towards a diverse array of functional groups. Furthermore, it also exhibited excellent performance in the difluoromethylation of some pharmaceutical molecules, natural products, as well as bioactive molecular derivatives, showcasing its broad applicability and synthetic potential. For example,  $\alpha$ -amino acid derivatives Boc-L-leucine can react with difluoroacetic acid with a yield of 75%. Likewise, the protocol has broad practicality, and (+)-nootkatone successfully reacted with difluoroacetic acid on a larger scale (4.0 mmol) with a yield of 80%. The reaction process was amplified using an expandable continuous flow reaction device, which greatly improved the reaction speed compared with the "single pot" method. A comprehensive suite of experiments, encompassing free radical trapping, free radical clock, isotope labeling, and electron paramagnetic resonance (EPR) spectroscopy, were conducted to gain a deeper understanding of the reaction mechanism, ultimately leading to the proposal of a plausible reaction pathway. As shown in **Scheme 3**, difluoroacetic acid **3-1** and  $\text{Fe}(\text{acac})_3$  formed  $\text{Fe}(\text{III})$ -carboxylate chromophore **3-2** *in situ*, and then the complex **3-2** was photoexcited to the LMCT state to obtain  $\text{Fe}(\text{II})$  complex and carboxyl radical **3-3**, followed by decarboxylation to release the key intermediate difluoromethyl radical **3-4**. Subsequently, **3-4** engaged in radical addition with the substrate alkenes to gain radical intermediate **3-5**, then received a hydrogen atom from  $\text{Ar-SH}$  ( $\text{Ar} = 2,4,6$ -triisopropylphenyl) to yield the target product **3-6** and  $\text{ArS}$  radical intermediate. After this,  $\text{ArS}$  radical oxidized the  $\text{Fe}(\text{II})$  complex to  $\text{Fe}(\text{III})$  and regenerated  $\text{Fe}(\text{III})$ -carboxylic acid complex **3-2** and  $\text{ArS}^-$ , finally realizing the catalytic cycle.

Currently, the synthesis of fluoroalkylated quinolinones still has strict requirements for reaction conditions, usually requiring expensive metal catalysts and excessive oxidants, and the choice of fluoroalkyl radical sources is also limited (Lin et al., 2017). To overcome these difficulties, Yang's group developed a practical method for the efficient synthesis of fluoroalkylated quinolinones in 2024 (Scheme 4) (Song et al., 2024). The carboxylic acids underwent visible-light-driven LMCT process and decarboxylation to generate fluoroalkyl radicals, which reacted with *N*-(2-cyanophenyl)-*N*-methylacrylamides **4-3** via free radical addition/cyclization cascade process to access fluorinated nitrogen heterocyclic derivatives. The fluoroalkylated quinolinone **4-6** was synthesized in an 87% yield by combining **4-3**, difluoroacetic acid (5 equiv.),  $\text{Fe}(\text{OH})(\text{OAc})_2$  (0.02 mmol, 10 mol%) and  $\text{Na}_2\text{CO}_3$  (10 mol%) in the mixture solvent of MeCN and  $\text{H}_2\text{O}$ , under the condition of  $\text{N}_2$  atmosphere and irradiation with a 390 nm blue LED light for 12 h at ambient temperature. Optimization experiments indicated that when using other iron catalysts instead of  $\text{Fe}(\text{OH})(\text{OAc})_2$ , it caused a decrease in yield. In the aspect of light source, increasing or decreasing the irradiation wavelength resulted in a decrease in the yield of the product. Control experiments proved that the photocatalyst, inert atmosphere, and light irradiation were essential for the transformation. Attempts at a gram-scale continuous flow reaction were also made using a photocatalytic device, and obtained the product with a moderate yield (66%), having a good application prospect. The study also showed the extensive reaction range of fluoroalkyl carboxylic acids. Most of these anionic acids with high oxidation potential can react smoothly and achieve excellent yields, including other acids with medium yields, which could prove that this method can effectively solve the problem of high oxidation potential. Simultaneously, it could also obtain the product of trifluoromethyl radical addition. The radical scavengers 2,6-di-*tert*-butyl-4-methylphenol (BHT) and TEMPO significantly inhibited the response, suggesting that the reaction may have undergone a free radical process. Furthermore, an isotope labeling experiment was conducted, involving the substitution of  $\text{H}_2\text{O}$  with  $\text{H}_2^{18}\text{O}$  in the solvent, conclusively demonstrating that the carbonyl group originated from the hydrolysis of the imine. Drawing upon these findings and phenomena observed during the condition screening, a plausible reaction mechanism was elucidated in **Scheme 4**. Initially,  $\text{Fe}(\text{OH})(\text{OAc})_2$  formed a trivalent iron complex in the presence of the solvent  $\text{CH}_3\text{CN}$ . Subsequently, it reacted with fluoroalkyl carboxylic acid anions to generate complex **4-1**, which was further converted into the excited state intermediate **4-2\*** under blue LED irradiation. Then, a key LMCT process occurred in this excited complex **4-2\*** through inner electron transfer, generating a  $\text{Fe}(\text{II})$  complex ( $\text{L}_n\text{Fe}^{\text{II}}$ ) and a carboxyl radical, which furnished the key fluoroalkyl radical **4-2** after decarboxylation. Then the fluoroalkyl radical combined with **4-3** to form imine radical intermediate **4-4**. An imine anion **4-5** was generated via a SET process between **4-4** and the  $\text{Fe}(\text{II})$  complex, along with the regeneration of the trivalent iron complex to close the photoredox cycle. Finally, **4-5** rapidly abstracted a hydrogen proton to produce the imine hydrolyzed by water in the solvent to deliver the desired fluoroalkylated quinolinone **4-6**.

In 2024, Niu and coworkers from Zhengzhou University proposed an innovative approach for fluoro-polyhaloalkylation of



non-activated olefins unlocking the LMCT of iron optically active species by Brønsted acid, activating inert polyhalogenated carboxylic acid salts ( $C_nX_mCOO^-$ ) to release polyhalogenated alkyl radicals, and achieved the fluoro-polyhaloalkylation of olefins through alkenes capture and radical fluorination (Scheme 5) (Jiang et al., 2024). By harnessing inexpensive trifluoroacetic anhydride (TFAA), isopropanol, oxygenated diphenyl and acetonitrile, a reaction system of Brønsted acid and trifluoroacetic acid was established. This

system, when coupled with commercial  $Fe(acac)_3$  as the metal catalyst, Selectfluor as the radical fluorinating agent, along with blue LED irradiation, enabled the successful execution of fluoro-trifluoromethylation reactions with exceptional regional selectivity and moderate to high yields. Further stoichiometric investigations revealed that under the irradiation of blue LED,  $Fe(CF_3COO)_3$  unlocking and releasing  $CF_3$  radicals depended on the presence of a strong Brønsted acid, and only when  $Fe(CF_3COO)_3$  was in





## 2.2 Photoinduced copper-catalyzed fluoroalkylation

In 2023, Wang and Li's group disclosed a novel strategy of Cu(I) initiated cross-coupling reaction for the monofluoroalkylation of terminal alkynes under light irradiation (Scheme 6) (Hu et al., 2023). With readily available monofluoroalkyl trifluoromethanesulfonate as a fluorinating agent to avoid using highly toxic fluorinated reagents, this catalytic system has shown mild reaction conditions, a wide range of substrates, and strong compatibility of functional groups. This method could also apply to the late-stage modification of biologically active molecules. Control experiments exhibited that light irradiation, copper catalyst, and ligand L11 were all crucial factors in the catalytic system. The reaction was completely inhibited by radical scavengers TEMPO or BHT and could detect TEMPO and BHT addition products by HRMS, which demonstrated that this catalytic cycle involved in a radical pathway. Based on these mechanistic experiments, a rationalized mechanism was illustrated in Scheme 6. At the beginning,  $L_nCuX$  reacted with substrate alkyne 6-1 under the condition of base to afford Cu(I) complex 6-2, which was then transformed into excited state 6-3 under light excitation. In the meantime, fluoroalkyl triflate 6-4 was converted to iodide 6-5 *in situ* in the existence of TBAI. Then the excited copper complex 6-3 and iodide 6-5 generated Cu(II) complex 6-6 and alkyl radical 6-7 through a SET process. Subsequently, the generated radical 6-7 was rapidly intercepted by 6-6 to yield the intended product 6-8, and then regenerated Cu(I) species to continue the next copper catalytic cycle.

## 2.3 Cobalt-catalyzed fluoroalkylation by LMCT

Co complexes have also been studied as photocatalysts in organic synthesis. For example, in 2018, Zysman-Colman and Hanan synthesized  $[Co(dgpy)_2]^{3+}$  and  $[Co(dgpz)_2]^{3+}$  complexes, which served as very strong photo oxidants and can be applied in the trifluoromethylation of polycyclic aromatic hydrocarbons (Pal et al., 2018). In 2023, Kuehner and coworkers also achieved similar transformations using Co complexes (Scheme 7) (Kuehner et al., 2023). Unlike previous work, Kuehner's work was achieved by the light induced activation of Co- $CF_3$  intermediates, which were generated *in situ* and can simultaneously act as chromophores and organometallic reaction centers. Optimization of reaction conditions showed this reaction obtained a higher yield in the presence of  $(OCO)Co(MeCN)$  and Umemoto's S-(trifluoromethyl)dibenzothiophenium triflate 7-1 with a 10-fold excess of reaction substrate in MeCN under irradiation with 440 nm blue LED for 6 h. The reaction yield decreased significantly when the electron cloud density of the ring was low. A workable mechanism was described in Scheme 7,  $[(OCO)Co^{II}]$  7-2 firstly reacted with Umemoto's reagent 7-1, and then net  $CF_3^+$  was added to Co(II) complex 7-2 to produce the photoactive  $(OCO \cdot)Co^{III}(CF_3)$  substance 7-3. Next, visible light irradiation induced the homolysis of Co- $CF_3$  bond of intermediates 7-3, generating Co(III) intermediate 7-5 and trifluoromethyl radical. The radical was

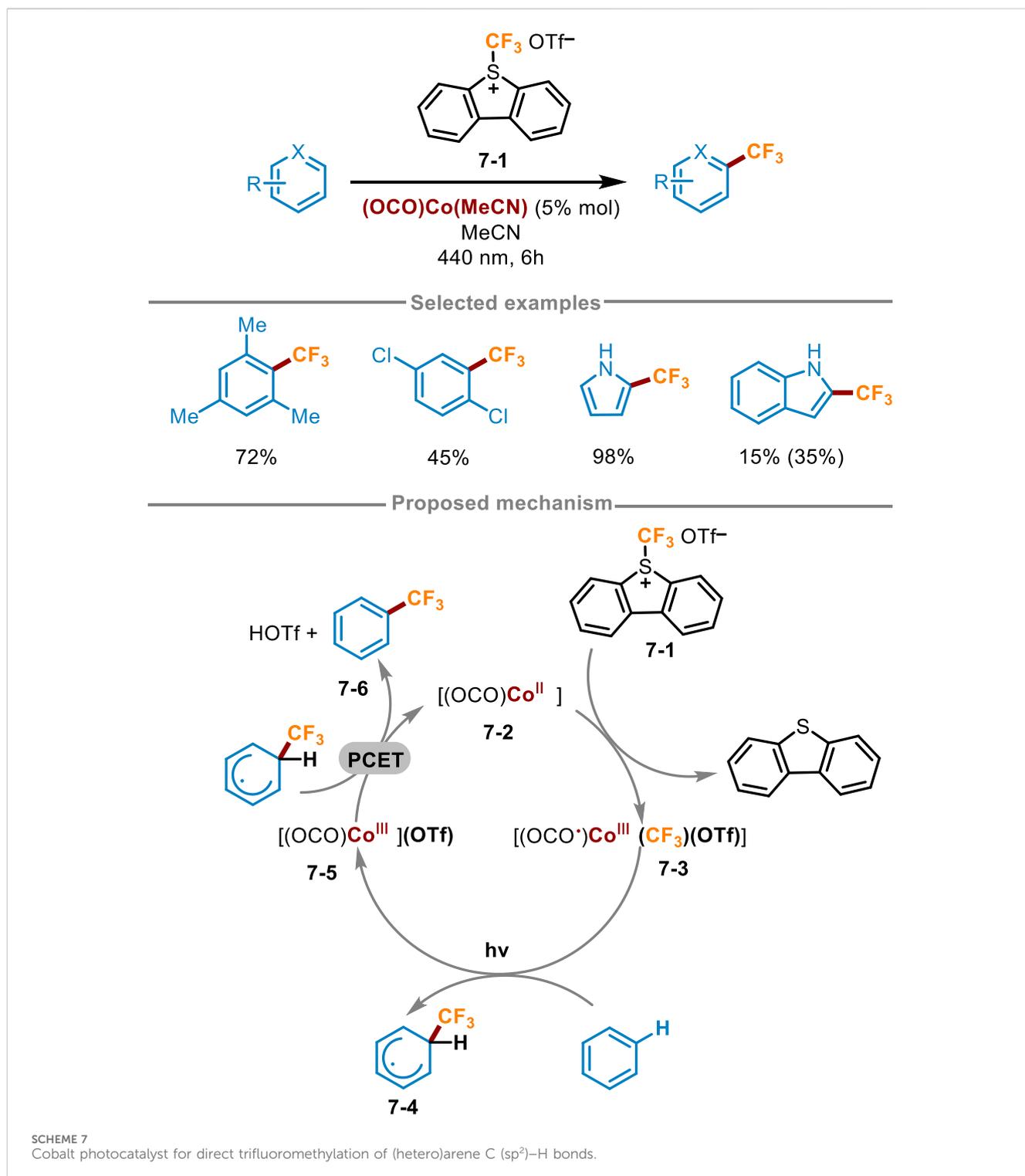
trapped by aromatic hydrocarbons to form the initial state cyclohexadiene radical 7-4. Afterward, the expected product 7-6 was delivered through the net proton-coupled electron transfer (PCET) process between 7-4 and 7-5, along with the regeneration of the Co(II) species to close the photoredox catalytic cycle.

## 2.4 Bismuth-catalyzed fluoroalkylation by LMCT

In 2023, Josep Cornella and coworkers reported the trifluoromethylation of C(sp<sup>2</sup>)-H of (hetero)arenes harnessing Bi catalyst under visible light irradiation (Scheme 8) (Tsuruta et al., 2023). This reaction method utilized aromatics or heteroaromatics as substrates,  $CF_3SO_2Cl$  as  $CF_3$  reagent, 10 mol% Bi(I) as a catalyst, and 465 nm visible light in  $CHCl_3$  solvent at 30°C. The catalytic method can directly modify various heterocyclic aromatic hydrocarbons with different functional groups. Through <sup>19</sup>F NMR and HRMS could observe the trifluoromethyl-TEMPO adduct, suggesting that generated trifluoromethyl radical upon light irradiation. The experiment with or without light proved that light irradiation was a necessary condition for Bi-O bond homolysis to generate  $CF_3$  radicals. According to mechanistic studies, a feasible catalytic cycle mechanism was formulated and presented in Scheme 8. Foremost, through radical oxidation addition (OA) of the fluorinating agent  $CF_3SO_2Cl$  8-1 to Bi(I) catalyst 8-2, the low-valent Bi(I) catalyst 8-2 was converted into Bi(III) intermediate 8-3. Then the Bi-O bond of Bi(III) complex 8-3 was photoinduced homolysis through the ligand-to-ligand charge transfer (LLCT) process, producing  $CF_3SO_2$  radical and Bi(II) radical 8-6, followed by the release of  $CF_3$  radical 8-4 and  $SO_2$ . Then  $CF_3$  radical 8-4 was added to (hetero)aromatic hydrocarbons to yield radical intermediate 8-7. Through HAT process, the radical 8-6 extracted a hydrogen atom from 8-7 to rearomatize and deliver trifluoromethylation products 8-8 and Bi complex 8-9. Finally, 8-9 released a molecule of hydrogen chloride through ligand coupling or alkali-promoted deprotonation to complete the catalytic cycle.

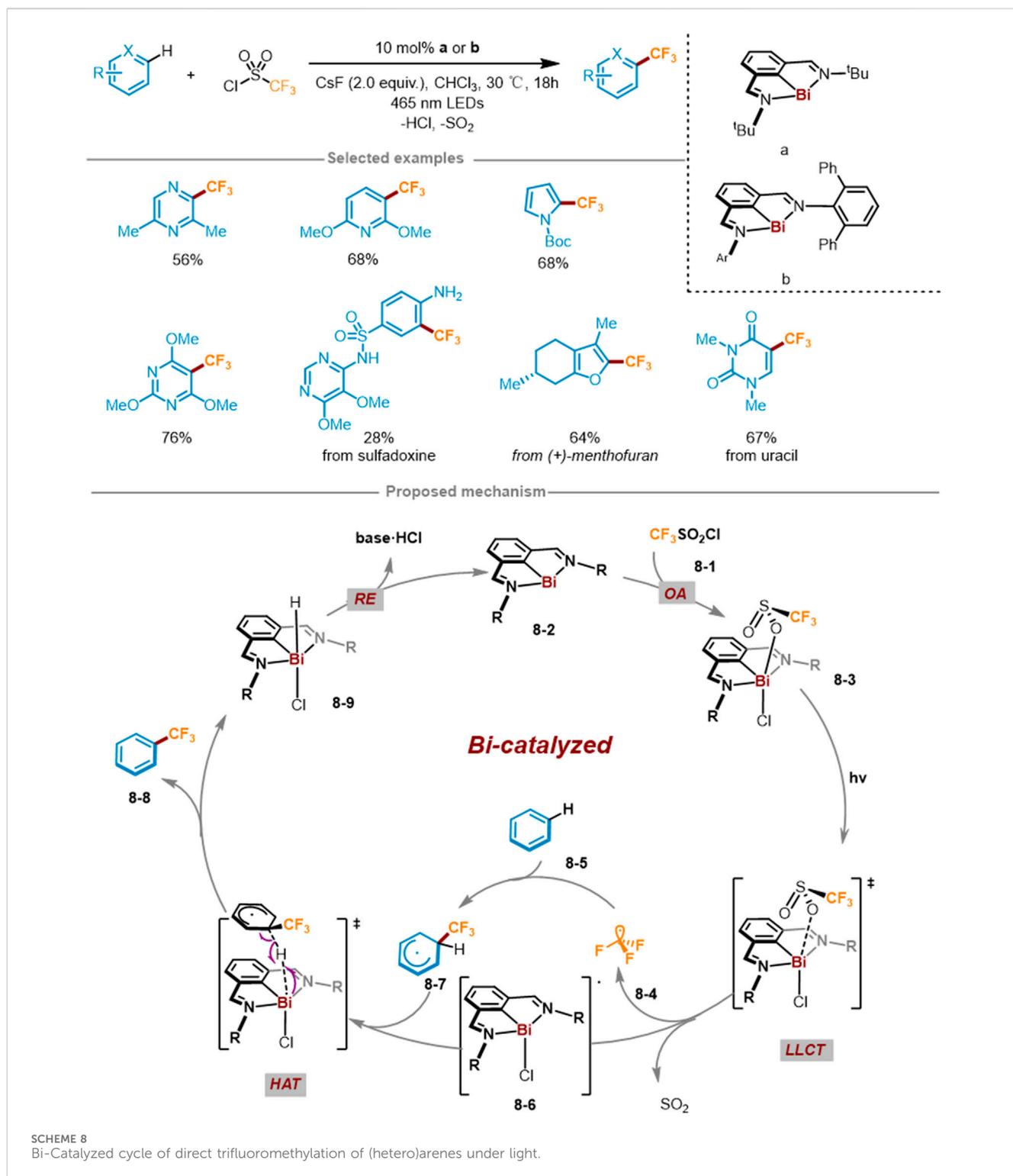
## 2.5 Silver-catalyzed fluoroalkylation by LMCT

Due to the transfer of electron density towards the metal center, only electrophilic metals with high valence states can participate in LMCT photochemistry. Ag(I) is a strong oxidant [ $E^\circ = 0.799$  V vs. normal hydrogen electrode (NHE)], while Ag(II) has a d<sup>9</sup> electron configuration and its 4d sublayer has empty orbitals, thus possessing stronger oxidation ability ( $E^\circ = 1.980$  V vs. NHE) (Grochala and Mazej, 2015). However, the electrophilic metals in the previous study did not include Ag(II). Based on the above situation, Daniel G. Nocera's research group at Harvard University introduced a detailed introduction to a new electrooptic oxidation-reduction method in 2023 (Scheme 9) (Campbell et al., 2024), which utilized LMCT photochemistry coupled with Ag(II) and Ag(I) oxidation to transfer perfluoroalkyl



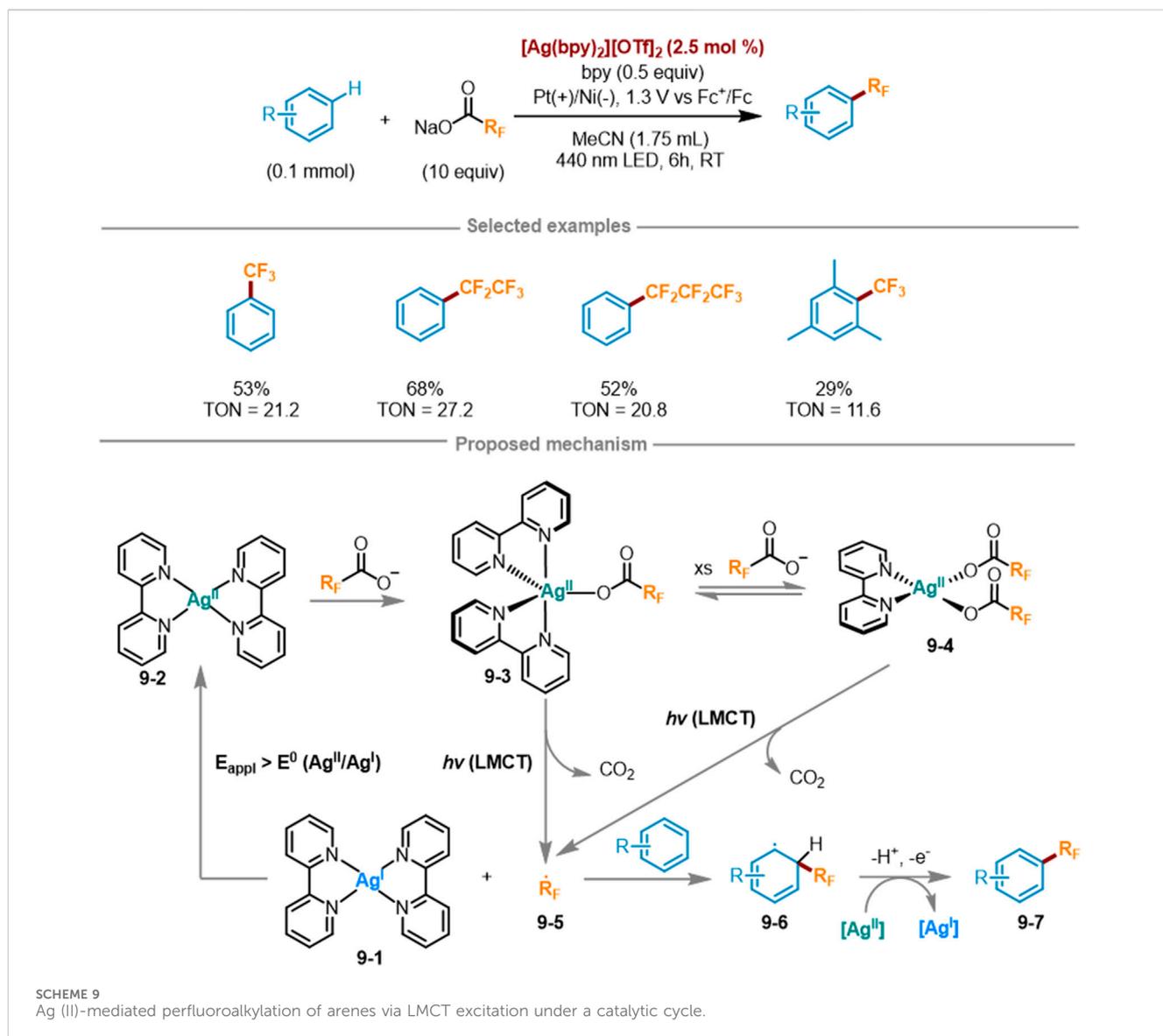
radicals to aromatic hydrocarbons. This method used visible light to excite LMCT transitions to fill this empty orbital, Ag(II) metal centers can be utilized as photo oxidants to activate challenging substrates. This method can also be extended to other long-chain perfluoroalkyl carboxylates including  $R_FCO_2^-$ . In a three-electrode split cell, under a bias voltage of 1.3 V versus  $Fc^+/Fc$ , the trifluoromethylation of benzene was attained at 21.2 turnovers in the presence  $Na(TFA)$  as a limiting reagent (10 equiv.) and

2.5 mol%  $[Ag(bpy)_2][OTf]_2$ , 0.5 equivalent of bpy mixed with one equivalent of benzene for photoredox reaction ( $\lambda_{exc} = 440$  nm). The bis (trifluoromethyl) benzene product can also be afforded with a yield of 11%. The possible rational mechanism was as follows: at an applied potential of  $[E_{app}] > E^\circ (Ag(II/I))$ , the low-valent Ag(I) complex **9-1** was oxidized to Ag(II) complex **9-2**. Subsequently, **9-2** combined with a fluoroalkyl carboxylate anion to yield Ag(II)- $CO_2R_F$  complex **9-3**, which may further react with



another molecule of fluoroalkyl carboxylate anion to form  $\text{Ag}(\text{bpy})(\text{O}_2\text{CCF}_3)_2$  **9-4**. Under excitation at a wavelength of 440 nm, both **9-3** and **9-4** was induced to the LMCT state, triggering photolysis and a rapid decarboxylation reaction to generate fluoroalkyl radicals **9-5** and  $\text{CO}_2$ . Fluoroalkyl radicals **9-5** can easily engage in addition reactions with aromatic

hydrocarbons to create  $\text{C}(\text{sp}^2)\text{-R}_\text{F}$  bonds, generating aromatic radicals **9-6**, which were then oxidized by a second equivalent of  $\text{Ag}(\text{II})$  to form fluorinated aromatic hydrocarbons **9-7**. Then the  $\text{Ag}(\text{I})$  photoproduct underwent electrochemical reoxidation back to the  $\text{Ag}(\text{II})$  photoreactant, achieving the photoelectrocatalytic cycle.



### 3 Conclusion and outlook

In the past decade, researchers have made significant progress in fluoroalkylation of various compounds via photocatalytic or electrochemical ways. In this review article, we take a comprehensive overview of recent research advancements concentrating on visible light-induced LMCT process to realize the fluoroalkylation of various substrates, such as alkenes, (hetero)arene, and terminal alkynes. The reactions were classified by different metal catalysts (Fe, Cu, Co, Bi, Ag). These schemes mostly utilize cheap and easily available fluoroalkyl carboxylic acids or these salts as reactants to introduce the required fluoroalkyl groups, including  $\text{CF}_3$ ,  $\text{CF}_2\text{H}$ ,  $\text{CFHR}$ , and  $\text{C}_m\text{F}_n$  etc. They usually have mild conditions, high atomic economy, wide range, and potential ability of late-stage modification, which overcome the limitations of previous methods.

However, although significant progress being made in this field, considering the importance of the synthesis and research

and development of fluorinated drugs, it still a crucial issue to continuously develop more economical and efficient strategies to introduce fluoroalkyl groups into compounds. At present, the substrates of LMCT-mediated fluoroalkylation strategies are limited to aryl and heteroaryl reactive systems, olefins. We believe that the LMCT-mediated strategy can expand the range of substrates, including more challenging inert compounds and valuable complex bioactive molecules. For instance, substrates can be expanded to carbonyl derivatives (such as aldehydes, ketones, alkyl aryl ketones, esters, and amides), polycyclic aromatic hydrocarbons (PAHs), benzyl compounds, and allyl compounds. These provide further opportunities for delivering the more valuable compounds with fluoroalkyl groups. In addition, LMCT-mediated asymmetric fluoroalkylation also needs to be further investigated. Photocatalytic fluoroalkylation by ligand-to-metal charge transfer is a relatively new research field, and we believe this review can provide valuable guidance for researchers

in this field to stimulate the development of novel synthetic schemes for fluoroalkylation.

## Author contributions

JL: Writing—original draft. ZC: Writing—review and editing. JB: Funding acquisition, Writing—review and editing. XH: Writing—review and editing. QD: Writing—review and editing. HZ: Investigation, Writing—original draft. CM: Funding acquisition, Supervision, Writing—review and editing.

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## Conflict of interest

Author ZC was employed by Chongqing Aoshe Bio-Chemical Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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