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Visible Light-Induced Aromatic Difluoroalkylation

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Abstract: Difluoroalkylated aromatics are important structural motifs in pharmaceutical and agrochemical applications. Herein, we report their synthesis by a mild, efficient, and convenient method using visible light photoredox catalysis. A variety of unactivated aromatics were difluoroalkylated with ethyl 2-bromo-2,2-difluoroacetate ($BrCF_2CO_2Et$) in the presence of the triscyclometalated Ir complex *fac*-[Ir(ppy)$_3$] under visible light irradiation at room temperature. It is shown that reaction outcomes containing the CF_2CO_2Et moiety can be converted to a variety of other CF_2-containing aromatics, demonstrating the synthetic utility of the present method.

Keywords: aromatics; difluoroalkylation; heteroaromatics; iridium; visible light

The incorporation of fluoroalkyl groups into organic molecules has been of great importance due to their impact on the physical and biological properties of the material.[1] In particular, difluoroalkylation to generate compounds containing $-CF_2H$ or various $-CF_2-$ groups has been useful in the preparation of pharmaceuticals, agrochemicals, sugars, and enzyme inhibitors.[2] Introduction of a functionalized CF_2 moiety such as $-CF_2CO_2Et$ not only can alter the properties of the molecules but can also provide a CF_2 building block because the moiety can undergo further modification into various CF_2-containing functional groups such as a difluoromethyl group (CF_2H), as shown in Figure 1.[3,4]

While a variety of difluoroalkylation methods have been demonstrated including transition metal-catalyzed or UV-mediated processes [Figure 2, Eq. (1) and Eq. (2)],[5] it is still desirable to develop more efficient and environmentally friendly transformations. Visible-light photoredox catalysis emerges as the promising alternative to the existing methods, as recently demonstrated by the Qing group and the Wang group for the difluoroalkylation of electron-rich heteroaromatics [Figure 2, Eq. (3)].[6] Herein, we present a strategy for the difluoroalkylation of aromatics employing ethyl 2-bromo-2,2-difluoroacetate in the presence of a triscyclometalated Ir catalyst as the visible light photoredox catalyst [Figure 2, Eq. (4)].[7,8] This radical-based reaction does not require prefunctionalization of the aromatics and proceeds under mild reaction conditions (room temperature/pressure). Mechanistic studies have also been performed to establish that the key catalytic process of the photoredox catalytic cycle involves oxidative quenching of the photoexcited catalyst. In addition, the synthetic utility of the products was demonstrated by their modification into various CF_2-containing molecules.

We started the investigation of aryl difluoroalkylation using 1,4-dimethoxybenzene **1a** as a model compound and ethyl 2-bromo-2,2-difluoroacetate ($BrCF_2CO_2Et$) to produce the difluoroalkylated product **2a** (Table 1). The reaction mixture in DMF was photoirradiated under blue LEDs (7 W) at room temperature with different photoredox catalysts and bases. It was found that the use of *fac*-[Ir(ppy)$_3$] and KO-*t*-Bu produced the best yields among various combinations involving the catalysts {[Ru(bpy)$_3$]Cl$_2$, [Ru(phen)$_3$]Cl$_2$, [Ir(ppy)$_2$(dtbbpy)]PF$_6$, and Ir(dFppy)$_3$; bpy = 2,2′-bipyridine, phen = 1,10-phenanthroline, ppy = 2-phenylpyridinato, dtbbpy = di-*tert*-butyl-2,2′-bipyridine, dFppy = 2-(1,4-difluorophenyl)-pyridinato} and bases (TMEDA, DBU, K_3PO_4, and K_2HPO_4) (entries 1–9). The effects of other parameters, such as solvents, concentrations, and the stoichiometry of the reagents on the reaction, were also examined.[9] The reaction showed the best reactivity with 3 mol% *fac*-[Ir(ppy)$_3$], 3 equivalents of

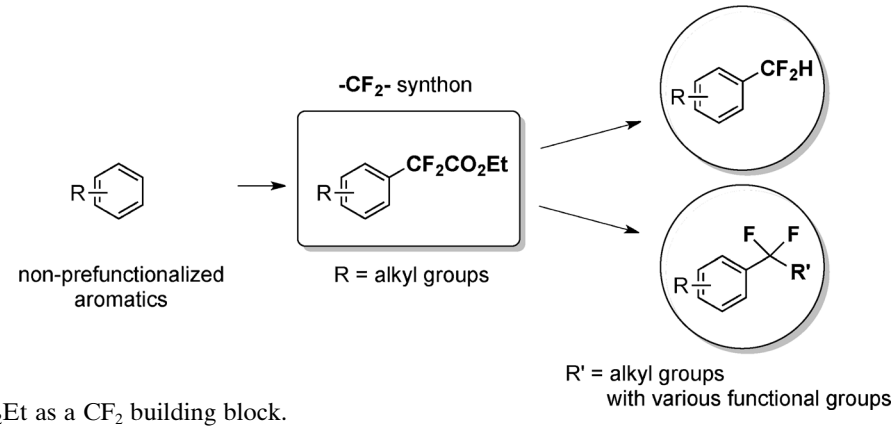


Figure 1. Aryl-CF_2CO_2Et as a CF_2 building block.

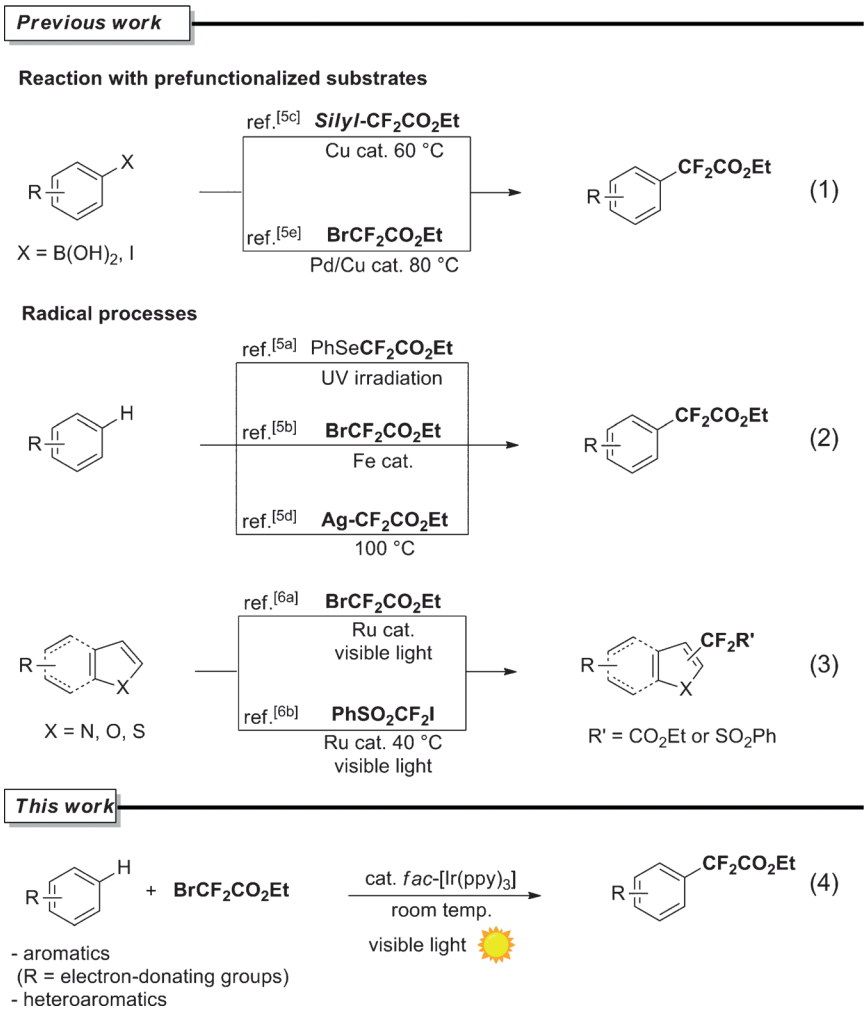
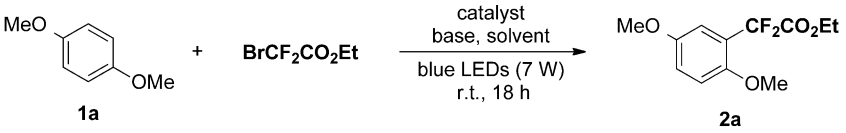


Figure 2. Methods for the synthesis of aryl-CF_2CO_2Et compounds.

$BrCF_2CO_2Et$, and 1.5 equivalents of KO-*t*-Bu in DMSO at a concentration of 0.25 M (entries 10–16). Control experiments showed that the reaction required both visible light[10] and a photocatalyst (entries 17 and 18).

With the optimized conditions in hand, we evaluated the utility of our difluoroalkylation method with a broad range of non-prefunctionalized aromatics (Table 2). This mild and convenient method allowed for the difluoroalkylation of a variety of electron-rich

Table 1. Optimization of reaction conditions for the synthesis of difluoroalkylated aromatics.[a]



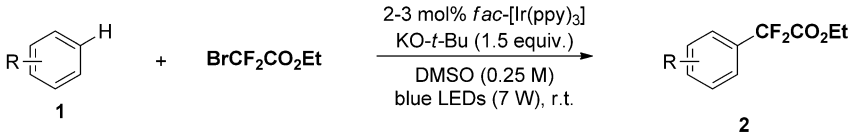
Entry	Photocatalyst (2 mol%)	Base (2 equiv.)	Solvent (0.25 M)	Yield [%][b]
1	$[Ru(bpy)_3]Cl_2$	TMEDA	DMF	8
2	$[Ru(phen)_3]Cl_2$	TMEDA	DMF	trace
3	$[Ir(ppy)_2(dtbbpy)]PF_6$	TMEDA	DMF	15
4	$Ir(dFppy)_3$	TMEDA	DMF	5
5	*fac*-$[Ir(ppy)_3]$	TMEDA	DMF	20
6	*fac*-$[Ir(ppy)_3]$	DBU	DMF	trace
7	*fac*-$[Ir(ppy)_3]$	K_3PO_4	DMF	36
8	*fac*-$[Ir(ppy)_3]$	K_2HPO_4	DMF	10
9	*fac*-$[Ir(ppy)_3]$	KO-*t*-Bu	DMF	35
10	*fac*-$[Ir(ppy)_3]$	K_3PO_4	DMSO	52
11	*fac*-$[Ir(ppy)_3]$	KO-*t*-Bu	MeCN	trace
12	*fac*-$[Ir(ppy)_3]$	KO-*t*-Bu	DMSO	60
13	*fac*-$[Ir(ppy)_3]$	KO-*t*-Bu	DMSO (0.1 M)	32
14	*fac*-$[Ir(ppy)_3]$	KO-*t*-Bu	DMSO (0.5 M)	44
15	*fac*-$[Ir(ppy)_3]$ (3 mol%)	KO-*t*-Bu	DMSO	80
16	***fac*-$[Ir(ppy)_3]$ (3 mol%)**	**KO-*t*-Bu (1.5 equiv.)**	**DMSO**	**81**
17	*fac*-$[Ir(ppy)_3]$ (no light)	KO-*t*-Bu	DMSO	trace
18	—	KO-*t*-Bu	DMSO	trace

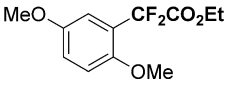
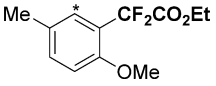
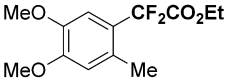
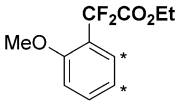
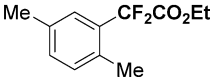
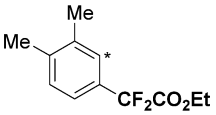
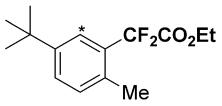
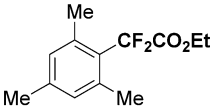
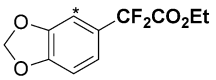
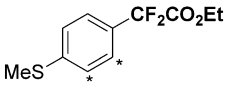
[a] *Reaction conditions:* **1a** (0.1 mmol), $BrCF_2CO_2Et$ (0.3 mmol).
[b] The yields were determined by gas chromatography and ^{19}F NMR spectroscopy with internal standards of dodecane and 4-fluorotoluene, respectively.

aromatics with high efficiencies. The regioselectivity pattern observed in the transformation was consistent with that anticipated for a radical mediated aromatic substitution process.[8a,11,12] Alkyl and alkoxy substituents such as −OMe worked as *ortho*/*para*-directing groups in the process with the electron-deficient carbon-centered CF_2 radical.[13] The selective addition of $^{\bullet}CF_2CO_2Et$ at the *ortho/para* positions of the aromatics can occur due to the favorable formation of more stable conjugated radical and carbocation intermediates. In addition to the regioselectivity, another salient feature of this transformation is the lower reactivity of the difluoroalkylated product toward the second reaction resulting in monodifluoroalkylation. In the same context, difluoroalkylation of electron-deficient aromatics was unsuccessful, and the reaction of less electron-rich substrates such as toluene showed low conversion rate (30% after 18 h). In addition, aromatics containing alkenyl substituents did not undergo selective aryl-difluoroalkylation because the alkene moiety was also reactive toward a radical-mediated process with the CF_2 radical. As an example, the reaction of 1-methoxy-4-vinylbenzene provided a mixture of products from bromodifluoroalkylation,[8b,c] alkenyl-difluoroalkylation, and aryl-difluoroalkylation.[14]

To gain insight into the reaction mechanism, we conducted Stern–Volmer experiments for 50 μM *fac*-$[Ir(ppy)_3]$. Phosphorescence decay traces of *fac*-$[Ir(ppy)_3]$ were monitored at 520 nm employing the time-correlated single-photon-counting (TCSPC) technique after nanosecond photoexcitation at 377 nm with varying concentrations of $BrCF_2CO_2Et$. As shown in [Figure 3 (a)], the phosphorescence life-

Table 2. Difluoroalkylation of aromatics.[a]



Entry		Product	Yield (%)[b]	Ratio[c]
1	**2a**		78	-
2[d]	**2b**		91	3:1
3	**2c**		73	-
4[d]	**2d**		79	6:1:2 (*o*:*m*:*p*)
5	**2e**		68	-
6[d]	**2f**		65	1.5:1
7[d]	**2g**		78	20:1
8	**2h**		74	-
9[d]	**2i**		69	5:1
10[d]	**2j**		78	4:1:5 (*o*:*m*:*p*)

[a] *Reaction conditions:* **1** (0.5 mmol), $BrCF_2CO_2Et$ (1.5 mmol), 18–24 h.
[b] The given yields are isolated yields obtained by the average of two runs.
[c] The ratios were determined by ^{19}F NMR spectroscopy, gas chromatography, and NOE experiments.
[d] The minor regioisomeric position is labelled with "*".

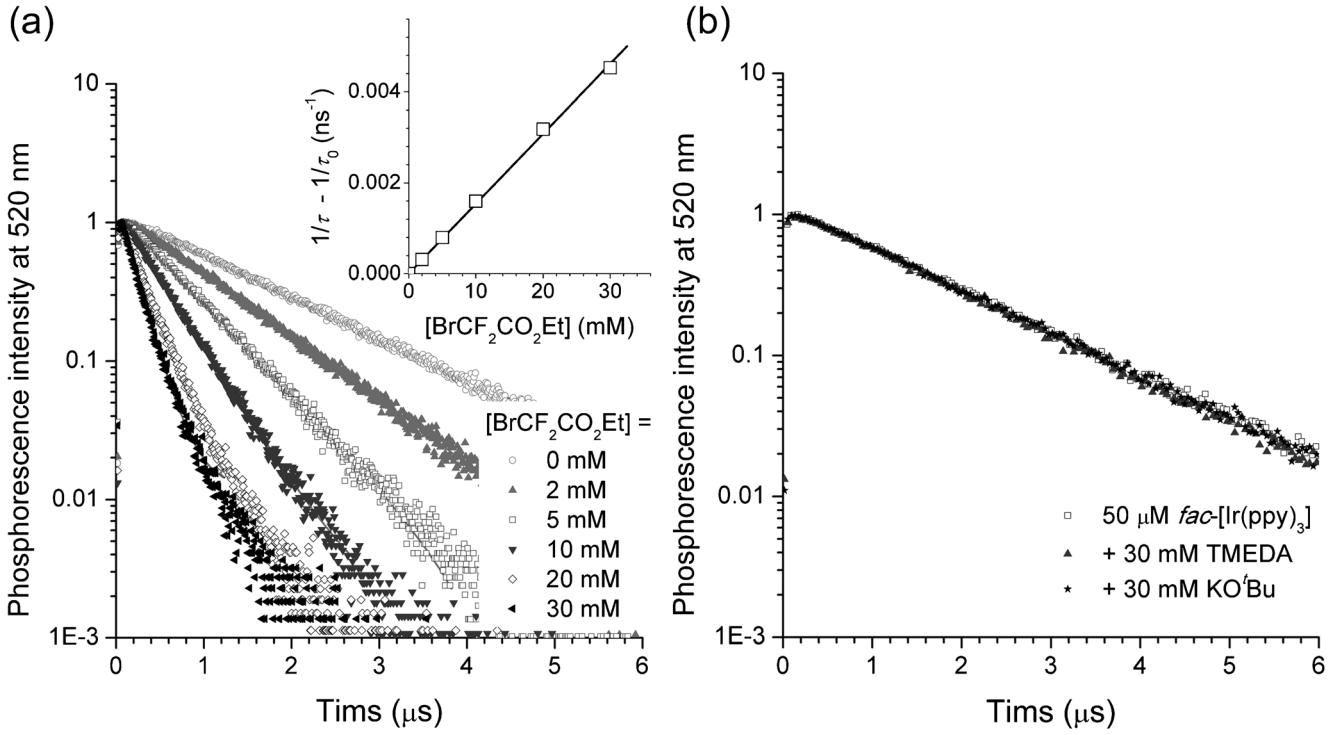


Figure 3. Phosphorescence quenching experiments for 50 μM *fac*-[Ir(ppy)$_3$] in Ar-saturated DMSO solutions with (a) 0–30 mM $BrCF_2CO_2Et$ and (b) 30 mM KO-*t*-Bu (triangles) or 30 mM TMEDA (circles). Phosphorescence decay traces of *fac*-[Ir(ppy)$_3$] were monitored at $\lambda_{em} = 520$ nm after the nanosecond pulsed excitation (temporal resolution = 8.0 ns) under $\lambda_{ex} = 377$ nm. Inset Figure is a plot of electron transfer rate ($1/\tau - 1/\tau_0$; where τ and τ_0 are phosphorescence lifetimes of *fac*-[Ir(ppy)$_3$] in the presence and absence of $BrCF_2CO_2Et$, respectively) as a function of the concentration of $BrCF_2CO_2Et$. The gray line is a linear fit of the data points, and the slope corresponds to the rate constant for electron transfer ($k_{eT} = 1.5 \times 10^8\,M^{-1}s^{-1}$).

time (τ_{obs}) decreases in proportion with the concentration of $BrCF_2CO_2Et$. This decrease in τ_{obs} is due to electron transfer from the photoexcited Ir complex to $BrCF_2CO_2Et$ and is caused by the fact that the driving force for the one-electron transfer is as high as 1.34 eV (see the Supporting Information, Figure S1, for details of the calculation). The rate constant for electron transfer (k_{eT}) was determined to be $1.5 \times 10^8\,M^{-1}s^{-1}$ [Figure 3 (a)], approaching the diffusion-limited regime. In sharp contrast, the phosphorescence decay trace is not affected by the presence of 30 mM TMEDA and 30 mM KO-*t*-Bu [Figure 3 (b)]. These results indicate that reductive quenching of the photoexcited Ir complex by the one-electron donor (i.e., TMEDA) can be ignored, and that the photocatalytic step does not involve participation of the Brønsted base (i.e., KO-*t*-Bu).

Based on these results, we propose a plausible mechanism for the difluoroalkylation of aromatics (Figure 4). Photoexcitation of *fac*-[Ir(III)(ppy)$_3$] by visible light produces [Ir(IV)ppy$^{\bullet-}$(ppy)$_2$] through a metal-to-ligand charge-transfer (MLCT) transition.[15] This transient species is oxidatively quenched by one-electron transfer to $BrCF_2CO_2Et$, producing $[Ir(IV)(ppy)_3]^+$ and the key intermediate $^{\bullet}CF_2CO_2Et$.

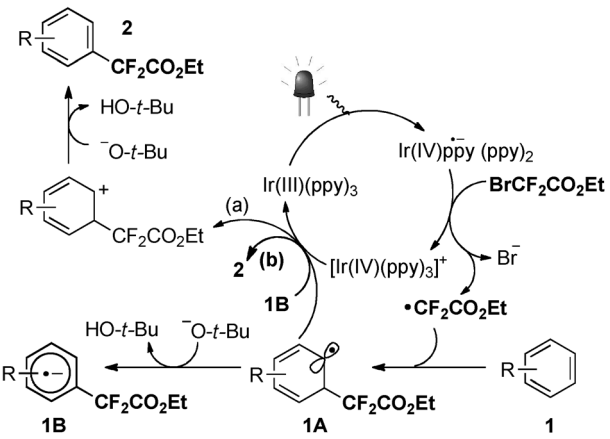
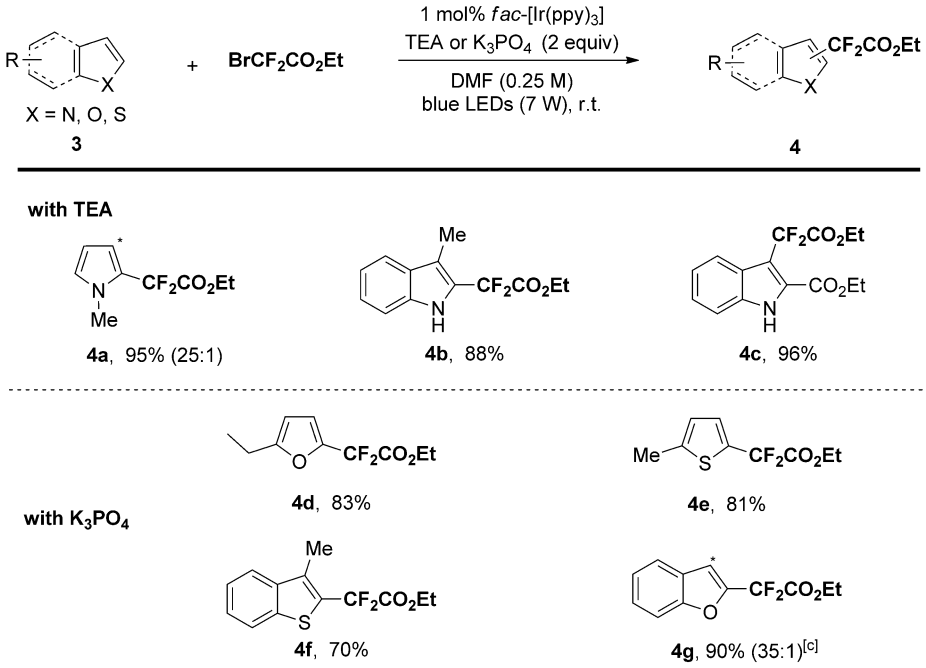


Figure 4. Proposed mechanism for the aryl-difluoroalkylation.

The addition of $^{\bullet}CF_2CO_2Et$ to an aromatic compound generates the difluoroalkylated radical species **1A** which can undergo two possible pathways. First, a one-electron transfer from **1A** to $[Ir(IV)(ppy)_3]^+$ regenerates $[Ir(III)(ppy)_3]$ and forms a carbocation intermediate. Subsequent deprotonation by $^{-}$O-*t*-Bu completes the reaction providing the desired difluor-

Table 3. Difluoroalkylation of heteroaromatics.[a,b]



[a] *Reaction conditions:* **3** (1.0 mmol), $BrCF_2CO_2Et$ (2.0 mmol), TEA or K_3PO_4 (2.0 mmol), 16–18 h.

[b] The given yields are isolated yields based on an average of two runs.

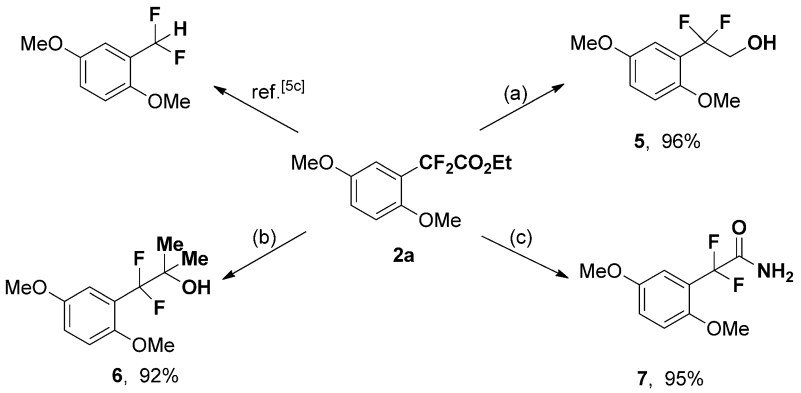
[c] The minor regioisomeric position is labelled with "*", and the ratio was determined by ^{19}F NMR spectroscopy and gas chromatography.

oakylated product **2** [pathway (a)]. Alternatively, deprotonation of **1A** can occur to produce the radical anion species **1B**.[16] Reductive one-electron transfer to $[Ir(IV)(ppy)_3]^+$ regenerates $[Ir(III)(ppy)_3]$ and yields **2** [pathway (b)]. It is also noted that radical propagation between $BrCF_2CO_2Et$ and **1A** or **1B** cannot be ruled out, although the mechanism requires further resolution.

Difluoroalkylation was also applied to heteroaromatics, and the process was optimized (see the Supporting Information, Tables S2 and S3). The reactivity of heteroaromatics was higher than that of aromatics, requiring less catalyst loading and less $BrCF_2CO_2Et$. As for heteroaryl difluoroalkylation, TEA and K_3PO_4 were used as bases and DMF was used as the solvent. A variety of heterocycles were reacted with the radical ($^{\bullet}CF_2CO_2Et$) which was generated in the presence of 1 mol% *fac*-$[Ir(ppy)_3]$ in DMF (0.25 M) under visible light irradiation (Table 3). The k_{eT} value for one-electron transfer from the photoexcited *fac*-$[Ir(ppy)_3]$ to $BrCF_2CO_2Et$ was determined employing the TCSPC technique to be $3.1\times10^8\,M^{-1}s^{-1}$ (Supporting Information, Figure S2). The use of TEA showed the best reactivity in the reaction of pyrroles (**4a**) and indoles (**4b**, **4c**), while K_3PO_4 was used for furans (**4d**), thiophenes (**4e**), benzothiophenes (**4f**), and benzofurans (**4g**). Reactions were highly efficient and gave difluoroalkylated products in good to excellent yields with high regioselectivities.

To demonstrate the synthetic utility of the products obtained from our methodology, a difluoroalkylated compound **2a** was shown to be successfully transformed into a variety of CF_2-containing compounds by conventional organic reactions (Scheme 1). Besides a known process from RCF_2CO_2Et to RCF_2H by hydrolysis and decarboxylation,[5c] we conducted the following reactions and generated three kinds of CF_2-compounds in excellent yields: (a) hydride reduction, (b) Grignard reaction, and (c) amide formation *via* nucleophilic acyl substitution with NH_3.[17]

In summary, an efficient and convenient method for the synthesis of difluoroalkylated aromatics, which are important structural motifs in pharmaceutical and agrochemical products, has been developed by visible-light photoredox catalysis. A variety of unactivated aromatics, including heteroaromatics, were difluoroalkylated with $BrCF_2CO_2Et$ as the CF_2R source in the presence of *fac*-$[Ir(ppy)_3]$ under visible-light irradiation at room temperature. Stern–Volmer experiments suggested that the photoredox catalytic cycle involved an oxidative quenching pathway. In addition, the synthetic utility of the products was demonstrated by their modification into various CF_2-containing molecules through conventional organic reactions. We an-



Scheme 1. Versatile transformations of **2a**. *Reaction conditions:* (a) $NaBH_4$ (1.5 equiv.), EtOH, 24 h. (b) MeMgBr (2.1 equiv.), THF, 0 °C → room temperature, 3 h. (c) NH_3, MeOH, room tempeature, 13 h.

ticipate that our protocol will be an efficient and convenient alternative to conventional difluoroalkylation methods.

Experimental Section

Synthesis of Ar-CF_2CO_2Et Compounds

An oven-dried, resealable test tube equipped with a magnetic stir bar was charged with an aromatic compound (0.5 mmol), sealed with a silicone septa screw-cap, and degassed by alternating vacuum evacuation and argon backfill. A solution of *fac*-[Ir(ppy)$_3$] (3.0 mol%, 0.015 mmol) in DMSO (2.0 mL, 0.25 M) and KO-*t*-Bu (1.5 equiv., 0.75 mmol) was then added to the tube. $BrCF_2CO_2Et$ (3 equiv., 1.5 mmol) was then added into the reaction mixture. The test tube was stirred under argon and irradiated by blue LEDs at room temperature. The reaction was allowed to proceed for 18–24 h, and reaction progress was checked by TLC or gas chromatography. The reaction mixture was then diluted with ethyl acetate and washed with an NH_4Cl solution and brine. The organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by flash column chromatography to give the aryl-CF_2CO_2Et compound.

Synthesis of HetAr-CF_2CO_2Et Compounds

An oven-dried, resealable test tube equipped with a magnetic stir bar was charged with a heteroaromatic (1.0 mmol), sealed with a silicone septa screw-cap, and degassed by alternating vacuum evacuation and argon backfill. A solution of *fac*-[Ir(ppy)$_3$] (1.0 mol%, 0.001 mmol) in DMF (4.0 mL, 0.25 M) and TEA in the case of **4a**–**4c** or K_3PO_4 in the case of **4d**–**4g** (2.0 equiv., 2.0 mmol) were then added to the tube. $BrCF_2CO_2Et$ (2.0 equiv., 2.0 mmol) was then added into the reaction mixture. The test tube was stirred under argon and irradiated with blue LEDs at room temperature. The reaction was allowed to proceed for 16–18 h, and reaction progress was checked by TLC or gas chromatography. The reaction mixture was then diluted with ethyl acetate and washed with an NH_4Cl solution and brine. The organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by flash column chromatography to give the heteroaryl-CF_2CO_2Et compound.

Acknowledgements

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[9] Table S1 in the Supporting Information shows effects of more parameters.

[10] As for a visible light source, the use of a fluorescent lamp instead of a blue LED strip resulted in less reactivity with longer reaction time.

[11] Examples on radical-mediated aromatic substitution process, see: a) L. J. Allen, P. J. Cabrera, M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607; b) H. Kim, T. Kim, D. G. Lee, S. W. Roh, C. Lee, *Chem. Commun.* **2014**, *50*, 9293.

[12] NOE experiments were conducted to determine the structures of major isomers. See the Supporting Information.

[13] The reaction of anisole (**2d**) gave the *ortho*-product as the major one, while that of 1,3-benzodioxole (**2i**) provided the *para*-product as the major one. A similar tendency was observed in the visible light-induced trifluoromethylation, see ref.[8a]

[14] The results of reaction are presented in Scheme S1 in the Supporting Information.

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[17] We also synthesized CF_2-containing amide product **8** by using **4a**. See the Supporting Information.

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