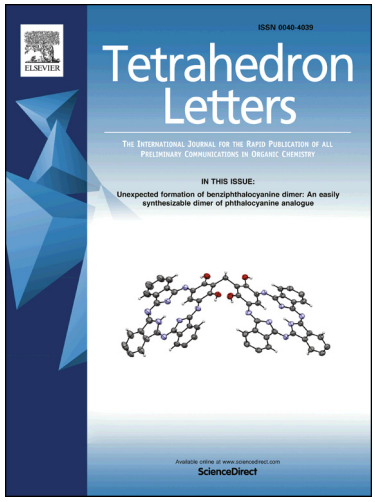

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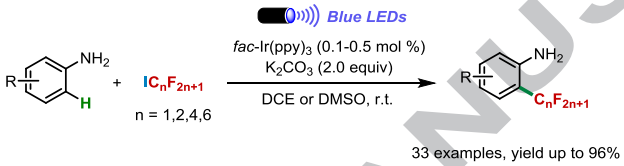

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ABSTRACT

A mild, operationally simple method for direct perfluoroalkylation and trifluoromethylation of anilines through visible-light-mediated photoredox catalysis from broadly available perfluoroalkyl iodides and free anilines is described. The method provides a facile route for application in drug discovery and development.

The introduction of fluorinated groups into organic molecules can dramatically alters their intrinsic properties.[1] In particular, perfluoroalkyl (R_F) groups, including trifluoromethyl group, are important structural motifs found in many commercial pharmaceuticals, agrochemicals, and functional materials due to their unique characteristics.[2] Considerable efforts have been made to develop effective methods for incorporating perfluoroalkyl groups into aromatic compounds over the past decades.[3] Traditionally, transition-metal-mediated cross-couplings serve as a common approach to construct aryl-R_F linkages. Recently, the transition-metal-catalyzed fluoroalkylations with aryl halides or aryl metals have emerged as an efficient strategy to access fluorinated compounds.[4] However, such a strategy suffers from the prefunctionalization of (hetero)arenes. Alternatively, the direct perfluoroalkylation of simple (hetero)arenes based on the transition-metal induced single-electron-transfer (SET) reaction[5] or sulfinatodehalogenation reaction[6] has been recognized as a more straightforward strategy. Despite of importance of these reactions, only electron-rich (hetero)arenes are suitable substrates. Hence, new methods to efficiently access perfluoroalkylated (hetero)arenes remains highly desirable.

Inspired by our recent visible-light-promoted synthesis of difluorooxindoles[7] and other previous reports,[8, 9] herein, we report an efficient method to access perfluoroalkylated anilines via a photoredox catalytic process from readily available perfluoroalkyl iodides and free anilines. The reaction allows the perfluoroalkylation and trifluoromethylation of a variety of free anilines, including electron-withdrawing substituents containing substrates with high efficiency and good regioselectivity.

We began our initial study by choosing 4-iodoaniline **1a** and readily available perfluorohexyl iodide **2a** as the model substrates under photochemical conditions toward synthesis of perfluorohexylated aniline (Table 1). The use of aniline as a substrate is because amine group can serve as a versatile functional group for further transformations. To our delight, when the reaction was conducted in 1,2- dichloroethane (DCE) with $Ru(bpy)_3(PF_6)_2$ (0.5 mol %) as a photoredox catalyst and K_2CO_3 (2 equiv) as a base, the sole *ortho*-perfluoroalkylated product **3a** was provided in 45% yield after irradiation by a blue light-emitting diode (LED) bulb (12 w) for 24 h (entry 1). Switching the photocatalyst from $Ru(bpy)_3(PF_6)_2$ to $Ru(bpy)_3Cl_2$ could improve the yield of **3a** to 63% (entry 2). Encouraged by these results, a survey of the reaction parameters, such as catalyst, base and solvent were conducted (entries 3-14). *fac*-$Ir(ppy)_3$ was found to be superior to $Ru(bpy)_3Cl_2$, providing **3a** in a 80% yield (entry 3). The combination of DCE and K_2CO_3 was still the best choice. Other bases and solvents showed less effective (entries 4-9, 11-14). Increasing the ratio of **1a**/**2a** from 2/1 to 3/1 benefited the reaction efficiency and afforded **3a** in 89% yield (entry 10). Finally, an optimal yield of **3a** (91% upon isolation) was obtained by decreasing the loading amount of photocatalyst to 0.1 mol% (entry 16). To the best of our knowledge, this is the lowest photocatalyst loading in visible-light-promoted fluoroalkylation reactions. No reaction was observed in the absence of either photocatalyst or light source, thus demonstrating that a visible-light-promoted photoredox process was involved in the reaction (Table 1, entries 17-18).

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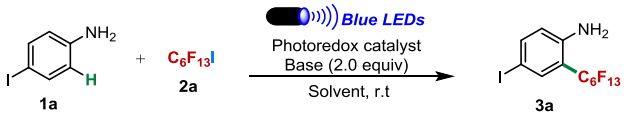
Table 1. Representative results for optimization of direct perfluorohexylation of 4-iodoaniline **1a**.

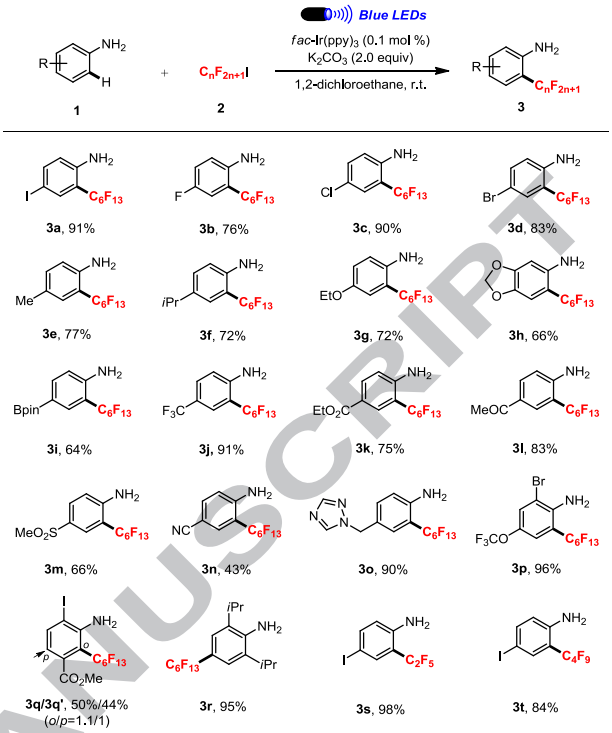


Entry	Photocatalyst(mol%)	Base(equiv)	Sovent	Yield (%)[b]
1	$Ru(bpy)_3(PF_6)_2$ (0.5)	K_2CO_3	DCE	45
2	$Ru(bpy)_3Cl_2$ (0.5)	K_2CO_3	DCE	63
3	*fac*-Ir(ppy)$_3$ (0.5)	K_2CO_3	DCE	80
4	*fac*-Ir(ppy)$_3$ (0.5)	Na_2CO_3	DCE	72
5	*fac*-Ir(ppy)$_3$ (0.5)	Cs_2CO_3	DCE	72
6	*fac*-Ir(ppy)$_3$ (0.5)	$NaHCO_3$	DCE	38
7	*fac*-Ir(ppy)$_3$ (0.5)	K_2HPO_4	DCE	24
8	*fac*-Ir(ppy)$_3$ (0.5)	Na_2HPO_4	DCE	6
9	*fac*-Ir(ppy)$_3$ (0.5)	None	DCE	NR
10	*fac*-Ir(ppy)$_3$ (0.5)	K_2CO_3	DCE	89[c]
11	*fac*-Ir(ppy)$_3$ (0.5)	K_2CO_3	DCM	83[c]
12	*fac*-Ir(ppy)$_3$ (0.5)	K_2CO_3	DMF	53[c]
13	*fac*-Ir(ppy)$_3$ (0.5)	K_2CO_3	Dioxane	26[c]
14	*fac*-Ir(ppy)$_3$ (0.5)	K_2CO_3	DMSO	84[c]
15	*fac*-Ir(ppy)$_3$ (0.25)	K_2CO_3	DCE	92[c]
16	*fac*-Ir(ppy)$_3$ (0.1)	K_2CO_3	DCE	95(91)[c]
17	None	K_2CO_3	DCE	NR[c]
18	*fac*-Ir(ppy)$_3$ (0.1)	K_2CO_3	DCE	NR[c,d]

[a]Reaction conditions (unless otherwise specified): **1a** (0.8 mmol, 2.0 equiv), **2a** (0.4 mmol, 1.0 equiv), DCE (4 mL), argon atmosphere, blue LEDs (12 w), room temperature, 24 h.
[b]Determined by ^{19}F NMR using fluorobenzene as an internal standard; Value within parentheses is the yield of isolated product.
[c]**1a** (1.2 mmol, 3.0 equiv) was used.
[d]The reaction was conducted in the absence of blue LEDs light source. NR=No Reaction.

To demonstrate the substrate scope of this method, a variety of free anilines **1** were examined (Scheme 1). Substrates bearing electro-neutral and electro-donating groups underwent the perfluoroalkylation smoothly and furnished products in good to excellent yields. It is noteworthy that even for the electron-withdrawing groups substituted anilines, good yields of corresponding perfluorinated products were still obtained (**3j-3n**, **3q**), thus highlighting the generality of current method. The reaction exhibited good functional group tolerance, many important functional groups, such as alkoxycarbonyl (**3k**), ketone (**3l**), mesyl (**3m**), cyano (**3n**) and *N*-heterocycle (**3o**), were all compatible with the reaction conditions. Remarkably, the successful formation of aryl halides- and aryl boronate-containing perfluorinated products provided good opportunities for downstream transformations (**3a**, **3c**, **3d** and **3i**). However, a mixture of regio-isomers with almost 1/1 ratio (*ortho*/*para*) was obtained when methyl 3-amino-4-iodobenzoate was examined (**3q**). While, only *para*-substituted perfluoroalkylated aniline was formed when di-*ortho*-substituted aniline was employed as a substrate (**3r**). Additionally, it is also possible to prepare other perfluoroalkylated anilines through this method. As shown in **3s** and **3t**, perfluorinated ethyl and butyl iodides were also applicable to the reaction and led to corresponding products in high to excellent yields.

Table 2. Visible-light-mediated direct perfluoroalkylation of free anilines.[a]

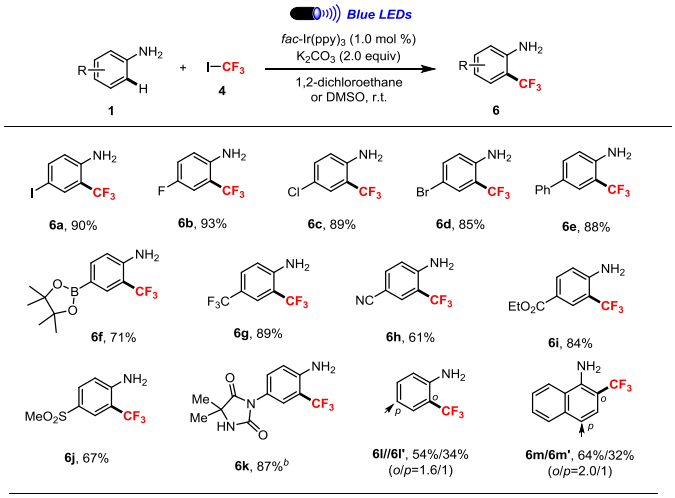


[a] Reaction conditions (unless otherwise specified): aniline **1** (1.2 mmol, 3.0 equiv), **2** (0.4 mmol, 1.0 equiv), K_2CO_3 (2.0 equiv), *fac*-Ir(ppy)$_3$ (0.1 mol %), 1,2-dichloroethane (4 mL), argon atmosphere, blue LEDs, room temperature, 24 hours. All reported yields are those of the isolated products.

The CF_3 group is an omnipresent motif found in many pharmaceuticals, agrochemicals, materials, and industrial chemicals. Despite well-established trifluoromethylation reactions, the straightforward and selective introduction of such a valuable group onto (hetero)aromatic rings with readily available and inexpensive fluorine sources remains highly desirable. With respect to trifluoromethylation of anilines, although CF_3I is an useful and inexpensive trifluoromethylating reagent,[10] the routine use of it by synthetic chemists remains a problem due to its intrinsic, gaseous phase at room temperature, which makes its accurate measurement cumbersome. We found that the stock solution of CF_3I in DCE or DMSO could be stored at room temperature without decline of the titer, thus making its manipulating process convenient and practical. Utilization of this stable and conveniently manipulated trifluoromethyl iodide solution, we were able to rapidly optimize the reaction conditions for direct trifluoromethylaiton of anilines (for details see supporting information).

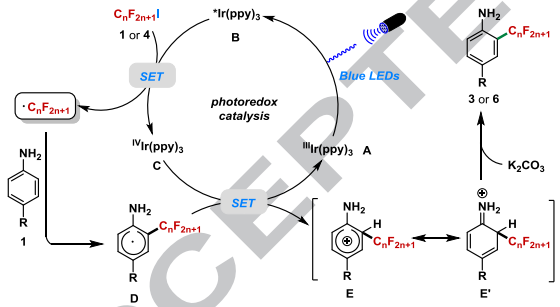
The direct trifluoromethylation of anilines also proceeded smoothly with 1.0 mol% of *fac*-Ir(ppy)$_3$ as a catalyst (Table 3). A wide range of free anilines furnished the corresponding products in good to high yields under these modified reaction conditions. Substrates bearing electron-withdrawing groups also led to good yields (**6g-6j**). Again, good functional group tolerance was observed (**6a-6d**, **6f-6k**). However, when basic aniline was examined, a mixture of *ortho*- and *para*-trifluoromethyl substituted anilines with a ratio of 1.6/1 (*ortho*/*para*) was obtained (**6l**). Similar finding was also observed when naphthalen-1-amine was examined (**6m**).

Table 3. Visible-light-promoted direct trifluoromethylation of free anilines.[a]



[a]Reaction conditions (unless otherwise specified): free anilines **1** (1.2 mmol, 3.0 equiv), CF_3I **4** (a solution in 1,2-dichloroethane, 0.4 mmol, 1.0 equiv), K_2CO_3 (2.0 equiv), *fac*-Ir(ppy)$_3$ (1 mol %), 1,2-dichloroethane (4 mL, together with CF_3I solution), argon atmosphere, blue LEDs, room temperature, 24 hours. All reported yields are those of the isolated products. [b]The reaction was conducted in DMSO with a solution of CF_3I in DMSO.

On the basis of previous report,[8a] a possible mechanism is shown in Scheme 1. The photoredox catalytic cycle is initiated from the excited state of the photocatalyst *[Ir(ppy)$_3$] (**B**) with blue LEDs. Subsequent single electron transfer from **B** to RFI generates perfluoroalkyl radical and $Ir^{(IV)}$(ppy)$_3$ (**C**). The newly formed radical intermediate reacts with free aniline to produce intermediate **D**, which is oxidized by **C**, followed by the abstraction of a proton with the base to provide the perfluoroalkylated products **3** and **6**.



Scheme 1. Proposed reaction mechanism

In conclusion, we have developed a photoredox-based method for facile perfluoroalkylation of free anilines from readily available perfluoroalkyl iodides. The reaction can also extend to trifluoromethylation of free anilines with high efficiency and good functional group tolerance, thus providing a facile route for application in medicinal chemistry.

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Supplementary Material

Detailed experimental procedures, and characterization data for

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Highlights

The reaction proceeds under mild conditions from broadly available perfluoroalkyl iodides and free anilines with high efficiency, broad substrate scope and high functional group tolerance.

The method provides a facile route for application in drug discovery and development.