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Photoredox Polyfluoroarylation of Alkyl Halides via Halogen Atom Transfer

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Abstract

Polyfluoroarene moieties are of interest in medicinal chemistry, agrochemicals, and material sciences. Herein, we present the first polyfluoroarylation of unactivated alkyl halides via a halogen atom transfer process. This method converts primary, secondary, and tertiary alkyl halides into the respective polyfluoroaryl compounds in good yields in the presence of amide, carbamate, ester, aromatic, and sulfonamide moieties, including derivatives of complex bioactive molecules. Mechanistic work revealed that this transformation proceeds through an alkyl radical generated after the halogen atom transfer.

Graphical Abstract

Organofluorine scaffolds are pivotal frameworks in various applications such as pharmaceuticals, material sciences, and pesticides and for positron emission tomography imaging (Scheme 1A).[1] Fluorine atoms in a bioactive molecule can provide many beneficial properties such as increased membrane penetration and enhanced activity and can promote chemical or metabolic stability.[2] Thus, the way to incorporate polyfluoroarenes into compounds has attracted considerable attention.[3,4] Metal-catalyzed cross-couplings between Ar_F—H and aryl, alkenyl, or alkynyl groups have been explored.[3-5] Strategies that proceed

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Supporting Information

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^{1}H and ^{13}C{1H} NMR spectra, GS—MS spectra, and additional information on the substrate scope and its limitations (PDF)

via nucleophilic aromatic substitution, such as the defluorinative functionalization of readily available polyfluoroarenes, often require the use of strong organometallic species such as Grignard, organolithium, or organozinc reagents.[6] These harsh reaction conditions limit the functional group compatibility and reduce the complexity of possible molecular scaffolds.

Recently, photoredox-catalyzed polyfluoroarylation has been developed to enable mild and selective C—C bond formations, but the number of alkylation strategies remain limited.[7] The Weaver group reported various photoredox functionalizations of C—F bonds in polyfluoroarenes, including a photocatalytic alkylation using alkenes as starting materials (Scheme 1B).[7d] In 2021, the Ritter group developed an alkylation of polyfluoroarenes via the radical decarboxylation of carboxylic acids.[7e] Finally, the Hu group reported a dual photo- and copper-catalyzed decarboxylative coupling of aliphatic *N*-hydroxyphthalimide (NHPI) esters with Ar_F—Zinc reagents.[7f]

Despite the progress made in the alkylation of polyfluoroarenes, the direct use of unactivated alkyl halides under metal-free conditions would significantly expand the scope and diversity of alkyl chains amenable for coupling compared to alkyl carboxylic acids, NHPI esters, and alkenes. Indeed, not only do alkyl halides represent one of the largest classes of building blocks in organic chemistry but they are also readily accessible from alcohols, another large chemical feedstock. Yet, access to alkyl radicals from alkyl halides remains challenging.[8]

As part of our interest in transition-metal-free cross-coupling reactions[9] and inspired by the recent work of Leonori, Juliá, and Doyle,[10] who demonstrated the ability of α-amino radicals to generate alkyl radicals from alkyl halides through halogen atom transfer processes (XAT), we present here the first example of a photoredox direct polyfluoarylation of unactivated alkyl halides via XAT (Scheme 1C). This metal-free transformation uses an α-aminoalkyl radical as the halogen abstracting reagent to obtain privileged alkyl polyfluoroarenes with wide functional group compatibilities, including esters, amides, carbamates, and sulfonamides.

We started our investigation with perfluorobenzene (**1a**) and 3-iodobutyl 4-methoxybenzoate (**2a**) as model substrates (Table 1, entry 1) in the presence of 4CzIPN as the photocatalyst and triethylamine as the halogen abstracting agent (Table 1). Initial screens showed the formation of the desired product in various solvents (entries 1–3), with 1,4-dioxane providing the best results (44%) when the reaction was performed at higher concentrations (entry 4). Screening of bases showed that increasing the steric bulk around the nitrogen using diisopropylethyl amine (DIPEA) reduced the yield to 34% (entry 5). Using structurally rigid bases such as DABCO (entry 6) completely shut down the reactivity. Increasing the amount of Et_3N (entries 7 and 8) led to small but noticeable increases in the yield. Similarly, increasing the amount of polyfluoroarene to 5 and 10 equiv (entries 9 and 10, respectively) further increased yields, affording the desired product in a 60% isolated yield (entry 10). Switching LED lamps from 440 to 427 nm (entry 11) reduced the yield to 38%. In the absence of either base (entry 12) or light (entry 13), the desired product was not observed. Finally, other common photocatalysts such as eosin Y (entry 14) or iridium-based catalysts (entry 15) provided the desired product in lower yields, 38% and 58%, respectively (see the Supporting Information for the full table of optimization on pages S7-S9).

We continued our investigations by exploring the scope of alkyl halides (Scheme 2). Ester moieties are well-tolerated in product **3** (60%). Cyclic and heterocyclic alkyl halides (**4–6**) afforded the desired products in good yields. Importantly, both alkyl iodides and alkyl bromides engage efficiently in this cross-coupling (42–70% yields), while alkyl chlorides remained unreactive. The reaction could also proceed with Boc-protected azetidines and piperidine motifs in 50% and 80% yields, respectively (**7** and **8**, respectively), which are important motifs in drug discovery.[11] The ability of this method to tolerate Boc protecting groups further emphasizes the synthetic utility of this approach. Thus, we continued exploring the piperidine amide motif,4-iodo-1-benzoylpiperidine (**9–14**), bearing various substituents. Electron-donating and electron-withdrawing groups were well-tolerated (65–85%). Aromatic halogens in the para position were also compatible with this method, as well as halogens in the meta position, affording products **15** and **16** in 55% and 75% yields, respectively. Importantly, the orthogonal reactivity of these aryl halides through this coupling process may enable further functionalization of the products via Suzuki or Negishi cross-coupling reactions. Ortho substitutions and heteroaromatics such as thiophene afforded products **17** and **18** in moderate to good yields (55–65%). Less stable primary alkyl radicals afforded products in **19–21** in low but synthetically useful yields (20–45%).[12] Notably, 1-adamantyl iodide, a tertiary alkyl iodide, also gave desired product **22** in a 30% yield. Finally, to highlight the late-stage functionalization potential of the method, compounds derived from commercially available bioactive molecules (ibuprofen, probenecid, and naproxen) were polyfluoroarylated to generate products **23–25**, respectively, in good to excellent yields (50–89%). These functionalizations could be broadly applied to other bioactive compounds containing alcohol moieties that could be readily transformed into their halogen counter parts.[13]

Next, we turned our attention to explore the scope of polyfluoroarenes **26–33** (Scheme 3). Substituted polyfluoroarenes generate inseparable mixtures of regioisomers due to unselective radical addition to different positions.[14] However, the reaction tolerates bromo and chloro substitutions, affording products **26** and **27**, respectively, in good to excellent yield (70–85%). It is worth indicating that alkylation occurred chemoselectively at the location of fluorine atoms with no observable substitution at the bromide or chloride, differentiating this method from previous methodologies.[7d] Polyfluoroheteroarenes such as pentafluoropyridine also gave product **28** in a moderate yield (60%). Electron-withdrawing CF_3 (**29**), secondary amides (**30** and **31**), and sulfonamide **32** were well tolerated, affording the corresponding products in 85%, 75%, 65%, and 40% yields, respectively. Finally, 1,2,4,5-tetrafluoro-3-(trifluoromethyl)benzene also benefitted from the chemoselective alkylation, providing product **33** in a 66% yield with no observable substitution at the location of the hydrogen.

To explore the reaction mechanism, a series of control experiments were performed (Scheme 4). As expected, a carbon-centered radical generated from (3-iodopropyl)-benzene was confirmed by the formation of the cyclic byproduct **35** (Scheme 4A). Furthermore, the use of radical trapping agents such as 2,2,6,6-tetramethyl-peperidinylxoyl (TEMPO) only afforded a trace amount of product **4** (Scheme 4B). The use of other trapping agents (1,1-DPE, 1,4-DNB, and BHT) also produced similar results. Importantly, two radical intermediates

were successfully trapped as TEMPO and 1,1-DPE adducts (**36–38**) and observed by GC-MS. The cyclohexane alkyl radical was trapped with both TEMPO (**36**) and 1,1-DPE (**37**). Additionally, the triethylamine radical at the α-position was also trapped using 1,1-DPE as product **38**. These experiments indicate that alkyl and triethylamine radicals are involved in this transformation.

To further understand the mechanism of the reaction and determine the sequence of each step, we performed a series of fluorescence quenching experiments involving the photocatalyst (Scheme 4C and Supporting Information S27). The addition of polyfluoroarene **1a** or alkyl halide **2a** does not quench fluorescence of the excited state of the photocatalyst (Scheme 4C1 and C2). On the other hand, the addition of Et_3N (Scheme 4C3) leads to a substrate-dependent quenching, indicating that the excited state of 4CzIPN initially reacts with Et_3N via a single-electron transfer. This observation is in accordance with previous XAT reactions developed by Leonori and Juliá.[10a,b]

On the basis of the above obtained results and previous reports,[7e,10] we propose a reaction mechanism in Scheme 5. First, photoexcited 4CzIPN oxidizes Et_3N to form radical cation **I**. Fast deprotonation[15] of **I** generates an α-aminoalkyl radical species **II** capable of performing the XAT with iodocyclohexane, which generates alkyl radical **III** and α-iodoamine **IV** (**II** and **III** can be trapped with 1,1-DPE and TEMPO; Scheme 4B). The irreversible dissociation of **IV** into iminium iodide **V** provides a XAT driving force. Radical species **III** then reacts with polyfluorobenzene to form the aryl radical intermediate **VI** via radical nucleophilic aromatic substitution. The reduction of **VI** by radical anion $4CzIPN^{\bullet-}$ affords the aryl anion species **VII** and regenerates the photocatalyst. Finally, the loss of fluoride from **VII** generates the desired final product.

In summary, this work presents the first polyfluoroarylation of alkyl halides via a XAT process. The reaction shows good functional group compatibility with synthetically useful moieties such a Boc protecting groups, esters, amides, and sulfonamides, all of which are of great interest to medicinal chemistry. The transformation proceeds in moderate to excellent yields with I°, II° and III° alkyl halides building blocks and alkyl halides derived from bioactive compounds. This process provides a complementary and metal-free approach to current decarboxylative and hydrofunctionalization approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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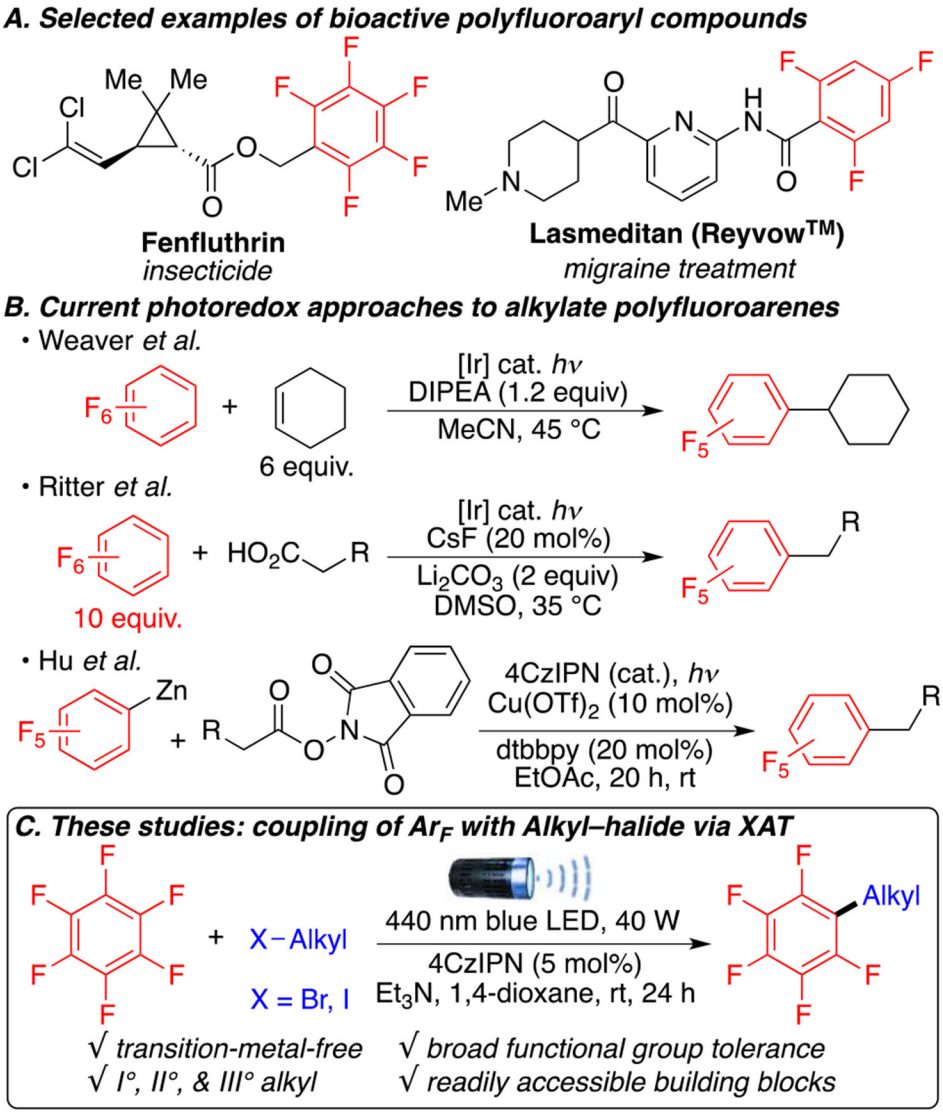
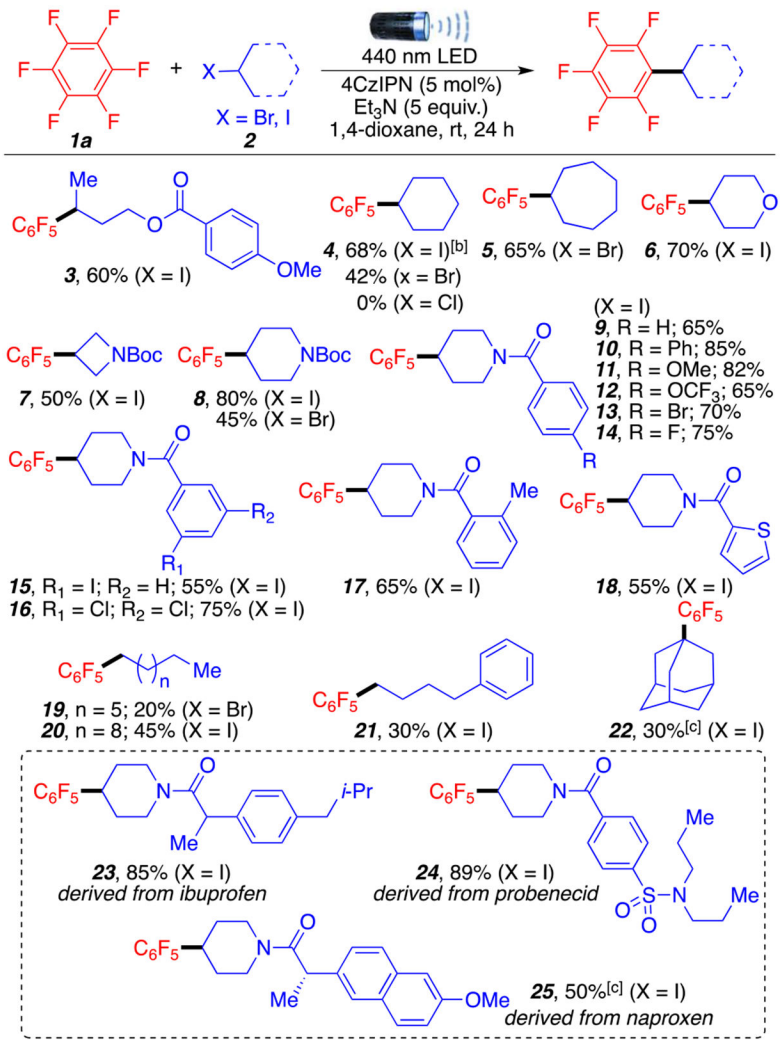


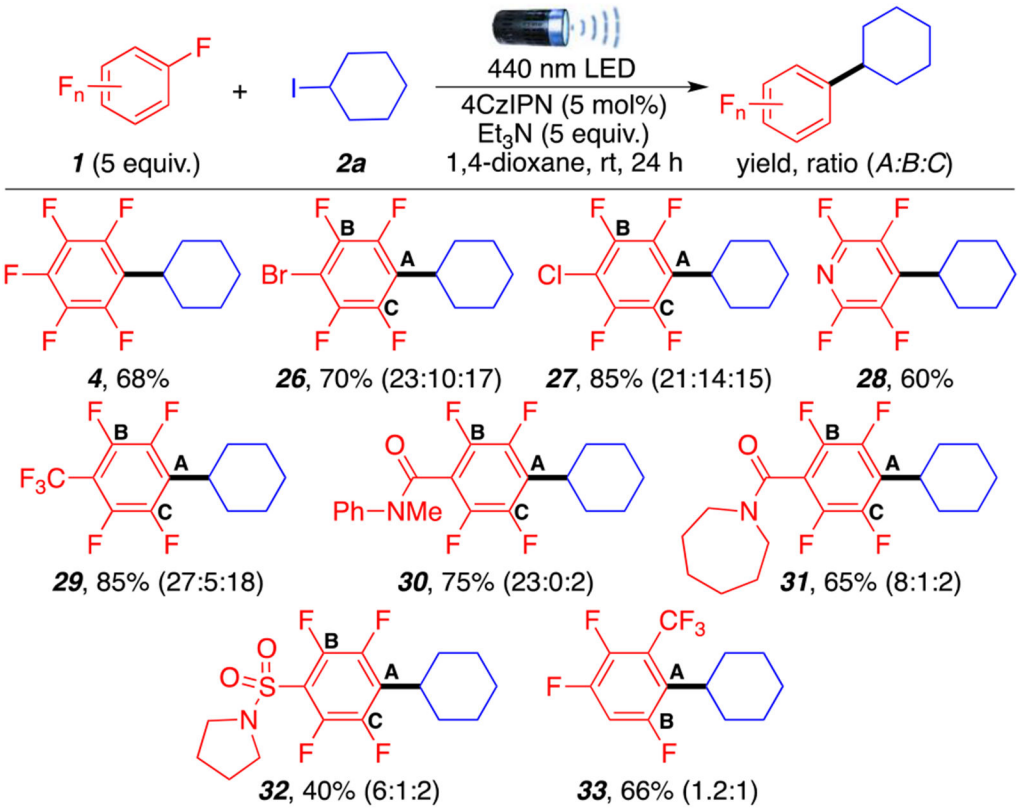
Scheme 1. Molecules of Interest and Current Technologies[a]

[a](A) Bioactive compounds of interest. (B) Photoredox methodologies to access alkylated polyfluoroarenes. (C) The presented halogen atom transfer (XAT) strategy.



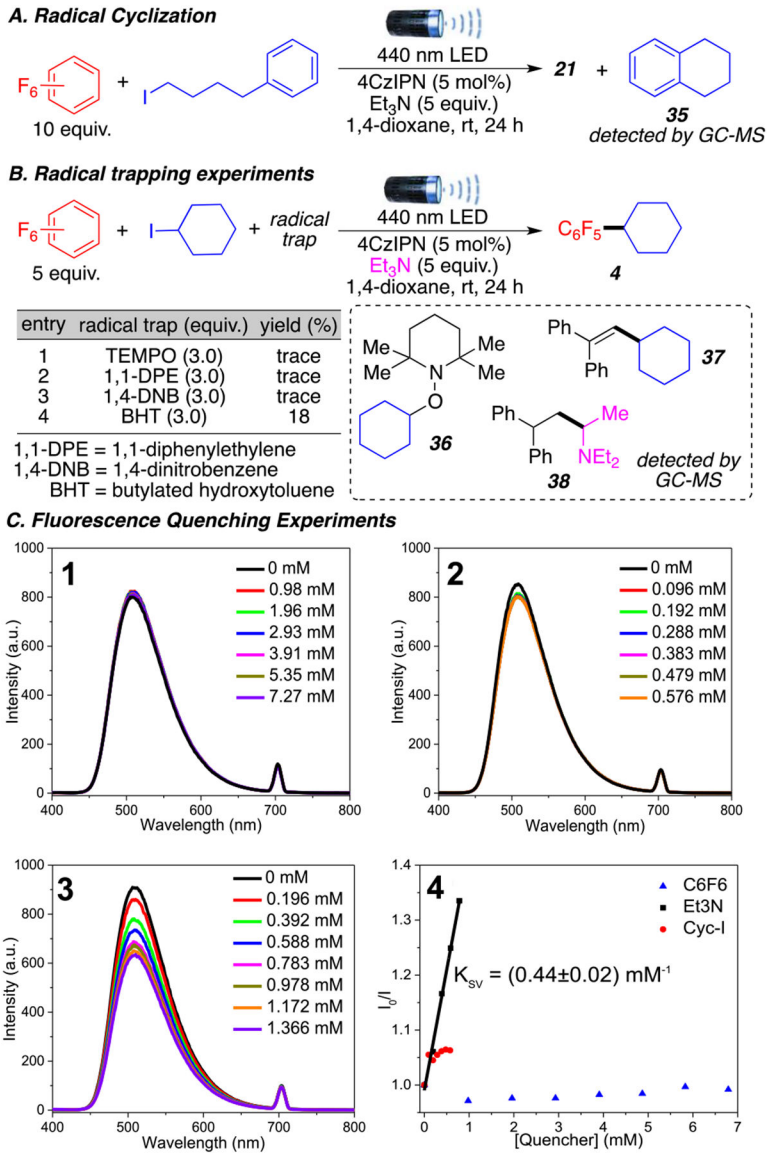
Scheme 2. Alkyl Halide Scope[a]

[a]Reaction conditions are as follows: **1a** (2.0 mmol, 10 equiv), 2 (0.2 mmol, 1 equiv), Et_3N (1.0 mmol, 5 equiv), 1,4-dioxane (0.4 mL), 4CzIPN (5 mol %), room temperature (temperature around reaction flask was 35 °C due to heating caused by the LED lamp), 24 h. All yields are isolated. [b]**1a** (5 equiv). [c]Reaction in DMSO (0.4 mL).



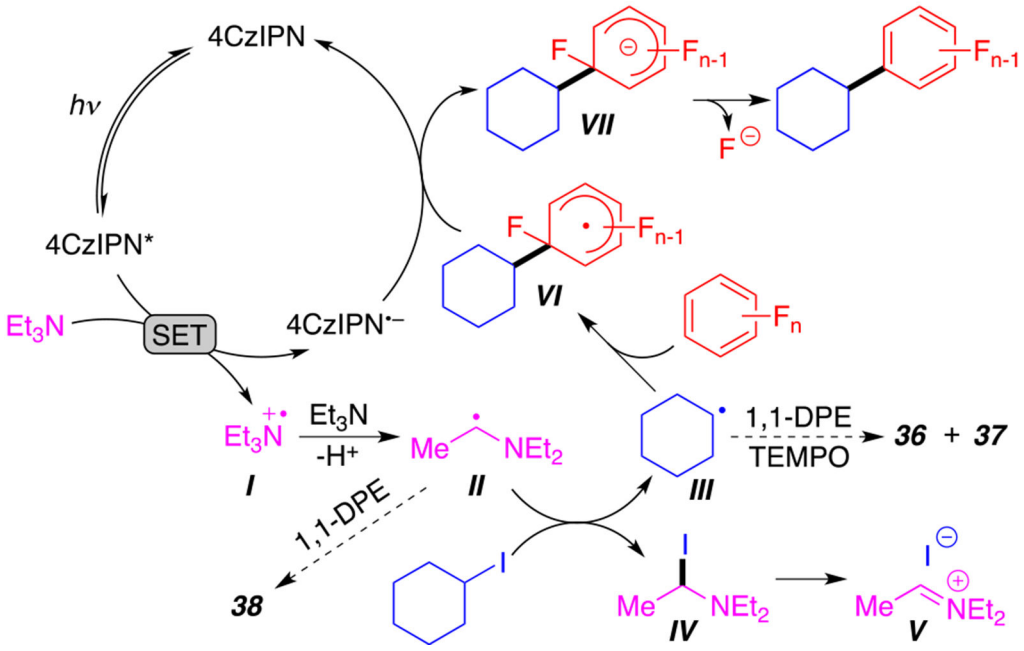
Scheme 3. Polyfluoroarene Scope[a]

[a]Reaction conditions are as follows : **1** (1.0 mmol, 5 equiv), **2a** (0.2 mmol, 1 equiv), Et^3N (1.0 mmol, 5 equiv), 1,4-dioxane (0.4 mL), 4CzIPN (5 mol %), room temperature (temperature around reaction flask was 35 °C due to heating caused by the LED lamp), overnight. All yields are isolated.



Scheme 4. Verification of the Presence of Radicals[a]

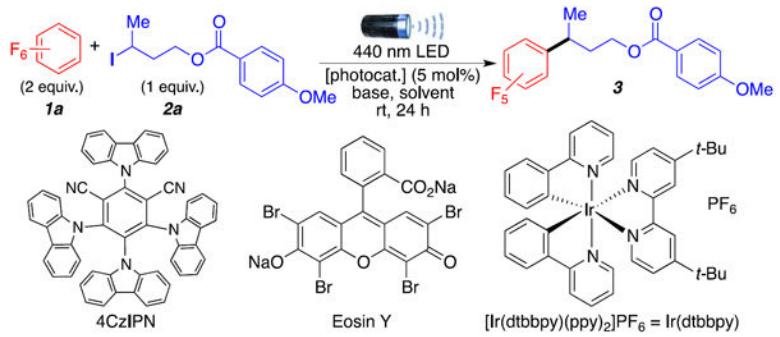
[a] (A) Cyclization byproduct experiment. (B) Radical trapping experiments. (C) Fluorescence spectra of 4CzIPN in 1,4-dioxane (0.01 mM) before and after the addition of different amounts of (1) C_6F_6, (2) iodocyclohexane, and (3) Et_3N. (4) The resulting Stern–Volmer plot.



Scheme 5.
Proposed Mechanism

Table 1.

Optimization of the Reaction and Its Conditions [a]



entry	base (equiv)	solvent (mL)	[photocatalyst]	yield (%)[b]
1	Et_3N (2.0)	CH_3CN (1.0)	4CzIPN	24
2	Et_3N (2.0)	DMSO (1.0)	4CzIPN	22
3	Et_3N (2.0)	1,4-dioxane (1.0)	4CzIPN	26
4	Et_3N (2.0)	1,4-dioxane (0.4)	4CzIPN	46
5	DIPEA (2.0)	1,4-dioxane (0.4)	4CzIPN	34
6	DABCO (2.0)	1,4-dioxane (0.4)	4CzIPN	0
7	Et_3N (3.0)	1,4-dioxane (0.4)	4CzIPN	48
8	Et_3N (5.0)	1,4-dioxane (0.4)	4CzIPN	50
9[c]	Et_3N (5.0)	1,4-dioxane (0.4)	4CzIPN	55
10[d]	Et_3N (5.0)	1,4-dioxane (0.4)	4CzIPN	62 (60)[e]
11[f]	Et_3N (5.0)	1,4-dioxane (0.4)	4CzIPN	38
12	–	1,4-dioxane (0.4)	4CzIPN	0
13[g]	Et_3N (5.0)	1,4-dioxane (0.4)	4CzIPN	0
14	Et_3N (5.0)	1,4-dioxane (0.4)	eosin Y	38
15	Et_3N (5.0)	1,4-dioxane (0.4)	Ir(dtbbpy)	58

[a] Optimal reaction conditions are as follows: **1** (2.0 mmol, 10 equiv), **2a** (0.2 mmol, 1 equiv), base (1.0 mmol, 5 equiv), 1,4-dioxane (0.5 mL), 4CzIPN (5 mol %), 440 nm LED (40 W), room temperature (temperature around reaction flask was 35 °C due to heating caused by the LED lamp), reaction flask capped under argon, 24 h.

[b] ^{1}H NMR yields using dibromomethane as internal standard.

[c] **1a** (5 equiv) was used instead of 2 equiv.

[d] **1a** (10 equiv) was used instead of 2 equiv.

[e] Isolated yield.

[f] A 427 nm LED (40W) was used instead of a 440 nm LED.

[g] The reaction was performed in the dark.