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Transition-Metal-Free Visible-Light Photoredox Catalysis at Room-Temperature for Decarboxylative Fluorination of Aliphatic Carboxylic Acids by Organic Dyes

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We report herein an efficient, general and green method for decarboxylative fluorination of aliphatic carboxylic acids. By using a transition-metal-free, organocatalytic photoredox system, the reaction of various aliphatic carboxylic acids with Selectfluor reagent afforded the corresponding alkyl fluorides in satisfactory yields under visible light irradiation at room temperature.

The increasing importance of organofluorine compounds in the pharmaceutical,[1] agrochemical and polymer industries has impelled the development of new methods for carbon-fluorine bond formation under mild conditions. However, site-specific monofluorination of organic molecules remains a challenging problem. In particular, radical fluorination, one of general strategies for site-specific formation of C(sp3)-F bonds, is emerging as a versatile tool.[2-5] In this strategy, the C-F bond is formed by the reaction between a carbon-based radical and an "atomic fluorine" source. For example, Li et al. reported a silver-catalyzed radical decarboxylative fluorination of organic acid.[5a] Very recently, Groves et al. introduced decarboxylative fluorination reaction based on the nucleophilic fluoride ion.[5d]

Recently, photoredox catalysis, which is a powerful molecule activation tool, has received great attention.[6-7] While many reports of fluorine incorporation utilizing photoredox catalysis focus on adding trifluoromethyl groups via C-C bond formation,[7] the direct visible light photoredox catalytic targeted monofluorination is rarely reported.[8]
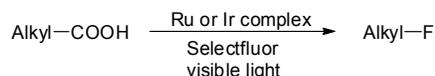
Sammis and co-workers have reported decarboxylative fluorination using a Ru(bpy)₃Cl₂ photocalalyst with Selectfluor, although the method is limited to aryloxyacetic acids and 500 W lamps. [8a] Very recently, MacMillan group reported elegant decarboxylative fluorination with Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆.[9]
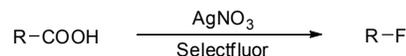
Scheme 1. Decarboxylative fluorination of aliphatic carboxylic acids.

We hypothesized that organic photoredox catalyst might be utilized in decarboxylative fluorination of the general aliphatic carboxylic acids with Selectfluor as a strong electrophilic reagent (Scheme 1). In this work, we reported that organic photocatalysts, such as 9-mesityl-10-methylacridinium perchlorate or Riboflavin,[10, 11] are able to efficiently promote the decarboxylative fluorination of aliphatic carboxylic acids affording monofluoroalkanes, aryl monofluoromethyl ethers or fluoroesters in good to excellent yields. To the best of our knowledge, this is the first example of decarboxylative fluorination of alkyl carboxylic acids catalyzed by organic dye as transition-metal-free photocatalyst under visible light.[9]

We envisioned that an organic photooxidant with appropriate redox potential might catalyze decarboxylative fluorination of inert general aliphatic carboxylic acids. For example, the photoexcited species *Mes-AcrClO₄ (9-Mesityl-10-methyl-acridinium perchlorate) has high oxidation potential (*$E_{1/2}^{red}$ = +2.08 V *vs* the saturated calomel electrode).[10] Our initial studies began with the attempted reaction of 1-tosylpiperidine-4-carboxylic acid and Selecfluor with 5 mol% Mes-AcrClO₄ in CH₃CN/H₂O of K₃PO₄ · 3H₂O under a 23 W compact fluorescent lamp. As expected, we observed 4-fluoro-1-tosylpiperidine in 58% isolated yield (Table 1, entry 1). And yet, the reaction catalyzed by less oxidizing Ru(bpy)₃Cl₂ almost did not provide fluorination product (Table 1, entry 2).[9] The Riboflavin, Eosin Y and Rhodamine B were also tested, but only Riboflavin gave a positive result (Table 1, entries 3-5). The base also affected this transformation

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COMMUNICATION   Journal Name

significantly (Table 1, entries 6-9). When 1.0 equivalent Cs_2CO_3 was used, the yield of isolated **2a** was dramatically improved.

Table 1. Photoredox Catalytic Decarboxylative Fluorination of Aliphatic Carboxylic Acid.[a]
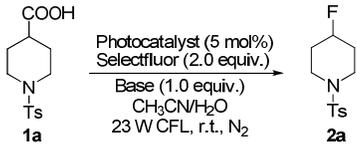
| Entry	Photocatalyst	Base	Yield [%][b]
1	Mes-AcrClO$_4$	K$_3$PO$_4$·3H$_2$O	58
2	Ru(bpy)$_3$Cl$_2$ • 6H$_2$O	K$_3$PO$_4$·3H$_2$O	trace
3	Riboflavin	K$_3$PO$_4$·3H$_2$O	55
4	Eosin Y	K$_3$PO$_4$·3H$_2$O	trace
5	Rhodamine B	K$_3$PO$_4$·3H$_2$O	trace
6	Mes-AcrClO$_4$	K$_2$HPO$_4$·3H$_2$O	62
7	Mes-AcrClO$_4$	Na$_2$CO$_3$	69
8	Mes-AcrClO$_4$	NaHCO$_3$	56
9	Mes-AcrClO$_4$	Cs$_2$CO$_3$	82
10[c, d]	Mes-AcrClO$_4$	Cs$_2$CO$_3$	80
11	Mes-AcrClO$_4$	none	no reaction
12[e]	Mes-AcrClO$_4$	Cs$_2$CO$_3$	no reaction
13	none	Cs$_2$CO$_3$	no reaction
14[f]	Mes-AcrClO$_4$	Cs$_2$CO$_3$	no reaction
15[g]	Mes-AcrClO$_4$	Cs$_2$CO$_3$	no reaction

[a] Unless otherwise noted, reactions were performed on 0.4 mmol scale using 5 mol% photocatalyst, 1.0 equiv base, 2.0 equiv Selecfluor, 3.0 mL CH$_3$CN/H$_2$O (v/v = 1/1), and a 23 W CFL as the light source, at room temperature, 60 h. [b] Yield of the isolated product. [c] Blue LEDs were used. [d] The quantum yield was 0.061. [e] N-Fluorobenzenesulfonimide instead of Selectfluor. [f] In the absence of light source. [g] In the presence of air.

When blue LEDs were used, the yield was not significantly increased (Table 1, entries 10). Note that no reaction proceeded in the absence of base (Table 1, entries 11). Replacing Selectfluor reagent with N-Fluorobenzenesulfonimide (NFSI) resulted in no reaction (Table 1, entry 12). Control experiments revealed that no reaction occurred in the absence of either the photocatalyst or the visible light source (Table 1, entries 13-14). And nitrogen atmosphere is essential to this catalytic system (Table 1, entries 15).

Having established effective conditions for decarboxylative fluorination, we next evaluated the scope of aliphatic carboxylic acids and the generality of this protocol. As shown in Scheme 2, primary, secondary, and tertiary alkyl carboxylic acids were all efficiently converted to the corresponding alkyl fluorides. The reactions of *N*-protected amino acids with Selectfluor proceeded smoothly, leading to the high-yield production of secondary alkyl fluorides **2b**-**2l**, respectively. Both phthaloyl and succinyl were well tolerated. In particular, *N*-protected amino acids with steric hindrance **2g** and **2l** also underwent highly efficient decarboxylative fluorination to afford the corresponding products. Although side reaction occurred when 2, 2-diphenylacetic acid was used, the moderate yield was observed for **2m**. Similarly, 1-tosylpiperidine-3-carboxylic acid was also competent substrate for this decaboxylative fluorination protocol

**Scheme 2**. Reaction Scope of Photocatalytic Decarboxylative Fluorination.[a, b]
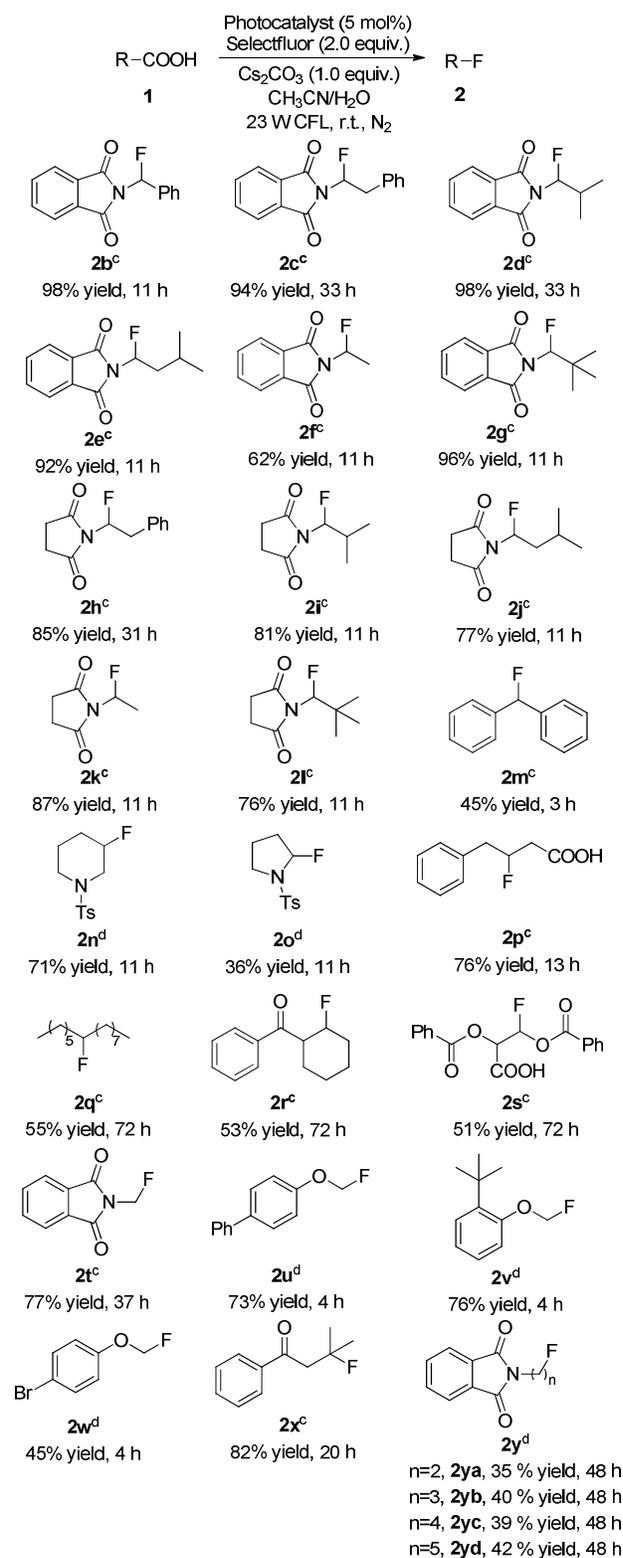
[a] Unless otherwise noted, reactions were performed on 0.4 mmol scale using 5 mol% photocatalyst, 1.0 equiv base, 2.0 equiv Selecfluor, 3.0 mL CH$_3$CN/H$_2$O (v/v = 1/1), and a 23 W CFL as the light source, at room temperature. [b] Yield

Journal Name

COMMUNICATION

of the isolated product. [c] Mes-AcrClO$_4$ was used. [d] Riboflavin was used.

in desired yield. However, when *N*-tosyl-*L*-proline was employed as a substrate, the corresponding alkyl fluoride **2o** was observed in a decreasing yield, due to the electron-rich amino group in alpha position. It is important to note that dicarboxylic acids underwent chemoselective decarboxylation to give the monofluorination products **2p** and **2s**. The unactivated acid **1q** was also subjected to the optimized condition in moderate yield. When aryloxyacetic acids were used in the decarboxylative fluorination, the resulted aryl fluoromethyl ethers **2u-2w** were obtained in moderate to good yields.

When **1r** was employed as a substrate, only β-decarboxylative fluorination happened, and β-fluoroketone was obtained. To our surprise, neither the α-position fluorination product nor α,β-unsaturated product was observed. It should be noted that, the corresponding fluoride of tertiary alkyl carboxylic acid **1x** was achieved in excellent yield. To our delight, unactivated primary alkyl acids **1y** were all efficiently converted to the corresponding alkyl fluorides.

A possible mechanistic pathway is proposed to illustrate the photoredox decarboxylative fluorination process (Scheme 3). The single electron oxidation of alkyl carboxylate in the presence of the excited state of photocatalyst has proven to be feasible according to the luminescence quenching experiment results (see Supporting Information). In the photoredox cycle, a carbon radical would be generated via immediate extrusion of CO$_2$. As a result, the fluorine atom would transfer from oxidizing Selectfluor to the alkyl radical.[9] The mechanistic pathway, which is very different from previous work,[8a, 9] has a great significance for the research of decarboxylative reaction catalyzed by organic photocatalyst via visible light.
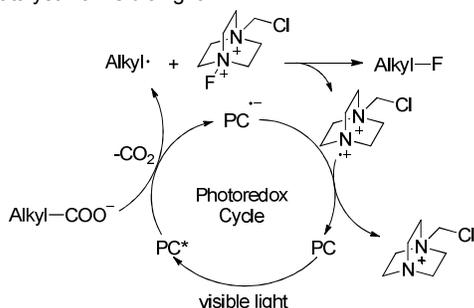
Scheme 3. Proposed Mechanism of Photoredox Catalytic Decarboxylative Fluorination of Aliphatic Carboxylic Acid.

In conclusion, we have developed an efficient, general and green method for decarboxylative fluorination of aliphatic carboxylic acids in aqueous solution with organic dyes as transition-metal-free photocatalyst, affording monofluoroalkanes, aryl monofluoroalkyl ethers or fluoroesters in good to excellent yields. Notably, the low cost of the safe fluorine reagent, easy access to the organic photocatalyst and very mild experiment conditions render this new transition-metal-free, photocatalytic radical fluorination in organic synthesis and industry.

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