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# Decarboxylative and Deaminative Alkylation of Difluoroenoxysilanes via Photoredox Catalysis: A General Method for Site-Selective Synthesis of Difluoroalkylated Alkanes

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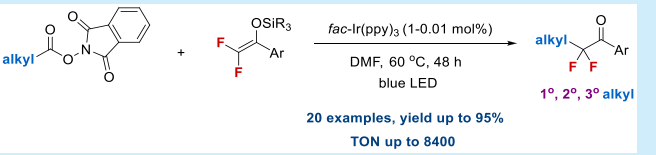
**ABSTRACT:** A general method for site-selective difluoroalkylation of alkyl carboxylic redox esters with difluoroenoxysilanes through photoredox-catalyzed decarboxylative reaction has been developed. The reaction can also be extended to aliphatic amine derived pyridinium salts. This method has the advantages of high efficiency, mild reaction conditions, and broad substrate scope, including primary, secondary, and sterically hindered tertiaryl alkyl substrates, providing a general and practical route for applications in organic synthesis and pharmaceutical studies.

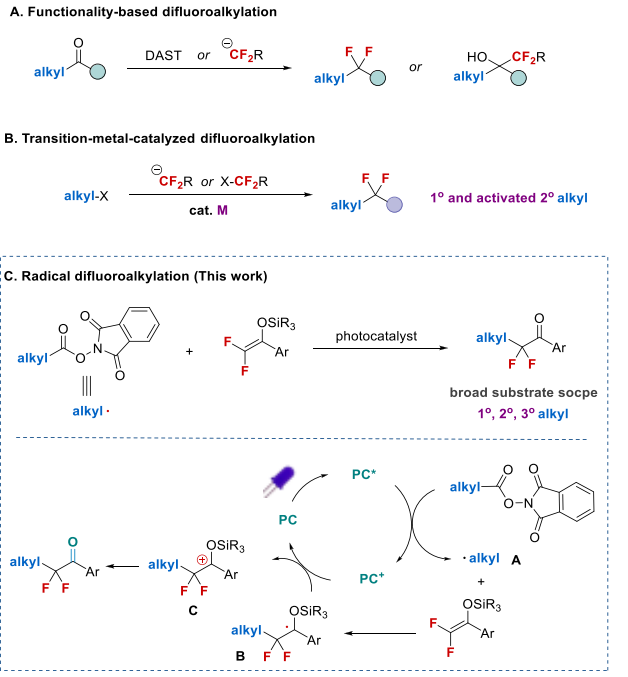





The site selective introduction of fluorinated functionality into organic molecules for precise molecular engineering has emerged as an important topic of organic synthesis, because of the widespread applications of organofluorinated compounds in pharmaceuticals, agrochemicals, and advanced functional materials.[1] The past decade has witnessed impressive achievements in the area, most of which focus on the site-selective fluoroalkylation of (hetero)aromatic compounds.[2] However, the site-selective fluoroalkylation, particularly, difluoroalkylation, of aliphatic substrates at unactivated position remains challenging.[2d,3] Due to the unique properties of difluoromethylene ($CF_2$) group, the site-selective introduction of the $CF_2$ moiety into an aliphatic chain can cause the conformational change, increase the dipole moment, and improve the metabolic stability of the bioactive molecules.[4] Specifically, the presence of a $CF_2$ adjacent to a carbonyl group can increase its electrophilicity, thus rendering the $\alpha,\alpha$-difluoroketones as the effective enzyme inhibitors.[5] As such, the site-selective difluoroalkylation has become a useful strategy in the drug discovery and development. For example, bioactive molecules bearing a $CF_2$ moiety have been used as cholesterol esterase inhibitor[6] and anticancer[7] and antivirus agents.[8]

Traditional methods to synthesize difluoroalkylated compounds include the transformation of the carbonyl groups, alkenes, and alkynes (Scheme 1A).[9] Despite the high efficiency of this functionality-based strategy, the introduction of a $CF_2$ at any position on the aliphatic chain through this strategy remains challenging due to its moderate functional group compatibility or relatively limited substrate scope. Recently, we developed a transition-metal-catalyzed difluoroalkylation strategy, providing an alternative approach to access difluoroalkylated alkanes (Scheme 1B).[10] However, the reaction of unactivated secondary and tertiary aliphatic substrates remains

**Scheme 1. Strategies for the Synthesis of Difluoroalkylated Alkanes**

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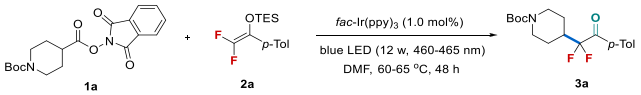
a hurdle. To overcome these limitations and meet the high demand of discovering new $CF_2$-containing bioactive molecules, a radical transformation would be an attractive strategy, as the radical reactions usually are not sensitive to the steric effect.[11] For practical applications, we sought to use inexpensive and widely available aliphatic carboxylic acids as the starting materials, which can be easily transformed into *N*-(acyloxy)phthalimides.[12] These redox esters can efficiently generate alkyl radicals via a single electron transfer (SET) pathway in the presence of photocatalyst.[13]

We hypothesized that once the alkyl radical **A** was generated between *N*-(acyloxy)phthalimide and the excited photocatalyst, the difluoroalkylated compound would be efficiently accessed with a suitable radical-trapping difluoroalkylating reagent, such as difluoroenoxysilane previously used for the visible-light-initiated difluoroalkylation of arene diazonium salts[14] (Scheme 1C). In this process, the newly generated alkyl radical **B** was oxidized by the photocatalyst to form a carbon cation species **C**, which subsequently underwent desilylation to produce the difluoroalkyl ketone. This radical strategy would enable difluoroalkylation of an array of unactivated primary, secondary, and tertiary aliphatic substrates, thus providing a general approach to access difluoroalkylated alkanes.

Accordingly, we chose aryl-substituted difluoroenoxysilanes **2** as the difluoroalkylating reagents. Due to the electron-withdrawing effect of the fluorine atom, these electron-deficient alkenes are favorable to reacting with a nucleophilic alkyl radical. We began our studies from the reaction of secondary alkyl carboxylic redox-ester **1a** with *p*-toyl substituted difluoroenoxysilane **2a** under photoredox reaction conditions (Table 1). We found that the use of commercially

**Table 1. Representative Results for Optimization of Photoredox-Catalyzed Decarboxylative Alkylation of Difluoroenoxysilane 2a with 1a[a]**



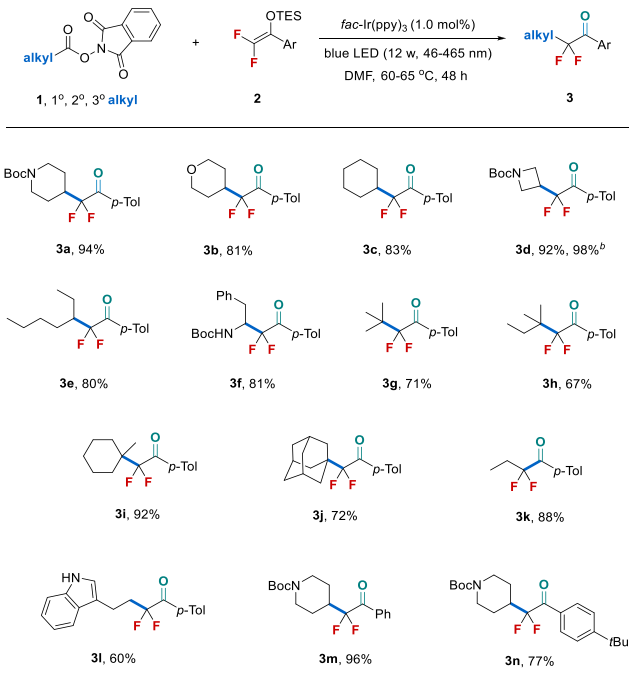

| entry | reaction conditions | yield (%), 3a[b] |
|---|---|---|
| 1 | Standard conditions | 94 (94) |
| 2 | $[Ir(dtbbpy)(ppy)_2]PF_6$ instead of *fac*-$Ir(ppy)_3$ | 76 |
| 3 | $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ instead of *fac*-$Ir(ppy)_3$ | 26 |
| 4 | $Ru(bpy)_3(PF_6)_2$ instead of *fac*-$Ir(ppy)_3$ | 8 |
| 5 | $CH_3CN$ instead of DMF | 87 |
| 6 | 1,4-Dioxane instead of DMF | 10 |
| 7 | reaction run at room temperature | 85 |
| 8 | w/o blue LED | 0 |
| 9 | w/o *fac*-$Ir(ppy)_3$ | 3 |

[a]Reaction conditions (unless otherwise specified): **1a** (0.5 mmol, 1.0 equiv), **2a** (1.5 mmol, 3.0 equiv). [b]Determined by $^{19}F$ NMR using fluorobenzene as an internal standard and number in parentheses is isolated yield.

available photocatalyst *fac*-$Ir(ppy)_3$ (1 mol %) in DMF under blue light (12 W, 460−465 nm) irradiation could provide the desired product **3a** in 94% yield upon isolation (entry 1). A slightly lower yield was obtained with $[Ir(dtbbpy)(ppy)_2]PF_6$ as the catalyst (entry 2). However, other photocatalysts, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and $Ru(bpy)_3(PF_6)_2$, led to poor yields (entries 3 and 4). Among the tested solvents, DMA and DMSO were comparable with DMF, and $CH_3CN$ was slightly less effective (entry 5, for details see the Supporting Information). But the ethereal solvent 1,4-dioxane almost suppressed the reaction (entry 6). Decreasing the reaction temperature to room temperature slightly diminished the reaction efficiency with an 85% yield of **3a** obtained (entry 7). Essentially, no reaction occurred in the absence of photocatalyst or blue light irradiation (entries 8 and 9), demonstrating that the [Ir]-catalyst and blue light play an essential role in promoting the reaction.

With the viable reaction conditions in hand, we examined the difluoroalkylation of a variety of redox-esters **1**. Overall, the reaction was not sensitive to the steric effect. Good to high yields were obtained with primary, secondary, and tertiary alkyl carboxylic esters. As illustrated in Scheme 2, cyclic secondary

**Scheme 2. Photoredox-Catalyzed Decarboxylative Alkylation of Difluoroenoxysilanes 2[a]**




[a]Reaction conditions (unless otherwise specified): **1** (0.5 mmol, 1.0 equiv), **2** (1.5 mmol, 3.0 equiv), DMF (5 mL) at 60 °C for 48 h. [b]Gram-scale reaction: **1** (4 mmol, 1.0 equiv), **2** (12 mmol, 3.0 equiv), DMF (40 mL) at 60 °C for 48 h.

alkyl redox esters furnished the corresponding products efficiently (**3a−3d**). High yields were obtained with piperidine-, tetrahydropyran-, and cyclohexane-derived substrates (**3a−3c**). A four-membered azetidine derivative was also applicable to the reaction, and an even higher yield (98%) was obtained by gram-scale synthesis (**3d**). Since $CF_2$ and azetidine are pharmaceutically relevant structural motifs, the current process may have potential applications in medicinal chemistry. The reaction was not restricted to the cyclic substrates, as the acyclic secondary alkyl redox esters underwent the difluoroalkylation smoothly (**3e** and **3f**). An unactivated secondary heptyl substituted ester provided the corresponding product **3e** with high efficiency. A phenylalanine-derived substrate was also a competent coupling partner with an 81% yield obtained (**3f**). The generality of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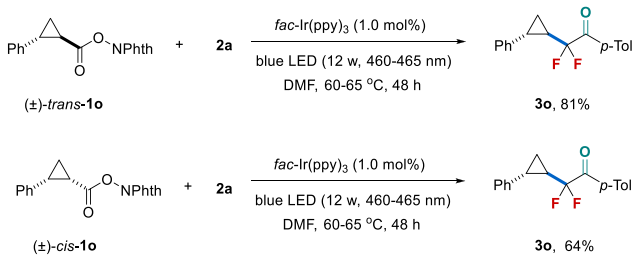
this method can also be demonstrated by difluoroalkylation of tertiary redox esters (**3g**−**3j**). Although the sterically hindered tertiary alkyl radicals are more stable and less reactive than primary and secondary alkyl radicals, high yields were still obtained. Pivalic acid and 2,2-dimethylbutanoic acid derived substrates underwent the difluoroalkylation efficiently (**3g** and **3h**), and even as high as a 92% yield of **3i** was provided. Adamantane carboxylate was also amenable to the reaction without difficulty (**3j**). With respect to primary alkyl redox esters, the corresponding difluoroalkylated products **3k** and **3l** could be readily prepared through the current process. In addition, difluoroenoxysilanes with different aryl substituents were also competent coupling partners (**3m** and **3n**), demonstrating the generality of this method further.

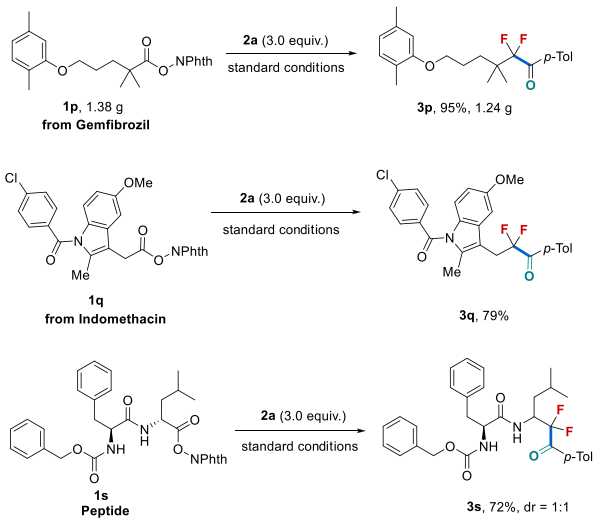
We also found that the reaction showed excellent *trans*-selectivity with cyclopropanecarboxylic acid derivatives as the coupling partner (Scheme 3). Both *trans*- and *cis*-2-phenylcyclopropane-1-carboxylic acid derived redox esters (**1o**) solely afforded *trans*-difluoroalkylated cyclopropane **3o** with high efficiency, indicating that a planar cyclopropyl radical is involved in the reaction.

**Scheme 3. *trans*-Selective Synthesis of 3o from *trans*- and *cis*-Redox-Esters 1o**



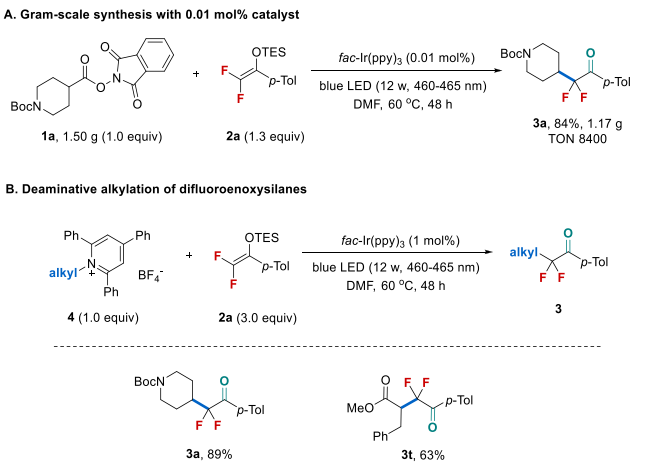

The utility of this method has also been demonstrated by the late-stage difluoroalkylation of pharmaceuticals and peptides. As shown in Scheme 4, gemfibrozil, a drug used for the treatment of hyperlipidemias, could be successfully modified by reaction of its redox-ester **1p** with difluoroenoxysilane **2a** in 95% yield on gram scale. Similarly, indomethacin derived substrate **1q** underwent the difluoroalkylation efficiently. Most remarkably, the dipeptide-based redox-ester **1s** also exhibited high reactivity, providing the $\alpha,\alpha$-difluoroalkyl ketone-containing peptide **3s** in 72% yield with 1:1 dr. Since $\alpha,\alpha$-difluoroketones are susceptible to forming ketal/hemiketal-type adducts with an enzyme active site, and the electron-withdrawing effect can stabilize the resulting tetrahedral adducts,[15] this method provides potential opportunities for applications in discovering a new enzyme inhibitor of medicinal interest.

**Scheme 4. Late-Stage Modification of Pharmaceuticals and Peptide**




Although considerable efforts have been made on the catalytic fluoroalkylation reactions, practical methods with a low catalyst loading to efficiently prepare fluoroalkylated compounds are rare.[16] In this context, gram-scale reaction of redox-ester **1a** and difluoroenoxysilane **2a** with 0.01 mol % of photocatalyst was conducted and provided the difluoroalkylated product **3a** in 84% yield (Scheme 5A). In this reaction, only 1.3 equiv of redox-ester **2a** was used, thus demonstrating the reliability and practicability of this protocol. In addition to alkyl carboxylic esters, the aliphatic amine derived pyridinium salts **4** were also applicable to the reaction (Scheme 5B). Piperidine-based pyridinium salt **4a** underwent the difluoroalkylation smoothly, leading to **3a** in a comparable yield. Pyridinium salt **4b** bearing a phenylalanine moiety was also a suitable substrate with the carboxylic ester intact (Scheme 5B, **3t**),[17] thus providing a complementary method to the decarboxylative process, in which the amine group was reserved (Scheme 2, **3f**).

**Scheme 5. Gram-Scale Synthesis with 0.01 mol % Catalyst Loading and Photoredox-Catalyzed Deaminative Alkylation of Difluoroenoxysilanes**




Importantly, the resulting difluoroalkylaryl ketones can serve as a versatile building block for diversified synthesis of fluorinated compounds. As depicted in Scheme 6A, the *p*-toyl acyl (*p*Me-$C_6H_4CO$) group could be readily removed to generate difluoromethylated alkanes **5**. Ketones **3** bearing cyclic or acyclic secondary alkyl groups all provided the corresponding products efficiently (**5a**−**5c**). Even tertiary alkyl substituted ketone **3p**, which is derived from the pharmaceutical gemfibrozil, underwent the reaction smoothly (**5d**), offering good opportunities for modification of the bioactive molecules further. Although the transition-metal-catalyzed difluoroalkylation represents a modern strategy to prepare fluorinated compounds,[2d,10] the difluoromethylation of tertiary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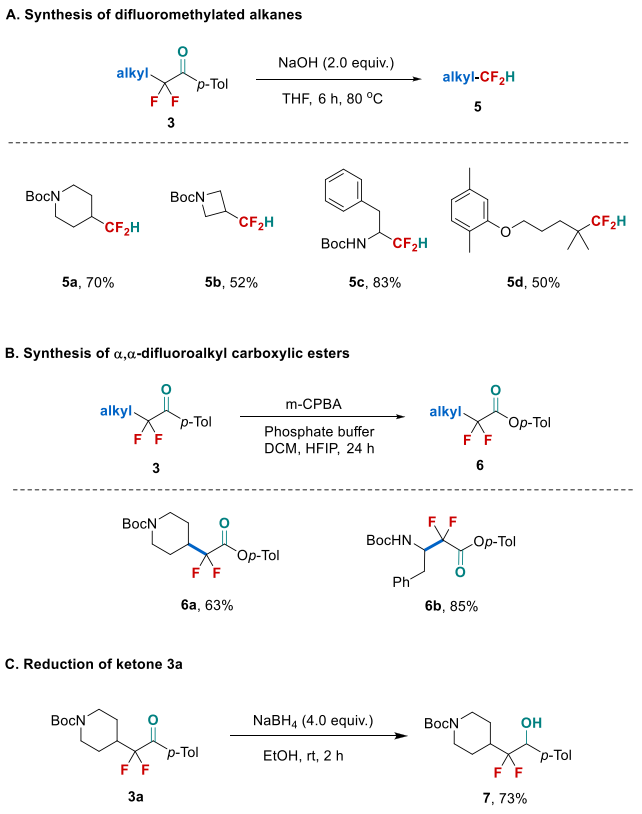
**Scheme 6. Transformations of Compound 3**




alkyl remains a challenging topic. The current process can overcome this limitation, thus featuring the advantages of this method.

The difluoroalkylaryl ketones can also be used for the preparation of $\alpha,\alpha$-difluoroalkyl carboxylic esters through Baeyer–Villiger oxidation (Scheme 6B). Given the important applications of fluorinated amino acids in medicinal chemistry and chemical biology,[18] the resulting protected fluorinated amino acid **6a** and $\alpha,\alpha$-difluoro-$\beta$-amino acid **6b** may have potential applications in the design of peptide based bioactive molecules. Furthermore, reduction of the ketone carbonyl group provided the alcohol efficiently (Scheme 6C), thus demonstrating the synthetic utility of this protocol further.

In conclusion, we have developed a general method to prepare difluoroakylated alkanes through photoredox-catalyzed decarboxylative and deaminative alkylation of difluoroenoxysilanes. The reaction proceeds under mild reaction conditions and allows difluoroalkylation of an array of primary, secondary, and tertiary alkyl carboxylic redox esters with high efficiency, excellent site selectivity, and broad substrate scope, including pharmaceuticals and peptides. The synthetic utility of this protocol has also been demonstrated by the gram-scale synthesis of difluoroalkylated alkane with low catalyst loading (0.01 mol %, 8400 TON), representing a practical method for fluoroalkylation. The resulting difluoroalkyl ketones can serve as a versatile building block for diversified synthesis of fluorinated compounds, including difluoromethylated alkanes bearing a quaternary carbon center that otherwise are difficult to prepare through conventional methods, thus paving a new way in the preparation of fluorinated compounds of interest in the medicinal chemistry and chemical biology.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02997.

Detailed experimental procedures, and characterization data for new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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