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Visible Light Promoted Deaminative Difluoroalkylation of Aliphatic Amines with Difluoroenoxysilanes

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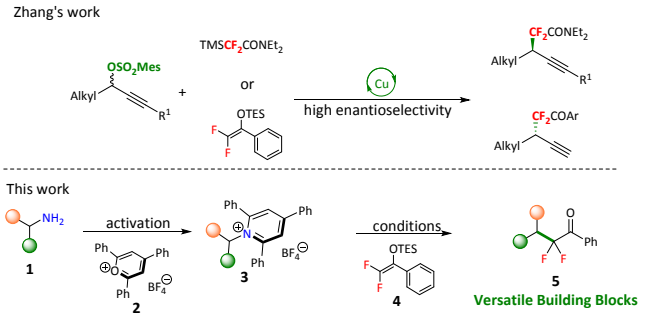
Abstract: A visible light promoted deaminative strategy for the difluoroalkylation reaction utilizing pyridinium-activated aliphatic primary amines and difluoroenoxysilane as substrates have been developed. This protocol is characteriazed by its mild reaction conditions, broad substrate scope, which converted a diverse array of amine-containing molecules to the alkyl-CF_2COPh products. Moreover, the resulting products can be easily transformed to a vast array of structurally novel and interesting difluoro-containing moieties, therefore providing a facile route for applications in medicinal chemistry and life science.

Due to the unique characteristics of the fluorine atom, fluorinated compounds played important roles in medicinal chemistry, agrochemistry and materials sciences.[1] Among the commonly encounted fluoro-containing functional groups, difluoromethylene (CF_2) groups are intriguing structural motifs, because they can be used as an isopolar-isosteric substitute for an oxygen atom or a carbonyl group, and can modulate the pKa value of neighboring groups such as hydroxy, thiol, or amine.[2] In addition, CF_2H group can act as a hydrogen bond donor.[3] Consequently, difluoromethylene groups are playing decisive roles as substituents in compounds with pharmacological activities.[4] Traditionally, the CF_2 group is generated by deoxyfluorination of a ketone with reagents such as N,N-diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor).[5] In the past 10 years, many effective and elegant difluoroalkylation protocols have been developed to introduce difluoromethylene into organic compounds.[6] Among them, transition-metal catalytic or photocatalytic strategies are particularly appealing owing to their atom economy and step economy. However, most of these well-developed methods are focused on the difluoroalkylation of (hetero)arenes [7] or unsaturated carbon-carbon systems [8].



Scheme 1 Methods for the difluoroalkylation of secondary C_{sp}^3.

Despite the tremendous progress on this field, the difluoroalkylation of C(sp^3) remain a challenge. To the best of our knowledge, only a few examples with limited substrate scope have been reported so far because of the lack of general and efficient strategies. [9] Recently, Zhang and co-workers reported a copper-catalyzed highly enantioselective difluoroalkylation of secondary propargyl sulfonates with $TMSCF_2CONEt_2$ [10] or difluoroenoxysilanes **(Scheme 1)**.[11] Despite the significant advances, those reactions were restricted to the propargyl positions. Given the unique properties of difluoromethylene group in pharmaceuticals containing C(sp^3)-CF_2R moieties, the development of a new mode for the construction of C(sp^3)-CF_2R will be of high demanding, to the medicinal chemistry and life science.

Primary amines are one of the most predominant functional groups found in a large number of organic molecules ranging from simple industrial raw materials to complex natural products, the development of new strategies for the construction of C(sp^3)-CF_2R through deaminative processes is of

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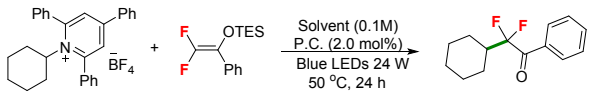
high importance. Katritzky salts are air and moisture stable reagents, which can be easily prepared in a single step via condensation of primary amines with 2,4,6-triphenylpyrylium tetrafluoroborate. Very recently, a variety of deaminative protocols employing Katritzky salts have been realized and allow selective transformations of abundant amino groups.[12] Here, we describe the first example of visible light promoted deaminative difluoroalkylation chemistry,[13] the resulting products can be further transformed to a diverse array of structurally novel and interesting difluoro-containing moieties, therefore providing a facile route for applications in medicinal chemistry and life science.

Table 1. Representative Results for the Optimization of the Visible Light Promoted Deaminative Difluoroalkylation of Amines. [a b]



3a 4 5a

Entry	Catalyst	Solvent	Yield (5a %)[b]
1	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA	68
2	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMF	36
3	$[Ir(dtbbpy)(ppy)_2]PF_6$	DME	11
4	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA:1,4-Dioxane (1:1)	73
5	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA : DME (1:1)	85
6	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA : THF (1:1)	85
7	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA : DME (1:3)	97
8	$Ir(ppy)_3$	DMA : DME (1:3)	19
9[c]	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA : DME (1:3)	75
10[d]	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA : DME (1:3)	----
11	----	DMA : DME (1:3)	----
12[e]	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA : DME (1:3)	97 (92)

[a] Reaction conditions (unless otherwise specified): 1a (0.1 mmol, 1.0 equiv.), 2 (0.2 mmol, 2.0 equiv.), P.C. (2.0 mol%), Solvent (1.0 mL), Blue LEDs 24 W, 50 °C, 24 h, under argon atmosphere. [b] NMR yield determined by ^{19}F NMR using p-Fluorotoluene as internal standard. [c] The reaction was performed at 35 °C. [d] The reaction was performed in the dark. [e] Reaction performed on a 0.2 mmol scale, 36 h, yield of isolated product given in parentheses.

Accordingly, we began this study by choosing Katritzky salts **3a** and difluoroenoxytriethylsilane **4** as the model substrate. (**Table 1**). Initially, a 68% of the desired product **5a** was obtained when the reaction of **3a** (0.1 mmol, 1.0 equiv) with **4** (2.0 equiv) was carried out under the irradiated of 24 W blue LEDs in DMA utilizing $[Ir(dtbbpy)(ppy)_2]PF_6$ (2 mol%) as photocatalyst at 50 °C for 24 h (**Table 1**, entry 1). Then, different reaction mediums were screened. Among the tested solvents, other amide solvents such as NMP and DMF were less effective (**Table 1**, entry 2， for details, see ESI). Poor yields were obtained when the reaction was conducted in DMSO or MeCN (for details, see ESI). Ethers (THF, 1,4-dioxane and DME) were also not effective solvents (**Table 1**, entry 3, for details, see ESI). To improve the reaction efficiency further, some co-solvent systems were tested, and an improved yield of **5a** was provided when DMA and ether solvents were used as co-solvent (**Table 1**, entries 4-6), and 85% yield was obtained when the reaction was performed in a co-solvent system of DMA/DME (1:1) or DMA/THF (1:1). After adjust the ratio of those co-solvent (DMA/DME or DMA/THF), the system DMA/DME (1:3) was proved to the best one, and 97% yield was provided (**Table 1**, entry 7, for details, see ESI). Other photocatalysts such as $Ru(bpy)_3Cl_2$, $Ir(ppy)_3$ or $[Ir(ppy)_2(bpy)]PF_6$ were also investigated, but failed to give satisfactory results **(Table 1**, entry 8, for details, see ESI). Finally, the effort of the reaction temperature was also examined, decreasing the reaction temperature to 35 °C deminished the reaction efficiency, and 75% yield was obtained (**Table 1**, entry 9). Control experiments demonstrated that both photocatalyst and visible light are essential for this transformation (**Table 1**, entries 10-11). When the reaction performed at 0.2 mmol scale, a comparable yield could be afforded (**Table 1**, entry 12).

With the optimized reaction conditions in hand, the scope of this photochemical deaminative difluoroalkylation reaction was explored. Various pyridinium salts derived from primary amines were successfully difluoroalkylated in satisfactory yields (**Table 2**). First, the reactivity of different sizes of aliphatic rings were examined, five-membered rings were less reactive, only moderate yield were obtained (**5b-c**). Other aliphatic rings, such as seven, eight or twelve- membered rings were suitable substrates, providing the desirable products in good yields (**5d-f**). The existence of difluoromethylene (CF_2) group on the ring does not interfere this protocol (**5g**). Interestingly, protected amino was also compatible with the reaction system (**5h**). Substrate derived from piperidine, the most prevalent nitrogen ring system found in medicinal chemistry, could difluoroalkylated smoothly in 81% yield (**5i**). In comparison, pyridinium salt of pyrrolidine was less effective, and only 45% yield was provided (**5j**). 60% yield was obtained when oxygen-containing saturated heterocycle was treated (**5k**). Then, straight-chain primary amines were tested, pyridinium salts from 2-amino-4-phenylbutane worked well to afford the corresponding products in 66% yield (**5l**). Amino acids, an important class of primary amines, are also common structural motifs found in life science and pharmaceuticals. Therefore, difluoroalkylation of those compounds were also conducted. Pleasingly, amino acids that have fluoro, chloro, *tert*-butoxy, protected amino, methylthio groups as substituents reacted with **4** very well, to afford the desirable products in 64-94% yields (**5m-u**). Moreover, substrates derived from diverse primary benzylic amines were also successfully difluoroalkylated and provide the desired products in 41-77% yield (**5v-5af**). 3-(Aminomethyl)pyridine was also compatible with the reaction system, affording **5ag** in 65% yield. The reaction was less reactive when the steric hindrance of the group adjacent to amino group was increased (**5ah**). Pyridinium salt linked with primary carbons were not suitable substrates because of unstable radical intermediate (**5ai**). To demonstrate the synthetic application of this methodology further, gram scale reactions for the synthesis of compounds **5e**, **5i** or **5t**) were conducted, and comparable yields were still obtained.

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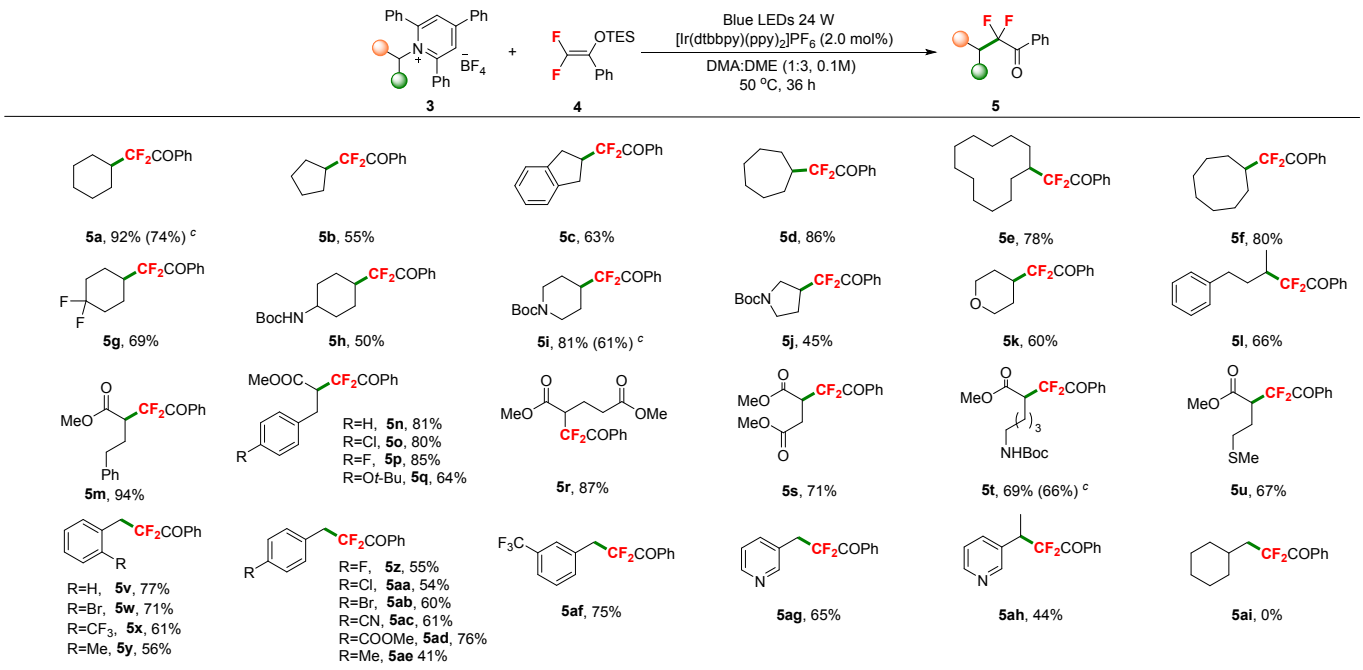
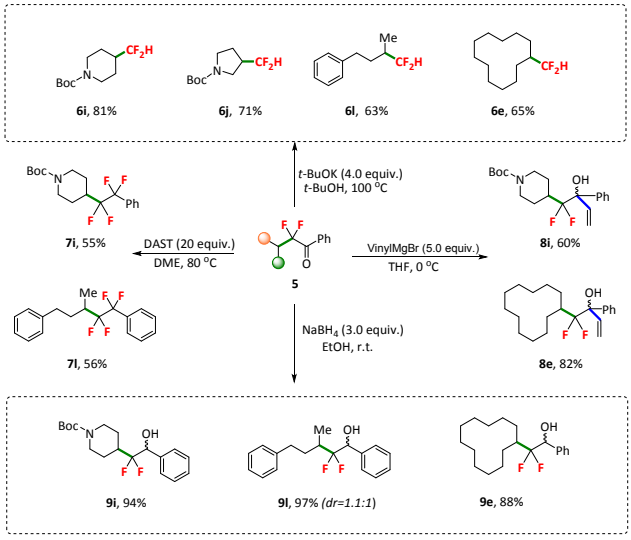
Table 2. Scope of the Visible Light Promoted Deaminative Difluoroalkylations. [a] [b]



[a] Reaction conditions (unless otherwise specified): **3** (0.2 mmol, 1.0 equiv.), **4** (0.4 mmol, 2.0 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.004 mmol, 2.0 mol%), DMA/DME (2.0 mL, v/v=1:3), Blue LEDs 24 W, 50 °C, 36 h, under argon atmosphere. [b] Yield of isolated product. [c] **3** (4.0 mmol, 1.0 equiv.), **4** (8.0 mmol, 2.0 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.08 mmol, 2.0 mol%), DMA/DME (16.0 mL, v/v=1:3), 50 °C, Blue LEDs 24 W, 72 h.

Having established suitable reaction conditions for the preparation of compounds **5**, the utility of this reaction can also be demonstrated by the further transformations. As shown in **Scheme 2**, compounds **5** can serve as versatile building blocks for the diversity-oriented synthesis. For instance, upon treatment with *t*-BuOK, the phenyl acyl (C_6H_5CO) can be easily removed to access difluoromethylated analogies in good yields which provide an alternative method for deoxyfluorination of aldehydes. The tetrafluoroethylene bridge (-CF_2CF_2-), which has many applications in both material and agrochemical, can be easily prepared by fluorination of the carbonyl group with DAST in moderate yields. The ketone could react with VinylMgBr, and versatile building blocks **8** could be provided in good yields. The compounds could also be converted to alcohols via reduction with high yields.

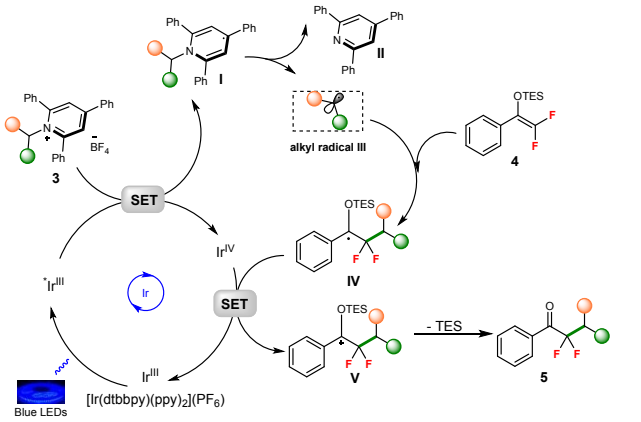
To shed light on the mechanism of this transformation, a series of experiments were conducted. The reaction was totally suppressed by the addition of a radical scavenger TEMPO (100 mol%), which suggests that the involvement of radical intermediates is likely during the reaction (for details, see ESI). A radical clock experiment employing Katritzky salts **10** as a substrate produced the ring opening product **11** in 14% yield (for details, see ESI). Finally, the calculated quantum yield value of Φ = 0.15, indicating the involvement of radical chain progress is unlikely.



Scheme 2 Transformation of Compounds 5.

On the basis of these preliminary results and previous reports, a plausible mechanism was proposed in **Scheme 3** for this transformation. Firstly, irradiation with visible light excites $[Ir(dtbbpy)(ppy)_2][PF_6]$ into a strong reductive species (i.e., $*[Ir(dtbbpy)(ppy)_2][PF_6]$ that performs a single electron transfer (SET) process to generate alkyl radical from Katritzky salt (**3**). Subsequent regioselective addition of alkyl radical to (**4**) lead to the carbon-radical intermediate (**IV**), which are further oxidized

to cation species (**V**) via a SET process with strong oxidant [$Ir^{(IV)}$]. Finally, the desiliconisation of (**V**) could afford the corresponding difluoroalkylated product (**5**).



Scheme 3 Proposed Plausible Reaction Mechanism.

In summary, a simple method for the visible light promoted deaminative difluoroalkylation reaction was developed. This protocol is characteriazed by mild reaction conditions and broad substrate scope, which converted a diverse array of amine-containing molecules to the alkyl-CF_2COPh products. Moreover, the resulting products can serve as versatile building blocks for the diversity-oriented synthesis, and a variety of structurally novel and interesting difluoro-containing moieties can be easily obtained by further transformations, therefore providing a facile route for applications in medicinal chemistry, life science and agrochemical.

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Conflicts of interest

There are no conflicts to declare.

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