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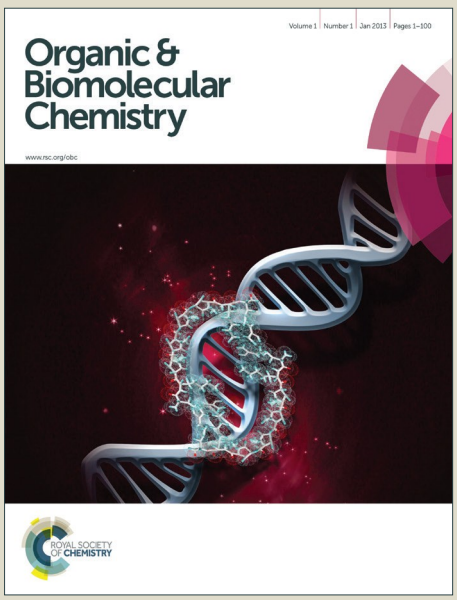

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Visible-Light Photoredox Intramolecular Difluoroacetamidation: Facile Synthesis of 3,3-Difluoro-2-Oxindoles from Bromodifluoroacetamides

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We report an operationally simple, visible-light-driven protocol for intramolecular C−H difluoroacetamidation of arenes for the synthesis of biological relevant 3, 3-difluoro-2-oxindoles at room temperature. Using *fac*-Ir(ppy)$_3$ as a photocatalyst and a 3W blue LED as a light source, an array of difluoroxindoles were prepared from rapidly available tertiary aryl bromodifluoroacetamides in moderate to excellent yields.

Fluorine-containing organic molecules can be extensively found in a number of biologically active natural products, pharmaceutically relevant candidates, agrochemical reagents, and functional materials.[1] It is an important and general strategy to introduce fluorine and fluorinated substitutes in the small molecule for structure-based drug development and pharmaceutical research. The fluorinated functional groups change their physiochemical properties significantly due to the enhanced chemical, physical, and metabolic stability of the fluorinated moiety.[2] Accordingly, there has been great interest and substantial effort in the synthesis of fluorine-containing small molecules.[3] Especially, various synthetic methods for the introduction of the *gem*-difluoromethylene group (CF_2) into organic compounds that have been well developed are consider as useful synthesis strategy for modification of biologically active compounds.[4]

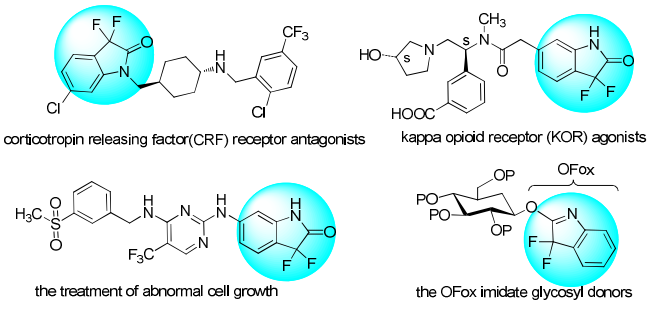
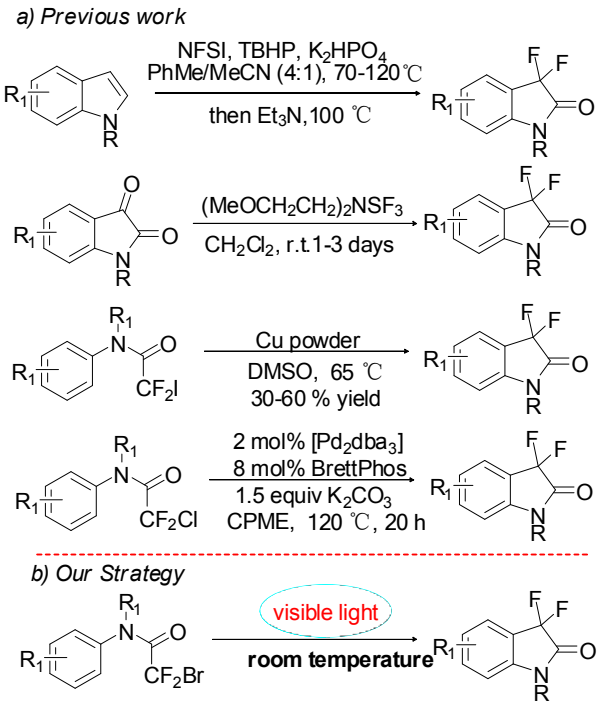


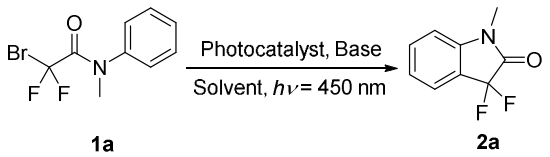
Fig. 1. Examples of biologically significant molecules containing 3, 3-difluoro-2-oxindoles.

Derivatives of oxindoles are an extremely important class of compounds due to their frequent appearance in a variety of naturally occurring compounds and their wide range of biological activities. Such as these kinds of compounds have been shown to display antimicrobial, antiviral, anticancer, and antiinflammatory activities.[5] The 3, 3-difluoro-2-oxindole ring system are of significant biological importance as bioisoteric analogues for biological studies in development of potential medicinal agents. Up to now, numerous natural compounds containing the 3, 3-difluoro-2-oxindoles ring moieties revealed potential utilities in biomedical studies.[6] Thus, search for efficiently synthetic methodologies to prepare these substrates are very meaningful for the detailed studies of their therapeutic application.[7] Generally, these types of difluoroxindoles could be obtained via nucleophilic fluorination of the corresponding isatin derivatives with diethylaminosulfur trifluoride (DAST) or Deoxofluor,[8a-8c] or by electrophilic fluorination of indoles with Selectfluor or NFSI.[8d] It is also possible to access difluoroxindoles via Cu-mediated intramolecular cyclization of iododifluoroacetamides in moderate yield.[9a] Very recently, Buchwald *et al.* used Pa-catalyzed C-H difluoroalkylation and BrettPhos as crucial ligand to construct difluoroxindoles derivatives.[9b] These valuable protocols have proven to be efficient for the preparation this kind of compounds. However, instability of the requisite reagents and bad to modest functional-group tolerance, expensive fluorination reagents, the production of a large excess of wastes from reaction systems, the synthesis difficulty of the required starting materials, as well as the requirement for rather high reaction temperature et al. remain impediments of these approaches. Therefore the development of more efficient and practical strategies in these areas is still highly desirable.



Scheme 1. Different protocols for the syntheses of 3, 3-difluoro-2-oxindoles.

Table 1. Optimization of reaction conditions



1a **2a**

Entry[a]	Solvent	Photocatalyst	Base	Yield(%)[b]
1	DMF	$Ru(bpy)_3Cl_2·6H_2O$	Na_2CO_3	58
2	DMF	$Ru(phen)_3Cl_2$	Na_2CO_3	62
3	DMF	$Re[phen(CO)_3]NCS$	Na_2CO_3	Trace
4	DMF	TBA-eosinY	Na_2CO_3	Trace
5	DMF	*fac*-$Ir(ppy)_3$	Na_2CO_3	91
6	CH_3CN	*fac*-$Ir(ppy)_3$	Na_2CO_3	Trace
7	DMF	*fac*-$Ir(ppy)_3$	Na_2HPO_4	72
8	DMF	*fac*- $Ir(ppy)_3$	$NaHCO_3$	41
9	DMF	*fac* -$Ir(ppy)_3$	K_2CO_3	59
10	DMF	*fac* -$Ir(ppy)_3$	K_2HPO_4	93
11[c]	DMF	--	K_2HPO_4	N.D.[e]
12[d]	DMF	*fac* -$Ir(ppy)_3$	K_2HPO_4	N.D.

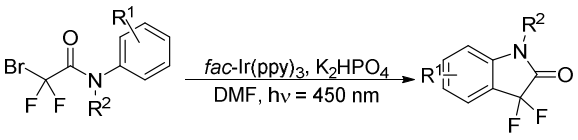
[a] Reaction conditions: a mixture of **1a** (0.20 mmol), base (0.24 mmol, 1.2 equiv), and photocatalyst (0.5 mol %) in solvent was irradiated with a 3 W blue LEDs at room temperature for 24 h [b] Isolated yield. [c] Irradiated without *fac*-$Ir(ppy)_3$. [d] The reaction was conducted in dark. [e] N.D. = not detected. DMF = *N, N*- dimethylformamide

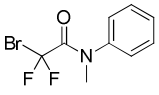
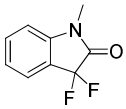
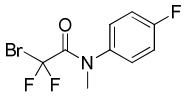
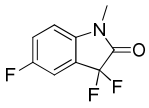
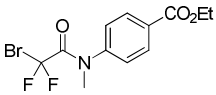
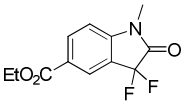
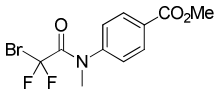
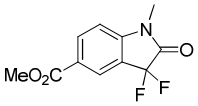
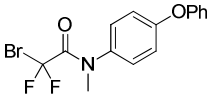
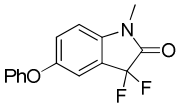
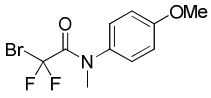
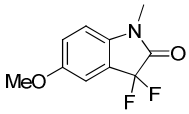
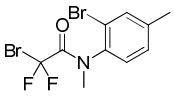
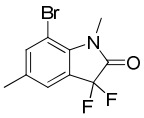
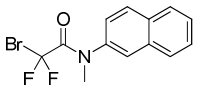
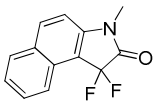
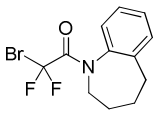
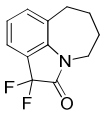
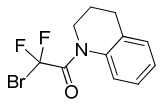
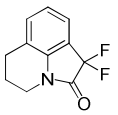
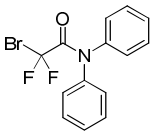
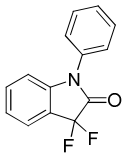
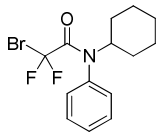
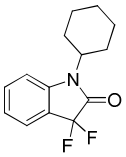
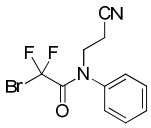
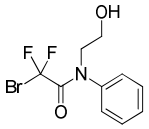
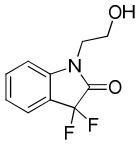
For the past few years, photocatalysis reactions, especially the use of visible light as a nearly non-polluting energy source to enable sustainable organic synthesis have attracted great interest.[10] Visible-light photocatalysis reactions avoided the disadvantage of high-energy ultraviolet radiation, and as the high transparency of most organic compounds in visible-light region, it is helpful to minimize side reactions which is often associated with the employment of UV light. Photoredox catalysis with transitional metal complexes has emerged as a powerful tool for redox reactions due to its ability to cause efficient photo-induced electron transfer processes under mild conditions. For instance, *fac*-$Ir(ppy)_3$, an Ir polypyridine complexe with high reducibility in the excited state has been well demonstrated by some valuable work that generated carbon-centered radicals from organohalides.[11] During the course of our investigations on the applications of photoredox catalysis in organic synthesis,[11h,12] we found a promising approach for synthesizing an array of substituted difluoroacetamidated arenes *via* intermolecular radical addition to arenes.[12a] We speculated that this strategy might also be effective for providing intramolecular aminocarbonyldifluoromethyl radical addition to arenes to afford biologically relevant 3,3-difluoro-2-oxindoles.[13]

Herein, We started our investigation by exploring the reaction of 2-bromo-2,2-difluoro-*N*-methyl-*N*-phenylacetamide (**1a**) in various photochemical conditions toward the synthesis of 3,3-difluoro-2-oxindoles. It was encouraging to see that the aimed product **2a** was obtained in 58% yield after 24 hours' irradiation (blue LEDs, λ = 450 nm) at room temperature when the reaction was performed in *N,N*-dimethylformamide (DMF) with $Ru(bpy)_3Cl_2·6H_2O$ as photocatalyst and Na_2CO_3 as base (Table 1, entry 1). Several photocatalysts were applied to this reaction to replace $Ru(bpy)_3Cl_2·6H_2O$ (Table 1, entries 2-5). It was found that when $Ru(phen)_3Cl_2$ was applied in this reaction conditions, the reaction yields rose to 62% (Table 1, entry 2), but when $Re[phen(CO)_3]NCS$ or organic photocatalyst TBA-eosinY was tested in the reaction (Table 1, entries 2-3), just trace amount of desired product was found. When *fac*-$Ir(ppy)_3$ was used in the reaction, the yields rose to 91% dramatically. Therefore we choose *fac*-$Ir(ppy)_3$ as the ideal photocatalyst. Other different bases including Na_2HPO_4, $NaHCO_3$, K_2CO_3, K_2HPO_4 were then tested (Table 1, entries 6-10), and the best result was achieved when K_2HPO_4 was introduced to the system. In this case we obtained the desired product **2a** in 93% isolated yield. In addition, when the reaction was carried out in the absecne of *fac*-$Ir(ppy)_3$ or in the dark (Table 1, entry 11 and 12), no conversion could be observed, which indicated that the reaction was indeed a visible-light-driven photoredox process.

With the optimized condition in hand, we examined the substrate scope of this visible-light-driven synthesis of 3,3-difluoro-2-oxindoles. A broad array of substituted 2-bromo-2,2-difluoro-*N*-phenylacetamides can efficiently convert to the corresponding 3,3-difluoro-2-oxindoles derivatives in moderate to excellent yields (Table 2, entries 1-14). When the electron-withdrawing groups such as fluoro, ethoxycarbonyl and methoxycarbonyl which located at *para* positions of the phenylacetamide, the aimed product **2b**, **2c**, **2d** can be produced

Table2 Scope survey of visible-light catalyzed synthesis of 3,3-difluoro-2-oxindoles.[a,b]

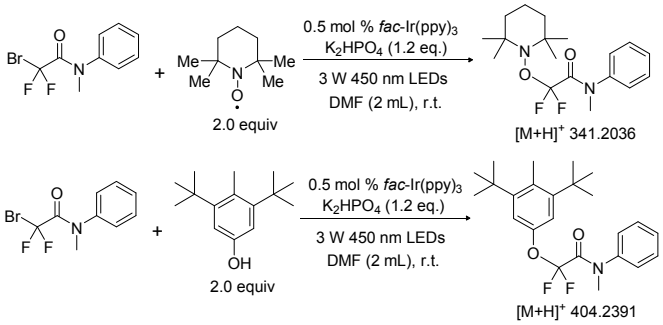


Entry	Substrate	Product	Yield (%) [c]	Entry	Substrate	Product	Yield (%) [c]
1	 **1a**	 **2a**	**93**	2	 **1b**	 **2b**	**97**
3	 **1c**	 **2c**	**93**	4	 **1d**	 **2d**	**90**
5	 **1e**	 **2e**	**76**	6	 **1f**	 **2f**	**69**
7	 **1g**	 **2g**	**40**	8	 **1h**	 **2h**	**57**
9	 **1i**	 **2i**	**79**	10	 **1j**	 **2j**	**92**
11	 **1k**	 **2k**	**88**	12	 **1l**	 **2l**	**80**
13	 **1m**	 **2m**	**85**	14	 **1n**	 **2n**	**90**

[a] Reaction conditions: a mixture of **1a** (0.20 mmol, 1.0 equiv), K_2HPO_4 (0.24 mmol, 1.2 equiv) and photocatalyst *fac*-Ir(ppy)$_3$ (0.5 mol %) in DMF (3 mL) was irradiated with a 3 W blue LEDs at room temperature for 24 h [b] Yield of isolated product.

smoothly in excellent yields (Table 2, entries 2-4). Moreover, this kind of reaction was successfully applied to the 2-bromo-2,2-difluoro-*N*-phenylacetamides with electron-donating groups at the arenes (Table 2, entries 5 and 6). The substrate with di-substituted aniline **1g** was also compatible with this new visible-light-driven cyclization approach, although the reaction proceeded less efficiently than mono-substituted cases (Table 2, entry 7). In general, arenes bearing electron-withdrawing substituents afforded higher yields than those with electron-donating groups. The lower transformation of 2-bromo-2,2-difluoro-*N*-phenylacetamides with electron-donating groups may be attributed to the inefficient electron transfer between the excited photocatalyst and the substrates.

Next, we examined 2-bromo-2,2-difluoroacetamides with different amine moieties instead of *N*-methylaniline. The reactions of 2-bromo-2,2-difluoro-*N*-methyl-*N*-(naphthalen-2-yl)acetamide (**1h**) generated **2h** as the only product (Table 2, entry 8). When tetrahydrobenzoazepine (**1i**) and tetrahydroquinoline (**1j**) were employed as the amine moiety of the substrate, tricyclic products **2i** and **2j** were formed in 79% and 92% yields, respectively (Table 2, entries 9 and 10). In addition, 2-bromo-2,2-difluoro-*N*-phenyl-acetamides possessing *N*-protecting groups such as phenyl(**1k**), cyclohexyl(**1l**), 2-cyanoethyl (**1m**) and 2-hydroxyethyl (**1n**) also resulted in satisfactory yields, highlighting the potential of the method in organic synthesis.

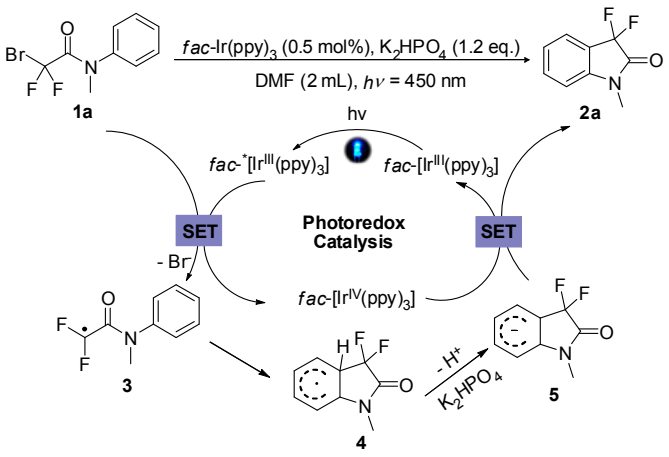


Scheme 3. Mechanism investigation

In order to understand the reaction mechanism and to verify the generation of the 2,2-difluoro-*N*-methyl-*N*-phenylacetamide radical **3** at the initial step of the reaction, the radical inhibitors such as BHT and TEMPO were introduced into the photochemical system, and no 3,3-difluoro-2-oxindole **2a** was detected in both cases. To our delight, the adduct of 2,2-difluoro-*N*-methyl-*N*-phenylacetamide radical **3** with the radical inhibitors were detected by ESI-HRMS, thus providing straightforward evidence of the formation of the radical **3** (Scheme 3).

Based on the radical trapped experimental results and our previous work in this field,[12] we proposed a possible mechanism. Visible-light irradiation of the photoredox catalyst *fac*-$Ir^{III}(ppy)_3$ produced the excited $^3[fac\text{-}Ir^{III}(ppy)_3]^*$, which can reduce 2-bromo-2,2-difluorophenylacetamide **1a** by single electron transfer (SET). The SET procedure generates electron-deficient radical **3** along with *fac*-$Ir^{IV}(ppy)_3$. Then intramolecular π-addition of the radical **3** produces a cyclohexadiene radical **4**. The α-proton of radical **4** is highly acidic[14] because it is activated by both the incorporation of the 2,5-cyclohexadienyl radical moiety into a larger aromatic system and the negative inductive effect of difluoroacetamide. Therefore, deprotonation of 4 should be occurred efficiently and give radical anion **5** with the aid of K_2HPO_4 . Finally, SET from radical anion 5 to *fac*-$Ir^{IV}(ppy)_3$ affords the desired product **2a** and regenerates the photocatalyst.

In summary, we have developed a catalytic and efficient method for the construction of 3,3-difluoro-2-oxindoles *via* visible light photocatalysis for the first time. The highlight of this photo-reaction is the operational simplicity, avoidance of



Scheme 4. Proposed Mechanism Cycle.

expensive fluorination reagent, complex ligand and high temperature. Moreover, this method is also an efficient method for the C-H difluoroalkylation with readily available starting materials.

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Notes and references

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