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A room temperature decarboxylation/C–H functionalization cascade by visible-light photoredox catalysis†

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An elegant approach to quaternary oxindole formation has been developed through a room temperature decarboxylation/radical C–H functionalization by visible-light photoredox catalysis.

The mild and efficient construction of multiple C–C bonds in a tandem process is a perennial topic of interest for organic chemists.[1] Carboxylic acid is one of the most common and readily available functional groups in chemistry.[2] In this context, we focused our attention on the development of visible-light-mediated decarboxylative tandem reactions,[3] as visible-light photoredox catalysis has received considerable attention in the last five years due to its significant advances compared with traditional photochemistry.[4] To the best of our knowledge, the photosensitized decarboxylation of carboxylic acids or the corresponding derivatives usually requires high-energy light irradiation.[5] Okada's group has reported a nice visible-light-mediated decarboxylative Michael addition of *N*-(acyloxy)phthalimides to electron deficient olefins by irradiation with a 500 W xenon lamp.[6] The phenyliodine(III) diacetate (DIB) is widely used in organic synthesis due to its easy availability and environmentally friendly nature,[7] but the decarboxylation of carboxylic acids with DIB typically requires high-energy light (and therefore the requirement of specialized photoreactors)[8] or elevated temperature (110–160 °C).[9,10] Herein, we document a novel visible-light-promoted room temperature decarboxylative tandem coupling of phenyliodine(III) dicarboxylate. This strategy provides a facile approach to 3,3-disubstituted oxindole, which is a privileged heterocyclic scaffold in a wide range of natural products and biologically active drugs (Fig. 1).[11] Although notable progress has been achieved in the construction of 3,3-disubstituted oxindoles, the reaction conditions are usually unsatisfactory (high temperature, strong base, high catalyst loading).[12] Therefore, the development of a convenient access to the family of oxindoles is of great interest.[13]

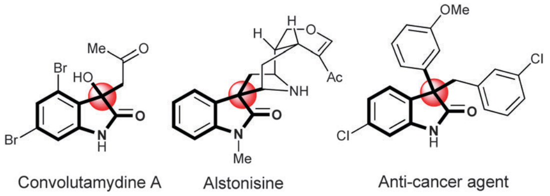
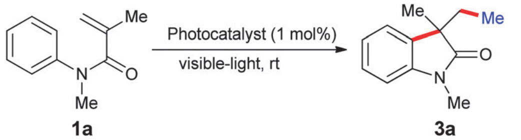


Fig. 1 The significance of the 3,3-disubstituted oxindole motif in natural products and biologically active reagents.

Initially, *fac*-Ir(ppy)$_3$ was chosen as the photocatalyst for the tandem reaction of *N*-methyl-*N*-phenylmethacrylamide **1a** and PhI(OAc)$_2$ **2a**.[14] To our delight, the decarboxylation/radical C–H functionalization cascade can occur at room temperature by irradiation with a 35 W fluorescent light bulb (Table 1, entry 1). Given the potential utility of this protocol, we focused our attention on optimizing the reaction conditions (Table 1, also see ESI† for details). When Ir(ppy)$_2$(dtbbpy)BF$_4$ and Ru(bpy)$_3$Cl$_2$ were used instead of *fac*-(ppy)$_3$, the yields were decreased (entries 4 and 5).[15] It was found that the optimal reaction should be catalyzed by 1 mol%

Table 1 Optimization of the tandem reaction[a]



Entry	Photocatalyst	Light	Solvent	*T*/h	Yield[b] (%)
1	*fac*-Ir(ppy)$_3$	+	MeCN	48	72
2	***fac*-Ir(ppy)$_3$**	**+**	**DMF**	**24**	**83**
3	*fac*-Ir(ppy)$_3$	+	DCM	36	66
4	Ru(bpy)$_3$Cl$_2$	+	DMF	24	30
5	Ir(ppy)$_2$(dtbbpy)BF$_4$	+	DMF	24	36
6	—	+	DMF	72	N.P.[c]
7	*fac*-Ir(ppy)$_3$	–	DMF	72	N.P.[c]

[a] Reaction conditions: **1a** (1.0 equiv.), DIB **2a** (3.0 equiv.), *fac*-Ir(ppy)$_3$ (1 mol%), DMF, 35 W fluorescent light bulb, rt. [b] Isolated yields. [c] N.P. no product. DMF = *N*,*N*-dimethylformamide; DCM = dichloromethane.

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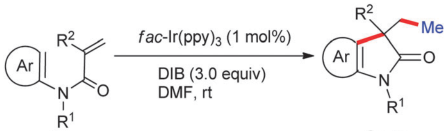
fac-Ir(ppy)$_3$ with DMF as the solvent by irradiation with visible light at room temperature (entry 2). If either visible-light or *fac*-Ir(ppy)$_3$ was absent, no **3a** could be formed (entries 6 and 7).

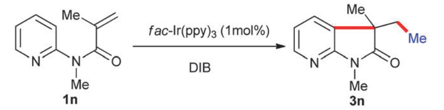
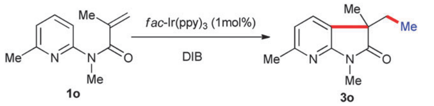
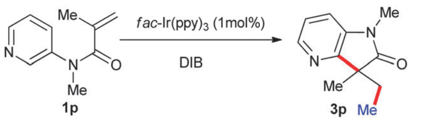
With the optimal reaction conditions in hand, the substrate scope was investigated, and the corresponding results are listed in Table 2. When various *N*-protected substrates **1a–e** were employed, the desired products **3a–e** could be obtained in 73–90% yields (entries 1–5). It was also found that the substrate bearing a strong electron-withdrawing group (**1j**) gave unsatisfactory results (entry 10), and **1f–i** could afford the desired products in good yields (entries 6–9). When the R^2 was switched from the methyl group to other alkyl groups, they uniformly furnished the desired products **3k–m** in good yields enabled by irradiation with visible-light (entries 11–13). Moreover, the tandem reaction had excellent chemoselectivity when different double bonds were incorporated in one substrate (entry 12). Notably, the pyridine group was also effective for the tandem alkylheteroarylation reaction (**1n–p**), and **1p** had good regioselectivity with only C2 C–H functionalization (entries 14–16).

Next, we applied this protocol to a variety of phenyliodine(III) dicarboxylates, and the results are summarized in Scheme 1. Carboxylic acids could easily undergo ligand metathesis with DIB, and the resulting compounds can be used without further purification. As can be seen in Scheme 1, the decarboxylation of carboxylic acids has substantial scope and the new method can expand the structural diversity of 3,3-disubtituted oxindoles. Various primary, secondary and tertiary aliphatic carboxylic acids bearing different functional groups were found to be compatible, and they can uniformly afford the desired oxindoles in good yields. Especially, when β-mono-substituted carboxylic acids were employed, **4d–e** could be obtained in satisfactory yields without the 1,2-H shift. Importantly, oleic acid was also effective to undergo the decarboxylation/C–H functionalization cascade (**4h**) while no intramolecular radical addition product of oleic acid was observed. It is worth mentioning that the introduction of an electron-withdrawing trifluoromethyl (CF$_3$) group into a known scaffold can tune the biological activity.[16] Therefore, some aliphatic carboxylic acids involving the CF$_3$ group were subjected to the optimal reaction conditions. Much to our delight, trifluoropropanoic acid and trifluorobutanoic acid except trifluoroacetic acid could proceed the tandem reaction smoothly (**4i–k**). Additionally, the α-chloropropanoic acid was also compatible

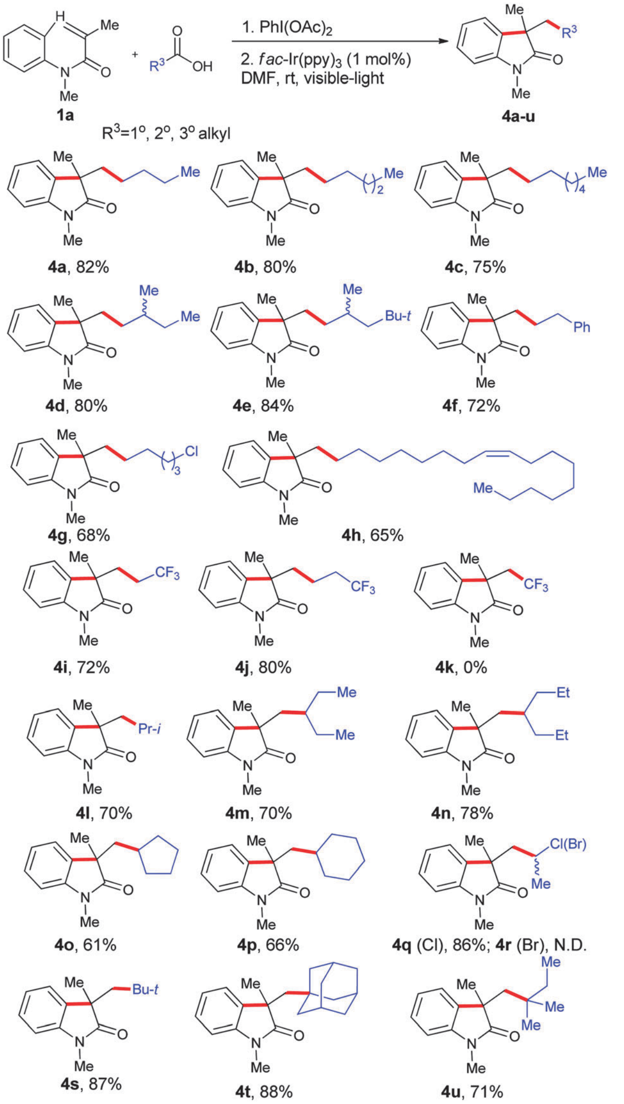
Table 2 The reaction scope^a



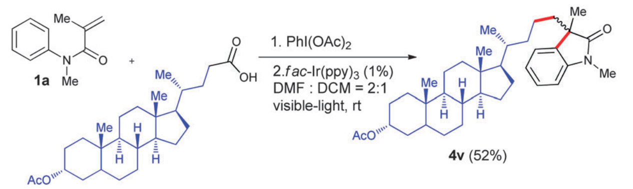
1a-q **3a-q**

Entry	Ar	R^1	R^2	1	3	Yield^b (%)
1^c	C$_6$H$_5$	Me	Me	**1a**	**3a**	83
2^d	C$_6$H$_5$	Et	Me	**1b**	**3b**	80
3^d	C$_6$H$_5$	i-Pr	Me	**1c**	**3c**	88
4^d	C$_6$H$_5$	Bn	Me	**1d**	**3d**	73
5^c	C$_6$H$_5$	Ph	Me	**1e**	**3e**	90
6^d	4-Me-C$_6$H$_4$	Me	Me	**1f**	**3f**	80
7^d	4-OMe-C$_6$H$_4$	Me	Me	**1g**	**3g**	76
8^d	4-Cl-C$_6$H$_4$	Me	Me	**1h**	**3h**	85
9^d	4-Br-C$_6$H$_4$	Me	Me	**1i**	**3i**	81
10^d	4-F-C$_6$H$_4$	Me	Me	**1j**	**3j**	<10
11^d	C$_6$H$_5$	Me	Et	**1k**	**3k**	82
12^c	C$_6$H$_5$	Me	Allyl	**1l**	**3l**	83
13^d	C$_6$H$_5$	Me	Bn	**1m**	**3m**	73
14^e	 fac-Ir(ppy)3 (1mol%) DIB **1n** **3n**					61
15^e	 fac-Ir(ppy)3 (1mol%) DIB **1o** **3o**					70
16^e	 fac-Ir(ppy)3 (1mol%) DIB **1p** **3p**					48

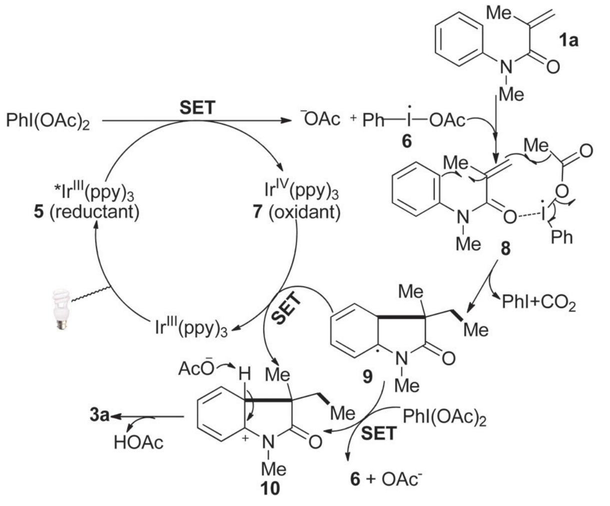
^{a} Reaction conditions: **1** (0.3 mmol), DIB **2a** (3.0 equiv.), *fac*-Ir(ppy)$_3$ (1 mol%), DMF (2.0 mL), 35 W fluorescent light bulb. ^{b} Isolated yields. ^{c} 24 h. ^{d} 36 h. ^{e} The reaction was carried out at 40 °C with 3.0 equiv. K$_2$HPO$_4$ for 40 h.



Scheme 1 The scope of phenyliodine(III) dicarboxylate. Reaction conditions: (1) aliphatic carboxylic acid (2.0 equiv.), PhI(OAc)$_2$ (1.0 equiv.); (2) **1a** (0.3 mmol), phenyliodine(III) dicarboxylate (3.0 equiv.), *fac*-Ir(ppy)$_3$ (1 mol%), DMF (2.0 mL), rt, 24–36 h, 35 W fluorescent light bulb. Isolated yields.



Scheme 2 The reaction of **1a** with the lithocholic acid derivative.



Scheme 3 Plausible mechanism.

by irradiation with visible-light, and the desired product **4q** could be obtained in 86% yield. However, when benzoic acid was used to undergo ligand metathesis with DIB, the resulting $PhI(OCOPh)_2$ did not work under the optimized reaction conditions due to its slower decarboxylation process and the decreased nucleophilicity of the aryl radical. To further demonstrate the generality of our protocol, lithocholic acid was tested, and it was found to stereoselectively undergo the tandem reaction to afford the desired oxindole **4v** (Scheme 2).

The plausible mechanism is shown in Scheme 3. Firstly, the excited-state $^*Ir^{III}(ppy)_3$ **5** that is formed under irradiation by visible-light could donate an electron to $PhI(OAc)_2$, giving the radical species **6**[17,8c] and a strong oxidant $Ir^{IV}(ppy)_3$ **7**[18] ($E_{1/2\text{red}} = +0.77$ V *vs.* SCE in CH_3CN). Subsequently, the carbonyl group-coordinated iodine radical species **8** could be yielded, which may undergo a decarboxylation/radical C–H functionalization cascade to give **9** and extrude CO_2 as well as PhI. Then, the resulting cyclohexadienyl radical **9** may be converted to the corresponding cation **10** by single electron transfer (SET) with $^{IV}Ir(ppy)_3$ **7** and complete the photoredox cycle. Alternatively, the cation **10** may be formed by SET with $PhI(OAc)_2$. Finally, **10** could be easily deprotonated by the acetate anion (OAc^-), generating the desired product **3a**.

In summary, we have developed an excellent tandem protocol for the formation of quaternary oxindole by means of visible-light photoredox catalysis, which possesses the ability to quickly couple to a number of readily available primary, secondary and tertiary aliphatic carboxylic acids. Further synthetic applications of visible-light-promoted tandem reactions to biologically interesting compounds and mechanistic work of the photoredox catalysis are under way in our lab.

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