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COMMUNICATION

Synthesis of oxindoles *via* visible light photoredox catalysis†

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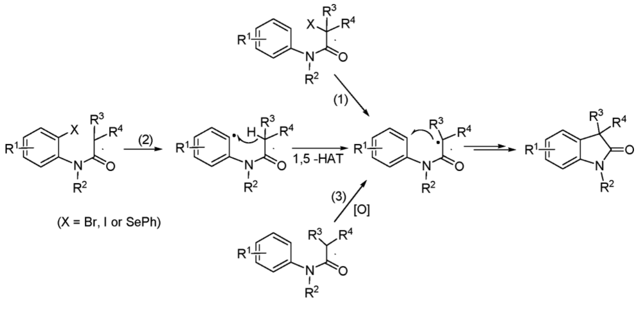
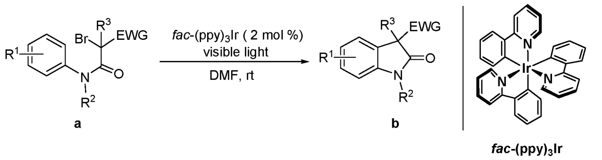
2-Electron-withdrawing-group-substituted 2-bromoanilides can be converted to the corresponding 3,3-disubstituted oxindoles with high efficiency under visible light irradiation by using *fac*-Ir(ppy)$_3$ as the photoredox catalyst. This protocol is suitable for the synthesis of oxindoles with chloro and bromo atoms attached to the phenyl ring.

Substituted oxindoles have long been of synthetic interest due to their existence in many biologically active molecules as well as their usefulness as important synthetic building blocks.[1] One effective methodology to construct the substituted oxindole ring structure involves the intramolecular homolytic aromatic substitution of hydrogen on the phenyl ring by amidoalkyl radicals (Scheme 1).[2] The amidoalkyl radicals can be generated by (1) halogen atom or phenylseleno group abstraction;[3,4] (2) generation of an aryl radical from *o*-halo-anilides followed by 1,5-hydrogen atom translocation (1,5-HAT);[5] or (3) single-electron oxidation of anilides.[6,7] These methods have been employed to prepare a variety of 3,3-disubstituted oxindoles. Herein, we wish to report a new protocol for the synthesis of substituted oxindoles based on approach (1) in Scheme 1 and visible light photoredoxcatalysis (Scheme 2).

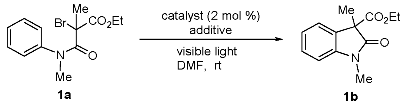


Scheme 1



Scheme 2

Table 1 Screening of the reaction conditions[a]



Entry	Catalyst	Additive (equiv.)	Conversion (%)	Yield (%)[b]
1	Ru(bpy)$_3$Cl$_2$	Et$_3$N (2)	70	35
2	Ru(bpy)$_3$Cl$_2$	^{i}Pr$_2$NEt (2)	100	60
3	Ru(bpy)$_3$Cl$_2$	Ph$_3$N (2)	17	14
4	Ru(bpy)$_3$Cl$_2$	none	<1	N.D.[c]
5	Ir(ppy)$_2$(dtbpy)PF$_6$	Ph$_3$N (2)	80	71
6	*fac*-(ppy)$_3$Ir	2,6-lutidine (2)	100	95
7	***fac*-(ppy)$_3$Ir**	**none**	**100**	**95**
8	*fac*-(ppy)$_3$Ir	none	*<1*[d]	N.D.[c]
9	none	none	<1	N.D.[c]

[a] A solution of 0.12 mmol of **1a** and 2.4 × 10^{-3} mmol of catalyst in DMF (2.4 mL) was irradiated at room temperature under argon atmosphere for 12 h. [b] Isolated yield. [c] Not determined. [d] Control experiment without irradiation under the otherwise same conditions.

Photocatalysis has long been of interest to organic chemists due to its capacity to initiate organic reactions in a green and sustainable way.[8] The recent employment of transitional metal photocatalysts such as Ru(bpy)$_3^{2+}$, Ir(ppy)$_2$(dtbpy)$^+$ and *fac*-Ir(ppy)$_3$ *etc.* enables the photo-induced electron transfer/energy transfer process to take place at visible light wavelengths, and hence significantly broadens the scope of photochemical reactions.[9] The studies by MacMillan *et al.*,[10] Stephenson *et al.*,[11] and Gagné *et al.*[12] demonstrate that visible light photoredox catalysis constitutes a mild and efficient means to generate free radicals from activated carbon–halogen bonds. This method is advantageous compared with the commonly used Bu$_3$SnH-based method in that the use of stoichiometric amounts of toxic reagents can be avoided. As a continuation of our interest in the synthesis of oxindoles,[13] we envisaged that this strategy could be applied to oxindole synthesis. As only the activated carbon–halogen bond would be cleaved under the reaction conditions, we hoped that substrates with a halogen atom attached to the phenyl ring could be tolerated.

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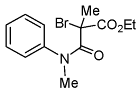
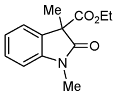
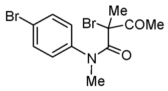
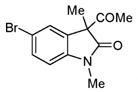
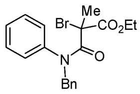
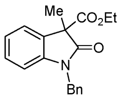
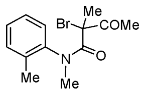
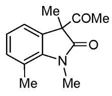
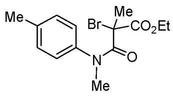
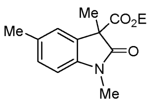
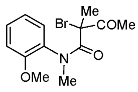
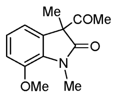
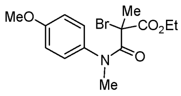
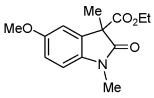
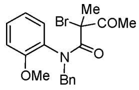
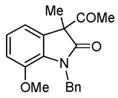
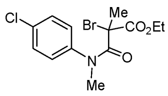
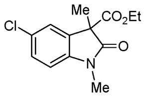
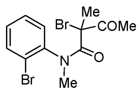
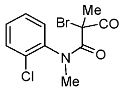
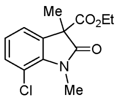
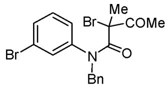
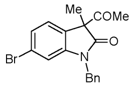
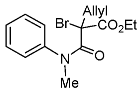
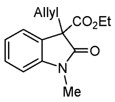
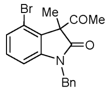
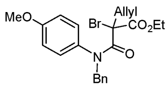
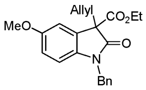
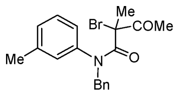
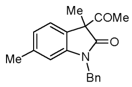
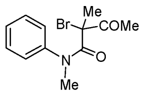
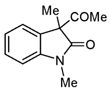
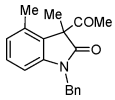
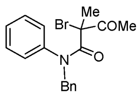
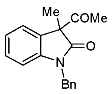
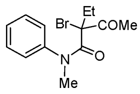
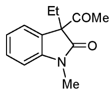
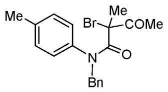
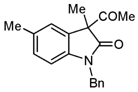
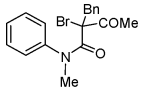
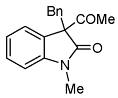
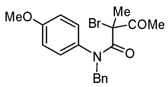
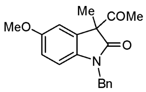
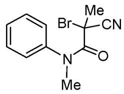
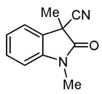
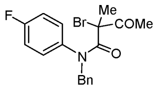
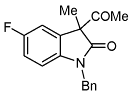
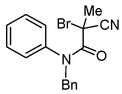
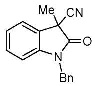
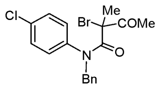
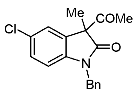
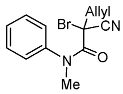
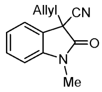
† Electronic supplementary information (ESI) available: General experimental procedure, characterization data, ^{1}H NMR and ^{13}C NMR spectra of compounds **1b–26b**. See DOI: 10.1039/c1ob06652h

Table 2 Synthesis of 3,3-disubstituted oxindoles **b** from compounds **a**[a]

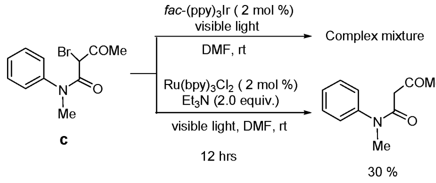
Entry	Substrate	Product(s)	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **1b**	95	15	 **15a**	 **15b**	81
2	 **2a**	 **2b**	88	16	 **16a**	 **16b**	80
3	 **3a**	 **3b**	95	17	 **17a**	 **17b**	93
4	 **4a**	 **4b**	94	18	 **18a**	 **18b**	81
5	 **5a**	 **5b**	93	19	 **19a**	Mixture[c]	—
6	 **6a**	 **6b**	80	20	 **20a**	 **20b**	28/70
7	 **7a**	 **7b**	98			 **20b'**	
8	 **8a**	 **8b**	85	21	 **21a**	 **21b**	27/64
9	 **9a**	 **9b**	96			 **21b'**	
10	 **10a**	 **10b**	98	22	 **22a**	 **22b**	86
11	 **11a**	 **11b**	95	23	 **23a**	 **23b**	87
12	 **12a**	 **12b**	98	24	 **24a**	 **24b**	98
13	 **13a**	 **13b**	96	25	 **25a**	 **25b**	89
14	 **14a**	 **14b**	92	26	 **26a**	 **26b**	92

[a] Reaction conditions: a mixture of 0.12 mmol of **a** and 2.4×10^{-3} mmol of *fac*-Ir(ppy)$_3$ dissolved in 2.4 mL DMF under argon atmosphere was irradiated with a 40 W household fluorescent lamp at room temperature for 12–16 h. [b] Isolated yield. [c] Pure product not obtained.

We commenced our study by subjecting compound **1a** to various irradiation conditions. Three commonly used transitional metal photocatalysts, $Ru(bpy)_3Cl_2$, $Ir(ppy)_2(dtbpy)PF_6$ and *fac*-$Ir(ppy)_3$, were chosen to initiate the reaction, and a 40 W household fluorescent lamp was used as the light source. The results are summarized in Table 1. All these three complexes were capable of effecting the reactions, but *fac*-$Ir(ppy)_3$ was found to be the most effective. With 2 mol% of *fac*-$Ir(ppy)_3$ as the photocatalyst, the reaction was complete in 12 h, giving rise to the desired product **1b** in excellent yield (Table 1, entries 6 and 7). It should be noted that the *fac*-$Ir(ppy)_3$-mediated reaction process does not need tertiary amines as a sacrificial reductant, as *fac*-$Ir(ppy)_3^*$ itself ($E_{1/2}$ = −1.73V, SCE in CH_3CN)[10c] can fulfil the reducing task. In addition, the reaction proceeded equally well in the presence or absence of 2,6-lutidine, indicating that the hydrogen bromide formed during the reaction does not influence the catalytic process.

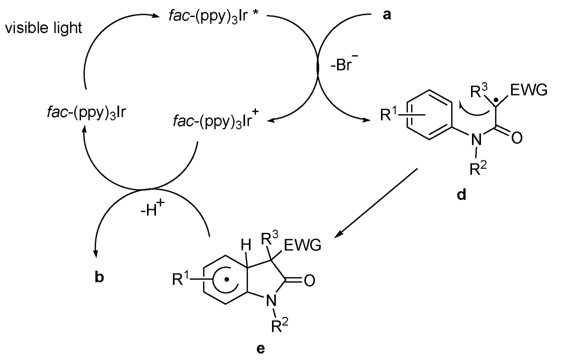
A variety of 3,3-disubstituted oxindoles was then prepared by employing this photoredox protocol. The results are listed in Table 2. The yields were generally high for substrates incorporating an electron-withdrawing group at the α-position, which is a prerequisite for the reaction to take place. It is noteworthy that 3-acetyl substituted oxindoles can be synthesized with high efficiency. These compounds are relatively unstable compared with their 3-ethylcarboxyl and cyano counterparts, and therefore the copper-catalyzed direct oxidative coupling[7] (approach (3), Scheme 1) is not suitable for their preparation. Although the oxidative coupling can be achieved by using Ag_2O as the oxidant, the yields were not satisfactory, and a stoichiometric amount of Ag_2O had to be used.[13a] This obstacle can be overcome by using the mild photochemical procedure. In addition, this protocol is tolerant of substrates containing a bromo atom on the phenyl ring (Table 2, entries 15 and 20), which is liable to loss with conventional free radical methods. However, when the substrate was **19a**, the reaction became complicated, and we failed to obtain the expected oxindole product in pure form (Table 2, entry 19). It is interesting to see that when compounds **20a** and **21a** were used as the substrates, the sterically more hindered **20b′** and **21b′** were obtained as the major products (Table 2, entries 20 and 21).

This protocol was also applied to effecting the reaction of compound **c**. However, we failed to obtain the corresponding 3-acetyl oxindole product from **c** (Scheme 3).



Scheme 3

A possible mechanism was proposed to rationalize the *fac*-$Ir(ppy)_3$-catalyzed photochemical synthesis of 3,3-disubstituted oxindoles (Scheme 4). The reaction is initiated by the single electron transfer between the visible light-excited *fac*-$Ir(ppy)_3$ and substrate **a**, which leads to the formation of the α-carbamoyl radical **d** and the oxidation of *fac*-$Ir(ppy)_3^*$ to *fac*-$Ir(ppy)_3^+$. Cyclisation of **d** results in the formation of **e**. The latter is converted to product **b** *via* single electron oxidation by *fac*-$Ir(ppy)_3^+$ and subsequent deprotonation, with *fac*-$Ir(ppy)_3$ being regenerated at the same time. In the cases of **20a** and **21a**, the unusual regioselectivity suggests that the electronic effect of the bromo or methyl group plays a predominant role in directing the free radical attack on the phenyl ring. Similar *ortho* selectivity has been observed before in studies concerning the addition of aryl radicals to arenes.[14]



Scheme 4

In summary, an efficient protocol based on *fac*-$Ir(ppy)_3$-mediated visible light photoredox catalysis has been developed for the synthesis of 3,3-disubstituted oxindoles from 2-electron-withdrawing-group-substituted 2-bromo-anilides. This procedure is advantageous in terms of high yield, mildness of reaction conditions and tolerance of functional groups.

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Notes and references

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