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PAPER

Visible-light-induced photocatalytic formyloxylation reactions of 3-bromooxindoles with water and DMF: scope and mechanism†

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The formyloxylation reaction of 3-bromooxindoles with water and *N*,*N*-dimethylformamide (DMF) has been developed in the presence of photoredox catalyst *fac*-Ir(ppy)$_3$ under irradiation of visible light at ambient temperature. The reaction provides a straightforward approach to pharmaceutically and synthetically useful 3-formyloxyoxindoles in high yields. The mechanism of this transformation 10 was investigated by fluorescence quenching experiments, "on-off" switching of the light source, labeling experiments, mass spectral analyses and *in situ* IR experiments.

Introduction

A major goal for the advancement of modern organic chemistry is the development of efficient, atom economical, 15 sustainable and selective methodologies that allow the rapid construction of structurally complex and functionally diverse molecular architectures from readily available starting materials.[1,2] In this regard, photoredox catalysis using visible light has emerged as a novel and powerful strategy for 20 molecular and bond activations to construct intricate molecules, and demonstrated great potential during the past several years.[3] The asymmetric alkylation of aldehydes and the [2+2] cycloaddition of enones constitute landmark achievements in this area,[4,5] which enabled other elegant 25 research studies.[6-9] Despite these significant advances, visible light photoredox catalysis has not reached its full potential. The implementation of clean and commercial available compounds into visible light photoredox catalysis toward intricate molecules is highly desirable.

30 *N*,*N*-dimethylformamide (DMF) which often serves as a polar reaction media, is also widely used as a multipurpose feedstock in organic synthesis.[10] Chemists have developed many new methods for the incorporation of DMF into small molecules forming basic building blocks for elaboration into 35 biologically relevant molecules and pharmaceutically important compounds. For example, Chang et al. reported a highly regioselective palladium catalyzed cyanation of aryl C-H bonds by employing DMF as the "C" source and ammonia as the "N" source of the -CN unit.[11] In 2010, the group of 40 Tsuji described an intermolecular hydroamidation of alkynes catalyzed by palladium using DMF as the reaction partner.[12] Notably, Jiao and co-workers realized an alternative way for the direct cyanation of indole and benzofuran rings using DMF as the "CN" source, leading to valuable aryl nitriles with 45 excellent selectivities.[13] Recently, other interesting reactions involving DMF as a precursor were also conducted.[14] The first example applying DMF to visible light photoredox catalysis was reported by the Stephenson group. They successfully converted alcohols to the corresponding bromides and iodides 50 via a Vilsmeier-Haack intermediate under mild reaction conditions.[15,16]

On the other hand, water has often been regarded as an ideal reagent as a result of its "green chemistry" features.[17] We envisioned that the development of new multicomponent 55 reactions that assemble DMF, water and other reactants into valuable compounds under the irradiation of visible light should be highly useful. As part of our ongoing research program directed at the applications of visible light photoredox catalysis for organic synthesis,[18] we disclose 60 herein a novel and efficient visible light induced radical addition/oxidation/hydrolysis cascade which gives 3-formyloxyoxindoles from 3-bromooxindoles, DMF and water (Scheme 1). This transformation can directly install a formyloxy group at the C3-position of oxindoles using DMF 65 as the "H, C, O" source and H$_2$O as the "O" source, and the corresponding products can be used in the synthesis of natural alkaloids and pharmaceuticals.[19-21] Mechanism studies have been performed by fluorescence quenching experiments, "on-off" switching of the light source, labeling experiments, mass 70 spectral analyses and in situ IR experiments.
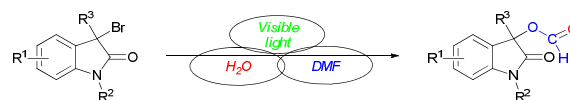
Scheme 1 Concept of the visible-light-induced photocatalytic formyloxylation reactions of 3-bromooxindoles with water and DMF.

75 ## Results and discussion

Reaction optimization

We commenced our investigation of the visible light photoredox three-component reaction using 3,5-dibromo-1,3-

dimethylindolin-2-one **1a** and DMF, along with 2 mol % photocatalyst *fac*-Ir(ppy)₃, and 18 W fluorescent household light bulb. This initial experiment gave the desired product **2a** in 62 % isolated yield after workup (Table 1, entry 1), and the structure of ₅ **2a** was unambiguously established by X-ray crystallographic analysis. Control experiments showed that trace amount of product, or no product at all, was obtained in the absence of either the photocatalyst or light source, which indicated that this transformation proceeded via a visible light catalytic pathway ₁₀ (entries 2-3). Encouraged by these preliminary results, we then embarked on optimizing the reaction conditions to improve the yield of **2a**. Firstly, an extensive screening of photocatalysts was conducted and it was found that *fac*-Ir(ppy)₃ was still the best choice (entry 1 *vs* entries 4-9). Subsequent investigation of the ₁₅ light source such as 3 W blue LEDs gave comparable results with somewhat prolonged reaction time (entry 10). When H₂O (5.0 equiv) was added into the reaction mixture, the model reaction was completed within 4 h and the yield was increased to 70 % (entry 11). Finally, doubling the water equivalent further reduced ₂₀ the reaction time to 2.5 h and increased the yield of **2a** to 79 %.

Table 1 Results of the experiments to optimize reaction conditions[a]

Entry	photocatalyst[b]	H₂O(x)	Time (h)	Yield[c] (%)
1	*fac*-Ir(ppy)₃	—	7	62
2	—	—	24	trace
3[d]	*fac*-Ir(ppy)₃	—	24	0
4	[Ru(bpy)₃Cl₂]·6H₂O	—	24	trace
5	Ir(ppy)₂(dtbbpy)PF₆	—	24	44
6	Ir(ppy)₂(bpy)PF₆	—	24	31
7	[Ir(dF(CF₃)ppy)₂(dtbbpy)](PF₆)	—	24	9
8	Ru(bpm)₃(BArF)₂	—	24	trace
9	Eosin Y	—	24	trace
10[e]	*fac*-Ir(ppy)₃	—	8	62
11	*fac*-Ir(ppy)₃	5	4	70
12	***fac*-Ir(ppy)₃**	**10**	**2.5**	**79**
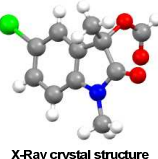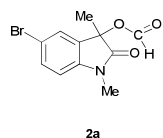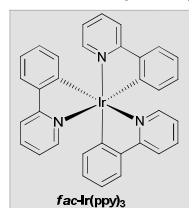
[a] The reactions were carried out on a 0.2 mmol scale of **1a** with 2 mol % of photocatalyst and H₂O (x equiv) in DMF (2.0 mL). [b] See the supporting information for the detailed structures of the photocatalysts. [c] Isolated yield. [d] Reaction was carried out in the dark. [e] 3 W blue LEDs was used as the light source. DMF: *N*,*N*-dimethylformamide.
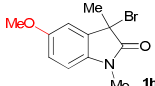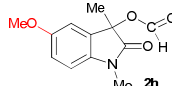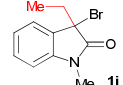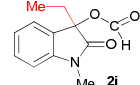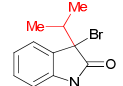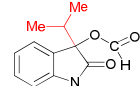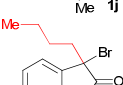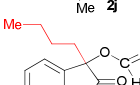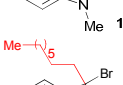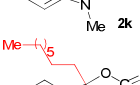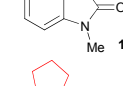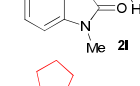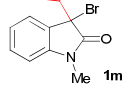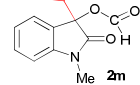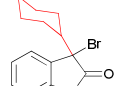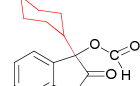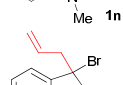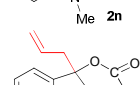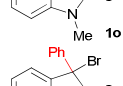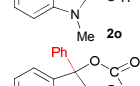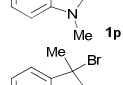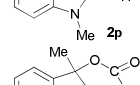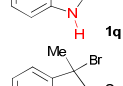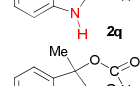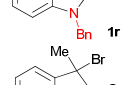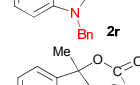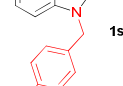
Substrate scope

The generality of the visible light induced assembly of 3-₂₅ bromooxindoles, DMF and water was investigated under the optimal reaction conditions using 2 mol % *fac*-Ir(ppy)₃. As shown in Table 2, this reaction tolerates a wide range of 3-bromooxindoles and various 3-formyloxyoxindoles were obtained in moderate to excellent yields upon isolation. For ₃₀ example, electron-withdrawing, electron-neutral and electron-donating substitution patterns on the aromatic rings all performed well, furnishing the corresponding products in 42-87 % yields (Table 2, entries 1-8). It is noteworthy that halogen substituents such as F, Cl, and Br on the benzene ring ₃₅ were compatible with the photoredox process. Products **2a**, **2c**-**2f** might be further modified at the halogenated positions using transition-metal catalyzed cross-coupling reactions.[22] Meanwhile, we have also tested the C-4-Br substituted substrate, unfortunately, we could not detect the desired ₄₀ product. It was also found that the group at the C-3 position of the oxindole skeleton might be extended to ethyl, isopropyl, butyl as well as longer-chain octyl group. These substrates reacted smoothly to give the desired products in good yields (93-96 % yields, entries 9-12). Cyclic substituents such as ₄₅ cyclopentyl and cyclohexyl are also suitable for this transformation and give good results (entries 13-14). In addition, the feasibility of this methodology could also be realized for 3-bromooxindoles bearing an allyl or a phenyl group at the C-3 position with somewhat lower yields (entries ₅₀ 15-16). Structural variation on the nitrogen protected groups did not affect the reaction efficiency and compounds containing *N*-H, Bn, 4-Me-Bn and allyl groups in **1q**-**1t** gave the products in 83-91% yields (entries 17-20), while the presence of an acylated group gave a complex mixture (entry ₅₅ 21).

Table 2 Substrate scope[a]

Entry	1	Time (h)	2	Yield[b] (%)
1[c]	**1a**	2.5	**2a**	79
2	**1b**	3	**2b**	79
3	**1c**	6	**2c**	68
4	**1d**	2.5	**2d**	84
5	**1e**	2.5	**2e**	83
6	**1f**	3.5	**2f**	42
7	**1g**	2.5	**2g**	87

Entry	Substrate	Time (h)	Product	Yield (%)
8	1h	10	2h	83
9	1i	3	2i	96
10	1j	3	2j	93
11	1k	4	2k	93
12	1l	8	2l	93
13	1m	3	2m	80
14	1n	3	2n	88
15	1o	3.5	2o	78
16	1p	11.5	2p	40
17	1q	2.5	2q	83
18	1r	2.5	2r	89
19	1s	3	2s	86
20	1t	3	2t	91
21	1u	—	—	N.D.

[a] Reactions were carried out on a 0.4 mmol scale of **1** with 2 mol% of *fac*-Ir(ppy)$_3$ and H$_2$O (10 equiv) in DMF (2.0 mL). [b] Isolated yield. [c] The reactions were carried out on a 0.2 mmol scale of **1a**. DMF: *N,N*-dimethylformamide; N.D.: Not determined.

Insight into the catalytic mechanism of the visible light induced formyloxylation reaction

While a precise reaction mechanism awaits further study, we now propose a possible catalytic cycle to explain the generation of 3-formyloxyoxindoles. As illustrated in Scheme 2, the photocatalyst *fac*-Ir(ppy)$_3$ was first excited to the highly active species *fac*-*Ir(ppy)$_3$ by the irradiation of visible light, which then reacted with alkyl bromide **1b**, resulting in the formation of radical intermediate **I** with the release of bromide ion and *fac*-Ir(ppy)$_3$$^+$ by an oxidative quenching cycle. Subsequently, radical addition reaction between intermediate **I** and *N,N*-dimethylformamide took place, giving the radical intermediate **II**. The next step may involve the oxidation of intermediate **II** to iminium ion **III** by two possible pathways: (a) intermediate **II** is oxidized by *fac*-Ir(ppy)$_3$$^+$ and regenerated the ground state *fac*-Ir(ppy)$_3$ to complete the catalytic cycle (path A); (b) intermediate **II** is oxidized by another molecule **1b**, affording iminium ion **III** and radical intermediate **I** through a chain-propagation mechanism (path B). Finally, hydrolysis of **III** gave the terminal product **2b** accompanying dimethylaminehydrobromide **3** as the byproduct. It is worth to mention that extra base was not needed to neutralize HBr, because the dimethylamine derived from DMF could serve as a base to capture the acid HBr.
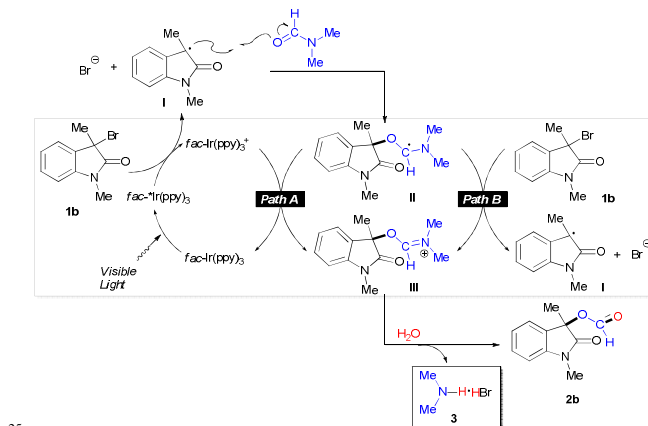
Scheme 2 Possible mechanism for the visible light induced three-component assembly of 3-bromooxindoles, DMF and water.

In order to shed some light on the above mechanism, a series of experiments including fluorescence quenching experiments, "on-off" switching of the light source and labeling experiments, MS analyses as well as in situ IR studies were carried out.

(1) Fluorescence quenching experiments. To get some insight into the proposed catalytic mechanism in which electron transfer from excited state *fac*-*Ir(ppy)$_3$ to substrate **1b** would occur, fluorescence quenching experiments (Stern-Volmer studies) of *fac*-Ir(ppy)$_3$ were carried out. We were pleased to observe that the fluorescence intensity decreased with increasing concentration of **1b** (Figure 1, a).[23] The maximum emission wavelength (λ_{em}) for *fac*-Ir(ppy)$_3$ was about 520 nm, and the data at this wavelength were selected for the Stern-Volmer plot (Figure 1, b). As shown in Figure 1, a linear relationship between I$_0$/I and the concentration of **1b**
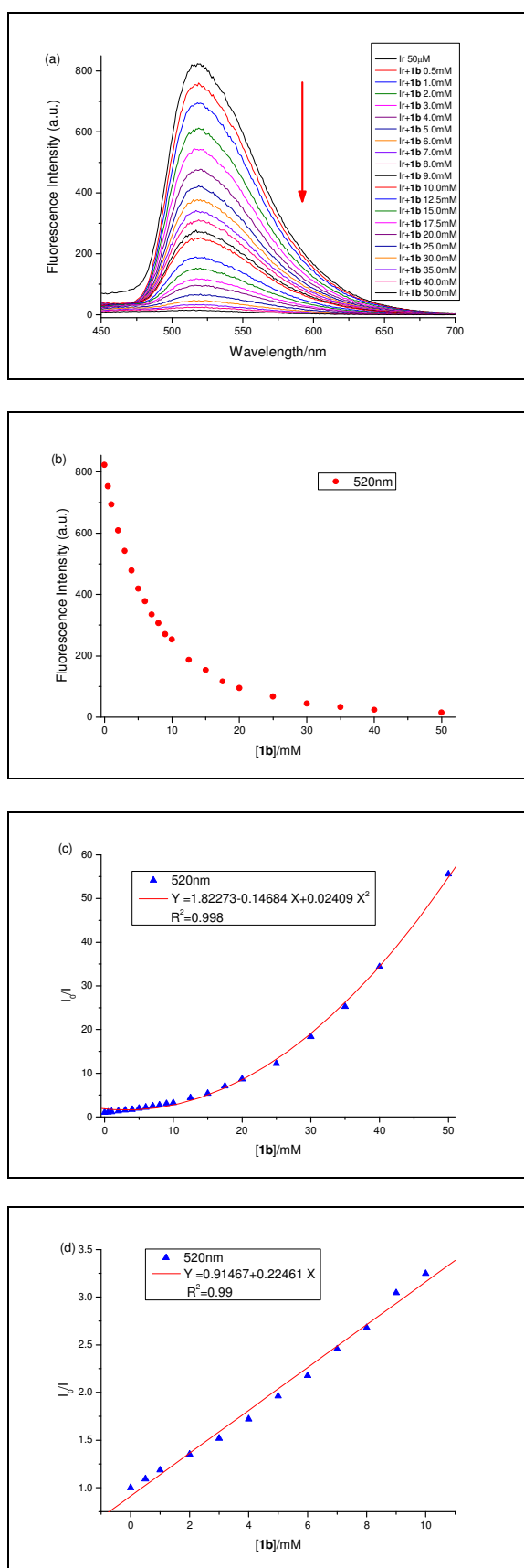
Figure 1 Fluorescence quenching (Stern-Volmer) studies between *fac*-Ir(ppy)$_3$ and **1b**.

was observed at low concentration (I$_0$ and I are the fluorescence intensities before and after the addition of **1b**, Figure 1, d). At high concentration, the Stern-Volmer plot exhibited an upward curvature, concave toward the *y*-axis (Figure 1, c). These results strongly indicate that the photoexcited state *fac*-*Ir(ppy)$_3$ was quenched by **1b** via electron transfer, and static and dynamic quenching might occur simultaneously in this reaction system.[24]

(2) "On-off" switching of the light source. As depicted in Scheme 2, a radical-chain propagation process was also possible for this visible light induced transformation (Scheme 2, path B). In order to get some information about this reaction pathway, we performed the experiment about the on-off switching of the light source in the reaction of **1b**, DMF and water. We initially removed the light source after 20 minutes when the yield of **1b** was approximately 13 % under the standard conditions (GC yield, using *n*-tetradecane as the internal standard).[23] It was found that no further progress was observed after stirring in the dark for 10 minutes (Figure 2). Importantly, the reintroduction of the visible light source for 20 minutes led to the further conversion of **1b** to the desired product **2b** in 34 % yield (GC yield). The "on-off" cycle could be repeated many times until the full consumption of **1b** took place. This phenomenon demonstrated that the visible light initiated three-component reactions demanded continuous irradiation with visible light, although the radical chain mechanism cannot be ruled out in this reaction system.[25]
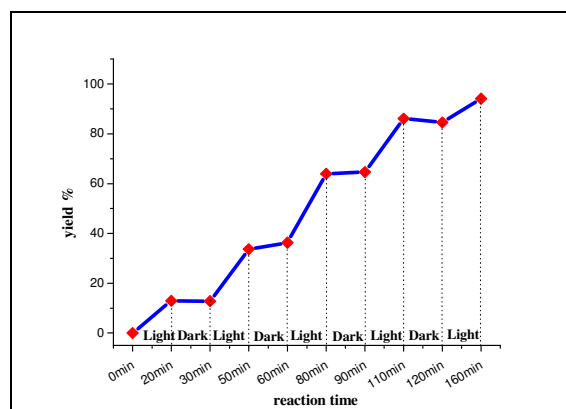
Figure 2 Time profile of visible light induced assembly of **1b**, DMF and water.

(3) Labeling experiments and ESI-MS analyses. To better understand the "C, H, O" source of the formyloxy group, we performed a series of labeling experiments. Treatment of **1b** with 10 equivalents of deuterium oxide under the optimal reaction conditions resulted in no deuterium product (Scheme 3, a). Interestingly, when *N,N*-dimethylformamide-d1 (98 atom % D) was used as the reaction partner, almost complete isotope incorporation occurred into the final product **2b** in 85% yield (Scheme 3, b). Thus, the hydrogen atom of the formyloxy group unambiguously originated from *N,N*-dimethylformamide (DMF). The deuterium product was further confirmed by HRMS analysis.[23]
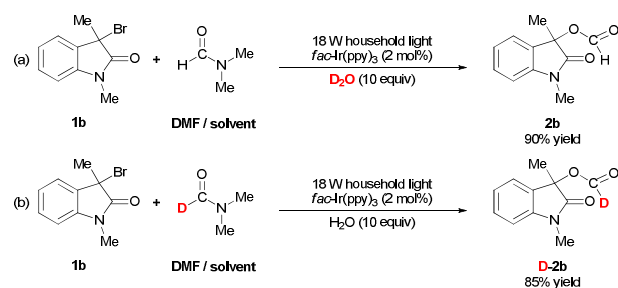
Scheme 3 Results of deuterium experiments.

Next, in order to confirm that the "C" of the formyloxy group at the C3-oxindole position also arose from DMF, we conducted the following C-13 labeling experiment. It was found that the carbon of the formyloxy group was wholly from DMF (Scheme 4), which implied that the carbonyl moiety of DMF is an efficient carbon source of "OCHO" in the present protocol. Meanwhile, mass spectrometric data was also recorded and integrated with the NMR spectroscopic analysis.[23] These results further support our proposed mechanism.
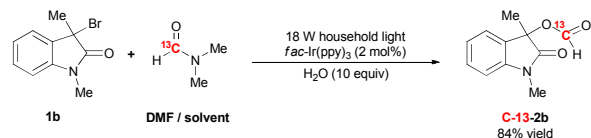
Scheme 4 Results of C-13 labeling experiment.

To better understand the source for the two oxygen atoms, we carried out O-18 labeling experiments (Scheme 5). Using water-18O (97 % atom) as the reaction partner, the O-18 labeling product was obtained in 81 % isolated yield under the optimized reaction conditions. However, we cannot identify which oxygen atom was labeled at this stage. So the O-18 labeling product was further hydrolyzed to the corresponding 3-hydroxyl oxindole **4** under basic conditions, and the O-18 labeling hydrolyzed product was not observed based on HRMS analysis. These results revealed that O^a was from DMF, and O^b originated from water.[23]

Scheme 5 Results of O-18 labeling experiments.

(4) Possible byproduct. As depicted in Scheme 2, the possible byproduct is dimethylaminehydrobromide **3**, which might be a salt dissolved in the aqueous phase during the workup process. To validate this proposal, we carefully studied the reaction of **1b** (Table 2, entry 2). Afte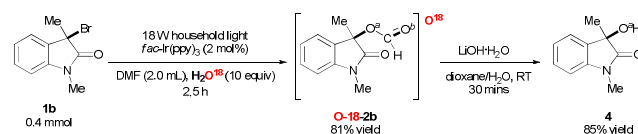r the reaction was complete (monitered by TLC), D_2O was added into the flask, then extracted with ethyl ether, and the aqueous phase was used to do the NMR experiment directly. As shown in Figure 3, besides DMF, only one signal (δ = 2.67 ppm) was observed (Figure 3, c). This signal could be assigned to

the two methyl protons of dimethylaminehydrobromide when compared with dimethylaminehydrobromide (δ = 2.68 ppm). On the other hand, dimethylaminehydrobromide **3** might be unstable at high temperature and released dimethylamine and hydrobromide, which were detected by GC-MS.[23] These results provide compelling evidence that dimethylaminehydrobromide **3** indeed existed in this process.
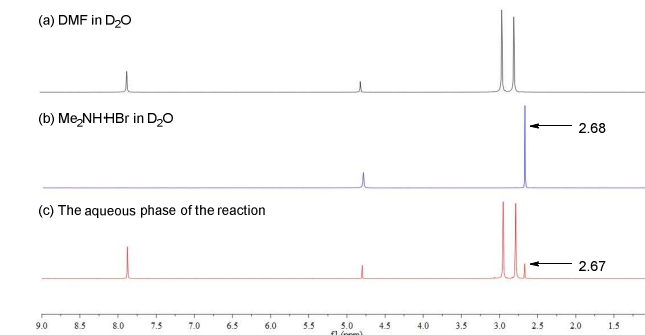
Figure 3 Results of the byproduct studies.

(5) In situ IR experiments. In order to get some insight into the kinetic behaviors of this transformation, the reaction of **1b** with DMF and water was monitored via in situ FTIR. It was very clear that from the 3D-FTIR spectrum (Figure 4, a), product **2b** was formed with the consumption of **1b**. From the kinetic profile of this reaction (Figure 4, b), a linear relationship between the concentration of **2b** and reaction time was observed at the beginning of this reaction, which indicated that the reaction rate is independent of **1b**. However, plot of **2b** formation vs time became a curved line with the progress of this reaction, which might result from the catalyst deactivation.[23,26]
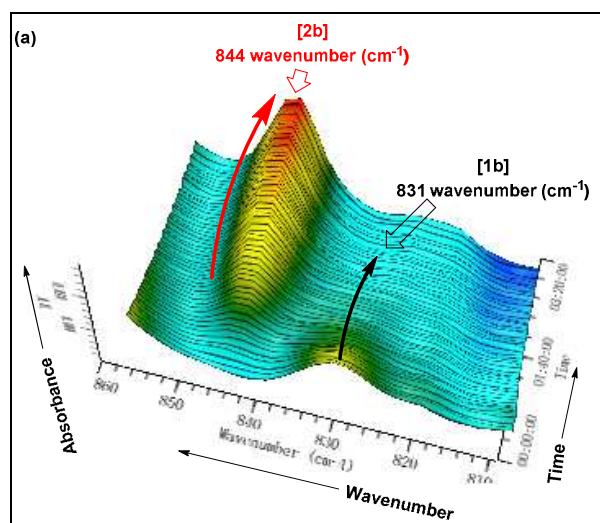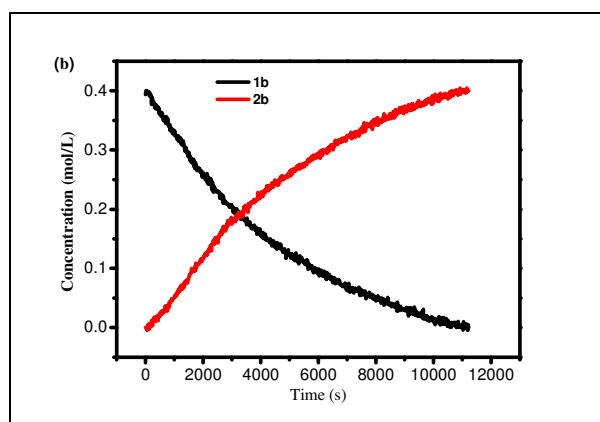
Figure 4 (a) Overall three-dimensional Fourier transform IR (3D-FTIR) profile of the three-component reaction. (b) Kinetic profile for the three-component reaction.

Conclusions

In summary, we have developed a visible light induced three component assembly of 3-formyloxyoxindoles from 3-bromooxindoles, DMF and water. Two green and sustainable natural resources, visible light and water were combined into one reaction system which opened new opportunities to visible light photoredox catalysis. The mild reaction conditions, broad scope of substrates, excellent functional group tolerance and high reaction efficiencies made this new protocol attractive, and a variety of 3-formyloxyoxindoles derivatives can be constructed in a highly concise fashion. Moreover, the detailed mechanism of this transformation was investigated based on fluorescence quenching experiments, "on-off" switching of the light source study, labeling experiments MS studies and in situ IR experiments. The application of this strategy to the synthesis of some promising candidates for drug discovery and the biological evaluation of these 3-formyloxyoxindoles are currently ongoing in our laboratory.

Experimental section

General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Organic solutions were concentrated under reduced pressure on a Büchirotary evaporator.Flash column chromatography (FC) was performed using 200-300 mesh silica gel. ^{1}H NMR spectra were recorded on Varian Mercury 600 (600 MHz) spectrophotometers. Chemical shifts (δ) are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Mercury 400 (100MHz) spectrophotometers ($CDCl_3$: 77.0 ppm) with complete proton decoupling. IR spectra were recorded on a BRUKER TENSOR 27 FT-IR spectrometer and are reported in terms of

frequency of absorption (cm^{-1}). GC-MS was performed on a Thermo DSQ II 2000. High Resolution Mass spectra were obtained from the Shanghai Mass Spectrometry Center (Shanghai Institute of Organic Chemistry). Melt points were measured on Büchi Melting Point B-545. Fluorescence spectra were collected on Cary Eclipse Fluorescence spectrophotometer. For the ReactIR kinetic experiments, the reaction spectra were recorded using an IC 15 from Mettler-Toledo AutoChem.

General procedure for visible light induced formyloxylation

To a 10 mL Schlenk tube equipped with a magnetic stir bar and rubber septum was charged with 3,5-dibromo-1,3-dimethylindolin-2-one **1a** (0.20 mmol, 1.0 equiv.), tris-(2-phenylpyridinato-C2,*N*)iridium(III) (*fac*-Ir(ppy)$_3$) (0.004 mmol, 0.02 equiv.), water (2.0 mmol, 10.0 equiv.), and DMF (2.0 mL).The mixture was degassed via the freeze-pump-thaw method and placed at a distance of ~5 cm from 18 W household light bulb. After the reaction was complete (2.5 h, monitored by TLC analysis), H_2O (5.0 mL) was added into the reaction mixture. Then, the mixture was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by FC (silica gel, PE:EtOAc = 10:1-5:1) to give the desired product 5-bromo-1,3-dimethyl-2-oxoindolin-3-yl formate **2a** (44.8 mg, 79 % yield) as a white solid.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and compound characterisation data, including X-ray crystal data for **2a** (CCDC937531). For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/b000000x/

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26 We also investigated the influence of light intensity on the reaction efficiencies, please see the supporting information for details.

Visible-light-induced photocatalytic formyloxylation reactions of 3-bromooxindoles with water and DMF: scope and mechanism

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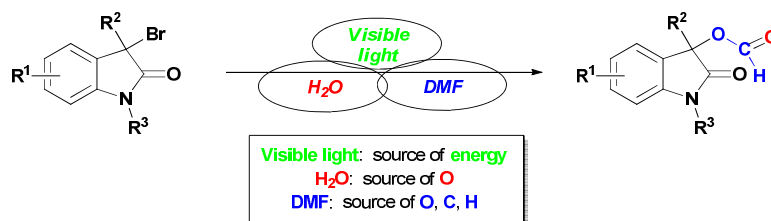
A highly efficient visible light induced formyloxylation reaction of 3-bromooxindoles was disclosed. Results of labeling experiments indicated that H_2O and DMF were incorporated into the terminal 3-formyloxyoxindoles. Fluorescence quenching experiments, "on-off" switching of the light source, mass spectral analysed as well as in situ IR experiments were performed to get some insight into the mechanism of this transformation.