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# Visible-light-mediated direct access to $\alpha$ -ketoamides by dealkylative amidation of tertiary amines with benzoylformic acids

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**Abstract:** A visible-light induced direct amidation of benzoylformic acids with tertiary amines has been explored. Tertiary amines underwent *N*-dealkylative amidation with  $\alpha$ -keto acid in the presence of [Ir{dFCF<sub>3</sub>ppy}<sub>2</sub>(bpy)]PF<sub>6</sub> and Cs<sub>2</sub>CO<sub>3</sub>, affording the corresponding  $\alpha$ -ketoamides in good yields under mild conditions. This transformation exhibits a wide substrate scope and provides a facile synthetic approach to  $\alpha$ -ketoamides.

#### Key words: Amidation, Photoredox, a-Ketoamides, Visible-light

α-Ketoamides are important functional motifs for the synthesis of pharmaceuticals, chemistry and bioactive natural products [1]. Thus, the development of mild and versatile synthetic methods for generating a-ketoamides has become a field of intense research effort. As carboxylic acids are stable, inexpensive and environmentally benign, a vast number of methods for the synthesis of  $\alpha$ -ketoamides via coupling carboxylic acid with amine have been developed [2]. The first direct amidation of carboxylic acid is reported by Grieco group in which they employ phenyl thiocyanate as nitrogen source (Scheme 1, a) [3]. Conventional protocols for amidation of carboxylic acid mostly depend on coupling reagent, which can first transform the acid into active species thus easy to couple with amines (Scheme 1, b) [4]. Later, further exploration indicates that formamides can also be used as a starting material in oxidative conversion of carboxylic acids to amines (Scheme 1, c) [5].

Tertiary amines are ubiquitous functionalities in nature, which can also serve as a source of nitrogen in the direct amidation of carboxylic acid. Wang's group first reported the Ag-catalyzed direct synthesis of  $\alpha$ -ketoamide using tertiary amines as nitrogen source at high temperature (120 °C) [6]. Later, Yin's group disclosed the copper-catalyzed amidation of acids with tertiary amines through C-N bond cleavage with the assistance of large excess amount of toxic CCl4 at a lower temperature (60 °C) [7]. Nevertheless, the development of energy efficient, environmental benign catalytic system for the direct synthesis of α-ketoamides through C-N bond cleavage under mild condition is highly desirable. In recent years, photosynthesis that converting the infinite solar energy to chemical energy have attracted tremendous research interest. Rueping's group reported the aerobic dealkylation of amines via Ir catalyst [8]. In addition, our group has developed a new protocol to dealkylative addition using tertiary amine as a starting material [9]. We envisaged that the application of tertiary amines as starting reactant through photoredox cycle is a favorable alternative for direct amidation. As part of our ongoing efforts on photoredox C-N cleavage coupling, we herein report the visible-light-mediated direct amidation of benzoylformic acids with tertiary amines through C-N bond cleavage under mild condition.



At the initial investigation, we selected benzoylformic acid 1a and triethylamine 1b as model substrate to optimize the reaction. Several conventional photocatalysts were screened in the presence of BrCCl<sub>3</sub> under blue LEDs irradiation. In general, the reactivity of iridium catalysts (Ir(ppy)<sub>3</sub>, [Ir(dtbbpy)(ppy)<sub>2</sub>]PF<sub>6</sub>,  $[Ir{dFCF_3ppy}_2(bpy)]PF_6)$  were better than  $[Ru(bpy)_3Cl_2] \cdot 6H_2O$ , organic dye (eosin Y and Rose Bengal) and acridinium salt (9mesityl-10-methylacridinium perchlorate) (Table 1, entries 1-6). Remarkably, [Ir{dFCF<sub>3</sub>ppy}<sub>2</sub>(bpy)]PF<sub>6</sub> gave 44% yield after 20 hours reaction. Encouraged by these results, we then embarked on screening different solvents, the results showed that the direct amidation proceeded best in DCM, whereas 7-24 % yield detected in MeCN, DMF, MeOH and only trace products were found in DMSO and THF (Table 1, entries 7-13). Having optimized catalyst and solvent in hand, we intentionally investigated the performance under a variety of base salts such as Cs<sub>2</sub>CO<sub>3</sub>, CsF, CsOAc, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>2</sub>HPO<sub>4</sub> and K<sub>3</sub>PO<sub>4</sub> (Table 1, entries 14-20). To our delight, Cs<sub>2</sub>CO<sub>3</sub> was found to be an effective additive that generated product in 62% yield. Control experiments showed that only trace product was observed in the absence of iridium catalyst or light. No product was found without oxidant BrCCl<sub>3</sub>, which indicated the oxidative reaction cycle is important for this reaction.



photocatalyst (3.0 mol%), base (2.0 equiv), solvent (2.0 mL), room temperature, using blue LEDs as the visible light source, 20 h. bDetermined by <sup>1</sup>H NMR yield using CH<sub>2</sub>Br<sub>2</sub> as internal standard. <sup>c</sup>Isolated yield. <sup>d</sup>Performed in the dark. eWithout BrCCl3.

carboxylic acid scope is under evaluation (Table 2). Initially, benzovlformic acids substituted with methyl group were examined in the reaction. For the carboxylic acid bearing orthoposition methyl group exhibited somewhat steric effect, and lower yields were observed (3b). Carboxylic acid bearing metaposition or para-position methyl group underwent amidation smoothly to give moderate yield 67-60% (3c-d). Gratifyingly, various functional groups were well tolerated, both electron donating- and electron withdrawing substituents at the para position of the phenyl moiety proceeded smoothly (Table 2). Halogen functional groups such as F, Cl and Br were welltolerated, leading to 50-55% yields (3e-h). In addition, benzoylformic acids substituted with tBu and OMe gave corresponding product in 61% and 63% yields (3i-j). Moreover, 2-naphthyl(oxo)acetic acid 1k and 1-naphthyl(oxo)acetic acid 1l also underwent amidation to generate  $\alpha$ -ketoamines in 61% and 60% yields, respectively.





<sup>a</sup>Reaction conditions: benzoylformic acids 1 (0.4 mmol), tertiary amine 2 (0.8 mmol), [Ir{dFCF<sub>3</sub>ppy}<sub>2</sub>(bpy)]PF<sub>6</sub> (0.012 mmol), BrCCl<sub>3</sub> (0.8 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.8 mmol), H<sub>2</sub>O (0.4 mmol), DCM (2.0 mL), room temperature, using Blue LEDs as the visible light source, 20 h. bIsolated yield.

To determine the possible intermediate of the reaction, we performed the reaction of benzoylformic acids with secondary amine under optimized reaction conditions. No desired amidation product was generated, and therefore the pathway involved dealkylation to secondary amine for amidation can be ruled out. On the basis of literature reports [8] and our experimental results, a plausible mechanism was proposed (Scheme 2). Initially, iridium catalyst was excited to generate the excited state under irradiation, which then undergoes single electron transfer (SET) with tertiary amine 2a to generate the radical cation 4 and Ir<sup>II</sup> metal complex. Meanwhile, the radical cation 4 undergoes dehydrogenation to afford iminium ion 5. Next, the iminium ion 5 was attacked by deprotonated carboxylic anions to the intermediate 6, which undergo a rearrangement to give the

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Scheme 2. Proposed plausible mechanism

In summary, we have developed an operationally convenient visible-light induced direct amidation of benzoylformic acids with tertiary amines under mild conditions. This protocol tolerates a variety of functional groups and provides an alternative procedure for the synthesis of  $\alpha$ -ketoamide derivatives. Further studies on the mechanism and applications of the reaction are currently underway in our laboratory.

#### **Experimental Section**

The 10-mL round-bottom flask was equipped with a magnetic stirrer bar. Afterwards, tertiary amine **1** (0.4 mmol), benzoylformic acids **2** (0.2 mmol),  $[Ir{dFCF_3ppy}_2(bpy)]PF_6$  (0.006 mmol), BrCCl<sub>3</sub> (0.6 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.4 mmol) and DCM (2 mL) were added. Then, the reaction mixture was sealed with stopper and placed in room temperature. A 5 w blue LED was placed at a distance of about 5 cm from the reaction vessel. After the reaction was complete (as monitored by TLC), the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the desired product **3**.

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# Highlights

(1) First example of operationally convenient

visible-light induced direct amidation of

benzoylformic acids with tertiary amines.

(2) Direct synthesis of a series of  $\alpha$ -ketoamide

derivatives under mild condition.

(3) The developed photocatalytic system can be

applied to a variety of benzoylformic acids bearing

different substitutes.

### **Graphical Abstract**

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