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Photoredox-Catalyzed Decarboxylative C–H Acylation of Heteroarenes

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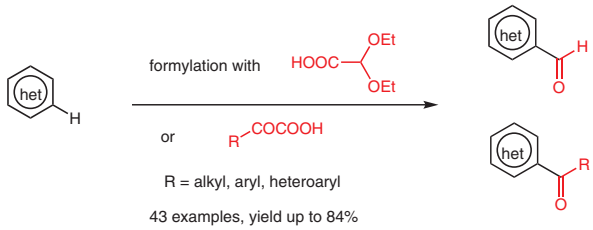

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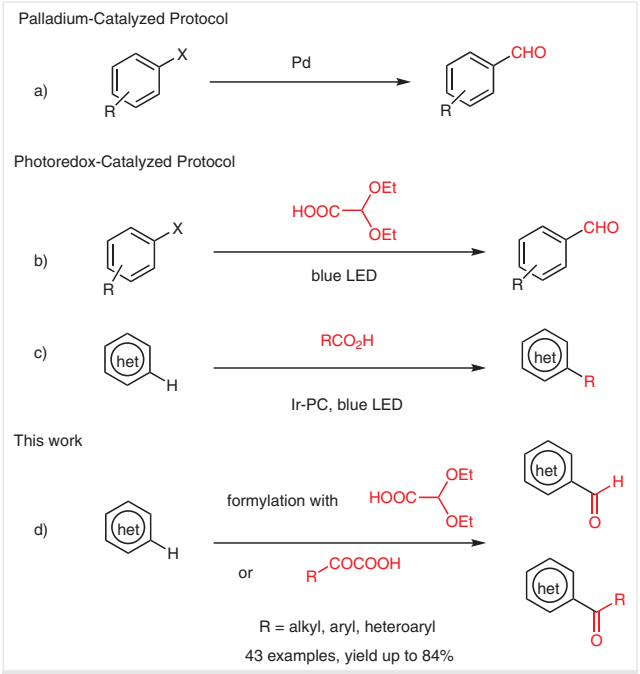
Abstract A mild, environmentally friendly, and regioselective acylation of heterocycles with inexpensive carboxylic acids is reported via photoredox catalysis. The strategy is highlighted with good functional group tolerance and substrate scope which could rapidly realize the acylation of various heterocyclic compounds.

Key words 2,2-diethoxyacetic acid, α-keto acids, heterocycles, C–H functionalization, acylation

Aldehydes and ketones are both prevalent compounds that can participate in various chemical transformations or serve as key synthons for complex scaffolds. Besides, they are also widely found in pharmaceuticals, fine chemicals, and natural products.[1] Direct activation and functionalization of C–H bonds in organic molecules to construct new C–C bonds provides a new synthetic strategy for organic synthesis.[2] However, it is still a challenging goal because of the relative inertness of the unactivated C–H bonds. Various available methods require strong oxidants or harsh conditions, limiting their application in the late-stage functionalization of complex molecules.[3]

Although aromatic aldehydes are widely applicable in synthetic chemistry,[4] methods to access them are to some extent limited. Classical methods such as Vilsmeier–Haack, Reimer–Tiemann, and Duff reactions[5] suffer from relatively poor regioselectivity due to the nature of aromatic electrophilic substitution reactions. Another alternative traditional approach to introduce an aldehyde group employs pre-functionalized organometallic reagents and *N*,*N*-dimethylformamide (DMF) at low temperature,[6] with low tolerance of functional groups as its drawback. In addition, more works are reported on the reductive formylation of aryl halides catalyzed by the transition metal palladium (Scheme 1, a),[7] the first of which was reported by Heck in 1974.[8] C–H acylation is a prevalent synthetic strategy for late-stage modification of heterocycles, the Minisci reaction is a commonly used heterocyclic acylation method that introduces nucleophilic acyl groups to electron-deficient heterocyclic aromatics.[9] However, the conditions of these reactions are either harsh or costly. Therefore, developing a mild, economical, and environmentally friendly formylation method is still urgent.



Scheme 1 C–H functionalization

Recently, visible-light photocatalysis has become a powerful synthetic tool for the construction of C–H and C–X bonds via single-electron transfer.[10] In particular, the use of carboxylic acids as radical precursors to construct C–C

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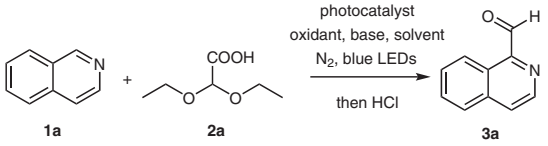
bonds has been the focus of recent interest.[11] Formylation of aromatic compounds has been realized through visible-light induced single-electron transfer, energy conversion, or hydrogen-atom-transfer processes. Wang reported a photochemical, regioselective hydroformylation reaction, in which a cheap organic dye 4CzIPN was employed as the photosensitizer (Scheme 1, b).[12] Hydroformylation results are also impressive from Doyle,[13] Wang,[14] and Li.[15] Glorius reported the use of inexpensive carboxylic acids as alkyl radical precursors of visible-light-induced Minisci reactions (Scheme 1, c).[11e] In addition, Minisci transformations using *N*-acyloxyphthalimides, alcohols, and peroxides as alkylating agents have recently been reported.[16] However, formylation of heterocyclic compounds under visible-light irradiation is rarely reported. Herein, we report a visible-light-induced formylation of heterocycles with 2,2-diethoxyacetic acid at room temperature without any photosensitizer (Scheme 1, d). Furthermore, a visible-light-induced acylation of heterocycles using α-keto acids has also been developed.

Initially, isoquinoline (**1a**) and 2,2-diethoxyacetic acid (**2a**) were selected as the model substrates for condition optimization. First, we screened the effect of different solvents (see Supporting Information) with ammonium persulfate (2 equiv) as the oxidant and cesium carbonate (2 equiv) as the base under the irradiation of 15 W blue LEDs. We were pleased to find that the reaction in dimethyl sulfoxide (DMSO) give the highest yield of **3a**. Subsequently, the influence of the catalyst was investigated (Table 1, entries 1–3). The reaction proceeded well to afford the desired product in high yield in the absence of any photocatalyst. Different oxidants were also tested which only resulted in lower yields of **3a** (Table 1, entries 4, 5). Then various bases were screened, and the results indicated that cesium carbonate could significantly improve the reaction efficiency (Table 1, entries 6–8). The highest yield of **3a** was finally obtained by increasing the amount of **2a** and oxidant (Table 1, entries 9, 10). Furthermore, control experiments showed that the reaction did not work well in the absence of light, oxidants, or bases (Table 1, entries 11–13).

With optimized reaction conditions in hand, we then focused on the substrate scope of the formylation reaction (Scheme 2). Generally speaking, this method provides a new route for the preparation of a series of formylated heterocycles in yields up to 80%. Reaction between isoquinoline **1a** and **2a** yielded the regioselective formylation product (**3a**, 73%). The corresponding products (**3b–f**,**h**) were obtained in good yields (53–72%) using isoquinolines bearing substituents such as Cl, CH_3, Br at their C4, C5, C6, C8 positions. The reaction was also proved applicable to C3-substituted isoquinolines and 4-Cl-, 4-CH_3-, 2-CH_3-substituted quinolines (products **3g**,**i–k**). The scope of heterocycle substrate was further extended to quinoxaline (**3l**, 53%), phenanthridine (**3m**, 80%), *N*-methylbenzimidazole (**3n**, 40%) and benzothiazole (**3o**, 37%) which proved that this transformation has a good generality.

Table 1 Optimization of Reaction Conditions[a,b]



1a 2a 3a

Entry	**2a** (eq)	Oxidant (eq)	Base (eq)	Yield (%)[b]
1	5	$(NH_4)_2S_2O_8$ (2)	Cs_2CO_3	45
2[c]	5	$(NH_4)_2S_2O_8$ (2)	Cs_2CO_3	43
3[d]	5	$(NH_4)_2S_2O_8$ (2)	Cs_2CO_3	19
4	5	$K_2S_2O_8$ (2)	Cs_2CO_3	24
5	5	$Na_2S_2O_8$ (2)	Cs_2CO_3	39
6	5	$(NH_4)_2S_2O_8$ (2)	K_2HPO_4	29
7	5	$(NH_4)_2S_2O_8$ (2)	K_2CO_3	40
8	5	$(NH_4)_2S_2O_8$ (2)	Na_2CO_3	38
9	5	$(NH_4)_2S_2O_8$ (3)	Cs_2CO_3	49
10	7	$(NH_4)_2S_2O_8$ (3)	Cs_2CO_3	73
11[e]	7	$(NH_4)_2S_2O_8$ (3)	Cs_2CO_3	19
12	7	none	Cs_2CO_3	0
13	7	$(NH_4)_2S_2O_8$ (3)	none	10
14[f]	7	$(NH_4)_2S_2O_8$ (3)	Cs_2CO_3	26

[a] General conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), $(NH_4)_2S_2O_8$(0.2 mmol), Cs_2CO_3(0.2 mmol), and DMSO (1 mL) under argon atmosphere, stirred under 15 W blue LEDs.
[b] Isolated yield.
[c] 4CzIPN was added.
[d] $[Ir[dF(CF_3ppy)]_2(dtbbpy)]PF_6$ was added.
[e] In the dark.
[f] Under air atmosphere.

Additionally, application to natural product caffeine also turned out to be successful, product **3p** was acquired in 20% yield.

The applicability of the method was further explored with different combinations of **1** and α-keto acids **4**. After the optimization of the reaction conditions and the proposition of a plausible mechanism (see Supporting Information), we subsequently explored the substrate scope (Scheme 3). Quinolines with both electron-donating and electron-withdrawing substituents exhibited excellent efficiency (products **5aa–fb**, 30–76% yield). Isoquinolines could also undergo this transformation smoothly (products **5g–o**, 45–81% yield), and quinoxaline and quinazoline were well tolerated (products **5p–r**). More types of heterocyclic substrates such as 4-*tert*-butylpyridine, phenanthridine, and benzoxazole were then examined, affording the corresponding benzoyl products (**5s–u**). Of the application to natural product caffeine was also successful (**5bb**, 41%).

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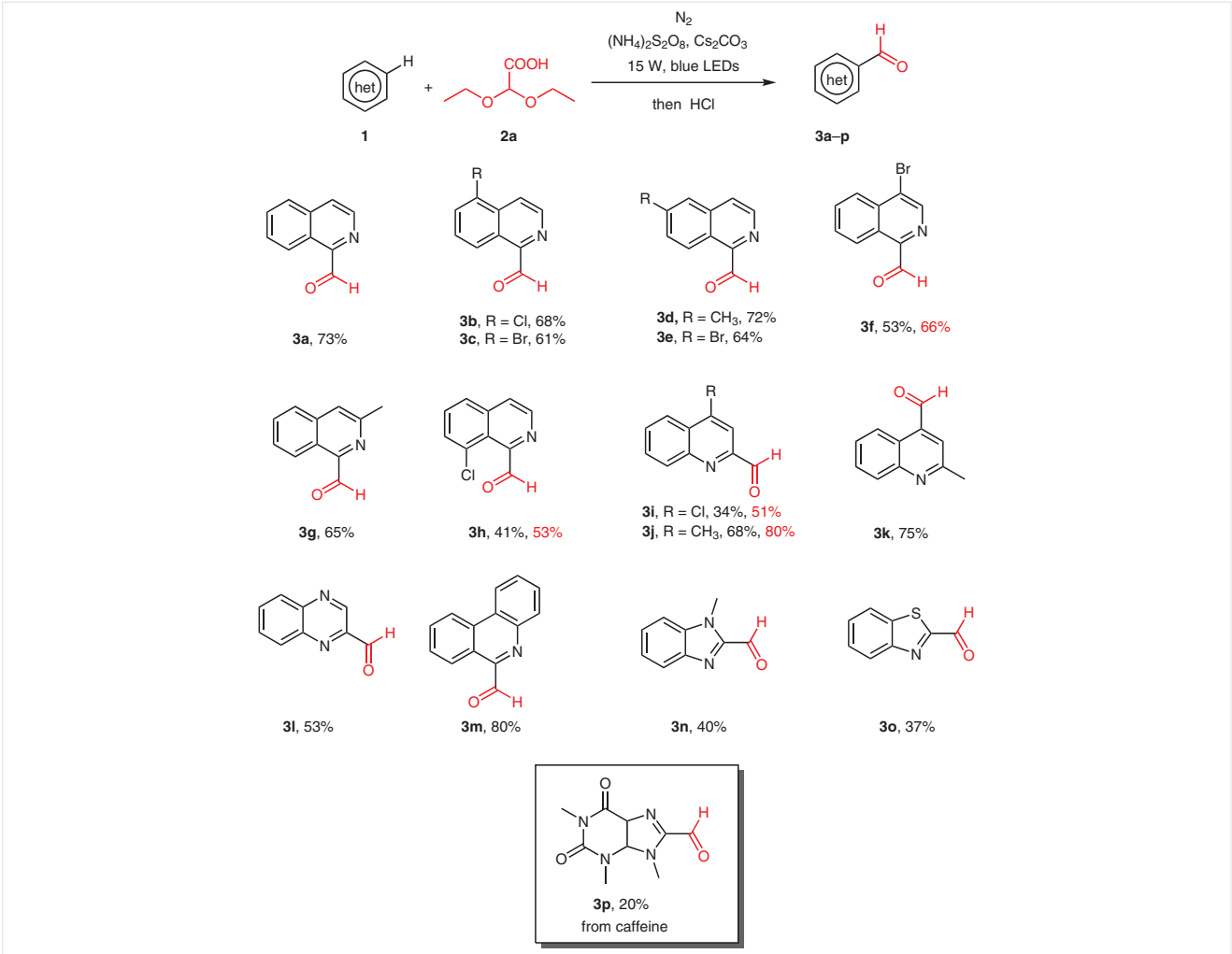

Scheme 2 Scope of heteroarenes formylation reaction.[a,b] [a]See Supporting Information for detailed procedures. [b] Isolated yields. Numbers in red are isolated yields based on recovered starting material.

Next, we studied the reactivity of different α-keto acids. The straight-chained or branched aliphatic α-keto acids smoothly gave the acylated products (**5v**,**w**) via decarboxylation. Similarly, heterocyclic keto acids also showed good reactivity (**5x**,**y**). Surprisingly, the corresponding functionalization of isoquinoline with trimethyl pyruvate gave the alkylated product **5z** with the loss of one molecule of carbon dioxide and carbon monoxide.

In order to explore the mechanism of the reaction, some control experiments were performed (Scheme 4). Under the optimal conditions, radical scavenger TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) was added before the reaction. Notably, product **6a** was not obtained (Scheme 4, b), suggesting that the reaction may proceed via a radical process. The reaction performed in the absence of ammonium persulfate also yielded no **6a** (Scheme 4, c), further illustrating the important role of ammonium persulfate.

Based on these experimental results and previous reports,[11e,17] a reasonable reaction mechanism is presented in Scheme 5. Under visible-light irradiation, $SO_4^{\bullet-}$ is formed after the homolysis of $S_2O_8^{2-}$. 2,2-Diethoxyacetate **2** was oxidized by $S_2O_8^{2-}$ to form radical **7**. Next, radical **7** adds to isoquinoline **1** to form intermediate **8**, which is further oxidized by ammonium persulfate to form the final product **6**. Acid-catalyzed hydrolysis of **6** produces the target product **3**.

In conclusion, we have developed a visible-light-induced C–H functionalization of heterocycles, which features mild and environmentally friendly conditions, broad substrate scope of N-containing heterocycles.[18] This method is a good complement to traditional acylation methods and allows direct functionalization of natural products.

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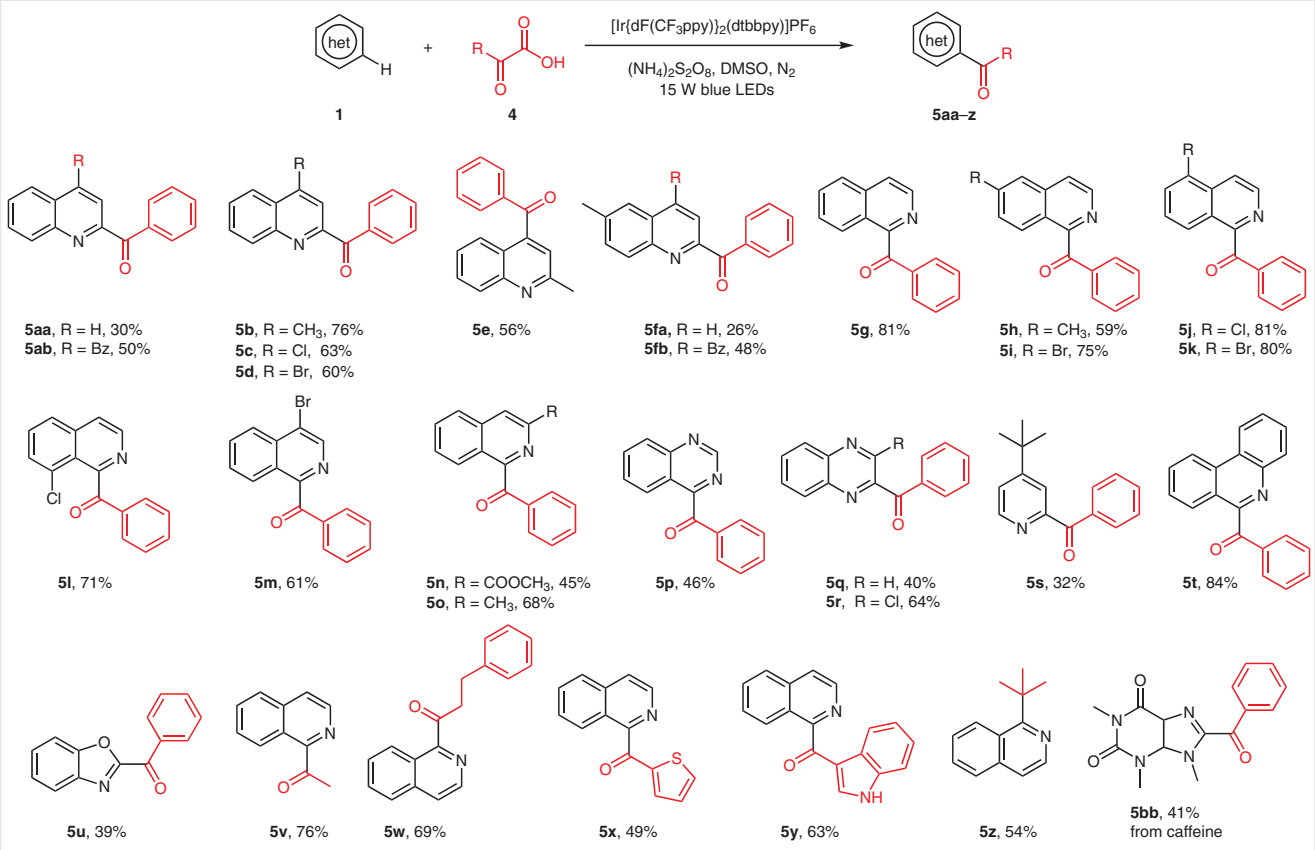
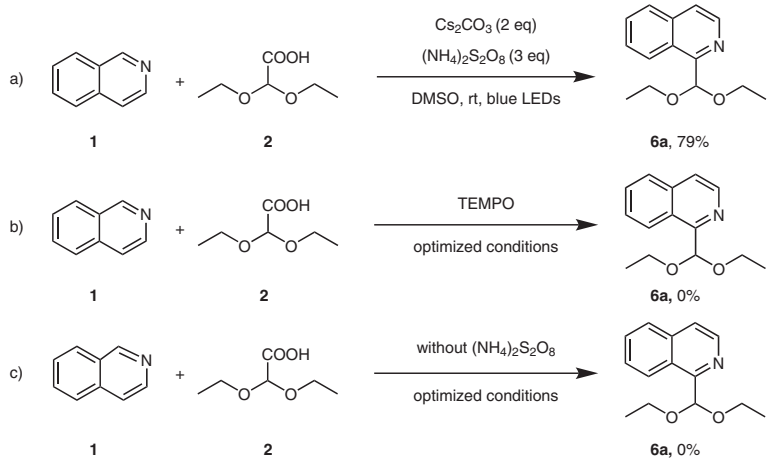


Scheme 3 Scope of heteroarenes and α-ketoacids.[a,b] [a] Reaction conditions: heteroarenes (0.1 mmol), α-keto acids (1mmol), [Ir{dF(CF_3ppy)}$_2$(dtbbpy)]PF_6 (0.2 mol %), $(NH_4)_2S_2O_8$ (0.2 mmol) and DMSO (1 mL) under argon atmosphere. [b] Isolated yield.



Scheme 4 Control experiments

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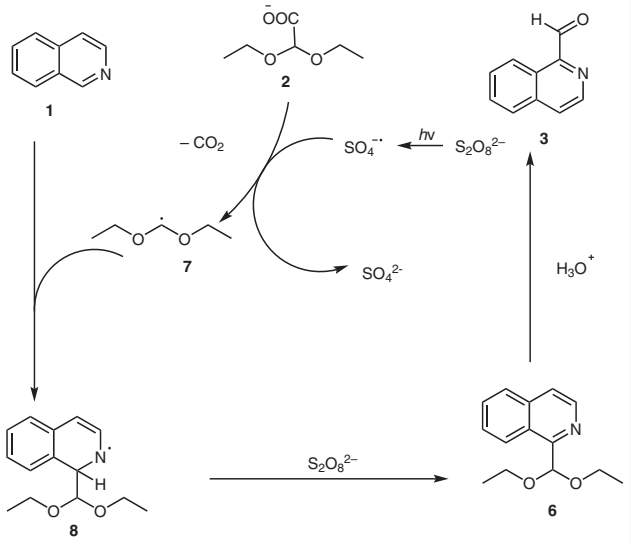

Scheme 5 Proposed mechanism

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609911.

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(18) **Procedure A for Compounds 3a–p**

Heterocycle (0.10 mmol), ammonium persulfate (0.30 mmol) and Cs_2CO_3 (0.20 mmol) were placed in a dry glass tube. Anhydrous DMSO (1 mL) and 2,2-diethoxyacetic acid (0.7 mmol) were injected into the tube by syringe under N_2 atmosphere. The solution was then stirred at room temperature under the irradiation of 15 W blue LEDs strip for 24 h. After completion of the reaction, the mixture was quenched by addition of 1.2 mL of 3.0 M HCl and stirred for another 20 h. Then saturated Na_2CO_3 solution was added to adjust pH to basic. The system was extracted with CH_2Cl_2, the combined organic layers were washed with brine, then dried over anhydrous Na_2SO_4. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with PE and EtOAc.

Isoquinoline-1-carbaldehyde (3a)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.38 (s, 1 H), 9.38–9.22 (m, 1 H), 8.74 (d, J = 5.5 Hz, 1 H), 7.97–7.82 (m, 2 H), 7.83–7.68 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.79, 195.74, 149.88, 142.54, 136.97, 130.88, 130.15, 127.05, 126.41, 125.80, 125.63. GC-MS (EI): 157.1, 129.1, 102.1, 75.0, 63.1, 51.1, 29.1.

Procedure B for Compounds 5a–z,bb

Heterocycle (0.10 mmol), ammonium persulfate (0.20 mmol), $[Ir\{dF(CF_3ppy)\}_2(dtbbpy)]PF_6$ (0.2 mol%), α-keto acids (1.0 mmol) were placed in a dry glass tube. Anhydrous DMSO (1 mL) was injected into the tube by a syringe under a N_2 atmosphere. The solution was then stirred at room temperature under the irradiation of 15 W blue LEDs strip for 12 h. After completion of the reaction, saturated Na_2CO_3 solution was added to adjust pH to basic. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with PE and EtOAc.

(4-Methylquinolin-2-yl)(phenyl)methanone (5b)

Brownish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dd, J = 14.0, 7.9 Hz, 3 H), 8.07 (d, J = 8.3 Hz, 1 H), 7.94 (s, 1 H), 7.77 (t, J = 7.6 Hz, 1 H), 7.72–7.65 (m, 1 H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 2.80 (s, 3 H).^{13}C NMR (151 MHz, $CDCl_3$): δ = 194.33, 154.52, 146.72, 145.78, 136.32, 133.18, 131.59, 131.27, 129.86, 129.08, 128.30, 128.27, 123.90, 121.43,19.08. GC-MS (EI): 247.1, 232.1, 218.1, 204.1, 140.0, 105.0, 77.1, 51.1, 28.1.

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