Visible-Light-Triggered Decarboxylative Alkylation of 8-Acylaminoquinoline with *N*-Hydroxyphthalimide Ester

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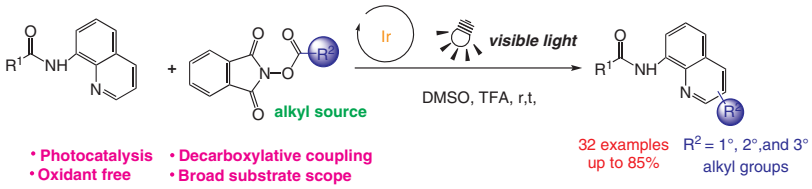

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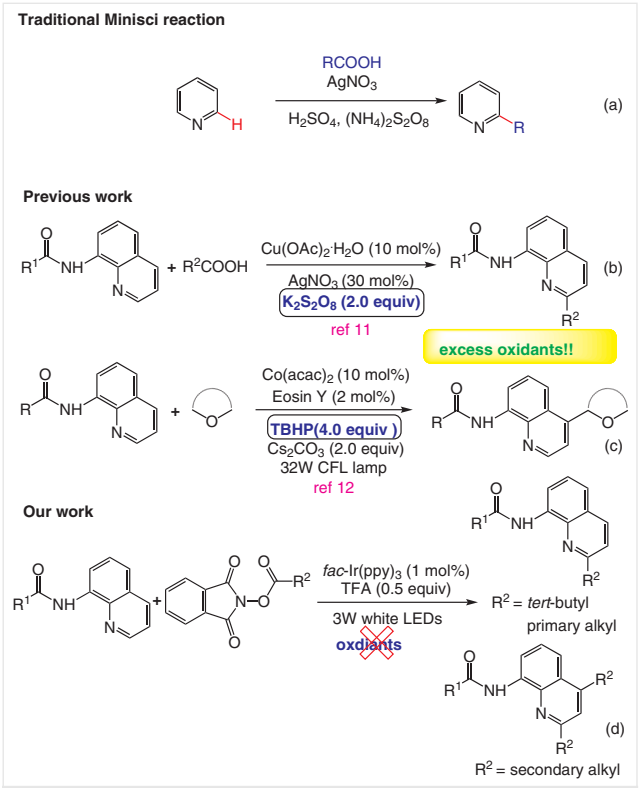
Abstract A facile protocol for visible-light-induced decarboxylative radical coupling of NHP esters with 8-aminoquinoline amides is reported, affording a highly efficient approach to synthesize a variety of 2-alkylated or 2,4-dialkylated 8-aminoquinoline derivatives. The reaction proceeds smoothly without adding any ligand, and provides the corresponding products containing a wide range of functional groups in moderate to excellent yields. This reaction uses readily available starting materials, and proceeds under mild conditions and with operational simplicity.

Key words 8-aminoquinoline, visible light, C–H alkylation, decarboxylation

As an important structural motif of heterocyclic molecules in natural products, quinoline derivatives have been widely applied to pharmaceutical science.[1] Particularly, 8-aminoquinolines exhibit several remarkable properties such as anti-Alzheimer and antimalarial activities.[2] In addition, 8-aminoquinoline amide was discovered as a bidentate directing group by Daugulis.[3] Therefore, it is of great importance to develop highly efficient methods for the preparation of substituted 8-aminoquinoline derivatives. The direct C–H functionalization of 8-aminoquinolines has gained significant interest in organic synthesis, and many successful examples including C–H halogenation,[4] alkylation,[5] nitrification,[6] esterification,[7] phosphonation[8] and carboxylation[9] on the C5 position have been achieved. The Minisci reaction,[10] in which carboxylic acids serve as the alkyl source (Scheme 1a), was likely to be a feasible method to lead to the alkylation of 8-aminoquinoline on the different positions (C2 or C4). This hypothesis has been demonstrated by Xia's group[11] through the use of strong oxidizing conditions (combination of $AgNO_3$ and $K_2S_2O_8$) (Scheme 1b), affording a series of 2-cycloalkyl-8-aminoquinolines;



Scheme 1 Strategies for the synthesis of alkylated 8-aminoquinoline derivatives

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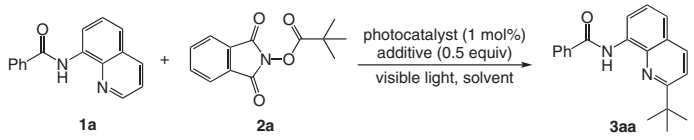
however, primary alkyl acids did not participate in the reaction. Recently, Ranu[12] reported a cobalt-catalyzed selective remote C-4 alkylation of 8-aminoquinoline amides via C–H activation with irradiation with a CFL lamp (Scheme 1c). Consequently, it is highly desirable to investigate both mild and convenient methods for synthesizing alkylated, especially primary-alkylated, 8-aminoquinoline derivatives, which could further promote the application of 8-aminoquinolines in new drug discovery and synthesis.

During the past decade, with the higher demand for developing green and sustainable chemistry, visible-light-induced catalysis, which has the advantage of environment-friendliness, mild conditions, and low-energy irradiation, has received increasing attention.[13] According to previous reports,[14] the alkyl *N*-hydroxyphthalimide (NHP) ester generated via condensation between NHPI and carboxylic acid, was shown to be an effective alkyl source because it could be easily reduced under photocatalytic conditions to donate a variety of alkyl radicals while releasing CO_2 and phthalimide. With this idea in mind, a visible-light-mediated radical type decarboxylative alkylation of 8-aminoquinoline by employing NHP esters was envisioned to solve the problem of a lack of effective methods for synthesis of chain alkylated 8-aminoquinoline derivatives.

As a part of our ongoing research on developing green methods for C–H functionalization,[15] herein, we described a facile visible-light-induced photoredox alkylation between 8-aminoquinoline amides and alkyl NHP esters through a radical type decarboxylative coupling process, affording an oxidant-free method for the preparation of 2-alkyl and 2,4-dialkyl 8-aminoquinoline amides under mild conditions (Scheme 1d).

To explore and optimize the reaction conditions, *N*-(quinolin-8-yl) benzamide (**1a**) and *tert*-butyl NHP ester (**2a**) were chosen as the model substrates. Initially, photocatalysts such as $Ru(bpy)_3Cl_2$, *fac*-Ir(ppy)$_3$, Eosin Y, Rhodamine 6G, and Rose Bengal were selected as catalysts to carry out the decarboxylative coupling reaction. Fortunately, the 2-*tert*-butyl product **3aa** was obtained, albeit in a relatively low yield (21%), when the reaction was irradiated with 3 W blue LEDs for 12 hours at room temperature under nitrogen atmosphere by employing *fac*-Ir(ppy)$_3$ as the photocatalyst and DMSO as the solvent (Table 1, entry 2), whereas none of the other screened photocatalysts cata-

Table 1 Optimization of the Reaction Conditions[a]



Entry	Photocatalyst	Solvent	Additive	Yield (%)[b]
1	$Ru(bpy)_3Cl_2$	DMSO	–	trace
2	*fac*-Ir(ppy)$_3$	DMSO	–	21
3	Eosin Y	DMSO	–	N.D.
4	Rhodamine 6G	DMSO	–	N.D.
5	Rose Bengal	DMSO	–	trace
6	*fac*-Ir(ppy)$_3$	DMSO	TFA	63
7	*fac*-Ir(ppy)$_3$	DMSO	DIPEA	15
8	*fac*-Ir(ppy)$_3$	DMSO	citric acid	trace
9	*fac*-Ir(ppy)$_3$	MeCN	TFA	trace
10	*fac*-Ir(ppy)$_3$	DCE	TFA	N.D.
11	*fac*-Ir(ppy)$_3$	acetone	TFA	17
12[c]	*fac*-Ir(ppy)$_3$	DMSO	TFA	81
13[d]	*fac*-Ir(ppy)$_3$	DMSO	TFA	39
14[e]	*fac*-Ir(ppy)$_3$	DMSO	TFA	N.D.
15[f]	*fac*-Ir(ppy)$_3$	DMSO	TFA	N.D.

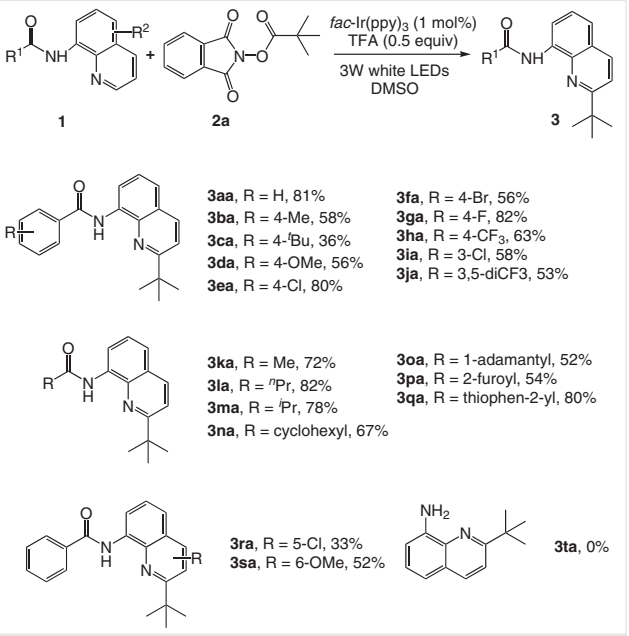
[a] Reaction conditions: a mixture of **1a** (0.1 mmol), **2a** (0.2 mmol), photocatalyst (1 mol%), additive (0.05 mmol), solvent (3 mL) was irradiated with CFL lamps under nitrogen atmosphere at room temperature for 12 h.
[b] Isolated yield.
[c] White LEDs instead of blue LEDs.
[d] Green LEDs instead of blue LEDs.
[e] Without irradiation.
[f] Without nitrogen atmosphere.

lyzed the reaction (entries 1–5). To further improve the yield of target product **3aa**, several additives were then examined. To our delight, the yield of **3aa** increased to 63% when the reaction was conducted in the presence of 0.5 equiv of TFA (entry 6). Other additives, such as DIPEA and citric acid, did not give a satisfactory result (entries 7, 8). Subsequently, a variety of other commonly used solvents were also investigated for this transformation (entries 9–11). However, the experimental results revealed that the reaction did not proceed well when carried out in MeCN, DCM or acetone, and DMSO was still found to be the best choice.

It was also pleasing to find that the yield of **3aa** increased sharply from 63 to 81% (Table 1, entry 12) when the blue LEDs were replaced with white LEDs; only low yield was obtained when green LEDs were employed as light source (entry 13). The reaction failed to initiate without any irradiation (entry 14). It is worth noting that the reaction did not proceed without the protection of nitrogen (entry 15). On the basis of the screening of the reaction conditions, it was clear that this cross-coupling reaction should be performed in the presence of *fac*-Ir(ppy)$_3$ in DMSO with the irradiation of 3 W white LEDs at room temperature under nitrogen atmosphere (Table 1, entry 12).

With the optimized conditions in hand, a series of 8-aminoquinoline derivatives were then applied to this C(sp^2)–C(sp^3) bond formation to yield the corresponding alkylated 8-aminoquinoline derivatives via the decarboxylative coupling with *tert*-butyl NHP. As summarized in Scheme 2, this method was found to be applicable to a wide range of 8-aminoquinoline amides and afforded the desired coupling products **3aa–sa** in moderate to good yields. Firstly, a series of 8-aminoquinoline amides bearing different protecting groups on the amino moiety were studied for this reaction. The results showed that the protecting groups have no obvious influence on the reaction. Substrates containing electron-donating groups (Me, *t*Bu, OMe) or electron-withdrawing groups (Cl, Br, F, CF$_3$) on the benzene ring of **1** were all well tolerated and afforded the desired C2-*tert*-butyl substituted products **3ba–ja** in moderate to good yields. By comparison of **3ea** and **3ia**, it also could be concluded that the substrates with substituents at different positions of the benzene ring exhibited similar reactivity. Furthermore, the substrate scope of this process with respect to aliphatic amides was evaluated under the optimized reaction conditions. The 8-aminoquinoline amides bearing either noncyclic alkyl groups such as methyl- (**3k**), *n*-Pr- (**3l**) and *i*-Pr- (**3m**), or the cyclic alkyl group (cylcohexyl, adamantyl) (**3n**, **3o**), all exhibited excellent tolerance for this transformation, providing the corresponding products **3ka–oa** in yields of 52–82%.

Heterocyclic amides containing furan (**3p**) or thiophene (**3q**) moieties also showed good suitability and gave the desired products in satisfactory yields. Moreover, to extend the substrate scope, 8-aminoquinoline derivatives bearing

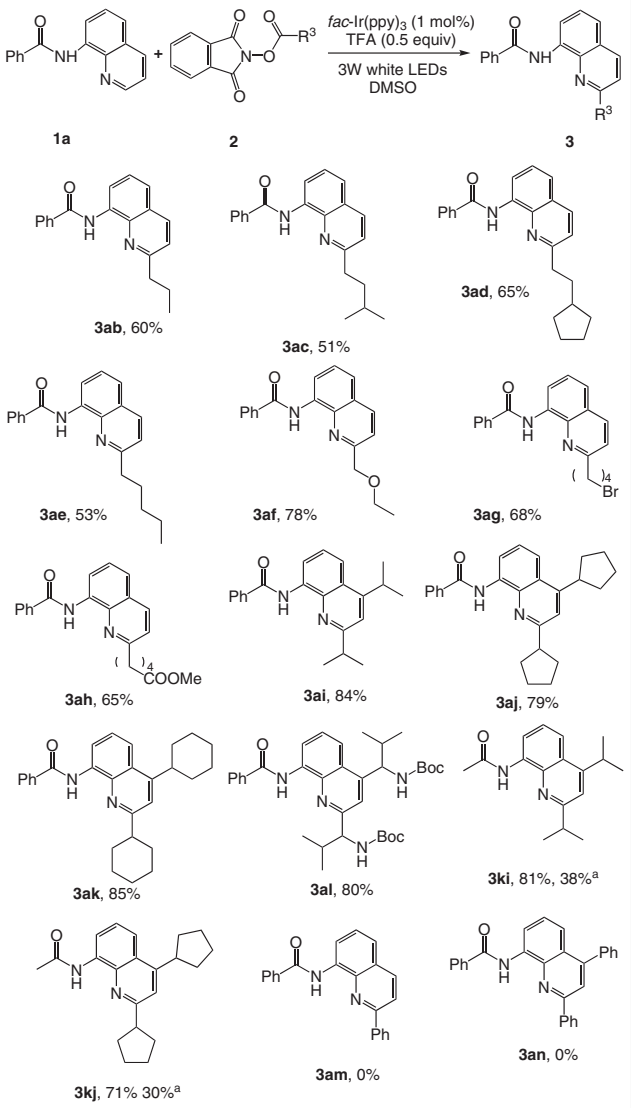


Scheme 2 Substrate scope of 8-aminoquinolines and alkyl NHP esters. *Reagents and conditions*: **1** (0.5 mmol), **2a** (1 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), TFA (0.25 mmol), DMSO (3 mL), with irradiation with white CFL lamps in nitrogen atmosphere at room temperature for 12 h.

substituents on the quinoline ring were also studied. Both 5-Cl (**3ra**) and 6-OMe (**3sa**) derived products could be obtained in moderate yields under the standard reaction conditions. Unfortunately, when *N*-free protected 8-aminoquinoline was subjected to the standard reaction conditions, no corresponding product could be detected.

Subsequently, we continued to investigate the substrate generality with a range of representative NHP esters via decarboxylative coupling with **1a** under the standard conditions. The results are summarized in Scheme 3. The primary alkyl NHP esters all showed good tolerance for this reaction, affording the corresponding alkylated products **3ab–ae** in moderate yields.

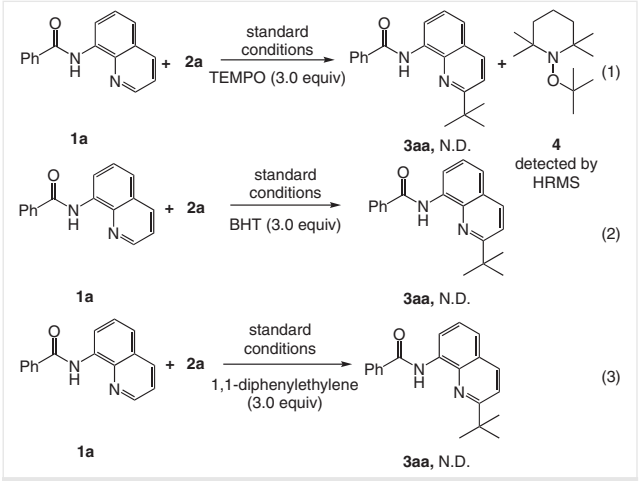
Moreover, primary alkyl NHP esters with additional hetero atoms such as oxygen (**2f**) or halogen (**2g**) were also well tolerated for this transformation, and the desired products **3af–ah** could be obtained in satisfactory yields. Substrates with ester groups (**2h**) also exhibited good reactivity, providing the corresponding product **3ah** in 65% yield. When secondary aliphatic carboxylic NHP esters such as isopropyl (**2i**), cyclopentyl (**2j**), cyclohexyl (**2k**) and *N*-Boc-L-norvalinyl (**2l**) were employed to react with **1a**, no C-2 monoalkylated product could be obtained. Instead, 2,4-disubstituted products **3ai–al** were isolated in good yields. Similar results were found when 8-acetylaminoquinoline **1k** was used under the reaction conditions (**3ki**, **3kj**). We tried to reduce the amount of NHP ester to 1 equivalent, and products **3ki** and **3kj** were still obtained in lower yields. Notably, neither 2-aryl-substituted *N*-(quinolin-8-



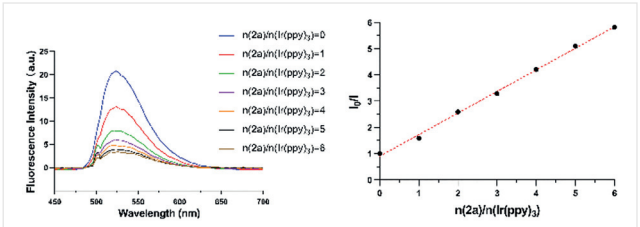
Scheme 3 Substrate scope of alkyl NHP esters. *Reagents and conditions*: **1a** (0.5 mmol), **2** (1 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), TFA (0.25 mmol), DMSO (3 mL), with irradiation with white CFL lamps in nitrogen atmosphere at room temperature for 12 h. [a] NHP ester (1 equiv) was used.

yl)benzamide product (**3am**) nor 2,4-disubstituted byproduct (**3an**) were found under the standard conditions.

Control experiments were carried out to gain insight into the mechanism (Scheme 4). Firstly, the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was applied to the model reaction system and we found that this decarboxylative coupling reaction was completely inhibited (Scheme 3, Eq. 1). Meanwhile, the adduct **4** of alkyl radical and TEMPO was detected by HRMS. Similar results were obtained when other radical scavengers 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 1,1-diphenylethylene were employed in the same reaction system (Scheme 3, Eq. 2 and 3). Additionally, Stern–Volmer experiments (Scheme 5) were performed and the results indicated that Ir(ppy)$_3^*$ could be quenched with alkyl NHP esters, suggesting that the reaction might proceed through an oxidative quenching pathway (for details, see the Supporting Information).



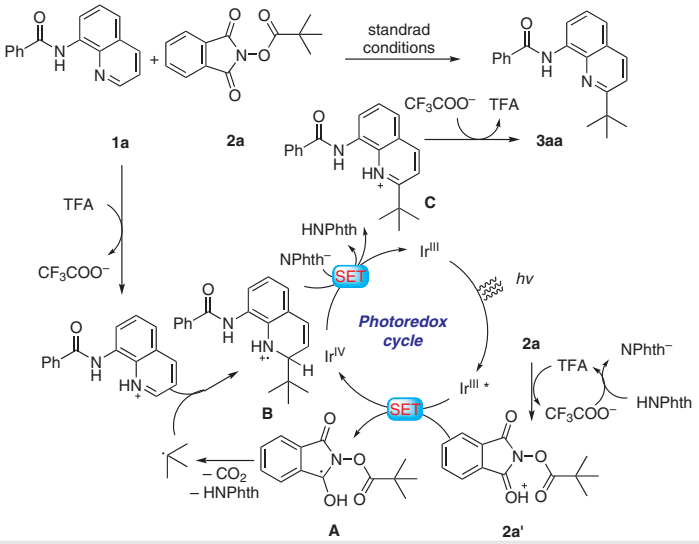
Scheme 4 Control experiments



Scheme 5 Stern–Volmer experiments

According to the observations described above and to previous reports,[15a,b] a plausible mechanism for this decarboxylative coupling reaction is proposed in Scheme 6. Firstly, the photocatalyst *fac*-Ir(ppy)$_3$ is irradiated to give its activated species Ir(ppy)$_3^*$, which can donate an electron to the protonated NHP esters **2a′** to form the radical **A**. After elimination of phthalimide and carbon dioxide, radical **A** could transform into the *tert*-butyl radical, which then undergoes a regioselective addition to the TFA-protonated **1a** to generate the key intermediate **B**. A proton on the C2 position of **B** is then removed by the phthalimide anion. The deprotonated product gives Ir^{4+} an electron in a SET step and is transformed into the intermediate **C**. Finally, **C** is transferred into the desired product **3aa** by facile elimination of TFA.

In conclusion, we have succeeded in developing a novel visible-light-induced C–H alkylation of 8-aminoquinolne amides by employing alkyl NHP esters as the alkyl source, preparing a variety of alkyl-substituted 8-aminoquinoline derivatives.[16] Remarkably, this transformation has been shown to be compatible with a wide range of alkyl NHP esters, and a variety of 8-aminoquinoline derivatives bearing



Scheme 6 Proposed mechanism

various functional groups also exhibited good tolerance for this transformation. Mechanistic studies have revealed that this decarboxylative coupling reaction proceeds through a radical process.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691579.

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(16) **Synthesis of 3; Typical Procedure for 3aa**: A 10 mL Schlenk-tube was charged with *N*-(quinolin-8-yl)benzamide (**1a**; 124 mg, 0.5 mmol), *tert*-butyl NHP ester **2a** (247 mg, 1.0 mmol), *fac*-Ir(ppy)$_3$ (6 mg, 0.015 mmol), trifluoroacetic acid (29 mg, 0.25 mmol) and DMSO (3.0 mL). The tube was evacuated and back-filled with N_2 for three times. The mixture was then irradiated with 3 W white CFL lamps and stirred for 12 hours at room temperature. After the reaction finished, the reaction was quenched with water (10 mL) and the mixture was extracted with DCM (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (ethyl acetate/hexane, 1:200) to afford **3aa** (123 mg, 81%) as a white solid; mp 131.0–132.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.04 (s, 1 H), 8.92 (d, *J* = 7.1 Hz, 1 H), 8.20–8.11 (m, 3 H), 7.68–7.48 (m, 6 H), 1.55 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 156.3, 148.6, 144.4, 137.1, 136.5, 134.0, 126.6, 126.0, 121.3, 119.0, 116.3, 114.8, 112.4, 38.3, 30.1. HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2O$: 305.1648; found: 305.1638.