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Visible-Light-Driven Regioselective Decarboxylative Acylation of *N*-Methyl-3-phenylquinoxalin-2(1*H*)-one by Dual Palladium−Photoredox Catalysis Through C−H Activation

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ABSTRACT: We report herein an efficient visible-light-promoted approach for the regioselective decarboxylative C−H acylation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones using α-oxo-2-phenylacetic acids *via* dual palladium−photoredox catalysis. The reactions were carried out at room temperature in the presence of 24 W blue LEDs. The established protocol tolerated a wide range of functional groups and enabled the synthesis of several acylated *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones in good to excellent yields. The proposed mechanism for this transformation was supported by control experiments.

INTRODUCTION

Visible-light photoredox catalysis has proven to be a powerful tool for organic transformations through C−C and C-heteroatom bond formation under mild reaction conditions.[1] Unlike the well-explored two-electron transfer traditional methods, single-electron transfer (SET)-mediated visible-light-driven protocols activate the functional groups of reaction substrates and result in several important organic conversions, overcoming the drawback associated with a single catalytic system.[2] Interestingly, the combination of visible-light photoredox catalyst and transition metal catalyst as dual catalyst has gained profound attention in accelerating various organic reactions that are not accessible through a single catalytic system.[3] In the last decade, several protocols have been reported demonstrating the successful merger of photoredox catalysis with transition metal catalysis for the installation of significant functional groups at specific positions of organic molecules.[4] Moreover, most of the developed dual catalytic systems are more focused toward the use of bimetallic systems, which involve the combination of Ru- and Ir-based complexes as photoredox catalysts with transition metals such as Cu, Ni, and Pd.[5] However, the involvement of dual metallaphotoredox systems of organic dyes as photoredox catalysts blended with transition metals, still has a significant scope to be explored in organic transformations because organic dyes are cheaper and easier to modify compared to Ru- and Ir-complex-based photocalysts.[6] Recent progress in the application of dual photoredox catalysts for selective C−H bond functionalization has realized the significance of the merger of Pd catalysts with photoredox dyes for selective decarboxylative acylation reactions of heterocyclic molecules.[7]

Quinoxalin-2(1*H*)-ones and their derivatives, in particular, 3-substituted derivatives, have shown promising biological and chemical properties. Anticancer,[8] antiherpes,[9] antiviral,[10] antithrombotic,[11] antitrypanosomal,[12] antihistamine,[13] and antiplasmodium[14] are some of the important pharmaceutical properties exhibited by quinoxalin-2(1*H*)-one derivatives. In addition, 3-substituted quinoxalin-2(1*H*)-ones also act as multidrug resistance antagonists,[15] antidiabetic glycogen phosphorylase inhibitors,[16] aldose reductase inhibitors,[17] smooth muscle relaxant caroverine,[18] modulators of PAS kinase,[19] MAO-A inhibitors,[20] and calcium channel blockers, etc.[21] Owing to the significance of 3-substituted quinoxalin-2(1*H*)-ones, several powerful and convenient protocols have been designed for their preparation.[22] However, the approaches for the selective functionalization of the C−H bond of the 3-substituted benzene ring of 3-arylquinoxalin-2(1*H*)-ones are limited. Our group developed transition metal-catalyzed approaches for the selective functionalization of 3-arylquinoxalin-2(1*H*)-ones *via* selective activation of Csp^2-H bonds (Scheme 1a−c).[23] Extending our efforts further in this direction based on the significance and scope of Pd-based dual photoredox catalysis, and our extensive literature survey on α-keto acid (2-oxo-2-phenylacetic acids) as a substantial acyl surrogate,[24] we hypothesized to carry out the regioselective decarboxylative Csp^2-H acylation of 3-arylquinoxalin-2(1*H*)-

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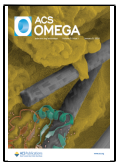

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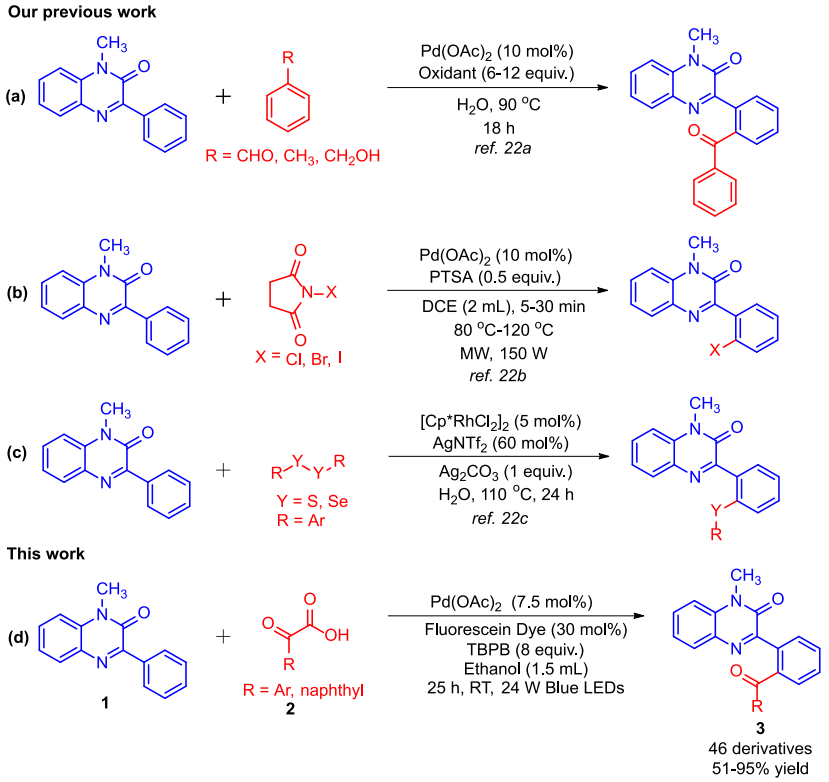
Scheme 1. Previous Transition Metal-Catalyzed Approaches for the Selective Functionalization of 3-Arylquinoxalin-2(1*H*)-ones *via* Selective Activation of Csp^2–H Bonds (a–c), and Present Work (d)



ones. The reactions were carried out between 1-methyl-3-phenylquinoxalin-2(1*H*)-ones and α-keto acids using a dual photoredox catalyst obtained by merging of palladium catalyst with visible-light photoredox catalyst, i.e., fluorescein dye (Scheme 1d). However, to the best of our knowledge, this is the first report for the regioselective decarboxylative acylation of 3-arylquinoxalin-2(1*H*)-ones with α-keto acids under the dual photocatlysis driven from an organic dye (fluorescein) as a photoredox catalyst and a Pd catalyst in the presence of visible-light at room temperature.

RESULTS AND DISCUSSION

Initial study was performed by reacting 1-methyl-3-phenylquinoxalin-2(1*H*)-one (**1a**) with 2-oxo-2-phenylacetic acid (**2a**) under 24 W blue LEDs in the presence of 10 mol % $PdCl_2(PPh_3)_2$ as metal catalyst, 40 mol % fluorescein dye as photocatalyst, and 6 equiv of *tert*-butyl peroxybenzoate (TBPB) oxidant in air for 15 h. Unfortunately, only traces of the desired product **3a** could be seen on thin layer chromatography (TLC) (Table 1, entry 1). However, replacement of catalyst $PdCl_2(PPh_3)_2$ with $Pd_2(dba)_3$ catalyst could result in the desired product in 38% yield (Table 1, entry 2). Afterward, other palladium catalysts, such as $PdCl_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $Pd(TFA)_2$, were screened (Table 1, entries 3–6). Interestingly, an improved product yield was obtained when $Pd(OAc)_2$ was used as the catalyst (Table 1, entry 5). Moreover, replacement of $Pd(OAc)_2$ with other metals, i.e., Co-, Ru-, Rh-, and Ir-based catalysts was ineffective (Table 1, entries 7–11). After exploring various catalysts, we switched to explore the role of oxidants. In this regard, several oxidants, such as $(NH_4)_2S_2O_8$, $K_2S_2O_8$, TBHP (aqueous as well as in decane), DTBP, and H_2O_2, were screened but none of these could facilitate the reaction (Table 1, entries 12–17). Even the combination of $(NH_4)_2S_2O_8$ and $K_2S_2O_8$ with $AgNO_3$ was also examined but the reaction could not deliver the desired product (Table 1, entries 18 and 19). In addition to these oxidants, oxygen was screened, but it could not initiate the reaction (Table 1, entry 20). Finally, 10 mol % $Pd(OAc)_2$ and 6 equiv of TBPB were found to be effective catalyst and oxidant, respectively.

Subsequently, other solvents and photoredox dyes were explored to improve the reaction yield further in the presence of $Pd(OAc)_2$ as the catalyst and TBPB as the oxidant (Table S1). Solvents, such as ethanol, methanol, 1,4-dioxane, DMF, toluene, DCE, and THF, were used for the reaction (Table S1, entries 1–7). Delightfully, all of the screened solvents could deliver the desired product, and 60% product yield was obtained in ethanol (Table S1, entry 5). Apart from fluorescein, other dyes, such as Eosin Yellow, Rose Bengal, Rhodamine 6G, and Methylene Blue, were also screened for this transformation; however, these dyes could not render the desired products (Table S1, entries 8–11). However, when Acridine Red was used as a photocatalyst, only 30% product yield was obtained (Table S1, entry 12).

Next, other parameters, such as equivalents of oxidant, mol % of catalyst, mol % of dye, reaction time, and amount of solvent, were screened in order to improve the product yield further (Table S2). In this regard, initially equivalents of TBPB oxidant varied from 6 to 8, and delightfully, an increase in the yield of the desired product was obtained (Table S2, entry 1). However, a further increase in the concentration of TBPB was unsuccessful as the product yield decreased from 67% to 42% (Table S2, entry 2). Multiple unidentified product formations were observed at higher concentrations of TBPB. This decrease in product yield while using 10 equiv of TBPB was

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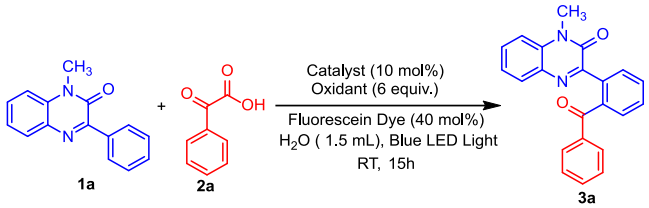
Table 1. Optimization to Study the Effect of Various Catalysts and Oxidants[a]



entry	catalyst	oxidant	yield (%)[b]
1	$PdCl_2(PPh_3)_2$	TBPB	traces
2	$Pd_2(dba)_3$	TBPB	38
3	$PdCl_2$	TBPB	5
4	$Pd(PPh_3)_4$	TBPB	30
5	$Pd(OAc)_2$	TBPB	55
6	$Pd(TFA)_2$	TBPB	51
7	$Co(acac)_3$	TBPB	traces
8	$RuCl_3{\cdot}xH_2O$	TBPB	NR[c]
9	$[RuCl_2(p\text{-cymene})]_2$	TBPB	NR[c]
10	[RhCl(cyclooctadiene)]$_2$	TBPB	NR[c]
11	$IrCl_3$	TBPB	traces
12	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	NR[c]
13	$Pd(OAc)_2$	$K_2S_2O_8$	NR[c]
14	$Pd(OAc)_2$	TBHP (aq)	17
15	$Pd(OAc)_2$	TBHP (decane)	18
16	$Pd(OAc)_2$	DTBP	traces
17	$Pd(OAc)_2$	H_2O_2	NR[c]
18	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (6)	NR[c,d]
19	$Pd(OAc)_2$	$K_2S_2O_8$	NR[c,d]
20	$Pd(OAc)_2$	O_2	NR

[a]Reagents and conditions: a mixture of 1-methyl-3-phenylquinoxalin-2(1*H*)-one (1 mmol), phenylglyoxylic acid (3 mmol), catalyst (10 mol %), fluorescein dye (40 mol %), and oxidant (6 equiv) was stirred in water solvent at room temperature for 15 h under irradiation of 24 W blue LEDs. [b]Isolated yield. [c]No reaction (starting material was present unreacted). [d]Oxidants were taken along with $AgNO_3$.

due to the formation of multiple products in the presence of high concentration of the oxidant. Hence, 8 equiv of TBPB were found to be the best for this transformation. Then the effect of the $Pd(OAc)_2$ catalyst loading was examined. Unfortunately, at higher catalyst loading, inferior product yield was observed (Table S2, entry 3). Remarkably, with a decrease in catalyst loading up to 7.5 mol %, the desired product could be achieved in 75% yield (Table S2, entry 4). However, a further decrease in catalyst loading was not favorable for this transformation (Table S2, entry 5). After finding the best catalyst loading, we subsequently studied the effect of the concentration of photoredox catalyst fluorescein dye. We found 30 mol % of fluorescein to be the best for this reaction as this resulted in a maximum product yield of 79% (Table S2, entry 6). However, any further decrease in dye concentration was unfavorable (Table S2, entries 7−9). By fixing the reaction parameter as 7.5 mol % $Pd(OAc)_2$ as metal catalyst, 30 mol % fluorescein dye as photoredox catalyst, 8 equiv TBPB as oxidant, and ethanol as solvent, we tried to see the effect of reaction time. It was observed that with the increase in reaction time from 15 to 25 h, the desired product yield also increased from 79% to 95% (Table S2, entries 6 and 12). On the other hand, the product yield decreased up to 74% when the reaction was carried out for 12 h due to the incompletion of the reaction (Table S2, entry 13). Last, the amount of solvent was also evaluated, but any increase and decrease in the amount of solvent did not produce favorable results (Table S2, entries 14 and 15).

After optimizing reaction conditions, the scope of the reaction partners, such as 1-methyl-3-phenylquinoxalin-2(1*H*)-ones and α-keto carboxylic acids, was explored. Initially, the scope of keto acids was explored. Several phenylglyoxylic acids containing substituents, such as methoxy, methyl, fluoro, chloro, and bromo, were reacted with 1-methyl-3-phenylquinoxalin-2(1*H*)-one (Table 2, **3b−3g**). All the substrates delivered the desired products smoothly under optimized reaction conditions and yielded the respective products in moderate to good yield. A maximum of 95% yield was obtained in the case of unsubstituted phenylglyoxylic acid (Table 2, **3a**). Additionally, from the experimental results it was inferred that other substituents have no significant role in reaction outcomes as none of them could produce the product in better yield as compared to the unsubstituted α-keto acid (Table 2, **3a−3g**). Furthermore, these substituted α-keto carboxylic acids were treated with differently substituted 1-methyl-3-phenylquinoxalin-2(1*H*)-ones bearing substituents, such as -OMe, -Me, -Cl, and -F groups, on the 3-phenyl ring, i.e., ring B. 3-Phenylquinoxalin-2(1*H*)-one having electron-releasing groups (methoxy and methyl) at the *para*-position of ring B, delivered a slightly better yield than that of electron-withdrawing fluoro and chloro groups at that position (Table 2, **3h−3ab**).

We further examined the scope of differently substituted 1-methyl-3-phenylquinoxalin-2(1*H*)-ones, and this time various substituents were present on ring A (Table 2, **3ac, 3ad, 3ag−3ak**). Ring A equipped with a methyl group provided a better product yield than that with the chloro group. Interestingly, the inductive effect of substituents present on phenylglyoxylic acid played a significant role in this reaction. Better product yield was obtained with substituents with positive inductive effects (Table 2, **3ah−3aj**) as compared to those substituents with negative inductive effects. An increase in product yield was observed with the increase in the +I effect of the substituents present on phenylglyoxylic acid. A slight decrease in case of methoxy substituted group on phenylglyoxylic acid could be due to the −I effect of the -OMe group (Table 2, **3ak**).

3-Phenylquinoxalin-2(1*H*)-ones bearing substituents on both rings, i.e. rings A and B were also explored with substituted phenylglyoxylic acids (Table 2, **3ae, 3af, 3al−3at**). Interestingly, both substrates with a methyl group delivered the corresponding product in 89% yield (Table 2, **3an**). However, replacing the methyl group of keto acid by methoxy resulted in a considerable decrease of product yield (Table 2, **3ap**). Moreover, other substituents could not contribute as effectively as methyl and methoxy groups. 2-(Naphthalen-2-yl)-2-oxoacetic acid also delivered the corresponding products with 1-methyl-3-phenylquinoxalin-2(1*H*)-ones (Table 2, **3g, 3k, 3ab** and **3at**). The introduction of substituents at the *ortho*-position of ring B resulted in the inability to generate products (Table 2, **3ay** and **3az**), primarily due to the presence of significant steric hindrance at the *ortho*-position. Conversely, when the same substituents were positioned at the *meta*-position, notably improved results were obtained (Table 2, **3au**, **3av**).

Interestingly, heterocyclic analogs of 1-methyl-quinoxalin-2(1*H*)-one, such as 3-thiophene, resulted in the corresponding products in 70% yield (Table 2, **3aw**).

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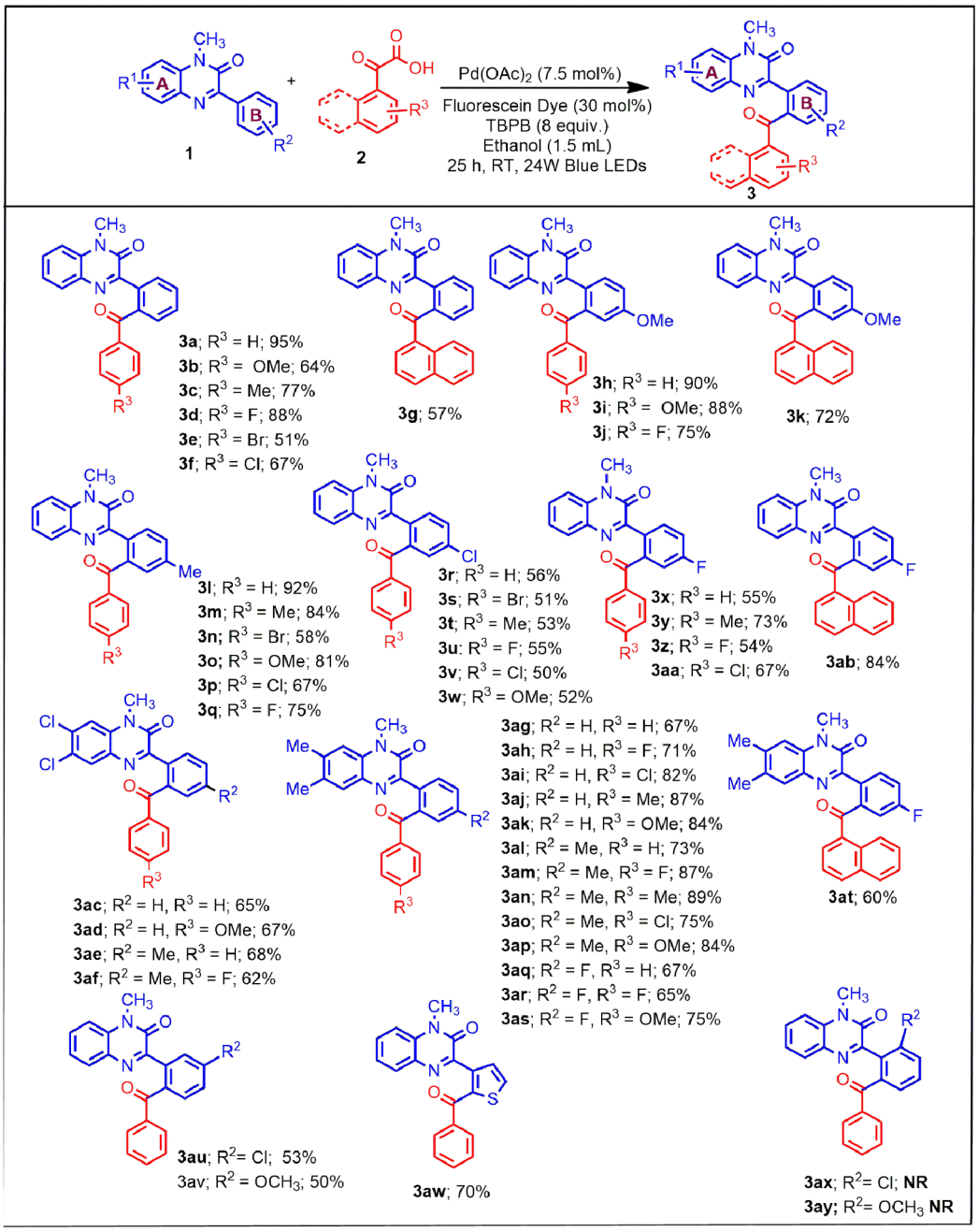
Table 2. Study of Substrate Scope for Decarboxylative Acylation of 1-Methyl-3-phenylquinoxalin-2(1*H*)-ones



To acquire a deeper understanding of the reaction pathway, various control experiments were performed (Scheme S1). When the reaction between 1-methyl-3-phenylquinoxalin-2(1*H*)-one and phenylglyoxylic acid was carried out in the presence of the radical scavenger reagent "TEMPO" (2,2,6,6-tetramethylpiperidine-1-oxyl, 5 mol %), the reaction was quenched completely and no acylated product was obtained (Scheme S1a). This result suggested the SET radical pathway for this transformation. The formation of the TEMPO-benzoyl adduct was confirmed by NMR spectroscopy to ensure the formation of benzoyl radical. Furthermore, when the reaction was carried out in the absence of $Pd(OAc)_2$ catalyst, no product formation was observed, revealing the need for Pd catalyst to enable this transformation (Scheme S1b). However, in the absence of TBPB oxidant, the product was obtained in just 30% yield (Scheme S1c). The product formation in the absence of TBPB could be due to the formation of acyl radicals by fluorescein dye in the presence of blue LED light.[7c] Furthermore, when the reaction was performed without blue LED light at room temperature, no product formation was seen (Scheme S1d). Intresetingly, at 50 °C, a 35% yield of product was obtained (Scheme S1e). Then, on−off experiment was performed to study the reaction profile. This experiment showed that the reaction proceeds only under irradiation of blue light, while the yield remains unchanged during the off conditions, indicating the need for consistent photoexcitation in facilitating this transformation (Figure S1).

On the basis of these experiments and literature reports,[25] a plausible reaction mechanism has been depicted in Scheme 2. The mechanism starts with the photoexcitation of fluorescein

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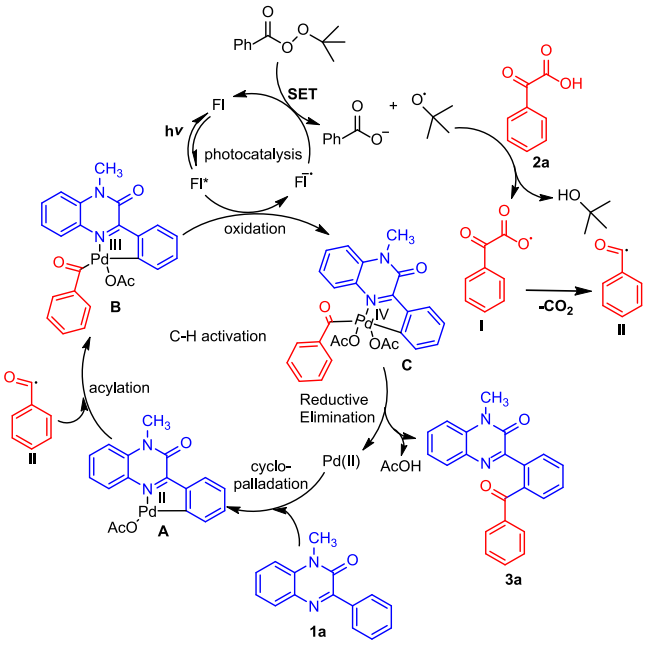
Scheme 2. Plausible Reaction Mechanism



dye (FI) to give its excited form FI*. Meanwhile, cyclopalladation between the Pd(II) catalyst and substrate **1a** delivers intermediate **A**. This intermediate **A** reacts with acyl radical **II** and affords the Pd(III) intermediate **B**. Next, intermediate **B** can undergo a single electron oxidation to render a Pd(IV) complex, which helps to reduce the excited species of fluorescein dye. The anion radical form of fluorescein closes the photocatalytic cycle by generating a *t*-butoxide radical through back electron transfer. The formed *t*-butoxide radical creates acyl radical **II** by the elimination of CO_2. Finally, reductive elimination from intermediate **C** takes places to produce the desired product **3a** and regenerates Pd(II) back.

To check the industrial applicability of this protocol, the reaction was also carried out at gram scale, and the corresponding product was obtained in 87% yield (Scheme S2).

CONCLUSION

In summary, we have disclosed the regioselective decarboxylative C−H functionalization of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones *via* photoredox/Pd-dual catalysis in the presence of visible light. This transformation involves mild reaction conditions, cheaper and readily available acylating agents, inexpensive and metal-free photocatalyst, and is operationally facile. The reaction demonstrated a wide substrate scope and furnished easy access to acylated *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones using 2-oxo-2-phenylacetic acids *via* C−H activation.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Compounds 3a−3at. An oven-dried 10 mL screw-capped reaction vial with a small stirring bar was charged with a mixture of 1-methyl-3-phenylquinoxalin-2(1*H*)-one 1 (1 mmol), α-oxo acid 2 (3 mmol), $Pd(OAc)_2$ (7.5 mol %), and TBPB (8 equiv) in ethanol (1.5 mL). The resulting mixture was stirred at room temperature for 25 h under irradiation of 24W blue LED light. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to ambient temperature, washed with 20 mL of saturated solution of $NaHCO_3$, and extracted with ethyl acetate (3 × 15 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to obtain the crude product. The crude product thus obtained was further purified on a silica gel column using hexane/ethyl acetate (8:2) as the eluent to afford pure targeted products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c06367.

Full experimental details and characterization data for all synthesized products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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