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Merging Photoredox with Palladium Catalysis: Decarboxylative *ortho*-Acylation of Acetanilides with *α*-Oxocarboxylic Acids under Mild Reaction Conditions

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Ⓢ *Supporting Information*

ABSTRACT: A room temperature decarboxylative *ortho*-acylation of acetanilides with *α*-oxocarboxylic acids has been developed via a novel Eosin Y with Pd dual catalytic system. This dual catalytic reaction shows a broad substrate scope and good functional group tolerance, and an array of *ortho*-acylacetanilides can be afforded in high yields under mild conditions.

ortho-Acylacetanilides are important structural motifs and synthetic intermediates in the preparation of natural products and pharmaceutically bioactive compounds, such as acridones, cinnolines, fluorenones, indoles, quinolones, and benzodiazepines.[1] Owing to their unique properties, the development of a practical synthetic strategy for their preparation is highly desirable. In the past decade, general methods for the synthesis of *ortho*-acylacetanilides via direct C−H activation and functionalization of aniline derivatives by using relatively nonhazardous acylating agents have been developed. Evidently, transition-metal-catalyzed direct C−H functionalization plays one of the most important roles in organic synthesis, which enables the construction of carbon−carbon and carbon−heteroatom bonds efficiently without the use of stoichiometric organometallic reagents.[2] In 2010, Ge disclosed an *ortho*-acylation of acetanilides through a Pd-catalyzed decarboxylative coupling of *α*-oxocarboxylic acids, and subsequently, a numbers of direct acylation of aromatic C(sp^2)−H bonds through Pd(II)-catalyzed decarboxylative cross-coupling with *α*-oxocarboxylic acids were reported.[3] In 2011, our group and others independently developed the oxidative cross-coupling of aldehydes with acetanilides.[4] After then, Yuan and Zhou showed that benzyl alcohols could act as the acylating agents.[5] Meanwhile, Sun, Kwong, and Zhang indicated that toluene could also act as the acyl precursors.[6]

Recently, visible light photoredox catalysis has emerged as a powerful tool in organic synthesis, which makes use of the photoredox catalyst that, upon excitation by visible light, engages in single electron transfer (SET) with the general functional groups, activating the substrates toward a diverse array of useful organic transformations.[7] More intriguingly, dual catalysis realized by combining visible light photoredox catalysis and transition-metal catalysis has recently attracted prominent attention. Exploration of the dual catalytic strategy has allowed the development of powerful organic transformations, which are not easily accessible and can overcome the drawbacks of a single catalytic system. Most recently, the successful merger of photoredox and transition metal catalysis has been demonstrated by Sanford,[8] MacMillan,[9] Glorius,[10] Rueping,[11] Molander,[12] and others[13] for the specific installation of unique functional groups, and which will be identified as a kind of useful synthetic method.

Based on our exploration in photoredox catalysis and inspired by the reported results,[14] we hypothesize that the decarboxylative *ortho*-acylation of acetanilides with *α*-oxocarboxylic acids can be realized by merging palladium catalysis with visible light photoredox catalysis. This assumed process has been carried out by using an Eosin Y and palladium dual catalytic system. It is important to note that an organic dye (such as Eosin Y) is cheaper and easier to modify compared with transition-metal photoredox catalysts, such as Ru- and Ir-complexes.[9−13] Herein, we report the first combination of organic dye (Eosin Y) as photoredox catalyst and palladium catalyst for the *ortho*-acylation of acetanilides with *α*-oxocarboxylic acids under visible light irradiation at room temperature.

An initial study was performed by using $[Ru(bpy)_3]Cl_2$ as a photoredox catalyst in Pd-catalyzed *ortho*-acylation of acetanilide (**2a**) with phenylglyoxylic acid (**1a**) in air under the irradiation of 3 W blue LED for 15 h. It was pleasing to find that the reaction does indeed proceed and afforded the desired acylation product **3a** in 36% yield (Table 1, entry 1). An improved yield (52%) of **3a** was obtained when an oxygen balloon was used instead of air atmosphere. In the absence of palladium or visible-light irradiation, none of the desired product was formed, and only a trace amount of the product was detected without $[Ru(bpy)_3]Cl_2$ (Table 1, entries 2−4). Subsequently, a number of photocatalysts, including Ru- and Ir-complexes and organic dyes, palladium sources, solvents, and molar ratio of substrates were examined to improve the reaction efficiency. It must be highlighted that the color of light emitting diode (LED) was used to match the absorption wavelength of photoredox catalyst. For

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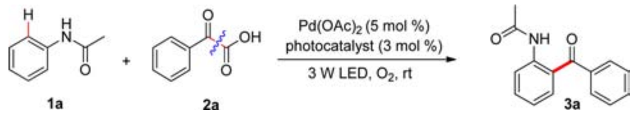
Table 1. Optimization of the Reaction Conditions[a]



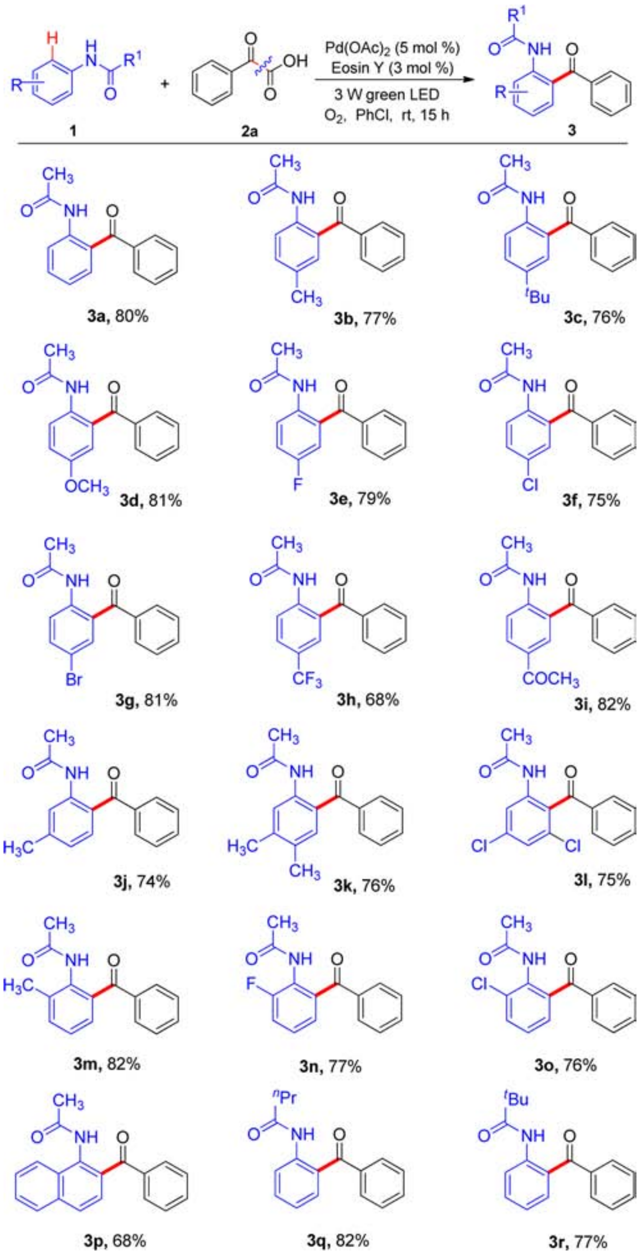
entry	photocatalyst	solvent	light source	yield[b] (%)
1	$Ru(bpy)_3Cl_2$	DCE	blue LED	36,[c] 52
2	$Ru(bpy)_3Cl_2$	DCE	blue LED	n.r.[d]
3		DCE	blue LED	trace
4	$Ru(bpy)_3Cl_2$	DCE	dark	n.r.
5	$Ir(ppy)_3$	DCE	blue LED	42
6	rose bengal	DCE	green LED	59
7	acridine	DCE	blue LED	62
8	methylene blue	DCE	green LED	49
9	fluorescein	DCE	green LED	trace
10	eosin Y	DCE	green LED	71, 72,[e] 42[f]
11	eosin Y	DCE	green LED	61[g]
12	eosin Y	DCE	green LED	49[h]
13	eosin Y	DCE	green LED	68[i]
14	eosin Y	DCE	green LED	66[j]
15	eosin Y	toluene	green LED	44
16	eosin Y	acetonitrile	green LED	57
17	eosin Y	DMF	green LED	42
18	eosin Y	1,4-dioxane	green LED	61
19	eosin Y	chloroform	green LED	63
20	eosin Y	chlorobenzene	green LED	80, 61,[k] 82[l]
21	eosin Y	chlorobenzene	green LED	61,[m] 82[n]
22	eosin Y	chlorobenzene	green LED	66,[o] 81[p]

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (5.0 mol %), photocatalyst (3.0 mol %), solvent (2.0 mL), rt, O_2, 3 W LED for 15 h. [b]Isolated yield. [c]Air atmosphere. [d]Without $Pd(OAc)_2$; n.r. = no reaction. [e]Eosin Y (5.0 mol %). [f]Eosin Y (1.0 mol %). [g]$Pd(TFA)_2$ (5.0 mol %). [h]$PdCl_2$ (5.0 mol %). [i]$Pd(CH_3CN)_2Cl_2$ (5.0 mol %). [j]$Pd(PPh_3)_2Cl_2$ (5.0 mol %). [k]$Pd(OAc)_2$ (3.0 mol %). [l]$Pd(OAc)_2$ (10 mol %). [m]**2a** (0.50 mmol, 1.0 equiv). [n]**2a** (1.0 mmol, 2.0 equiv). [o]10 h. [p]20 h.

example, blue light was used for $[Ru(bpy)_3]Cl_2$, while green light was used for Rose Bengal. Among the photocatalysts examined, Eosin Y showed the highest reactivity (Table 1, entries 5−10). For palladium sources, $Pd(OAc)_2$ was the best of choice (Table 1, entries 10−14). Solvent screening revealed that chlorinated solvents were better than others, and chlorobenzene was the most effective medium for the reaction, affording product **3a** in 80% yield (Table 1, entries 15−20). The loading of palladium and photoredox catalyst, the ratio of **1a** to **2a**, as well as the reaction time were optimized, which are outlined in Table 1 (entries 21 and 22).

Next, the generality of this *ortho*-acylation was investigated under the optimal reaction conditions. As summarized in Scheme 1, a broad range of substituted acetanilides were examined to be applicable to this transformation. In general, *m*- and *p*-substituted acetanilides with electron-donating and electron-withdrawing groups on the benzene rings could be applied to the reaction with **2a** and afforded the desired products (**3a**−**j**) in good yields. This reaction also proceeded well as acetanilides, possessing strong electron-withdrawing groups, such as trifluoromethyl and acetyl group at the *p*-positions (**3h** and **3i**). Furthermore, the reactions of *m*,*p*- and *m*,*m*-disubstitued acetanilides with **2a** generated good yields of the corresponding products (**3k** and **3l**). It should be noted that *o*-methyl, *o*-fluoro, and *o*-chloro substituted acetanilides reacted with **2a** to afford the corresponding products (**3m**−**o**) in 76−82% yields under the present conditions, but no reaction was found in $Pd(TFA)_2/(NH_4)_2S_2O_8$ system.[3] However, much more hindered *o*-substituted acetanilides [*o*-ethyl, *o*-(*iso*-propyl), and (*o*-*tert*-butyl) acetanilides], failed in the reaction under the current catalysts system. *N*-(Naphthalen-1-yl)acetamide reacted with **2a**, affording the desired product **3p** in 68% yield. Except acetanilides, *N*-phenylbutyramide and *N*-phenylpivalamide also underwent the *ortho*-acylation with **2a** to generate the desired products **3q** and **3r** in 82% and 77% yields, respectively.

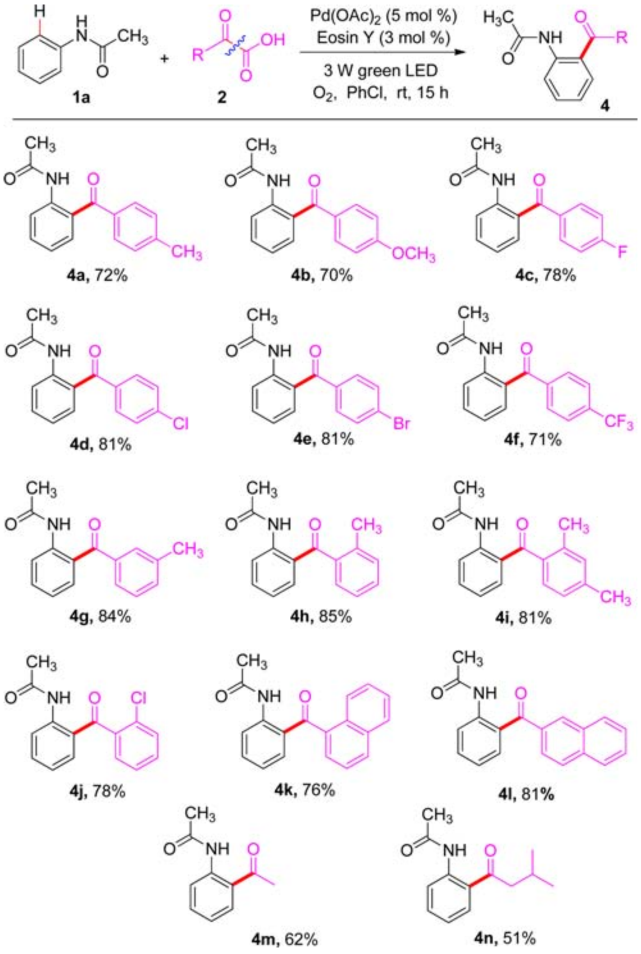
Scheme 1. Scope of Anilides[a,b]



[a]Reaction conditions: **1** (0.50 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (5.0 mol %), Eosin Y (3.0 mol %), chlorobenzene (2.0 mL), rt, O_2, 3 W green LED for 15 h. [b]Isolated yield.

As shown in Scheme 2, a variety of substituted phenylglyoxylic acids, including methyl, methoxy, halogen, and trifluoromethyl groups on the phenyl rings were compatible in the reaction with **1a** under the optimal reaction conditions, providing the desired products (**4a**−**g**) in high yields. It is worth noting that *ortho*-

Scheme 2. Scope of α-Oxocarboxylic Acids[a,b]

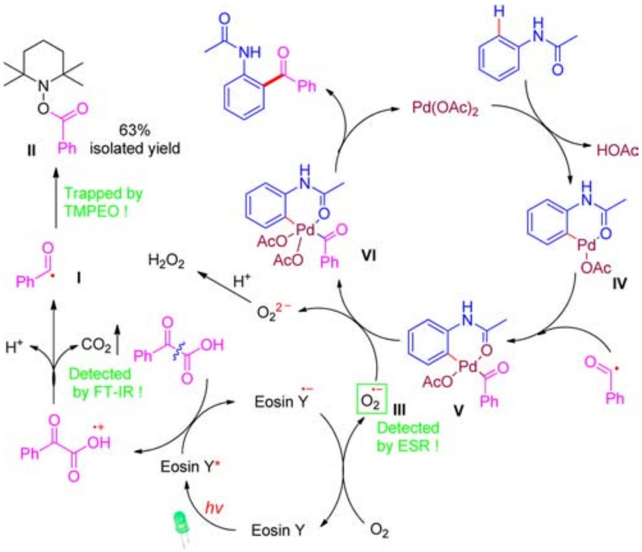


[a]Reaction conditions: **1** (0.50 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (5.0 mol %), Eosin Y (3.0 mol %), chlorobenzene (2.0 mL), rt, O_2, 3 W green LED for 15 h. [b]Isolated yield.

hindered phenylglyoxylic acids were also feasible coupling partners, leading to products **4h**−**j** in 78−81% yields. 1-Naphthyl and 2-naphthyl α-oxocarboxylic acids also gave good yields of the corresponding products **4k** and **4l**. Furthermore, aliphatic α-oxocarboxylic acids, such as 2-oxopropanoic acid and 4-methyl-2-oxopentanoic acid, were also compatible in this reaction, giving fair yields of **4m** and **4n**.

To understand this transformation, a plausible reaction pathway was proposed with phenylglyoxylic acid (**1a**) and acetanilide (**2a**), as shown in Scheme 3. At first, Eosin Y was excited to its excited state (Eosin Y)* under visible light irradiation. An oxidation of phenylglyoxylic acid with formed (Eosin Y)* generated benzoyl radical (**I**), which was trapped by 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to its adduct **II** in 63% isolated yield along with the formation of $(\text{Eosin Y})^{\bullet-}$. Subsequently, electron transfer from $(\text{Eosin Y})^{\bullet-}$ by molecular oxygen regenerated Eosin Y for next run and produced superoxide radical anion **III** ($O_2^{\bullet-}$), which was confirmed by electron spin resonance (ESR). However, the Pd-catalytic cycle could be initiated by a C−H activation of acetanilide to form a palladacycle intermediate **IV**, which reacted with the formed benzoyl radical (**I**) *in situ* to afford a Pd(III) intermediate **V**, followed by a one-electron oxidation via superoxide radical anion to generate a Pd(IV) intermediate **VI** along with the formation of O_2^{2-} and H_2O_2. Subsequently, a reductive elimination of **VI** to the desired product and Pd(II) catalyst occurs to complete the catalytic cycle.

Scheme 3. Plausible Mechanistic Cycle



In summary, a dual catalytic system for the *ortho*-acylation of acetanilides has been developed, and its applicability to a broad range of substrates was highlighted. In comparison with single transition-metal procedure, stoichiometric or overstoichiometric amounts of oxidants can be used instead by a photoredox catalyst and molecular oxygen system. It is important to note that Eosin Y used as photoredox catalyst makes this system both attractive and a more environmentally sound alternative. Moreover, a plausible reaction mechanism is proposed based on the control experiments and ESR studies. Further attempts to apply this new type of combined catalysis to other substrates and metal catalysts are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03192.

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

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Notes

The authors declare no competing financial interest.

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