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Acylation of Arenes with Aldehydes through Dual C−H Activations by Merging Photocatalysis and Palladium Catalysis

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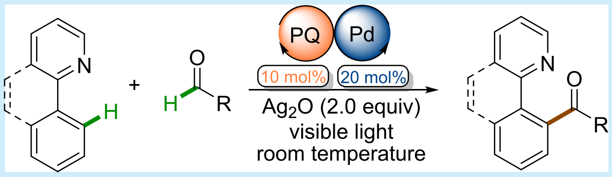
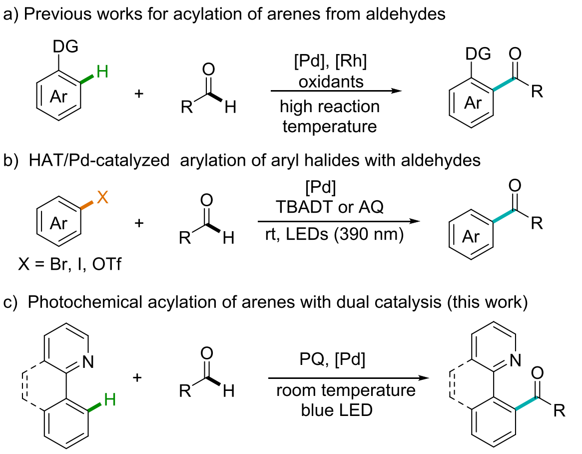
ABSTRACT: An acylation of arenes with aldehydes through dual C−H activations at room temperature is reported. The acylation was initiated by phenanthraquinone-catalyzed hydrogen atom transfer from aldehyde under visible light irradiation. The aldehyde-derived acyl radical merged with palladium-catalyzed activation of arenes to afford the cross coupling products.



Aryl ketones are important structural motifs widely found in natural products, pharmaceuticals, and functional materials.[1] Because of their importance, many synthetic protocols for aromatic ketones have been achieved. The Lewis acid-promoted Friedel−Crafts acylation of aromatics is one of the most classical methods for synthesis of aryl ketones, although the reaction suffers from poor regioselectivity and harsh conditions.[2] Beyond typical cross coupling methods, the C−H activation strategy provides a unique opportunity to construct carbonyl compounds without prefunctionalization steps.[3] Over the past several decades, transition metal-catalyzed oxidative C−H functionalization has been significantly developed for the preparation of complex molecules from simple starting materials with high atom efficiency.[4] The abundant aldehydes are commercially available and inexpensive and could serve as ideal acylation reagents for the synthesis of aryl ketones in the presence of *ortho*-chelating groups and strong oxidants (Scheme 1a).[5] Although of great significance, the use of an excess of oxidant (such as TBHP or PIDA) to generate acyl radicals and the requirement of a high reaction temperature limit their applications.

Scheme 1. Generation of Aryl Ketone via Acylation from Aldehydes


a) Previous works for acylation of arenes from aldehydes

b) HAT/Pd-catalyzed arylation of aryl halides with aldehydes

c) Photochemical acylation of arenes with dual catalysis (this work)

Because the chemical reactivity of electronically excited molecules differs fundamentally from that in the ground state, the photochemistry induced by visible light provides fresh opportunities to expand the potential of aldehydes.[6] It was determined that the formyl hydrogen of aldehyde could be abstracted by photoexcited tetrabutylammonium decatungstate (TBADT)[7] or anthraquinone (AQ)[8] to acyl radical through a hydrogen atom transfer (HAT) process. By merging the process with palladium catalysis, Zhang et al. recently realized the acylation of aryl halides under mild conditions (Scheme 1b).[9] Here we reported the photochemical regioselective arylation through direct double C−H activations of aldehydes and arenes under photocatalysis in conjunction with palladium catalysis.

Our initial investigations focused on the model photochemical acylation between 4-methylbenzaldehyde **1** and 2-phenylpyridine **2**. As shown in entry 1 of Table 1, when AQ was exploited as the photocatalyst for the generation of acyl radical and $Pd(OAc)_2$ as the transition metal catalyst, no coupling product was detected. Screening the possible photocatalysts identified that phenanthraquinone (PQ)[10] efficiently abstracted formyl hydrogen and the corresponding acylation product **3** was afforded in 82% yield (entry 2). In addition to Ag_2O, other oxidants [such as MnO_2, $Mn(OAc)_2$, O_2, $K_2S_2O_8$, etc.] for the recycling photocatalysis were also evaluated. However, these experiments resulted in much lower yields because aldehydes were very sensitive to these strong

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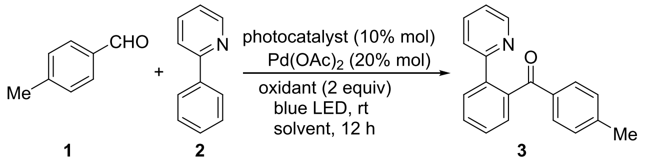
Table 1. Screening for the Optimal Conditions[a]



entry	photocatalyst	oxidant	solvent	yield[b] (%)
1	AQ	Ag_2O	CH_3CN	0
2	PQ	Ag_2O	CH_3CN	82
3	PQ	MnO_2	CH_3CN	69
4	PQ	$Mn(OAc)_2$	CH_3CN	58
5	PQ	air	CH_3CN	35
6	PQ	O_2 (1 atm)	CH_3CN	26
7	PQ	$K_2S_2O_8$	CH_3CN	25
8	PQ	Ag_2O	CH_2Cl_2	49
9	PQ	Ag_2O	DCE	55
10	PQ	Ag_2O	$CHCl_3$	52
11	PQ	Ag_2O	acetone	65
12	PQ	Ag_2O	DMF	0
13	PQ	Ag_2O	THF	0
14[c]	PQ	Ag_2O	CH_3CN	0
15	none	Ag_2O	CH_3CN	0

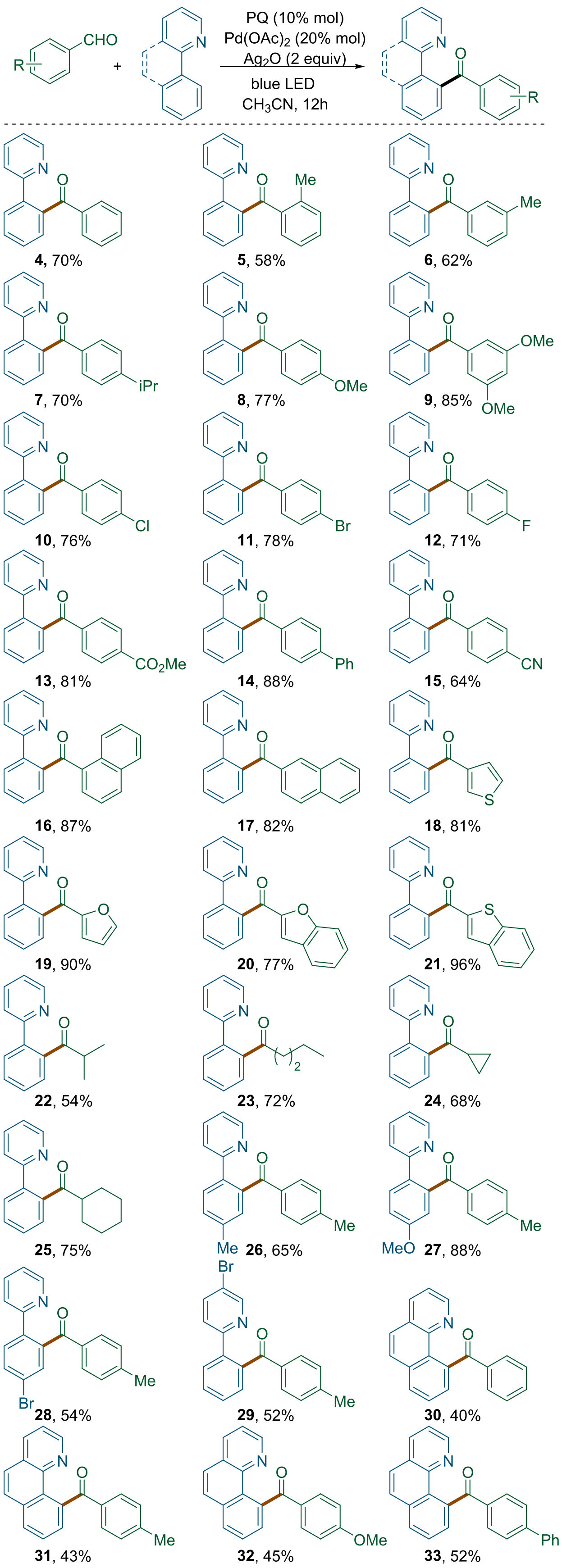
[a] Reaction conditions: **1** (0.5 mmol, 2.5 equiv), **2** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (0.04 mmol, 20 mol %), photocatalyst (0.02 mmol, 10 mol %), and oxidant (0.4 mmol, 2.0 equiv) in the solvent (4 mL) irradiated by blue LEDs under an argon at room temperature for 12 h. [b] Isolated yields by silica gel column chromatography. [c] The reaction was conducted in the dark while the mixture was being refluxed.

oxidants (entries 3−7). Further screening the solvents revealed that MeCN was optimal, lower yields were obtained in CH_2Cl_2, DCE, acetone, etc. (entries 8−11), and no products were harvested in DMF and THF (entries 12 and 13, respectively). The photochemical nature of this acylation was incontestably confirmed as essentially no product was observed when the controlled experiments were performed in the dark while refluxing or without a photocatalyst (entries 14 and 15).

With the optimized reaction conditions established, the scope of this photochemical acylation was investigated (Scheme 2). It was discovered that the acylation tolerated a wide range of substituents on the aromatic ring of benzaldehydes. The acylation of 2-phenylpyridine with non-substituted benzaldehyde (**4**) and aldehydes bearing electron-donating substituents on different positions, such as Me, *i*Pr, and OMe (**5**−**9**), proceeded well, and 70−85% yields were obtained. The halogen substituents (**10**−**12**) were also suitable for the acylation. In addition to the electron-donating groups, the substrates containing an electron-withdrawing group, such as 4-CO_2Me (**13**), 4-Ph (**14**), and 4-CN (**15**) groups, that were also examined for the acylation all afforded the product in good yields (64−88%). We next evaluated polycyclic aromatic aldehydes and found that both α- and β-naphthaldehyde (**16** and **17**, respectively) were efficient substrates. In addition, this acylation was also extended to heterocyclic aldehydes. Reactions with 3-thiophenaldehyde, 2-furanaldehyde, and 2-benzofuranaldehyde afforded products in high yields (**18**−**20**, respectively), especially for 2-benzothiophenaldehyde (**21**, 96% yield).

Moreover, we also found that this acylation was not limited to aryl aldehydes; aliphatic aldehydes were also reactive, and the corresponding products (**22**−**25**) were afforded with moderate yields. The substituted 2-phenylpyridine analogues

Scheme 2. Substrate Scope of Photochemical Acylation



were also exploited for the coupling reaction, and moderate yields were obtained (**26**−**29**). Finally, we investigated the reactivity of benzo[*h*]quinoline as the arene substrate with aryl aldehydes. It is worth noting that benzaldehyde or the *para*-substituted benzaldehydes containing different phenyl electron-donating or electron-withdrawing groups were also suitable for the PQ/palladium dual catalyzed acylation (**30**−**33**), albeit lower yields were obtained. Moreover, the acylation of 2-phenylpyridine (**2**) with 4-methylbenzaldehyde (**1**) was also conducted on a 2 mmol scale, and a 73% yield of product **3** was harvested after 24 h.

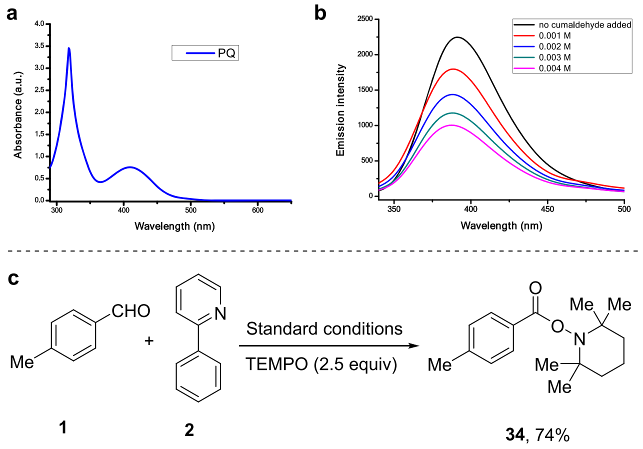
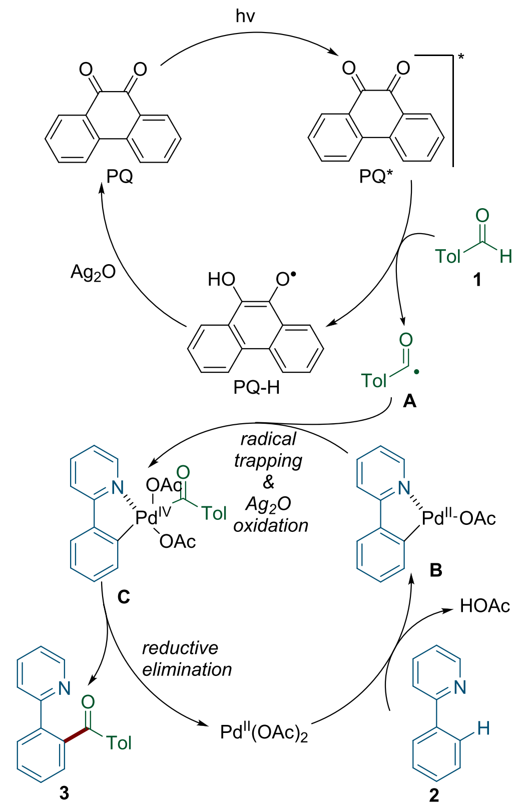


Figure 1. Mechanistic studies. (a) UV−vis absorption spectra of acetonitrile solutions (1×10^{-4} M) of PQ. (b) Quenching of the PQ emission (1×10^{-5} M in CH_3CN) in the presence of increasing amounts of **1**. (c) Radical trapping experiments with TEMPO.

To improve our understanding of the reaction mechanism, UV−vis experiments with PQ as the HAT photocatalyst were conducted (Figure 1a). Obvious absorption peaks of the buff solution of PQ in the visible light region as well as in the UV region were observed (Figure 1a). Because the fluorescence signal excited by visible light is very weak, the alternative emission at 395 nm excited by UV was measured. Stern−Volmer quenching studies revealed that the excited state of PQ was effectively quenched by cumaldehyde (Figure 1b). Moreover, the Stern−Volmer analysis revealed a linear correlation indicating a dynamic quenching of the excited PQ by cumaldehyde (Figure S3). These results indicated that the excited PQ was responsible for triggering the formation of the acyl radical from aldehyde. To verify that the acyl radical participated in the acylation reaction, the controlled experiment with radical scavenger TEMPO was conducted under the standard conditions. The reaction was completely suppressed, and no coupling product was formed. Instead, TEMPO-quenched product **34** was isolated in 74% yield (Figure 1c). These results suggested that an acyl radical was generated through a HAT process under the photochemical conditions and participated in the downstream palladium-catalyzed acylation.

Scheme 3. Proposed Mechanism of Acylation through the Dual Catalysis Process



On the basis of literature reports and experimental results, a plausible mechanism for the merging of the photocatalytic cycle and the palladium catalytic cycle is outlined in Scheme 3. The photocatalyst PQ was initially irradiated by visible light to reach an electronically excited state (PQ*). Then it abstracted a hydrogen from aldehyde **1** to generate an acyl radical **A** and PQ-H. PQ-H was oxidized by Ag_2O to recycle the photocatalyst. Meanwhile, 2-phenylpyridine **2** reacted with $Pd(OAc)_2$ through C−H activation to afford a five-membered palladacycle intermediate **B**.[11] Photogenerated acyl radical **A** was then trapped by palladacycle **B** followed by further oxidation with Ag_2O to form Pd(IV)[12] intermediates **C**. Finally, intermediates **C** underwent reductive elimination to release coupling product **3** and regenerate the Pd(II) catalyst.

In summary, we have developed an acylation protocol between aldehydes and arenes via merging photocatalysis and palladium catalysis. The photoexcited PQ abstracted a hydrogen atom from aldehydes to generate the acyl radical through a HAT process. Then it merged with a palladium-catalyzed C−H activation to afford the cross coupling products. In addition, the method utilized both aromatic and aliphatic aldehydes as an abundant acyl source to afford aryl ketones under mild reaction conditions, as well as tolerance for a broad range of functional groups.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01184.

Experimental procedures, ^{1}H and ^{13}C NMR spectra, and characterization data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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