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Dual Photoredox/Palladium-Catalyzed C–H Acylation of 2-Arylpyridines with Oxime Esters

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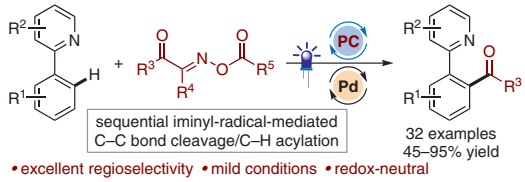

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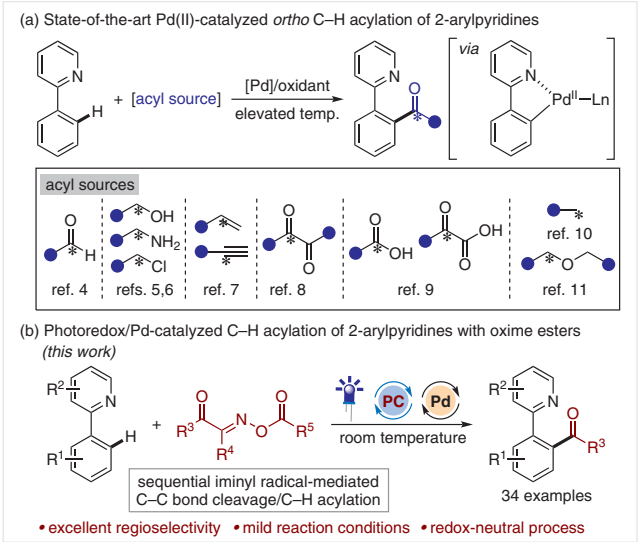
Abstract An unprecedented dual photoredox/palladium-catalyzed iminyl-radical-mediated C–C bond cleavage and directed *ortho* C–H acylation of 2-arylpyridines by using oxime esters is described. Oxime esters can serve as efficient acyl sources through formation of the corresponding acyl radicals by photoredox-catalyzed iminyl-radical-mediated C–C bond cleavage. This redox-neutral protocol features excellent regioselectivity, a broad substrate scope, and good functional-group tolerance with respect to both components, giving a broad range of aryl ketones with generally good yields.

Key words photocatalysis, palladium catalysis, C–H activation, acylation, iminyl radical, oxime esters

Over recent decades, palladium-catalyzed direct C–H activation/functionalization has been established as one of the most attractive and powerful platforms for the construction of various carbon–carbon and carbon–heteroatom bonds.[1] Because of the prevalence of benzophenone motifs in numerous pharmaceuticals, fragrances, and agrochemicals,[2] the palladium-catalyzed oxidative C–H acylation reactions of directing arenes have been particularly well explored.[3] There have been many advances in relation to the substrate scope, functional-group compatibility, and range of catalyst systems for these transformations. In this context, a wide variety of readily available acyl sources have been identified as being capable of coupling with palladacycle intermediates formed by C–H activation of 2-arylpyridines (Scheme 1a). Representative acyl sources include aldehydes,[4] alcohols,[5] arylmethyl amines and chlorides,[6] alkenes and alkynes,[7] diketones,[8] carboxylic acids and α-keto acids,[9] toluene derivatives,[10] and benzylic ethers.[11] Despite their advantages, most of these arene C–H acylation reactions still require stoichiometric oxidants and elevated temperatures (>80 °C). As a result, the quest for new acyl sources and the design of general room-temperature and redox-neutral methods for C–H acylation continues to be an important challenge for this area.



Scheme 1 State-of-the-art Pd(II)-catalyzed *ortho* C–H acylation of 2-arylpyridines, and a new reaction design

The field of nitrogen radical chemistry has recently witnessed a renaissance, triggered mainly by the introduction of visible-light photoredox catalysis for the formation of

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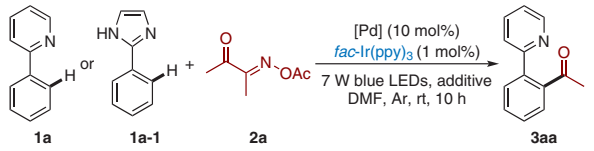
various open-shell nitrogen radical species under mild conditions.[12] In this area, our laboratory has also been interested in developing new methods that permit selective nitrogen-mediated reactions through the use of photoredox catalysis.[13] As part of this program, we recently disclosed that cyclic iminyl radicals generated from easily prepared oxime esters under visible-light-driven photoredox catalysis can undergo β-C–C bond cleavage to form cyanoalkyl radicals.[14,15] With radical species of this type, we developed a wide range of carbon–carbon and carbon–heteroatom bond-forming transformations toward the synthesis of diverse cyano-group-containing molecules. These radical processes are highly selective and proceed through a redox-neutral mechanism, such that no stoichiometric additives are required. Given that palladium-catalyzed radical chemistry has been well established,[16] we questioned whether the chemistry of iminyl radicals might be applied to palladium-catalyzed C–H functionalization of arenes. Moreover, the Wu group recently reported that acyclic α-keto oxime esters can undergo photocatalytic single-electron transfer (SET) reduction and β-fragmentation via the corresponding iminyl radicals, thereby permitting a range of radical transformations of alkenes.[17] Inspired by these studies and in consideration of the significant advantages of metallaphotoredox-catalyzed reactions,[18] we attempt to explore the possibility that α-keto oxime esters might serve as an effective class of acyl-radical precursors to participate in the acylation of 2-arylpyridines under dual photoredox/palladium catalysis (Scheme 1b). This strategy features mild reaction conditions and requires no external oxidant. Notably, the feasibility of our reaction design was recently corroborated by the investigations of the group of Wang and Li,[19] who showed that a combination of the photoredox catalyst Eosin Y or 9-mesityl-10-methylacridinium perchlorate with $Pd(TFA)_2$ permitted the efficient room-temperature decarboxylative *ortho*-acylation of acetanilides, azobenzenes, or azoxybenzenes in the presence of O_2 or air as an oxidant. Sanford and co-workers also reported that combining photoredox catalysis and palladium-catalyzed C–H activation permitted room-temperature aromatic C–H arylation with aryldiazonium salts as aryl-radical sources.[20] In addition, many other dual catalytic strategies for C–H functionalization have been reported.[21] Here, we describe how we translated our idea into experimental reality.

Initially, we selected 2-phenylpyridine (**1a**), and butane-2,3-dione *O*-acetyloxime (**2a**) as the model substrates to explore the feasibility of the target *ortho* C–H acylation (Table 1).[22] To our delight, when the reaction was performed in the presence of the photocatalyst *fac*-Ir(ppy)$_3$ (1 mol%) and $Pd(TFA)_2$ (10 mol%) in DMF at room temperature under irradiation by 7 W blue LEDs for ten hours, the desired reaction occurred to give the expected product **3aa** in 21% yield, albeit with moderate conversion (Table 1, entry 1). Extending the reaction time to 24 hours slightly increased the yield to 30% (entry 2). It has been well documented that metal salts as additives typically play an important role in palladium-catalyzed C–H functionalization.[23] We therefore screened a range of commonly used silver salts (entries 3–6), and we found that AgOTf (2.0 equiv) provided an obvious enhancement in the yield, giving a 42% yield of **3aa** (entry 5). Moreover, an increase in the amount of AgOTf to 2.5 equivalents significantly improved the reaction efficiency, with **3aa** being isolated in 75% yield (entry 7). At the current stage, we are unsure of the role of AgOTf in the process; however, mechanistic studies are currently ongoing to elucidate this in more detail.[24] Compared with $Pd(TFA)_2$, other palladium salts [$Pd(OAc)_2$ and $PdCl_2$] gave lower yields (entries 8 and 9). Finally, the results of a series of control experiments showed that the photocatalyst, palladium salt, and visible light are all essential to the *ortho* C–H acylation reaction (entries 10–12). We further examined other N-heterocycles as directing groups, as illustrated by the case of 2-phenylimidazole (**1a-1**); however, its reaction did not proceed under the standard conditions (entry 13).

Table 1 Condition Optimization[a]



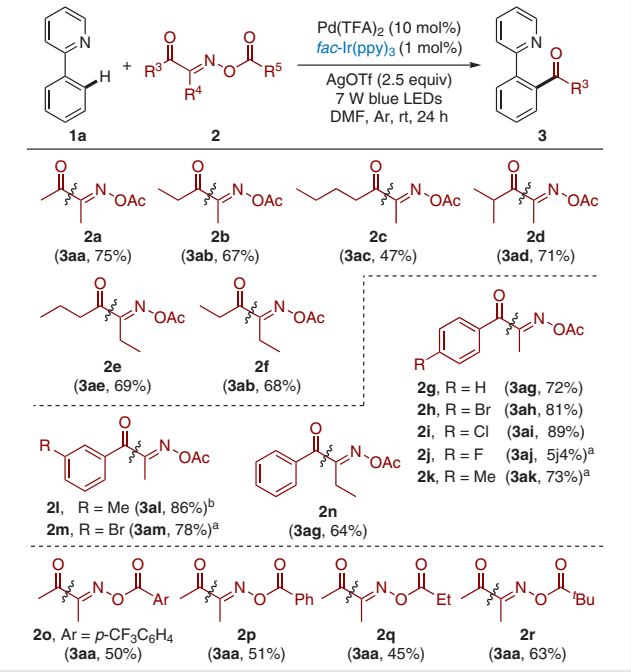
1a 1a-1 2a 3aa

Entry	Reactant	[Pd]	Additive (equiv)	Yield[b] (%)
1	**1a**	$Pd(TFA)_2$	–	21
2[c]	**1a**	$Pd(TFA)_2$	–	30
3[c]	**1a**	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	28
4[c]	**1a**	$Pd(TFA)_2$	AgOAc (2.0)	26
5[c]	**1a**	$Pd(TFA)_2$	AgOTf (2.0)	42
6[c]	**1a**	$Pd(TFA)_2$	AgTFA (2.0)	32
7[c]	**1a**	**$Pd(TFA)_2$**	**AgOTf (2.5)**	**82 (75)[d]**
8[c]	**1a**	$Pd(OAc)_2$	AgOTf (2.5)	64
9[c]	**1a**	$PdCl_2$	AgOTf (2.5)	55
10[c]	**1a**	–	AgOTf (2.5)	NR[e]
11[c,f]	**1a**	$Pd(TFA)_2$	AgOTf (2.5)	NR
12[c,g]	**1a**	$Pd(TFA)_2$	AgOTf (2.5)	NR
13[c]	**1a-1**	$Pd(TFA)_2$	AgOTf (2.5)	NR

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), Pd catalyst (10 mol%), additive, DMF (2.0 mL), rt, 7 W blue LEDs, 10 h.
[b] NMR yield.
[c] 24 h.
[d] Isolated yield.
[e] NR = no reaction.
[f] Without a photocatalyst.
[g] Without visible-light irradiation.

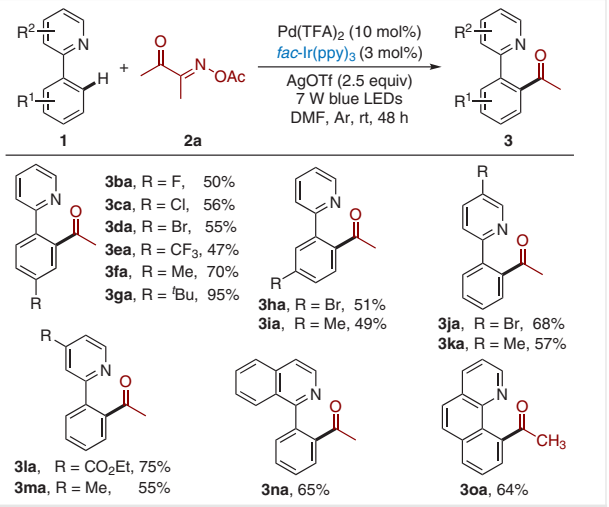
With the optimized conditions in hand, we first investigated the substrate scope of the acyl radical precursor by using a range of oxime esters **2** (Scheme 2). In addition to

2a, oxime esters **2b–d** bearing linear or branched alkyl chains reacted well with **1a** to give the corresponding products **3ab–ad** in yields of 47–71%. As shown in the cases of **2e** and **2f**, variation of the iminyl group (R^4) was tolerated, and the expected products **3ae** and **3ab** were obtained in good yields with release of propionitrile during the course of acyl-radical formation. Notably, a variety of aryl acyl radicals generated from oxime esters **2g–m** with electronically diverse substituents (H, Br, Cl, F, or Me) at the *para*- or *meta*-position of the phenyl ring all participated in the reaction smoothly after a prolonged reaction time or in the presence of 3 mol% of photocatalyst. The desired products **3ag–am** were obtained in yields of 54–89%. Again, the reaction of **2n** also worked well to afford **3ag** in 64% yield. In agreement with our previous study,[14] structural modification of the acyl moiety on the oxime had somewhat of an effect on the reaction. For example, oxime esters **2o–r** also provide to be suitable for the reaction, albeit with a lower reaction efficiency, leading to product **3aa** in 45–63% yield, probably as result of their inherent redox potential.



Scheme 2 Scope of the oxime esters. Isolated yields based on **1a** are reported. [a] 48 h. [b] 48 h, 3 mol% of *fac*-Ir(ppy)$_3$.

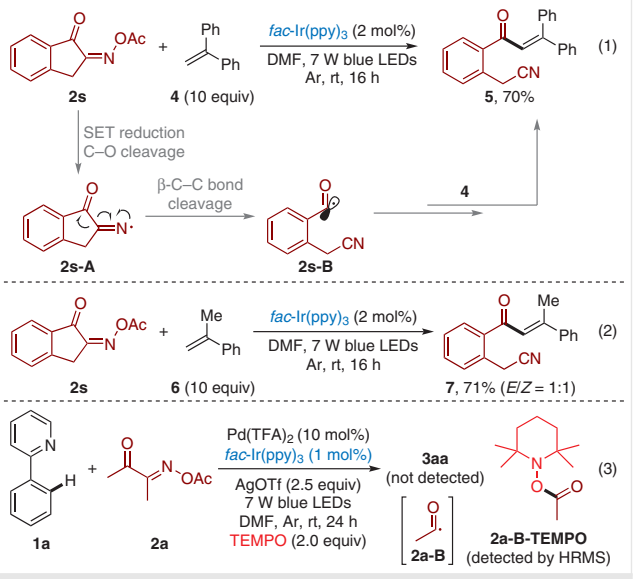
Next, we proceeded to examine the scope of the 2-arylpyridine under the standard conditions; however, the reactions proceeded slowly. In contrast, the reaction efficiency was significantly increased when 3 mol% of the photocatalyst was used with an extended reaction time of 48 hours (Scheme 3). It appears that a diverse set of electronically and sterically diverse functional groups on the phenyl ring are well tolerated. For instance, substrates **1b–i** with electron-withdrawing or electron-donating groups at various positions of the aromatic ring *para* or *meta* to the pyridinyl group, reacted readily with **2a** to give **3ba–ia** in yields of 47–95%. As shown in the case of **3ea**, the presence of the strongly electron-withdrawing group CF_3 resulted in an obvious decrease in the yield. Furthermore, the reactions of substrates **1j–m** with electronically diverse functional groups (Br, Me, CO_2Et) on the pyridine ring also proceeded smoothly to give **3ja–ma** in good yields. We were pleased to find that other directing groups such as quinoline also facilitated the *ortho* C–H acylation: as such, products **3na** and **3oa** were isolated in yields of 65% and 64%, respectively. Note that halogen atoms Cl and Br on the arene or pyridine ring were fully compatible with the current catalytic system, suggesting that Pd(0) species are not intermediates in this process.



Scheme 3 Scope of 2-arylpyridines. Isolated yields based on **1** are reported.

To gain some insight into the mechanism, we then carried out control experiments with the cyclic oxime ester **2s** (Scheme 4). We found that **2s** reacted smoothly with 1,1-diphenylethylene (**4**) and α-methylstyrene (**6**) under the conditions that we previously developed for the generation of iminyl radicals from oxime esters.[14] The corresponding α,β-unsaturated ketones **5** and **7** with acetonitrile group in the *ortho*-position of the phenyl ring were obtained in good yields. These results, together with our previous studies[14] and the work of the Wu group,[17] suggest that a cyclic iminyl radical **2s-A** might be involved in the process; this radical is formed by SET reduction of **2s** followed by C–O cleavage. Subsequently, radical **2s-A** might trigger β-C–C bond cleavage to form the relatively more-stable acyl radical **2s-B**. In addition, upon addition of the radical scavenger TEMPO in a stoichiometric amount under the standard conditions, the model reaction between **1a** and **2a** was completely inhibit-

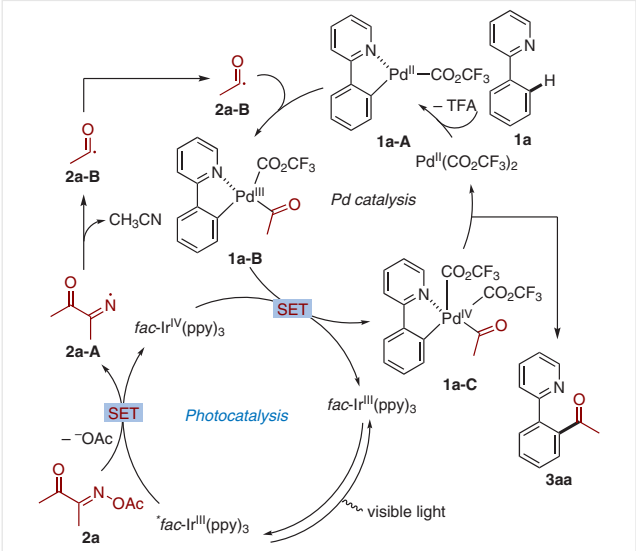
ed, and the corresponding radical-trapping adduct **2a-B-TEMPO** was detected. This observation indicated that acyl radical **2a-B** might be involved in this process.



Scheme 4 Mechanistic study

On the basis of these experimental results and reports in the literature,[15,19,20] a plausible mechanism for the reaction of **1a** and **2a** is proposed, as shown in Scheme 5. First, irradiation of the photocatalyst *fac*-Ir(ppy)$_3$ produces an excited state **fac*-Ir(ppy)$_3$ that undergoes a SET with oxime ester **2a** to form the iminyl radical **2a-A** upon C–O bond cleavage. Iminyl radical **2a-A** then undergoes further β-C-C bond cleavage to form the more stable acyl radical **2a-B**. Meanwhile, **1a** undergoes pyridine-directed electrophilic palladation to generate the five-membered cyclopalladated complex **1a-A**.[25] We hypothesize that, at this stage, **1a-A** reacts with acyl radical **2a-B** to furnish a Pd(III) intermediate **1a-B**; this is followed by another SET oxidation by the oxidizing-state *fac*-Ir^{IV}(ppy)$_3$ to form the Pd(IV) complex **1a-C**, closing the photocatalytic cycle. Finally, C–C bond-forming reductive elimination of **1a-C** occurs to yield the desired product **3aa** with regeneration of the Pd(II) catalyst, completing the palladium-catalysis cycle.

In summary, we have developed the first example of a dual photoredox and palladium-catalyzed iminyl-radical-mediated C–C bond cleavage and directed *ortho* C–H acylation of 2-arylpyridines by using oxime esters without any external oxidant.[26] This room-temperature redox-neutral protocol features excellent regioselectivity, a broad substrate scope, and good functional-group tolerance with respect to both components, providing practical access to a range of aryl ketones. We expect that this strategy will find application in the design of many new synthetically useful reactions.



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-0040-1707252.

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(26) **1-(2-Pyridin-2-ylphenyl)ethanone (3aa); Typical Procedure**
A 10 mL, flame-dried, round-bottomed Schlenk flask equipped with a magnetic stirrer bar was charged with **1a** (0.2 mmol, 31.04 mg), **2a** (0.4 mmol, 57.26 mg), AgOTf (0.5 mmol, 128.47 mg), *fac*-Ir(ppy)$_3$ (0.002 mmol, 1.31 mg), and Pd(TFA)$_2$ (0.02 mmol, 6.65 mg). The flask was evacuated and backfilled with Ar three times, and the mixture was irradiated with 7 W blue LED strips until the reaction was complete (24–48 h; TLC). The mixture was then poured into a separatory funnel containing 20 mL of sat. aq NaCl and washed with CH_2Cl_2 (20 mL). The organic layers were separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel) to give a colorless oil; yield: 29.6 mg (75%).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 4.4 Hz, 1 H), 7.78 (t, *J* = 7.7 Hz, 1 H), 7.60 (dd, *J* = 12.9, 7.7 Hz, 2 H), 7.53 (t, *J* = 6.9 Hz, 2 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.27 (t, *J* = 5.9 Hz, 1 H), 2.23 (s, 3 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.1, 157.6, 149.2, 141.5, 138.8, 136.7, 130.3, 129.1, 128.6, 127.6, 122.5, 122.3, 30.5. HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}NO$: 198.0913; found: 198.0918.

