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Site-Selective C–H Acylation of Pyridinium Derivatives by Photoredox Catalysis

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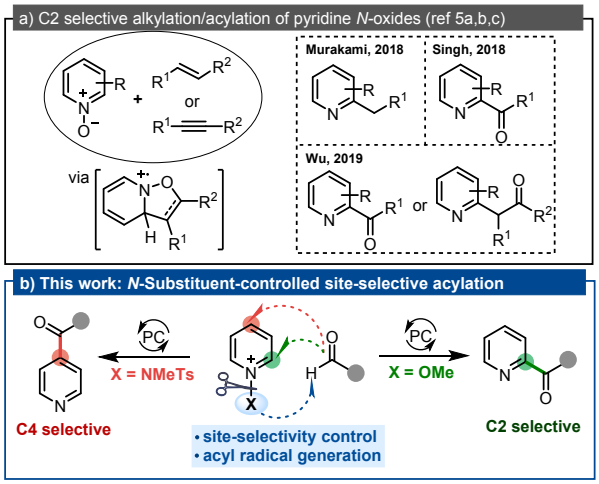
ABSTRACT: A strategy for visible-light-induced site-selective C–H acylation of pyridinium salts was developed by employing *N*-methoxy- or *N*-aminopyridinium salts, offering a powerful synthetic tool for accessing highly valuable C2- and C4-acylated pyridines. The methoxy or amidyl radicals photocatalytically generated from the pyridinium salts can undergo hydrogen atom abstraction from readily available aldehydes to form acyl radicals, which can engage in addition to pyridinium substrates. Remarkably, the use of *N*-methoxypyridinium salts preferentially gives the C2-acylated pyridines, and the site selectivity can be switched from C2 to C4 by using *N*-aminopyridinium salts. The utility of this transformation was further demonstrated by the late-stage functionalization of complex biorelevant molecules and by application of acyl radicals to photocatalytic radical cascades.

KEYWORDS: photochemistry, acyl radical, acylated pyridine, site-selectivity, pyridinium salt.

Acyl pyridines are frequently used as privileged cores in the pharmaceutical and fine chemical research fields.[1] Unlike electron-rich (hetero)arenes, acylation of the pyridine core *via* the conventional Friedel–Crafts reaction is fundamentally problematic due to the decreased electron density in the aromatic system and the addition of an acylating agent to the nitrogen atom,[2] which requires a nonclassical strategy. The pyridine scaffold contains multiple reactive sites, and selective functionalization of pyridines can afford a powerful synthetic method for access to chemical modification of the pyridine-containing biorelevant compounds.[3,4] As a result, there is a growing demand for synthetic methods that can site-selectively functionalize pyridine derivatives in a predictable and controllable manner under mild conditions. Importantly, several approaches have achieved functionalization of the C2 position of the pyridine core using pyridine *N*-oxides.[5] For example, the Murakami group demonstrated the photocatalyzed C2-alkylation of pyridine *N*-oxides through the cleavage of cyclized radical cation intermediates (Scheme 1a).[5a] Using alkynes as acyl group precursors, Singh et al. reported the Ag-catalyzed oxidative acylation of pyridine *N*-oxides.[5b] Furthermore, the photoinduced divergent C2-alkylation and acylation of pyridine *N*-oxides with alkynes were achieved by the Wu group.[5c]

Despite these advances, these reactions remain limited mainly to the introduction of the acyl group to the C2-position of the pyridine moiety, and the introduction of a carbonyl group at the C4-position of pyridines remains a challenge and has yet to be realized with meaningful selectivity.[6] In this context, the development of a mild method that enables the controlled acylation of the specific C–H bonds in pyridine scaffolds (C2 vs. C4) is highly desirable. Acyl radicals are versatile and useful intermediates for a broad range of chemical reactions.[7] For the direct generation of acyl radicals from readily available aldehydes, the photochemical approach has been proposed as a green route, which could be employed to drive Giese-type addition to activated alkenes and Minisci-type acylation of heteroarenes (e.g., isoquinoline).[8] To convert aldehydes into acyl radicals, radical species generated from

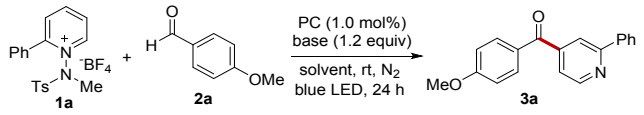
Scheme 1. Design Plan for the Site-Selective Acylation of Pyridine Scaffolds



hydrogen atom transfer (HAT) reagents such as persulfates and peroxides are generally required to abstract the hydrogen atom from the aldehyde.[9] Recently, quinuclidine has emerged as a HAT organocatalyst that efficiently abstracts the aldehydic hydrogen atom to form the acyl radical.[10] Furthermore, Wu and coworkers demonstrated that excited Eosin Y directly abstracts the hydrogen atom from aldehydes to form acyl radicals.[11]

Drawing inspiration from photocatalyzed radical reactions, we imagined the possibility of controlling the reaction sites by tuning the steric and electronic differences of the pyridinium salts, which can differentiate and amplify the site-discriminating interactions with acyl radicals. We speculated that the oxo functionality of the acyl radical could engage in the electrostatic attraction with the nitrogen of *N*-methoxy pyridinium salt[12,13] to afford C2-acylated pyridines, and this intrinsic preference could be overcome by the use of *N*-aminopyridinium salt to avoid an unfavorable clash at the C2 position between the *N*-methyl tosyl group and the approaching acyl radical. In addition, we questioned whether the methoxy or amidyl radicals[14] generated from the fragmentation of the pyridinium salts could function as efficient HAT reagents by abstracting a hydrogen atom from an aldehyde. Considering that the bond dissociation energy (BDE) of the C–H of aldehydes is approximately 88 kcal/mol, the BDEs of the O–H bond in MeOH (~104 kcal/mol) and the N–H bond in TsNHMe (~101 kcal/mol) are large enough to engage in a HAT event with an aldehyde.[15] As outlined in Scheme 1b, we discovered that the *N*-substituent of pyridinium salts is capable of determining the reaction site in the acylation reactions: *N*-aminopyridinium salts display a strong preference for the C4-position, whereas *N*-methoxypyridinium salts favor the addition of acyl radicals to the C2-position.

Table 1. Optimization for Reaction Conditions[a]

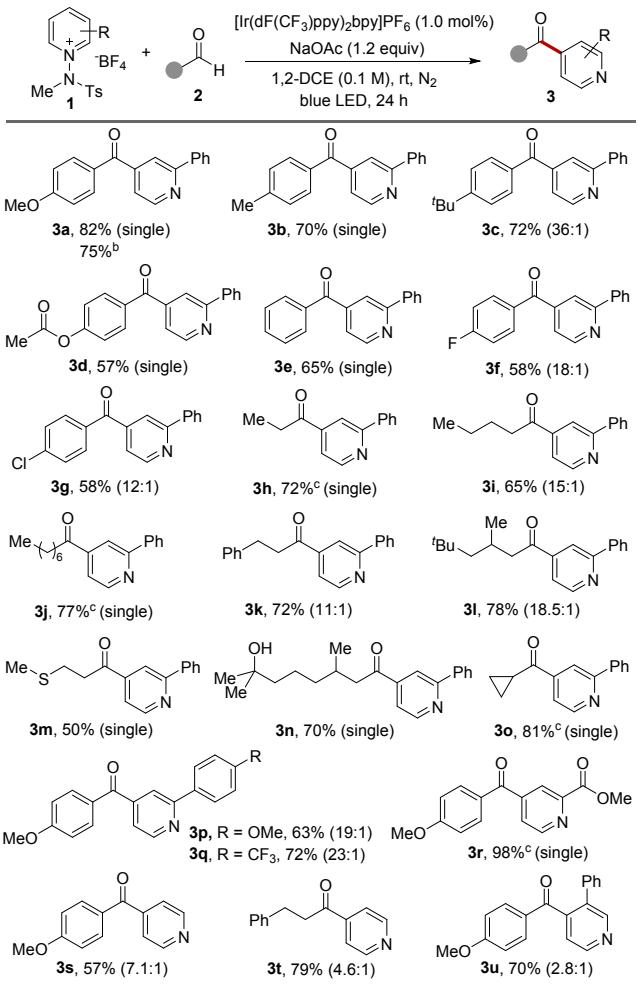


entry	photocatalyst	base	solvent	yield(%)[b]
1	$[Ir(dF(CF_3)ppy)_2bpy]PF_6$	-	1,2-DCE	30
2	$[Ir(dF(CF_3)ppy)_2bpy]PF_6$	$NaHCO_3$	1,2-DCE	59
3	**$[Ir(dF(CF_3)ppy)_2bpy]PF_6$**	**NaOAc**	**1,2-DCE**	**84**
4	$Ir(ppy)_3$	NaOAc	1,2-DCE	24
5	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	NaOAc	1,2-DCE	23
6	EosinY	NaOAc	1,2-DCE	68
7	$[Ir(dF(CF_3)ppy)_2bpy]PF_6$	NaOAc	MeCN	79
8	$[Ir(dF(CF_3)ppy)_2bpy]PF_6$	NaOAc	1,4-dioxane	33
9	-	NaOAc	1,2-DCE	NR
10[c]	$[Ir(dF(CF_3)ppy)_2bpy]PF_6$	NaOAc	1,2-DCE	NR
11[d]	$[Ir(dF(CF_3)ppy)_2bpy]PF_6$	NaOAc	1,2-DCE	NR

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), photocatalyst (1.0 mol%), base (0.12 mmol), and solvent (1.0 mL) with blue LED irradiation under N_2 atmosphere at rt for 24 h. [b]The yields were determined by ^1H NMR with an internal standard. [c]Reaction was performed in the dark. [d]TEMPO (3.0 equiv) was added.

To test the feasibility of our proposed approach, we initially investigated the photocatalytic reaction using *N*-aminopyridinium salt **1a** and *p*-anisaldehyde **2a** as model substrates under blue LED irradiation (Table 1). After evaluating some potential catalytic systems, we found that irradiation of the reaction mixture enabled the direct C4-acylation to afford the corresponding product **3a** (entry 1). The choice of base was critical for the reaction efficiency, and the use of NaOAc dramatically promoted the formation of **3a** (entries 1-3). Of the various photocatalysts tested, $[Ir(dF(CF_3)ppy)_2bpy]PF_6$ was most effective in terms of overall conversion and site selectivity (entries 3-6). Among the solvents screened, 1,2-DCE was most effective for this coupling reaction (entries 3, 7 and 8). We examined the influence of the light source, and blue LEDs gave the highest yield (see the Scheme S2 for details). After a systematic screening, the desired product **3a** was formed in 84% yield with the optimal conditions (entry 3). Mild room temperature conditions were sufficient for the construction of the scaffolds in the overall reaction process. Control experiments demonstrated that the photocatalyst and visible light were required for the successful reaction (entries 9 and 10). In the presence of TEMPO under optimal conditions, the desired product was not obtained, indicating that the possible involvement of radical intermediate in the reaction (entry 11). Stern–Volmer quenching experiments were performed with pyridinium salt **1a**, revealing that the quenching rate was directly proportional to the concentration of **1a** and the oxidative quenching cycle is presumably favored (see the Figure S1 and S2 for details).

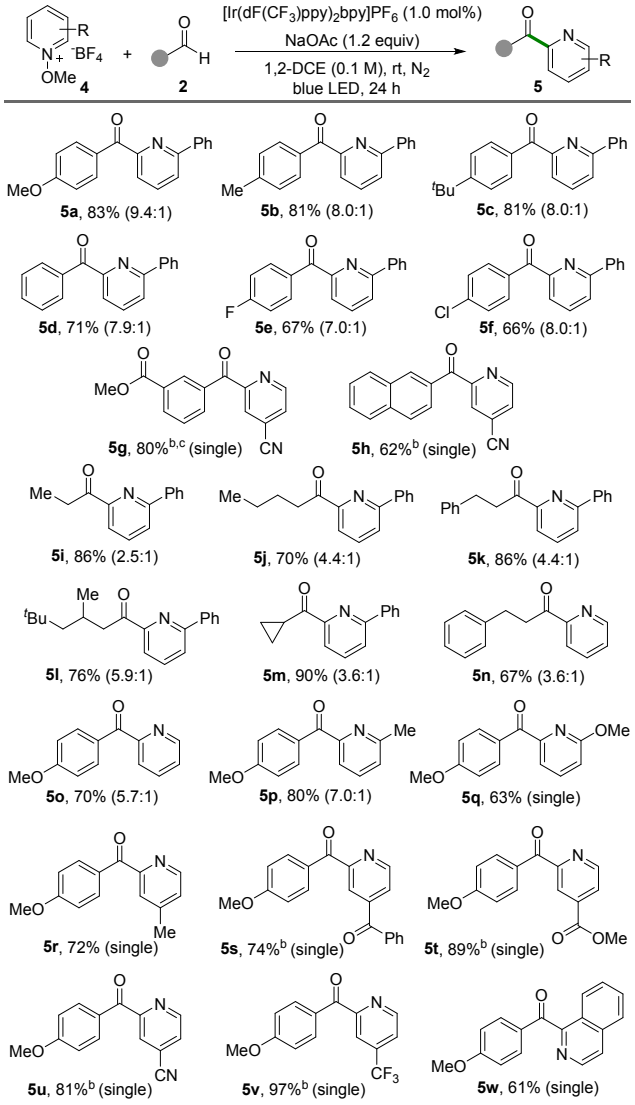
Scheme 2. C4-Selective Acylation Using *N*-Aminopyridinium Salts[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), PC (1.0 mol%), base (0.12 mmol), and solvent (1.0 mL) with blue LED irradiation under N_2 at rt for 24 h. Yields of isolated products. Isomeric ratios were determined by ^{1}H NMR analysis. [b]1.0 mmol scale. [c]**2** was used as the limiting reagent with **1** (2.0 equiv) in MeCN (0.1 M).

The simple optimized reaction conditions were then applied to a variety of aldehydes to establish the scope and generality of this method. As summarized in Scheme 2, a range of benzaldehydes bearing methoxy, methyl, butyl, ester, fluoro, and chloro groups were successfully engaged to afford the desired products with excellent C4-regiocontrol (**3a-3g**). We subsequently assessed the applicability of the current method with respect to various aliphatic aldehydes, and the utility of the present method was demonstrated by providing convenient access to prominent structural motifs featuring acyl pyridine units containing either linear or branched alkyl chains (**3h-3l**). Notably, alkyl aldehydes bearing alcohol, thioether, cyclopropyl groups were well tolerated in the present cross-coupling reactions and provided the desired ketones **3m**, **3n**, and **3o**, thereby significantly expanding the scope and synthetic utility of this reaction. In addition, we were pleased to observe that pyridyl groups possessing methoxy- or trifluoromethyl-substituted aryl (**3p**, **3q**) and ester (**3r**) groups reacted well to afford the desired C4-acylated pyridines under the optimized reaction conditions. The reaction with a substrate bearing C3-phenyl group provided a modest preference for the C4-acylated product (**3u**, 2.8:1 selectivity).

Scheme 3. C2-Selective Acylation Using *N*-Methoxypyridinium Salts[a]



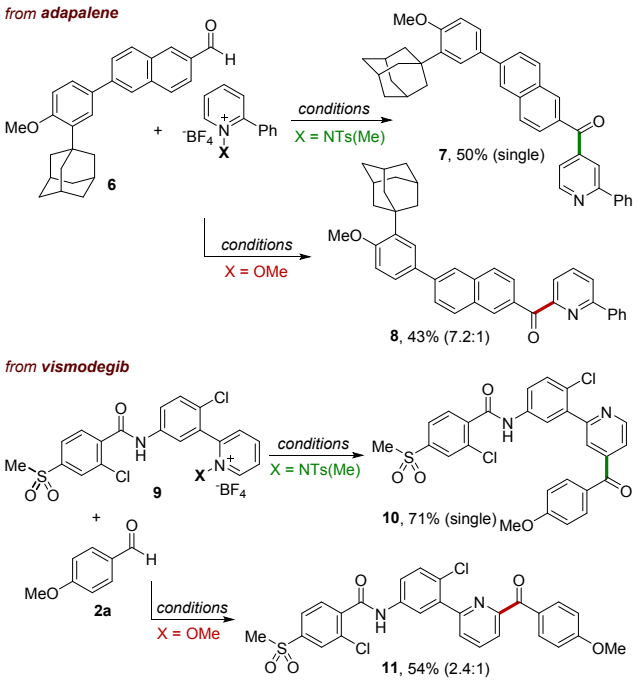
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), PC (1.0 mol%), base (0.12 mmol), and solvent (1.0 mL) with blue LED irradiation under N_2 at rt for 24 h. Yields of isolated products. Isomeric ratios were determined by ^{1}H NMR analysis. [b]**2** was used as the limiting reagent with **1'** (2.0 equiv) in MeCN (0.1 M). [c]$(NH_4)HCO_3$ was used instead of NaOAc.

Encouraged by the exciting results from C4-selective acylation, we next directed our attention to C2-selective acylation by investigating other *N*-substituents of pyridinium salts as summarized in Scheme 3. Remarkably, by switching the *N*-substituent to a methoxy group, the site selectivity changed from the C4-position to C2-position of the pyridine scaffold. Subsequently, the scope of this method was studied with respect to various benzaldehydes bearing either electron-rich or electron-deficient substituents, which successfully reacted with the pyridinium salts to afford the desired C2-acylated products (**5a-5h**). In a similar fashion, the current protocol can be extended to aliphatic aldehydes, affording the C2-acylated pyridine derivatives (**5i-5n**). In addition, pyridyl groups possessing methyl, methoxy, ketone, ester, cyano, and trifluoromethyl substituents reacted well to afford the desired

acylated pyridines with excellent C2-regiocontrol under the optimized reaction conditions (**5o-5v**).

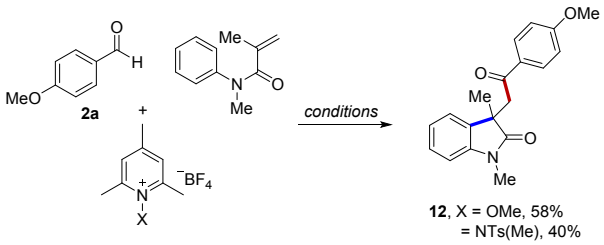
To further highlight the broad applicability of this site-selective synthetic method, we carried out the late-stage modifications of pharmaceutically relevant molecules. As illustrated in Scheme 4, when the aldehyde **6** derived from adapalene was subjected to the standard reaction conditions, site-selective acylation of the pyridinium scaffolds occurred under the present catalytic systems to yield the corresponding C4- and C2-products **7** and **8**, respectively with good functional group tolerance. In a similar manner, the site-selective acylation proceeded well when we applied the standard conditions to pyridinium compounds **9** derived from vismodegib.

Scheme 4. Late-Stage Site-Selective C-H Acylation of Complex Molecules



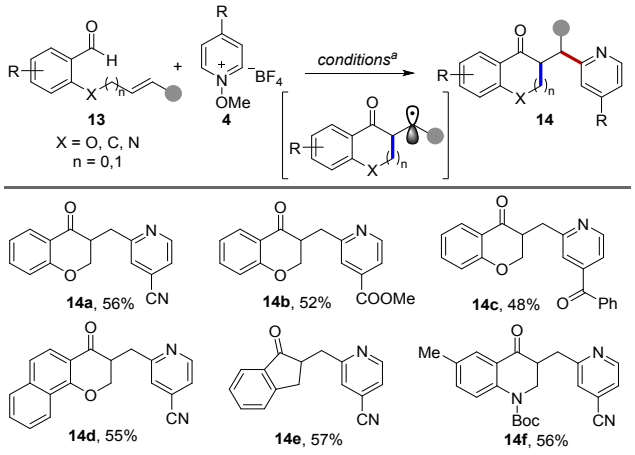
To clarify the reaction mechanism, several control experiments were performed. To determine whether the pyridine generated in situ by single electron transfer (SET) during the reaction could act as a substrate, we subjected mixtures of pyridinium salt **1a** and methyl nicotinate to the standard reaction conditions (see the Scheme S4 for the details). As anticipated, it was observed that only pyridinium salt **1a** was converted into the corresponding product **3a**. Next, the crucial step of the proposed mechanism is the photogeneration of acyl radicals by the HAT process from aldehydes to methoxy or amidyl radicals. In the presence of 2,4,6-trimethyl substituted pyridinium salt, the intermolecular acylation of an olefin and an intramolecular radical cyclization readily proceeded[16], leading to the formation of oxindole **12** (Scheme 5). These results validate that acyl radicals can be efficiently generated from aldehydes under the current catalytic system where both *N*-methoxy- and *N*-aminopyridinium salts serve as efficient HAT reagents.

Scheme 5. Photocatalytic Cascade Construction of Functionalized Oxindole



Having demonstrated the ability of the current photocatalytic system to generate acyl radicals, we next ventured to explore more challenging radical cascades to construct structurally complex pyridine-tethered chromanones. To this end, we prepared aldehyde substrates **13** linked to olefin chains, as illustrated in Scheme 6, which were subjected to the optimized conditions in the presence of pyridinium salt **4**. To our delight, the proposed cascade reactions comprising acyl radical formation, intramolecular radical cyclization, and interception by a pyridinium salt enable the rapid generation of valuable pyridine-tethered chroman-4-ones (**14a-14c**) and related derivatives (**14d-14f**).

Scheme 6. Application to Radical Cascades



[a]Reaction conditions: **13** (0.1 mmol), **4** (0.2 mmol), $[Ir(dF(CF_3)ppy)_2bpy]PF_6$ (2.5 mol%), $NaHCO_3$ (0.12 mmol), and MeCN (1.0 mL) at rt under N_2 for 16 h with blue LED irradiation. Yields of isolated products.

To gain more insight into the observed selectivity, density functional theory (DFT) calculations were carried out (see the SI for computational details). The site-selectivity is determined in the acyl radical addition step. In the case of the *N*-methoxypyridinium salts, our calculations indicate that the transition state leading to the C2-product is 1.4 kcal/mol lower in energy than the TS for the C4-product (Figure S8) because of attractive electrostatic interactions between the positively charged nitrogen atom of the *N*-methoxypyridinium substrate and oxo functionality of the acyl radical.[13] On the other hand, the *N*-methyl tosyl substituents on the *N*-amidopyridinium salt is sterically too bulky to allow the acyl radical to engage in favorable electrostatic attractions. As shown in Figure S9, the TS for the C4-product is found to be 2.4 kcal/mol lower in

energy than the TS affording the C2-product, which can be attributed to the greater steric demand of *N*-methyl tosyl group. In addition, when we conducted control experiments by subjecting substrates bearing a sterically smaller mesyl group, the site-selectivity was dramatically reduced (C4/C2 = 3.5:1), indicating the influence of substituents on site-selectivity (see the Scheme S7 for details).

A plausible mechanism for the current methods is proposed in Figure 1. The photoexcited Ir(III)-photocatalyst under blue LED irradiation undergoes the SET reduction of the *N*-alkoxy- or *N*-amino-pyridinium salt to generate the alkoxy or amidyl radicals. These radicals subsequently abstract the hydrogen atom from the aldehyde substrate to generate the acyl radical species **B**. Afterward, the acyl radical engages in cross-coupling with another pyridinium substrate to form radical intermediate **C**, which undergoes deprotonation and *N*-heteroatom bond cleavage to form the final product and release another alkoxy or amidyl radicals. The resultant radical initiates the radical chain pathway by generating the acyl radical. The quantum yield was determined to be relatively high at Φ = 18.7 (see the SI for the details), which indicates that the radical chain pathway is quite productive. In the process, an alternate reaction pathway involving rearomatization and reduction by SET events in the photoredox catalytic cycle can be envisioned to maintain the catalytic cycle. In both pathways, the base is required to deprotonate intermediates **C**, leading to the final products.

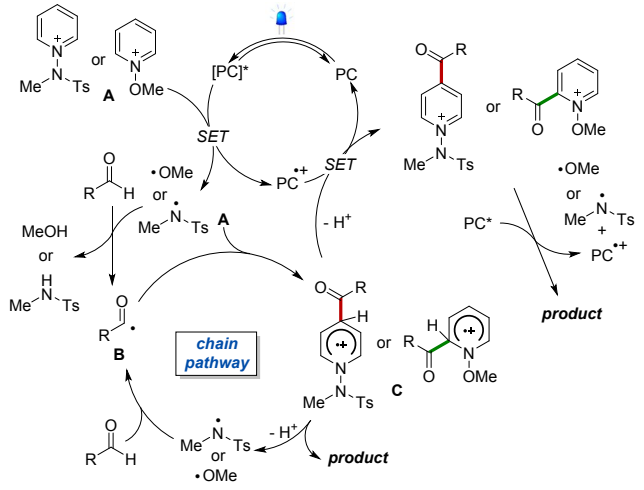


Figure 1. Plausible reaction mechanism

In summary, the use of pyridinium salts as both efficient HAT reagents and pyridine surrogates leads to photocatalytic site-selective C–H acylation of pyridine scaffolds. Remarkably, the site selectivity from acyl radical trapping with pyridinium salt can be controlled by the *N*-substituent on the pyridinium salt: the use of *N*-methoxypyridinium salts preferentially gives the C2-acylated pyridines, and the site selectivity can be switched from C2 to C4 by using *N*-aminopyridinium salts. This convenient and versatile method does not require an oxidant, and the utility of this transformation was further demonstrated by the late-stage functionalization of complex biorelevant molecules. Furthermore, using pyridinium salts as efficient HAT reagents, the current photocatalytic system provides access to acyl radicals that can be applied to other photocatalytic radical cascades.

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ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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