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Photoinduced Divergent Alkylation/Acylation of Pyridine *N*-Oxides with Alkynes under Anaerobic and Aerobic Conditions

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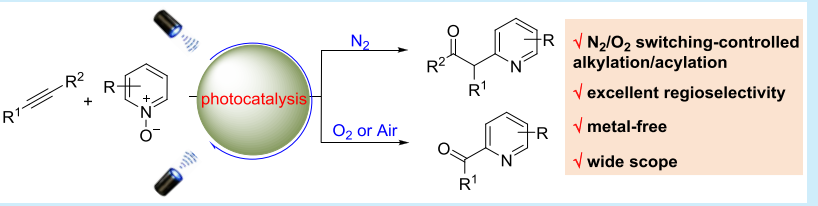
Supporting Information

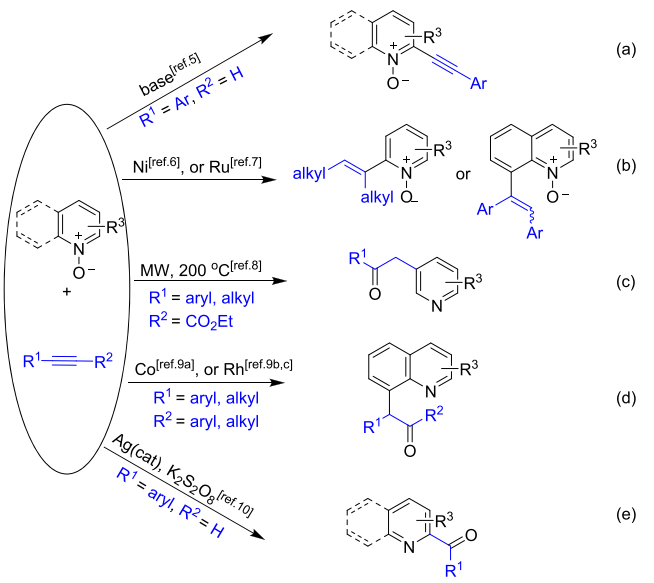


ABSTRACT: *Ortho*-alkylated and *ortho*-acylated pyridines have been conveniently synthesized from pyridine *N*-oxides and alkynes under visible-light-mediation in a metal-free manner. The alkynes served as both alkylating and acylating agents via switching between anaerobic and aerobic conditions. The overall strategy accommodates a broad scope of substituted pyridine *N*-oxides and alkynes, with excellent regioselectivity in a number of cases.

Synthesizing pyridine derivatives is of vital importance in organic and medicinal chemistry because pyridines are privileged structural motifs in natural products[1] and pharmaceutical agents.[2] In this context, transition-metal-catalyzed[3] or radical-mediated[4] direct C−H functionalization of pyridines has emerged as an efficient and atom-economical strategy to access this important family of heterocyclic compounds. However, low selectivity is normally a problem in those types of transformations. Compared with pyridines, pyridine *N*-oxides are readily available and are ideal alternatives for the preparation of pyridine derivatives with improved regioselectivity owing to their unique character.

Alkynes are versatile reactants in the selective functionalization of pyridine *N*-oxides (Scheme 1). Nucleophilic reaction of pyridine *N*-oxides with terminal alkynes in the presence of a base[5] delivered *ortho*-alkynylated pyridine *N*-oxides (Scheme 1a). The groups of Hiyama[6] and Matsuo[7] reported respectively alkenylation of pyridine *N*-oxides at the C-2 position and quinoline *N*-oxides at the C-8 position by transition-metal-catalyzed reactions (Scheme 1b). At 200 °C with microwave irradiation, Maulide et al. successfully realized the generation of *meta*-substituted pyridines to access metyrapone analogs using pyridine *N*-oxides and electron-deficient alkynes (Scheme 1c).[8] Quinoline *N*-oxides were found to undergo cobalt(III) or rhodium(III)-catalyzed coupling with alkynes to provide C-8 functionalized quinolines (Scheme 1d).[9] The *N*-oxide acted as a directing group to induce the C-8 functionalization of quinolines as well as a source of the oxygen atom in these transformations. In 2018, Singh et al. reported oxidative acylation of electron-deficient heteroarenes including pyridine *N*-oxides and quinolone *N*-oxides using terminal alkynes in the presence of a silver catalyst and excess potassium persulfate, $K_2S_2O_8$ (Scheme 1e).[10] Even though significant progress has been achieved, selective C-2 alkylation and acylation of pyridine *N*-oxides, especially in metal-free conditions, are still challenging and highly desirable.

Scheme 1. Functionalization of Pyridine/Quinoline *N*-Oxides with Alkynes



Visible-light-mediated photocatalysis has witnessed dramatic developments over the past decade, which has enabled previously unknown transformations.[11] Alkylation of pyridine *N*-oxides, induced by visible light, has been realized using alkenes and alkyltrifluoroborate potassium salts as alkylation

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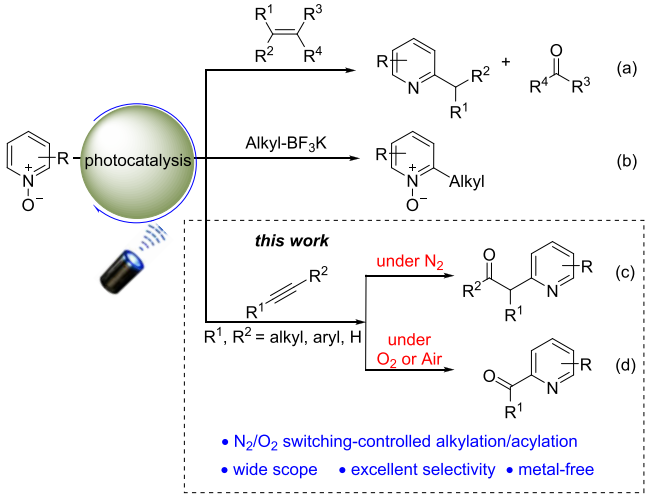
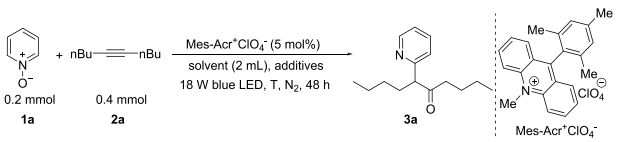
reagents (Schemes 2a,b).[12] As part of our continuing efforts in development of visible-light-promoted green synthesis,[13] we report herein a metal-free photoinduced divergent alkylation/acylation of pyridine *N*-oxides using alkynes as the alkylation and acylation reagents under anaerobic or aerobic conditions (Schemes 2c,d).

Scheme 2. Photoinitiated Functionalization of Pyridine *N*-Oxides



We initiated the study by alkylation of pyridine *N*-oxide (**1a**) with *n*-dec-5-yne (**2a**) in MeCN in the presence of the photocatalyst 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$ClO$_4^-$) under blue LED irradiation (Table 1). This led to the desired alkylated product (**3a**) which was obtained in 44% yield (entry 1), along with pyridine byproducts. The transformation was sensitive to pH. Addition of 0.5 or 1.0 equiv of pyridine resulted in a substantial decrease in yield (entries 2 and 3). Other bases, such as $NaHCO_3$, NaOAc, and K_3PO_4, showed similar detrimental effects (see the Supporting Information). In contrast, acids such as trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TfOH), and HBF_4, improved the reaction yield dramatically (entries 4–9). Nearly quantitative yields could be obtained with 20 mol% HBF_4 at 50 °C (entry 7). Further optimization showed that hexafluoroisopropanol (HFIP) could be employed to replace strong acidic additives to tolerate acid-labile functionalities, also with excellent yields (entry 10). As the solvent, acetone, which is greener and less costly than MeCN, was equally effective (entries 11 and 12). No product was obtained in the absence of either photocatalyst or light, demonstrating the need for all these components (see the Supporting Information).

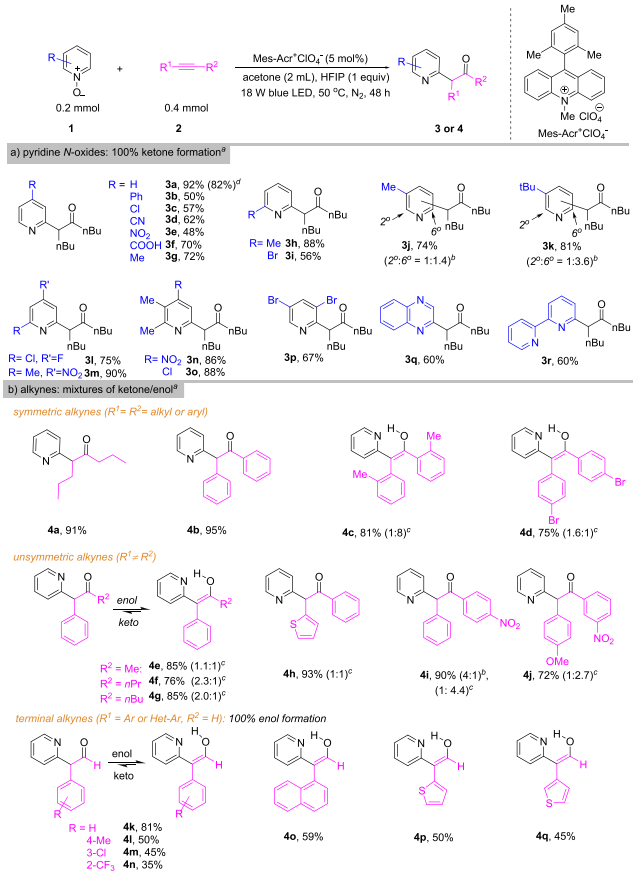
Table 1. Exploration of Optimal Conditions for Alkylation



entry	additives (*X* mol%)	*T* (°C)	solvent	yield (%)[a]
1	–	rt	MeCN	44
2	pyridine (50)	rt	MeCN	26
3	pyridine (100)	rt	MeCN	15
4[b]	aq. HBF_4 (50)	rt	MeCN	62
5[b]	aq. HBF_4 (5)	50	MeCN	80
6[b]	aq. HBF_4 (10)	50	MeCN	92
7[b]	aq. HBF_4 (20)	50	MeCN	>99
8	TFA (20)	50	MeCN	76
9	TfOH (20)	50	MeCN	92
10	HFIP (100)	50	MeCN	>99
11[b]	aq. HBF_4 (20)	50	acetone	>99
12	HFIP (100)	50	acetone	>99 (92)[c]

[a]Yields based on analysis of the crude ^{1}H NMR spectra using CH_2Br_2 as an internal standard. [b]Aq. HBF_4 (8.0 M in water) was applied. [c]The number in parentheses refers to isolated yield; rt = room temperature.

Scheme 3. Substrate Scope of Alkylation of Pyridine *N*-Oxides with Alkynes



[a]Isolated yields. [b]Ratios of regioisomers based on analysis of the crude ^{1}H NMR spectra. [c]Ratios of keto/enol. [d]Isolated yields at 6 mmol scale.

We then investigated the reaction scope of alkylation of pyridine *N*-oxides under the optimal conditions (Table 1, entry 12). As depicted in Scheme 3a, with *n*-dec-5-yne as a representative alkyne partner, a diverse range of substituted pyridine *N*-oxides provided alkylation products in good to excellent yields. *Ortho*- or *para*-substituents pyridine *N*-oxides underwent C-2 alkylation with excellent regioselectivity (**3a–3i, 3l–3o**), while mono *meta*-substituted pyridine *N*-oxides delivered a mixture of products (**3j, 3k**). The reaction tolerated many functional groups, such as halogens, nitriles, nitro compounds, and carboxylic acids. In addition, quinoxaline *N*-

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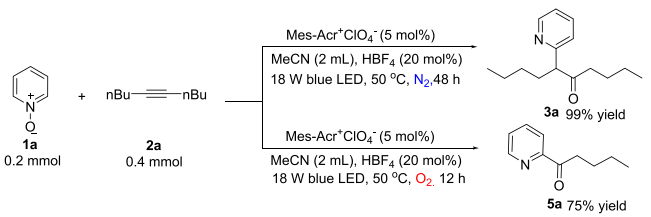
oxide and 2,2′-dipyridyl *N*-oxide could also be utilized to prepare the alkylated products (**3q**, **3r**) in good yield.

A remarkably broad scope of alkynes, including symmetrical, unsymmetrical, and terminal alkynes, were effective under the optimal conditions and provided *ortho*-substituted pyridine *N*-oxides in moderate to good yields with generally excellent regioselectivity (Scheme 3b). Electron-deficient (e.g., **4d**, **4i**, **4n**) and electron-rich arenes (e.g., **4c**, **4j**, **4l**), naphthalene arenes (**4o**), and heteroarenes such as thiophene (**4h**, **4p**, **4q**) were all well-tolerated. Most intriguing is the excellent selectivity achieved with unsymmetrical and terminal alkynes. Only one regioisomer, with aryl substituents located on the pyridine side, was generated with aryl alkyl disubstituted alkynes (**4e**–**4g**) and terminal alkynes (**4k**–**4q**). Notably, when aryl heteroaryl disubstituted alkynes were used, a single regioisomer (**4h**) was obtained in which the phenyl substituent was located at the opposite site of the pyridine moiety.[14] Changing the heteroaryl substituent to an aryl group led to a mixture of regioisomers (**4i**). However, a single isomer (**4j**) could still be obtained from the disubstituted alkyne bearing aryl substituents with a distinct difference in electron densities. Keto–enol tautomerization was observed in most of the products due to the intramolecular hydrogen bonding between the pyridine substituent and enol proton. In particular, the products generated from pyridine *N*-oxides and terminal alkynes were exclusively in the enol form (**4k**–**4q**).

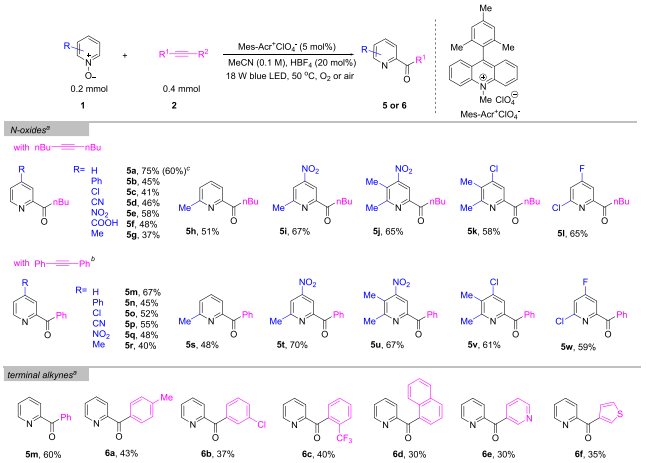
Compared with alkylation, acylation of pyridines has seen only limited development and only a few examples have been reported.[10,15] During the optimization of the alkylation, we found that *ortho*-acylated pyridines could be obtained in good yields with the same starting materials simply by switching the anaerobic conditions to aerobic (Scheme 4).

Scheme 4. Photoinduced Alkylation and Acylation of Pyridine *N*-Oxides



Under the aerobic conditions, use of 20 mol% HBF_4 and MeCN as the solvent gave products in slightly better yields compared to 100 mol% HFIP and acetone as the solvent, and the scope for acylation was subsequently evaluated. As illustrated in Scheme 5, with symmetric dialkyl alkynes, acylated pyridine products (**5a**–**5l**) were obtained smoothly in 35–75% yields[16] across a wide range of functional groups, including halogens, nitriles, nitro groups, and carboxylic acids. However, when diphenylethyne was used as the acylation reagent, the desired products were achieved in very low yields due to the oxidation of diphenylethyne under the photoredox conditions in the presence of O_2 (see the Supporting Information). To minimize the unwanted oxidation, acylation using diphenylethyne was first conducted under a N_2 atmosphere for 24 h and then in the presence of air for another 12 h. In this way, the acylated pyridines (**5m**–**5w**) were successfully obtained in 40%–70% yields. Finally, terminal alkynes could be directly applied under aerobic

Scheme 5. Scope of Acylation of Pyridine *N*-Oxides with Alkynes

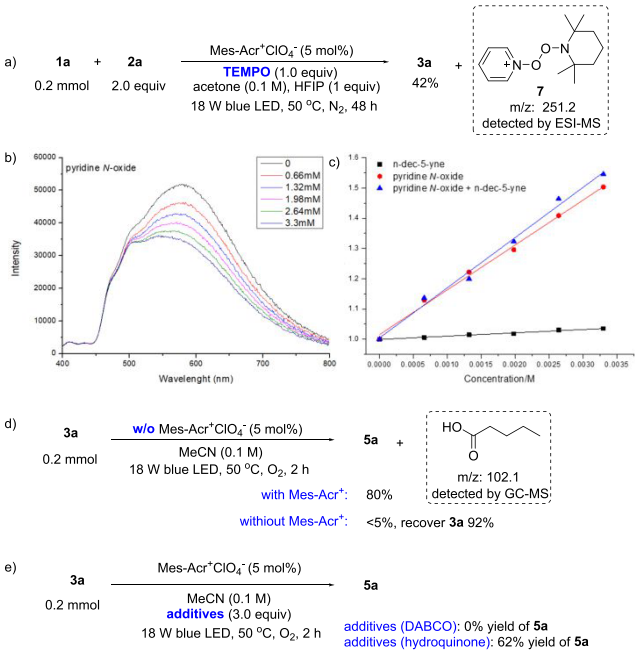


[a]Isolated products. [b]Reaction conditions: under N_2 for 24 h, then under air for another 12 h. [c]Isolated yields at 6 mmol scale.

conditions to obtain *ortho* acylated pyridine derivatives (**5m**, **6a**–**6f**) in moderate yields (30–60%).

A series of control experiments were performed to gain further insight into the nature of the alkylation and acylation reactions. A significantly lower yield of the alkylation product (**3a**) was obtained in the presence of 1 equiv of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), indicating a radical process (Scheme 6a). Notably, the formation of peroxide **7** was

Scheme 6. Control Experiments for Elucidation of the Mechanism



detected by ESI-MS, suggesting that pyridine *N*-oxide radicals might be involved. Stern–Volmer fluorescence quenching studies showed that light-activated photocatalyst Mes-Acr^{+}* ($E_{1/2}^{red}$* = +2.06 V vs SCE in MeCN) was quenched by pyridine *N*-oxide ($E_{p/2}$ = +1.75 V vs SCE in MeCN) rather than by the *n*-dec-5-yne ($E_{p/2}$ = +2.96 V vs SCE in MeCN,

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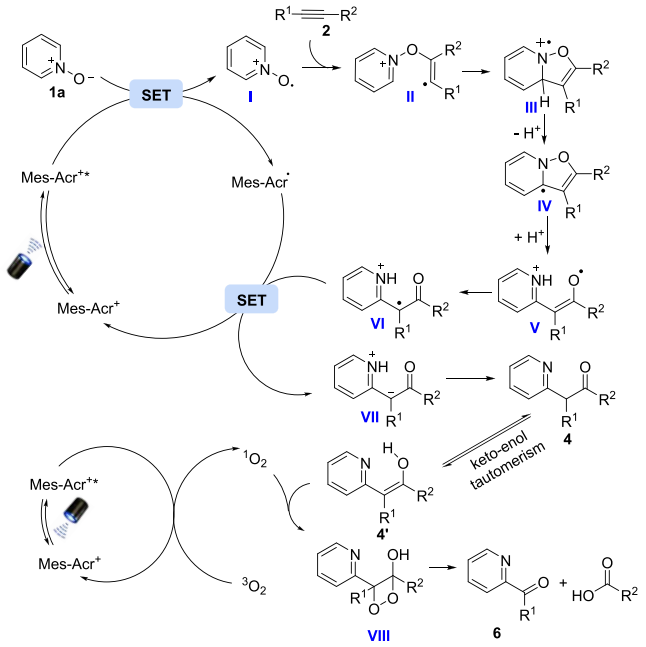
Scheme 6b and c).[17] It was expected that the acylation product (**5**) might be produced through a cascade reaction via compound **3**.[18] Indeed, when **3a** was subjected to the optimal aerobic acylation conditions, **5a** was obtained in 80% yield, along with the pentanoic acid byproduct (Scheme 6d). However, less than 5% yield of **5a** was generated in the absence of the photocatalyst. The fluorescence quenching study demonstrated a strong quenching effect by O_2 of light-activated Mes-Acr^{+}*, while **3a** showed no quenching effect (Figures S6, S7). However, only a moderate decrease in the yield was detected in the presence of excess hydroquinone, a radical quencher. This indicated that the transformation might not involve radical species. Addition of the singlet oxygen quencher 1,4-diazabicyclo[2.2.2]octane (DABCO) totally suppressed the reaction (Scheme 6e), suggesting that a singlet oxygen pathway played a major role in the formation of acylation products.[19]

A plausible mechanism was proposed in light of all the experimental data as shown in Scheme 7. As suggested by the

Scheme 7. Plausible Mechanism for Alkylation and Acylation



fluorescence quenching studies, a reductive quenching of photoexcited Mes-Acr^{+}* by pyridine *N*-oxide leads to the reduced Mes-Acr$^{•}$ and pyridine *N*-oxide radical **I**, which will add across alkyne **2** to form vinyl radical **II**. The more stable vinyl radical will be favored, leading to the site selectivity. Vinyl radical **II** then cyclizes to give the aminium cation radical **III**. Deprotonation and intramolecular 1,2-shift of one electron furnishes the α-amino radical **IV** and subsequent β-N−O bond scission driven by aromatization followed by protonation delivers vinyloxy radical **V**, which can tautomerize to α-ketyl radical **VI**. The addition of acidic additives may facilitate the cleavage of the N−O bond of intermediate **IV** to promote the formation of **V**. The α-ketyl radical **VI** can accept an electron from Mes-Acr$^{•}$ to turnover the photocatalytic cycle while delivering the anion intermediate **VII**, which affords the alkylation product **4** after proton transfer. Under an atmosphere of O_2 or air, the enol form **4′** of alkylation product will be further oxidized by singlet oxygen, produced from energy transfer between the light-excited photocatalyst and $^{3}O_2$. The acylation product **6** will be accomplished via a C−C bond cleavage of the intermediate **VIII**.[20]

In conclusion, we have developed a photoinduced alkylation/acylation of pyridine *N*-oxides to synthesize a variety of pyridine derivatives with alkynes as alkylating or acylating agents switching between anaerobic and aerobic conditions. Addition of acidic additives is important to achieve products in high yields. These protocols exhibit a broad scope across a range of pyridine *N*-oxides and alkynes, and are distinguished by their metal-free character and excellent regioselectivity achieved in a number of cases.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01940.

Detailed experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of final products (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(16) Under aerobic conditions, the generation of unacylated pyridine byproducts was detected, which could account for the relatively moderate yield of desired products.
(17) During the preparation of this manuscript, a related study of *ortho*-alkylation of pyridine *N*-oxides with alkynes by photocatalysis was reported; see: Markham, J. P.; Wang, B.; Stevens, E. D.; Burris, S. C.; Deng, Y. *Chem. - Eur. J.* **2019**, *25*, 6638−6644. However, we suggested an alternative mechanistic pathway. For detailed analysis, see the Supporting Information.
(18) The alkylation required a longer reaction time compared to acylation probably due to the presence of a dark color during the reaction process which limited the photon absorption. The reaction under O_2 was almost colorless.
(19) For singlet oxygen generation under photocatalytic conditions with Mes-Acr$^+$ClO$_4^-$, see: Griesbeck, A. G.; Cho, M. *Org. Lett.* **2007**, *9*, 611−613.
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