A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
GDCh
International Edition
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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201801305
Angew. Chem. 10.1002/ange.201801305

Link to VoR: http://dx.doi.org/10.1002/anie.201801305
http://dx.doi.org/10.1002/ange.201801305

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Photo-Catalyzed *Ortho*-Alkylation of Pyridine *N*-Oxides through Alkene Cleavage

Wang Zhou, Tomoya Miura,* and Masahiro Murakami*

Abstract: A photo-catalyzed reaction of pyridine *N*-oxides with alkenes gives *ortho*-alkylated pyridines with cleavage of the carbon–carbon double bond. Benzyl and secondary alkyl groups are incorporated at the *ortho*-position of pyridines in one-pot.

Pyridines are prevalent structural units in drug molecules.[1] Developing methods for the synthesis of alkylated pyridine have attracted an increasing interest since chemical modification of pyridine core, especially at later-stages, will offer a rapid access to the variants of clinical candidates that is particularly important in the drug discovery process.[2] Although the Minisci reaction is a powerful tool for direct radical alkylation of pyridine, harsh reaction conditions are required.[3] Recently, photo-catalyzed radical alkylation of pyridine has made great strides,[4] occurring under much milder reaction conditions. However, the control of the regiochemistry has been a problematic issue in the radical alkylation reactions.[4a,4b,5]

Pyridine *N*-oxides are a class of stable organic compounds which can act as versatile starting substances for the synthesis of pyridine derivatives.[6] It would be appealing if pyridine *N*-oxides are converted into *ortho*-alkylated pyridines using simple alkenes, which are abundant and easily available, as the alkylation reagents.[7,8] To date, however, there are reported only a few cases in which alkenes participate in alkylation of pyridine *N*-oxides.[9,10] Moreover, only electron-deficient alkenes can alkylate pyridine *N*-oxides. For example, perfluoropropene thermally reacts with pyridine *N*-oxide to afford tetrafluoroethyl-substituted pyridine through 1,3-dipolar cycloaddition followed by elimination of carbonyl fluoride (Figure 1a). Although pyridine *N*-oxides have polar nitrogen-oxygen bond, they are less reactive 1,3-dipoles for cycloaddition, probably because of the simultaneous disruption of aromaticity. We envisioned that a radical species photocatalytically generated from a simple alkene would be an alternative partner to alkylate pyridine *N*-oxide: A cation radical generated by photo-irradiation of an alkene in the presence of a photocatalyst[11] would be electrophilic enough to couple with pyridine *N*-oxide. The resulting tethered radical intermediate would undergo intramolecular *ortho*-addition, and the subsequent elimination of a carbonyl compound would afford the final product (Figure 1b).[12] Herein, we report one-step conversion of pyridine *N*-oxides into *ortho*-alkylated pyridines through photo-catalyzed alkene cleavage.

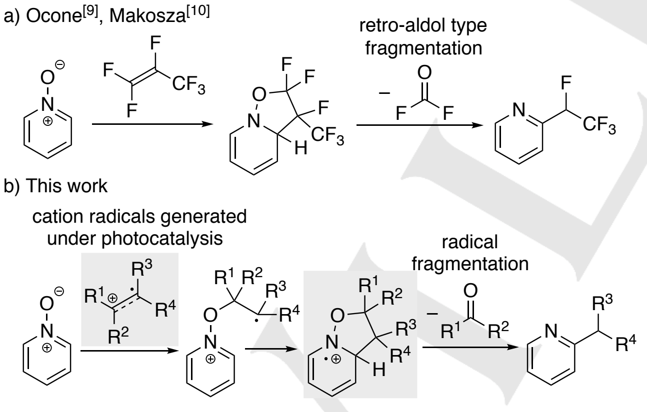
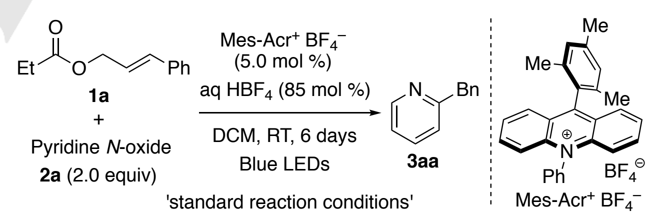


Figure 1. Synthesis of *ortho*-alkylated pyridines by reaction of pyridine *N*-oxides with a) perfluoropropene and b) alkene cation radicals.

A mixture of cinnamyl propionate (**1a**, 0.50 mmol), pyridine *N*-oxide (**2a**, 1.0 mmol), 9-mesityl-10-phenylacridinium tetrafluoroborate (Mes-Acr$^+$ BF_4^-, 5.0 mol %), and HBF_4 (42 wt% in H_2O, 85 mol %) in dichloromethane (2.0 mL) was irradiated with blue LEDs (446 nm, 18.4 W) for 6 days. 2-Benzylpyridine (**3aa**) was obtained in 69% yield after chromatographic isolation (Table 1, entry 1). The product **3aa** was formed in 60% NMR yield when the reaction was intercepted after 2 days (entry 2). Light and Mes-Acr$^+$ BF_4^- were indispensable for the reaction (entries 3 and 4). The reaction scarcely occurred in the absence of aq HBF_4 (entry 5). Other acids such as TfOH and TsOH gave inferior results (entries 6 and 7). No desired product but untouched starting materials were detected when the mixture was heated at 80 °C for 2 days without the photocatalyst nor photoirradiation (entry 8). No 1,3-dipolar cycloaddition product

Table 1. Photo-catalyzed reaction of cinnamyl propionate (**1a**) with pyridine *N*-oxide (**2a**).



Entry	Deviation from standard reaction conditions[a]	Yield of **3aa** [%][b]
1	none	71 (69)[c]
2	2 days reaction time	60
3	no light	0
4	no photocatalyst	0
5	no aq HBF_4	8
6	TfOH instead of aq HBF_4	54
7	TsOH·H_2O instead of aq HBF_4	45
8	no photocatalyst at 80 °C for 2 days	0

[a] Conditions: **1a** (0.50 mmol), **2a** (1.0 mmol), Mes-Acr$^+$ BF_4^- (5.0 mol %), aq HBF_4 (85 mol %), blue LEDs (446 nm, 18.4 W), DCM (2.0 mL), RT, 6 days. [b] NMR yields. [c] The number in parentheses refers to the isolated yield.

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie2018xxxxx.

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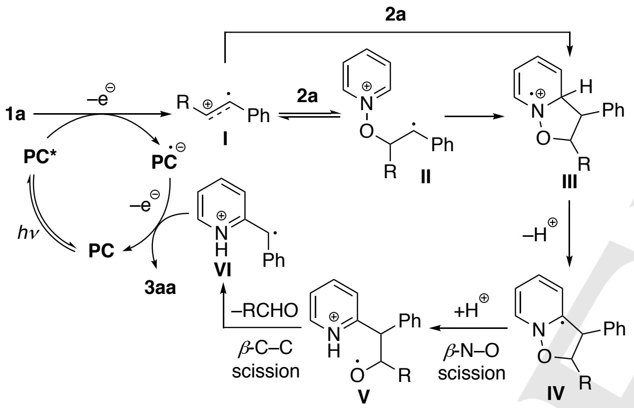
10.1002/anie.201801305

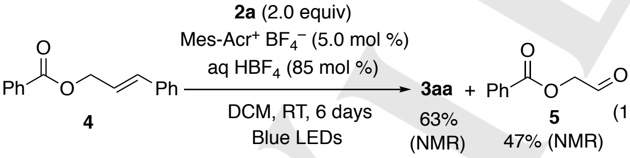
of **1a** with **2a** was detected by a crude NMR analysis. Moreover, the reaction did not proceed in the presence of 1.0 equivalent of 2,2,6,6-tetramethyl piperidine-1-oxyl (TEMPO). Thus, it was likely that the reaction was mediated by the photocatalyst which generated radical species.

We assume a mechanism shown in Scheme 1 for the formation of 2-benzylpyridine (**3aa**) from cinnamyl propionate (**1a**) and pyridine *N*-oxide (**2a**). Initially, a single-electron transfer occurs from the alkene **1a** to the excited photocatalyst **PC*** to generate a cation radical **I**.[11,13] Pyridine *N*-oxide (**2a**) adds across **I** in a way to form a benzylic radical **II**, which cyclizes to give rise to the aminium cation radical **III**. Or alternatively, **2a** reacts with **I** in a concerted way to give rise to the cation radical **III** directly. Deprotonation and intramolecular 1,2-shift of one electron delivers the α-amino radical **IV**.[14] β-N–O bond scission is driven by aromatization and the following protonation generates alkoxy radical **V**.[15] The subsequent β-C–C bond scission loses an aldehyde fragment,[16] furnishing benzylic radical **VI**, which accepts an electron to achieve photocatalyst turnover.[4b] The following tautomerization releases the final product **3aa**. A substoichiometric amount of HBF_4 presumably keeps the reaction conditions acidic enough to generate the protonated intermediate **V**.



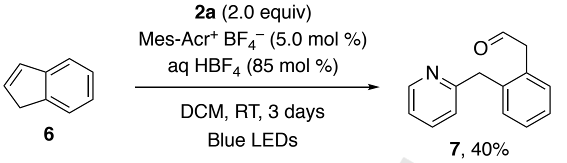
Scheme 1. Proposed mechanism. **PC** = photocatalyst, R = $EtCO_2CH_2$.

When cinnamyl benzoate (**4**) was employed, **3aa** and benzoyloxyacetaldehyde (**5**) were obtained in 63% and 47% NMR yields, respectively [Eq. (1)].



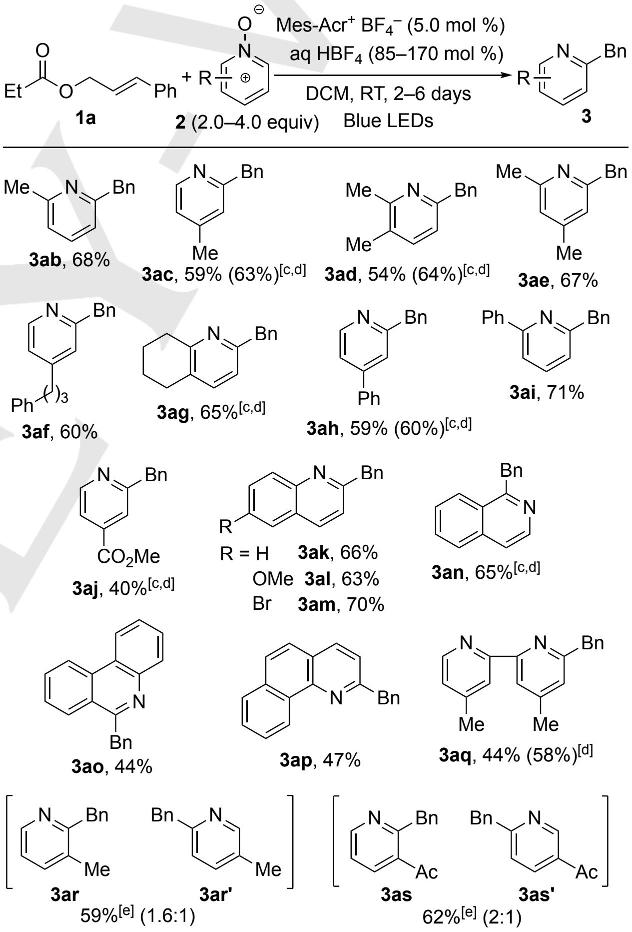
(1)

In addition, the pyridyl-substituted aldehyde **7** was produced from indene (**6**) and pyridine *N*-oxide (**2a**) [Eq. (2)]. These results support the fragmentation step forming an aldehyde (see the Supporting Information for more mechanistic study).



(2)

A variety of pyridine *N*-oxides were subjected to the photo-induced *ortho*-benzylation reaction (Scheme 2). Pyridine *N*-oxides possessing alkyl or phenyl substituents at *ortho*-, *meta*- and *para*-positions were suitable substrates, affording the *ortho*-benzylated products **3ab**–**3ai** in moderate to good yields. An ester group located at the *para* position retarded the reaction, giving **3aj** in 40% yield, probably because of its electron-withdrawing nature. Generally, the use of 4.0 equivalents of *N*-oxides and 170 mol % of aq HBF_4 shortened the reaction time (finished within 2 days) and slightly increased the yield (the yields in parenthesis of **3ac** and **3ad**). Notably, the substrate scope could be facilely expanded to *N*-oxides of quinolines **3ak**–**3am**, isoquinoline **3an**, phenanthridine **3ao**, 7,8-benzoquinoline **3ap**, and 2,2'-bipyridine **3aq**, which demonstrated the



Scheme 2. Photo-catalyzed deoxygenative benzylation of heteroaromatic *N*-oxides. [a] Conditions: **1a** (0.50 mmol), **2** (1.0 mmol), Mes-Acr$^+$ BF_4^- (5.0 mol aq HBF_4 (85 mol %), blue LEDs (446 nm, 18.4 W), RT, 2-6 days. [b] Isolated yields. [c] 4.0 equivalents of *N*-oxide (**2**, 2.0 mmol) were used. [d] HBF_4 (170 mol %) was used. [e] Cinnamyl acetate **1a**^{1} was used instead of **1a**.

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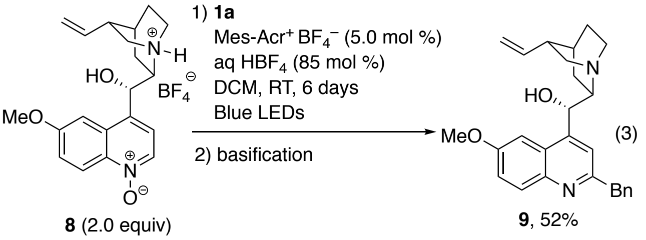
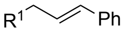
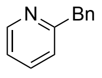
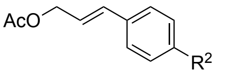
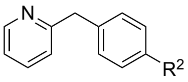
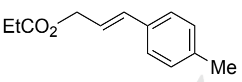
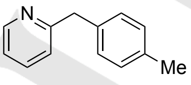
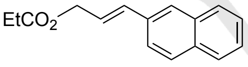
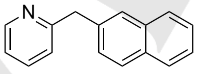
application of this protocol to derivatization of pyridine-containing compounds and ligands were possible. When pyridine *N*-oxide had one substituent at the 3-position, alkylation occurred at the 2- and 6-positions (**3ar**, **3ar'**, **3as**, and **3as'**). In these cases, a small amount of deoxygenation products of *N*-oxides were detected along with the formation of the major alkylation products.

To test the feasibility of this method for late-stage functionalization, quinidine *N*-oxide tetrafluoroboric acid complex (**8**) was subjected to the reaction conditions. An *ortho*-benzylation product **9** was produced in 52% yield without any protective manipulations for the alkenyl and hydroxyl groups [Eq. (3)].



The scope with respect to alkenes was also examined in the reaction with pyridine *N*-oxide (**2a**) (Table 2). Esters of cinnamyl alcohol, such as acetate (entry 1), formate (entry 2), dimethylcarbamate (entry 3), phosphonate (entry 4), and carbonate (entry 5) were all eligible to this transformation.

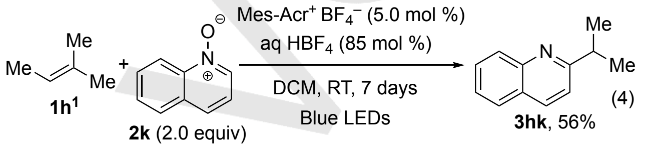
Table 2. Scope of alkene **1a^1**–**1g**[a]

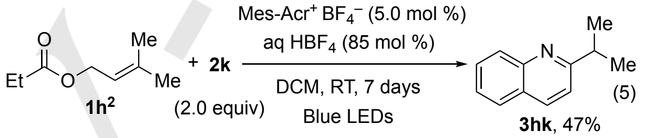
Entry	Alkene **1**[b]	Product **3**	Yield[c]
			
1	R^1 = AcO **1a^1**	**3aa**	66%
2	HCO_2 **1a^2**		52%
3	Me_2NCO_2 **1a^3**		66%
4	$(EtO)_2P(O)O$ **1a^4**		40%[d]
5	$MeOCO_2$ **1a^5**		53%[d]
6	H **1a^6**		59%[d]
			
7	R^2 = Cl **1b**	**3ba**	61%
8	F **1c**	**3ca**	62%
9	OAc **1d**	**3da**	55%
10	CO_2Me **1e**	**3ea**	39% (55%)[e]
11	 **1f**	 **3fa**	50%
12	 **1g**	 **3ga**	45%

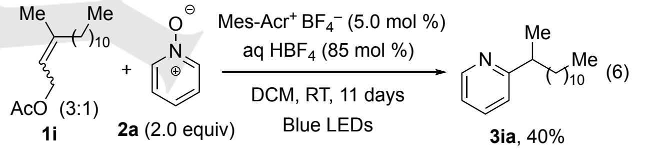
[a] Reaction conditions: **1** (0.50 mmol), **2a** (1.0 mmol), Mes-Acr$^+$ BF_4^- (5.0 mol %), aq HBF_4 (85 mol %), blue LEDs (446 nm, 18.4 W), RT, 2–7.6 days. [b] The *E*:*Z* ratios are over 20:1. [c] Isolate yield. [d] 4.0 equivalents of *N*-oxide and 170 mol % of HBF_4 were used. [e] Yield based on recovered starting material.

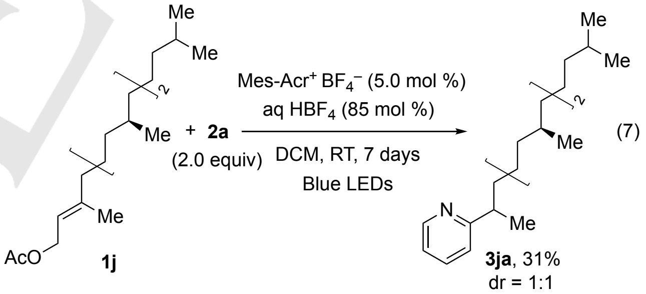
Simple β-methyl styrene also gave the product **3aa** (entry 6). The employment of cinnamyl acetates or propionates with varying substituents on the phenyl rings led to the production of pyridines **3ba**–**3ga** with different benzylic groups in moderate yields (entries 7–12).

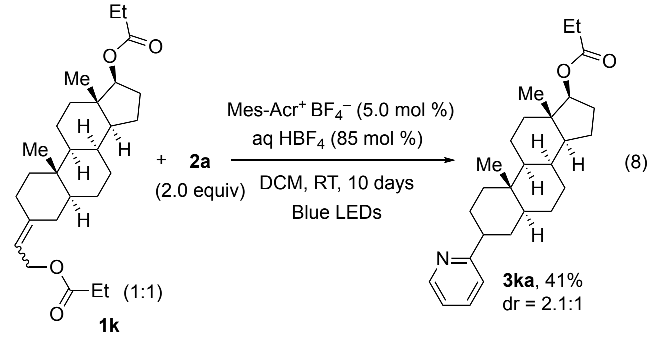
Notably, not only benzylic groups but also secondary alkyl groups could be introduced at the *ortho* position of pyridine, although the yield was moderate. Tri-substituted alkenes, 2-methyl-2-butene (**1h^1**) and 3-methyl-2-butenyl propionate (**1h^2**), participated in the reaction with quinoline *N*-oxide (**2k**) to produce *ortho*-isopropyl quinoline (**3hk**) [Eqs (4 and 5)]. Alkene having a long alkyl chain **1i** furnished product **3ia** [Eq. (6)]. Moreover, complex alkenes bearing multiple stereocenters were also compatible substrates for this transformation. Commercially available phytyl acetate (**1j**) was successfully converted into pyridine **3ja** [Eq. (7)]. A pyridine derivative of steroid **3ka** could be easily accessed, demonstrating the versatility of this method [Eq. (8)].











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In summary, we have developed a photo-induced alkylation reaction of pyridine *N*-oxides by using alkenes as alkylating reagents. This strategy was successfully applied to the reaction of a variety of *N*-oxides and alkenes, yielding pyridines having benzylic and secondary alkyl groups at the *ortho*-position.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research (S) (JP15H05756) and (C) (JP16K05694) from MEXT and JST ACT-C Grant Number JPMJCR12Z9, Japan. W.Z. acknowledges a JSPS postdoctoral fellowship for foreign researchers.

Keywords: alkene • C–C bond cleavage • photocatalysis • pyridine *N*-oxide • *ortho*-alkylation

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10.1002/anie.201801305

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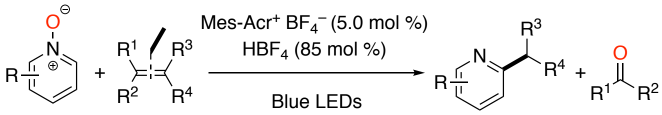

A photo-catalyzed reaction of pyridine *N*-oxides with alkenes gives *ortho*-alkylated pyridines with cleavage of the carbon–carbon double bond. Benzyl and secondary alkyl groups are incorporated at the *ortho*-position of pyridines in one-pot.

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Photo-Catalyzed *Ortho*-Alkylation of Pyridine *N*-Oxides through Alkene Cleavage

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