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Communication

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Visible Light-Driven C4-Selective Alkylation of Pyridinium Derivatives with Alkyl Bromides

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Supporting Information Placeholder

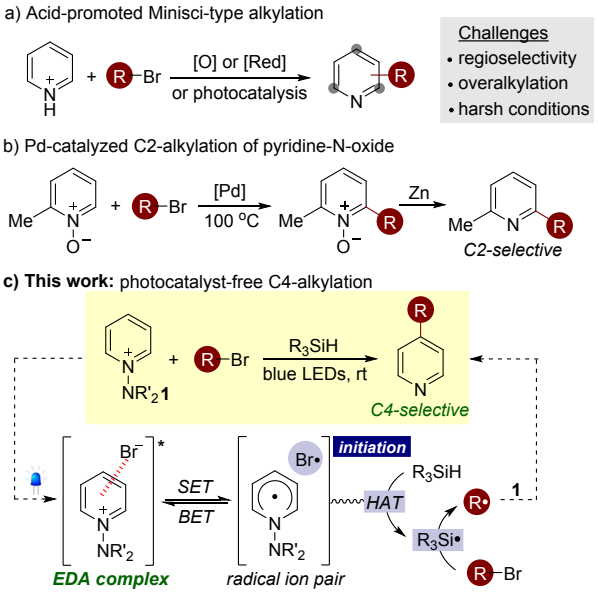
ABSTRACT: Reported herein is a general strategy for the photochemical cross-coupling between *N*-amidopyridinium salts and various alkyl bromides under photocatalyst-free conditions, granting facile access to various C4-alkylated pyridines. This approach exploits the intriguing photochemical activity of electron donor-acceptor (EDA) complexes between *N*-amidopyridinium salts and bromide, which provides a photoactive handle capable of generating silyl radicals and driving the alkylation process. The robustness of this protocol was further demonstrated by the late-stage functionalization of complex compounds under mild and metal-free conditions.

Pyridine is a valuable motif found in a wide range of natural products,[1] biologically active molecules,[2] and functional materials.[3] Along these lines, there is a growing demand for the regioselective introduction of alkyl groups to the privileged pyridine scaffolds.[4] Among synthetic strategies, direct C–H alkylation using readily available alkyl halides has emerged as an increasingly popular approach. For example, the tremendous efforts have led to various Minisci-type reactions with alkyl halides for the C−H alkylation of *N*-heteroarenes.[5] Despite these advances, however, the addition of alkyl radicals to the pyridines faces site selectivity issues involving two competitive pathways (C2 vs. C4) or/and overalkylation, which highlights the challenges for controlling the site-selective alkylation of pyridines (Scheme 1a). The Fu group successfully realized a palladium-catalyzed alkylation of pyridine *N*-oxides[6] using 2° and 3° alkyl bromides to afford C2-alkylated pyridine *N*-oxides (Scheme 1b).[6a] In addition, Zhou et al. applied a palladium-catalyzed alkylation to various heteroarenes.[6b] On the other hand, the introduction of alkyl groups at the C4-position of unbiased pyridines with alkyl halides remains a long-standing challenge in the field of synthetic chemistry.

Previously, our group reported a photocatalytic strategy for site-selective radical trapping with a pyridinium salt.[7] As with other photocatalyzed reactions, the photoactivation of the pyridinium salts relies on an external photocatalyst to trigger a single-electron transfer (SET) reduction for the generation of the reactive radical.[8] Recently, elegant synthetic strategies involving photon-absorbing electron donor-acceptor (EDA) complexes have been developed to promote photochemical transformations under photocatalyst-free conditions.[9] Drawing inspiration from the utility of this strategy, we imagined a new activation mode for pyridinium salts that would bypass the external photocatalyst, opens up novel reactivity to further expand the synthetic potential of pyridinium salts. On this basis, we questioned whether a pyridinium salt could be associated with a suitable electron-rich donor to generate the EDA complex and trigger the formation of radical species.[10] This study reveals the intriguing photochemical ability of the pyridinium salt-bromide complex upon light absorption, as it effectively undergoes SET to drive a new pattern of reactivity.

Based on the ability of silyl radicals to generate alkyl radicals through a silyl radical bromine abstraction from alkyl bromides,[11] we envisioned that the photon-absorbing EDA complex between pyridinium salt and bromide would activate $(TMS)_3SiH$, thus converting a variety of alkyl bromides into open-shell coupling partners. Notably, our finding that this EDA complex serving as an initiator of the chain pathway is key to the successful implementation of this process to maximize the efficiency of the desired cross-coupling. At the same time, sterically bulky *N*-substituent on the pyridinium salts provides regiochemical induction, favoring the C4-position.[7] Herein, we disclose the C4-selective alkylation of pyridine moieties with various alkyl bromides triggered by the photochemical activity of the pyridinium salt-bromide EDA complexes (Scheme 1c). The reaction proceeds with primary, secondary and tertiary alkyl bromides to provide facile access to valuable C4 alkylated pyridine-containing building blocks under mild and metal-free conditions.

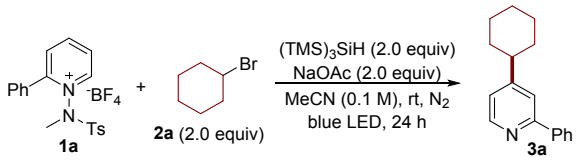
Scheme 1. Alkylation of Pyridine Scaffolds with Alkyl Bromides



We first screened a variety of anions and amines for their abilities to induce the formation of an EDA complex with *N*-amidopyridinium salt **1a**, analyzed by UV/Vis absorption spectroscopy. Our initial investigations revealed the formation of colored EDA complexes upon the treatment with several electron donors, such as TEA, hydroxide, and bromide (see the Supporting Information for details). Importantly, mixing **1a** and tetrabutylammonium bromide (TBAB) as a source of bromide caused a shift in the intensity of the peak corresponding to blue light irradiation, suggesting the formation of a photoactive EDA complex between **1a** and bromide anion. We then performed a series of Stern−Volmer experiments, which revealed that the photoexcited pyridinium salt **1a** is effectively quenched and linearly correlated with the concentration of bromide, supporting the notion that a reductive-quenching of **1a** could generate a bromine radical.

Considering the proposed chain mechanism, we surmised that only a small amount of bromine radical is needed for the initiation of this radical-mediated reaction. Indeed, a central factor in our strategy is the use of a suitable anion to engage fast back-electron transfer (BET)[9c,12] because a rapid intermolecular SET reduction would lead to significant consumption of starting substrate **1a** prior to coupling reactions. Notably, it was found that the photolysis of **1a** with the bromide generated a small amount of production of the photolytic product (see Scheme 2c). In contrast, replacing the bromide with other electron donors, such as TEA and hydroxide, led to substantial decomposition of **1a** (see Scheme S5 for detail). Together, these observations indicate that bromide is a suitable electron donor for inducing the formation of the EDA complex with **1a** and promoting the desired reactivity with only minimal sacrifice of **1a**.

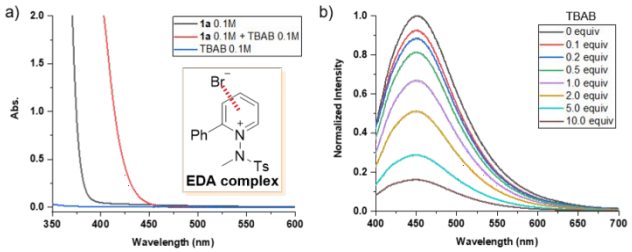
Table 1. Optimization of the reaction conditions[a]



entry	variations from standard conditions	yield (%)[b]
1	none	83
2	acetone instead of MeCN	80
3	1,2-DCE instead of MeCN	49
4	addition of ^{n}Bu$_4$NBr (0.5 equiv)	44
5	Et$_3$SiH instead of (TMS)$_3$SiH	NR
6	(EtO)$_3$SiH instead of (TMS)$_3$SiH	NR
7	without NaOAc	7
8	without (TMS)$_3$SiH	NR
9	without visible light irradiation	NR
10	addition of TEMPO (2.0 equiv)	NR

[a]Reactions were performed by using **1a** (0.1 mmol), **2a** (2.0 equiv), NaOAc (2.0 equiv), (TMS)$_3$SiH (2.0 equiv) in solvent (1.0 mL) under light irradiation using blue LED strips at rt under N_2 for 24 h. [b]Yields were determined by ^{1}H NMR analysis.

■ Absorption spectra and Stern-Volmer quenching of **1a**



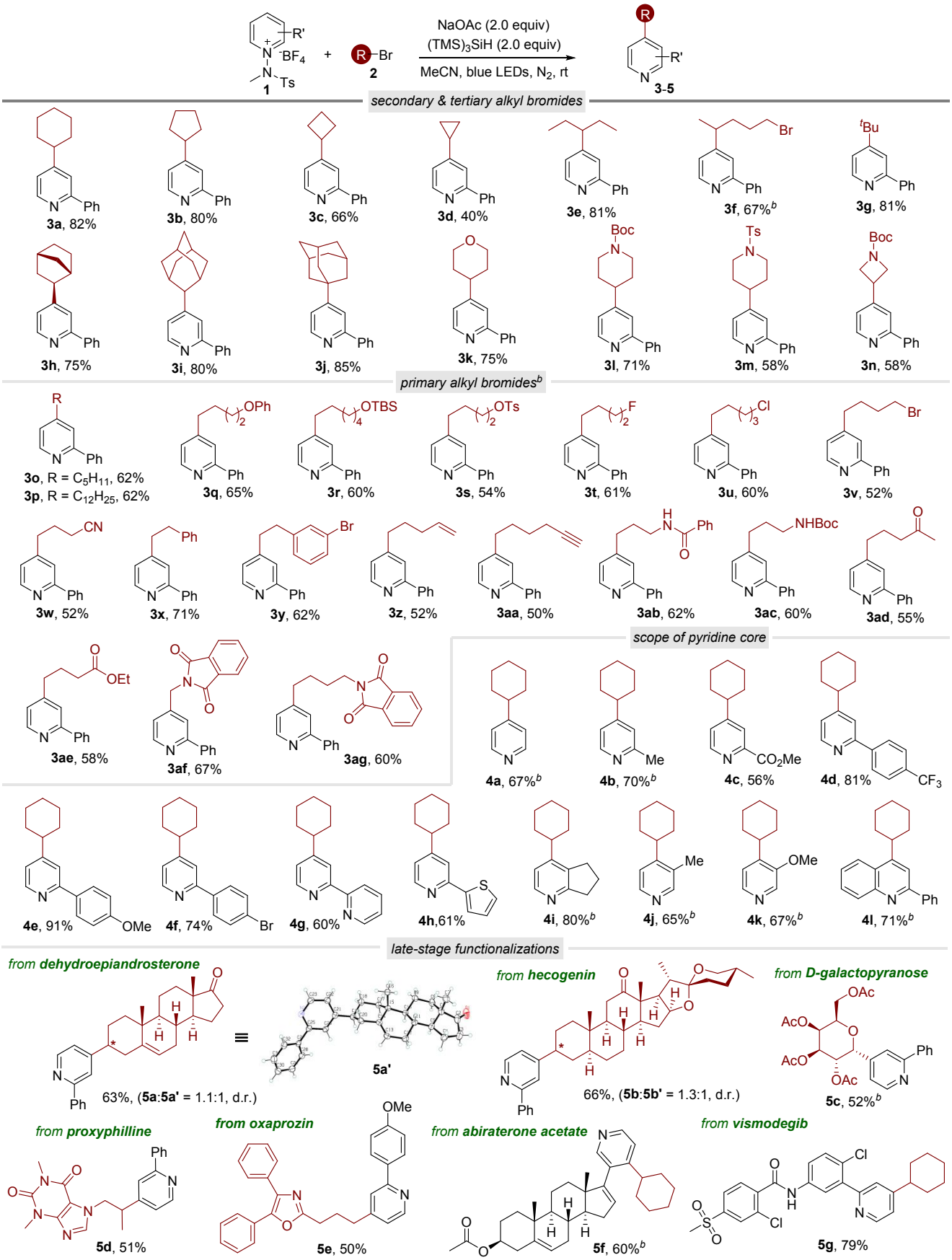
With this knowledge, we next evaluated the feasibility of the proposed reactions between **1a** and bromocyclohexane (**2a**) as model substrates in the presence of (TMS)$_3$SiH and NaOAc (Table 1, see the SI for details). To our delight, we observed a promising result under irradiation with blue LED strips at room temperature, indicating that only trace amounts of the bromide anion formed from in situ **2a** under irradiation[5c,11a-11d] can effectively initiate a radical chain reaction. Under these conditions, C4-alkylated product **3a** was produced in 83% yield as a single isomer. The addition of ^{n}Bu$_4$NBr as a bromide source decreased the product yield (entry 4), as the presence of bromide at a higher concentration with (TMS)$_3$SiH caused accelerated decomposition of **1a**. MeCN was the most effective of the solvents tested (entries 2 and 3). The employment of other silane sources that have higher Si–H bond dissociation energy than that of (TMS)$_3$SiH, failed to afford the desired product **3a** (entries 5 and 6).[13] Of the various bases tested, NaOAc displayed the best activity, and the reactivity was significantly decreased in the absence of the base (entry 7). Control experiments confirmed that visible light and (TMS)$_3$SiH are critical for this transformation (entries 8 and 9). When the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added to the standard reaction conditions, complete inhibition of the reaction was observed (entry 10).

With the optimized reaction conditions, a variety of alkyl bromides were subjected to the optimized reaction conditions to demonstrate the generality of this method (Table 2). This exploration exhibited that sterically encumbered substrates, such as cycloalkyl, linear alkyl, adamantyl, tetrahydropyranyl, piperidinyl, and azetidine bromides were shown to be competent coupling partners (**3a-3n**). Notably, for the dibromo substrate bearing both primary and secondary bromide groups, the reaction selectively takes place at the secondary aliphatic position, leaving the primary bromide intact (**3f**). Moreover, primary alkyl bromides bearing common functionalities, such as (silyl)ether, tosyl, fluoride, chloride, bromide, cyano, phenyl, vinyl, acetylenyl, amide, ester, ketone, carbamate, and phthalimide groups were well tolerated and afforded the desired alkylated products (**3o-3ag**), reflecting the mildness and high efficiency of the method. The functional groups that are active in cross-coupling reactions, such as chloro, bromo, tosyl, and ester groups, remained intact, potentially allowing for post-transformation modification. In addition, exclusive chemoselectivity for alkyl bromide was observed in the presence of aryl bromide, resulting in selective formation of a single mono-pyridylation product **3y** with aryl bromide untouched. Remarkably, in all cases, complete C4 regioselectivity was achieved, regardless of whether the alkyl bromides are primary, secondary, or tertiary, and none of the C2-alkyl pyridines were detected. Next, we explored the scope of the pyridine core. A broad range of pyridinium substrates bearing various functional groups, such as methyl, ester and substituted aryl groups at the C2-position, were selectively alkylated at the C4-position of the pyridines to afford the desired products (**4a-4f**). In addition, pyridinium salts bearing other heteroarenes, such as thiophene and pyridine can be employed (**4g** and **4h**). Notably, neither the efficiency of the reaction nor the selectivity were

hampered by C3 substituents (methyl and methoxy) under the current system, and the corresponding C4-alkylated products were obtained (**4i-4k**). Furthermore, this method could be extended to the alkylation of quinoline scaffold (**4l**).

To further demonstrate the versatility of this activation mode, the current transformation was applied to the late-stage functionalization of biorelevant targets. Specifically, dehydroepiandrosterone, hecogenin, oxaprozin, and proxyphylline could be selectively installed at the C4 position of pyridine scaffold (**5a-5e**).[14] Additionally, the site-selective alkylation proceeded well when substrates derived from pyridine-based drug, such as abiraterone acetate and vismodegib were employed (**5f** and **5g**). Given its generality, we expect this light-promoted protocol to be useful for fragment couplings leading toward a broad range of medicinal agents and complex targets.

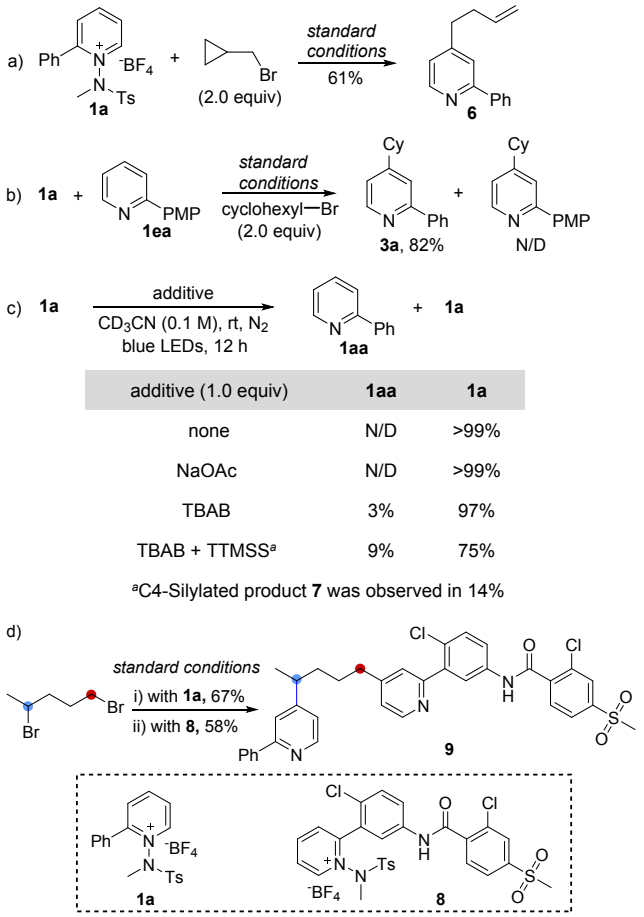
Table 2. Substrate Scope of the C4-Selective Alkylation[a]



[a]Reactions were performed with **1** (0.1 mmol), **2** (2.0 equiv), NaOAc (2.0 equiv), $(TMS)_3SiH$ (2.0 equiv) in MeCN (1.0 mL) under light irradiation using blue LED strips (465 nm) at rt under N_2 for 24 h. Yields of isolated products. [b]Using Kessil blue LED (440 nm).

To elucidate the reaction mechanism, we carried out a series of control experiments. When cyclopropylmethyl bromide was employed as the substrate, ring-opened linear product **6** was observed, which implies a radical ring-opening is involved (Scheme 2a). To determine whether the pyridine species generated by a single-electron reduction could act as a substrate, mixtures of **1a** and pyridine **1ea** were subjected to the standard reaction conditions, and alkylation occurred only at the pyridinium salt **1a** (Scheme 2b). Next, we investigated the feasibility of the photolysis of the pyridinium salt (Scheme 2c). Under blue LED irradiation, the photolysis of **1a** did not occur. On the other hand, upon addition of TBAB to the reaction mixture, we detected the formation of photolytic product **1aa**, which could be accelerated in the presence of $(TMS)_3SiH$. These results revealed that the photoinduced SET occurred between **1a** and bromide to generate bromine radicals. Finally, to showcase the synthetic utility of this transformation, we ventured to explore the sequential pyridylation reactions of the dibromo substrate by employing two different pyridyl sources **1a** and **8**. Gratifyingly, the pyridyl group and vismodegib were consecutively installed through two sequential processes to afford **9** (Scheme 2d).

Scheme 2. Control Experiments and Sequential Pyridylation



additive (1.0 equiv)	1aa	1a
none	N/D	>99%
NaOAc	N/D	>99%
TBAB	3%	97%
TBAB + TTMSS[a]	9%	75%

[a]C4-Silylated product **7** was observed in 14%

Based on these observations, we propose a reaction mechanism involving the initial formation of a photoactive pyridinium-bromide complex (Figure 1). Photoexcited EDA complex **I** undergoes an intramolecular SET to trigger the formation of a bromine radical that subsequently abstracts a hydrogen atom from $(TMS)_3SiH$, thus interrupting the BET.[9c] This process leads to the formation of a silyl radical that in turn, abstracts bromine from an alkyl bromide to produce the corresponding alkyl radical. The alkyl radical is then trapped at the C4 position of the *N*-amidopyridinium salt, and the regioselectivity is controlled by the *N*-substituent.[7] Next, the reaction is expected to proceed via deprotonation of cationic radical species **II** and C–N bond cleavage to deliver the desired product and amidyl radical. The photochemically generated amidyl radical initiates a new chain propagation manifold via a HAT event with $(TMS)_3SiH$. Indeed, this EDA complex serves as an effective initiator of the chain pathway, which explains the high value of quantum yield (Φ = 19.0).

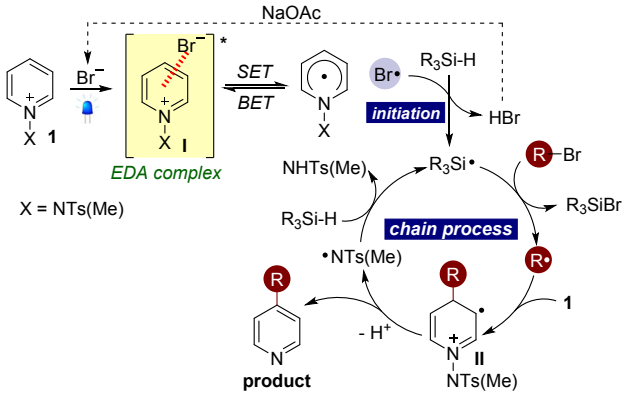


Figure 1. Proposed reaction mechanism.

In summary, we report a general strategy for the C4 selective alkylation of *N*-amidopyridinium salts with alkyl bromides without requiring an external photoredox catalyst. A photoexcited pyridinium salt-bromide complex is key to the success of this process, as it enables the generation of silyl radicals from $(TMS)_3SiH$. In the process, a variety of alkyl bromides can be converted to the corresponding alkyl radical coupling partners, allowing facile access to privileged C4-alkylated pyridine building blocks that would be difficult to prepare with conventional approaches. The utility of this protocol is further demonstrated by the late-stage functionalization of biorelevant compounds. This study demonstrates the potential of *N*-amidopyridinium salts to promote new photochemical reactions in synthetic chemistry.

ASSOCIATED CONTENT

Supporting Information

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

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(14) CCDC 1994429 (**5a'**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

TOC Graphic