Visible light induced alkene aminopyridylation using N-aminopyridinium salts as bifunctional reagents

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The development of intermolecular alkene aminopyridylation has great potential for quickly increasing molecular complexity with two valuable groups. Here we report a strategy for the photocatalytic aminopyridylation of alkenes using a variety of N-aminopyridinium salts as both aminating and pyridylating reagents. Using Eosin Y as a photocatalyst, amino and pyridyl groups are simultaneously incorporated into alkenes, affording synthetically useful aminoethyl pyridine derivatives under mild reaction conditions. Remarkably, the C4-regioselectivity in radical trapping with N-aminopyridinium salt can be controlled by electrostatic interaction between the pyridinium nitrogen and sulfonyl group of β-amino radical. This transformation is characterized by a broad substrate scope, good functional group compatibility, and the utility of this transformation was further demonstrated by late-stage functionalization of complex biorelevant molecules. Combining experiments and DFT calculations on the mechanism of the reaction is investigated to propose a complete mechanism and regioselectivity.

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Alkenes are ubiquitous in organic chemistry and the aminative difunctionalization of olefins is a convenient strategy for directly accessing nitrogen-containing molecules. However, adding hard Lewis basic amino functionalities to carbon–carbon double bonds that are of course soft Lewis bases on their own right is fundamentally problematic and requires a non-classical strategy because simply using an amino group as a nucleophile is not promising. Recently, photoredox catalysis proved to be highly efficient for generating N-centered radicals that could be employed to drive anti-Markovnikov-selective alkene carbo-, hydroxyl-, and fluorination/amidation reactions and form synthetically and biologically valuable linear amines. The pyridine moiety is a basic structural unit of numerous natural products, pharmaceuticals, agrochemicals, and fine chemicals. Therefore, a number of synthetic strategies have been explored to install pyridyl groups on molecules. Bringing together these two valuable but challenging methodological avenues, we questioned whether aminopyridylation of olefins can be achieved using the power of photoredox catalysis techniques to offer an efficient, direct, and environmentally benign synthetic route to these valuable products. The development of intermolecular alkene difunctionalization with a bifunctional reagent has great potential for quickly increasing molecular complexity in a single operation with high levels of atom and step economy.

The Minisci-type C–H alkylation of pyridines by directly adding alkyl radicals to the C2-position of the pyridine core is well-established, but overalkylation at the C6-position is a common problem resulting in mixtures of mono- and disubstituted products. Recently, the N-alkoxypyridinium salts emerged as easily accessible, versatile, and bench-stable pyridine surrogates that in principle may offer increased levels of selectivity and reactivity. For example, Herzon reported a cobalt-mediated reductive cross-coupling of alkenes with N-methoxypyridinium salts, and we developed remote C–H pyridylation reactions by using N-alkoxypyridinium salts as substrates. Unfortunately, these reactions were found to be modestly regioselective (C2 vs. C4) when secondary alkyl radicals were employed. Clearly, a key difficulty to overcome when developing the proposed alkene aminopyridylation lies in the regioselectivity of the two competing sites (C2 vs. C4) on the pyridinium salts.

The generation of N-centered radicals from N-aminopyridinium salts proved highly efficient in photocatalytic systems, although fragmentation of the prefunctionalized N-radical precursor by single electron transfer (SET) reduction results in an inevitable loss of pyridine as chemical waste. We envisioned that N-aminopyridinium salts may serve as bifunctional reagents to deliver both the aminyl radical and the pyryl group to an olefin. In this scheme, the aminyl radicals generated from a fragmentation of the N-aminopyridinium salt react with the alkene to form a new C–N bond and an adjacent β-amino radical. The resultant alkyl radical may then trap N-aminopyridinium salt to install a pyridyl group, affording synthetically and biologically valuable aminoethyl pyridines.

Results

Reaction discovery and optimization. We tested the viability of our proposed approach using vinyl ether as model reactants under blue LED irradiation, and selected data are enumerated in Table 1. After evaluating different reaction conditions, we were pleased to find that the use of Ir(ppy)3 in acetonitrile initiated 1,2-amination and pyridylation at room temperature to afford the desired product in 30% yield (entry 1), indicating that the proposed overall process involving tandem amination and pyridylation is possible. Notably, radical trapping with 2a occurs selectively at the C4 position of the pyridine core. Significant turnover was observed with the

![Fig. 1 Project background and design plan for photocatalytic aminopyridylation of olefins. a) Bioactive aminoethy heteroarenes. b) Acid-promoted Minisci-type alkylation of pyridine. c) Radical pyridylation using N-alkoxypyridinium salts. d) Aminopyridylation of olefins using N-aminopyridinium salts as bifunctional reagents. PC photocatalyst. Ts toluenesulfonyl](https://www.nature.com/naturecommunications)
In these calculations, the prototype reactant 2a, N-(methyltosyl)aminopyridinium, is employed to form the product 3b. As illustrated in Fig. 2, the proposed mechanism is fundamentally different from the previously studied alkylation reactions. The catalytic cycle is initiated by the excitation of the photocatalyst PC to \( \text{PC}^* \), which subsequently transfers a single electron to 2a to form the unstable N-pyridine radical 2a*. Homolytic cleavage of the –N–N bond liberates pyridine and produces the activated N-centered radical A. This reaction is calculated to have a step barrier of 7.8 kcal/mol and is irreversible with a driving force of 28.3 kcal/mol. From the N-centered radical A, we considered two plausible reaction pathways invoking the attack of either the alkene 1b or a second equivalent of the pyridinium 2a*. Interestingly, attacking 2a is both kinetically and thermodynamically disfavored and requires a step barrier of 21.3 kcal/mol associated with the transition state \( \text{p-A-TS}^\bullet \) to afford the putative intermediate \( \text{p-B}^\bullet \), found to be 11.6 kcal/mol higher in energy than A, as shown in red dotted line in Fig. 2. Our calculations indicate that the N-centered radical A prefers to attack the olefin substrate \( \text{1b} \) to give intermediate B with a barrier of only 8.5 kcal/mol and this step is energetically downhill by 7.3 kcal/mol. It is interesting that the N-centered radical A acts as an electrophile to attack the electron-rich olefin substrate in this instance, rather than behaving like a nucleophile that may have preferred to react with the electron-poor pyridinium substrate. Although it is easy to recognize electrophilic and nucleophilic reactants in closed-shell molecules, it is rather difficult to predict if radical species prefer to engage an electron-rich or an electron-poor substrate. Whereas DFT calculations can capture these effects, as we demonstrate, it is desirable to understand these results in a more intuitive sense.

The frontier molecular orbitals of A, 1b, and 2a displayed in Fig. 3 illustrate that the singly occupied molecular orbital (SOMO) of A is at –7.64 eV, whereas the highest \( \pi \) and the lowest \( \pi^* \) MOs of 1b are found at –6.61 and +0.56 eV, respectively. The analogous orbitals of 2a are located at –12.69 and –6.24 eV, respectively. Because the SOMO of A is closest in energy to the occupied \( \pi \) orbital of the olefin substrate 1b, as highlighted in blue in Fig. 3, these two MOs engage in a 2-orbital-3-electron interaction. As a consequence, the N-centered radical acts as an electrophile towards the olefin. The orbitals of the pyridinium substrate 2a, on the other hand, are much lower in energy because of the positive molecular charge and the closest frontier orbital to the SOMO of A is the \( \pi^* \) orbital, as highlighted in red in Fig. 3. Consequently, these two MOs give a 2-orbital-1-electron interaction and the radical acts as a nucleophile towards the pyridinium substrate. The strengths of these interactions are governed by the overlap of the interacting orbitals and their energy difference. Large orbital overlap and small energy difference will increase the interaction strength. As illustrated in Fig. 3, the energy difference of the interacting frontier orbital is 1.04 eV for the olefin 1b, whereas 1.41 eV is found for the pyridinium substrate. Moreover, the \( \pi \) orbital of the olefin is much more localized than the \( \pi^* \) orbital of the pyridinium, thus the orbital overlap will give notable preference to the olefin. Thus, both components favor the radical-olefin interaction, which explains the transition state and intermediate energies presented above.

To push the reaction forward, it is necessary that the alkyl radical B attacks a pyridinium species to form an unstable cationic radical intermediate C that can be deprotonated to afford the neutral radical species D. Note that the deprotonation transition state was not specifically modeled, but we assume this step to be fast and unproblematic considering the small kinetic isotope effect (Fig. 8a, \( K_{\text{H}}/K_{\text{D}} = 1.2 \)). The final product is formed by –N–N bond cleavage to extrude the aminyl radical, which can
Fig. 2 Propose reaction pathway and related free energy profile. a Proposed reaction pathway. b Free energy profile for the formation of 3b that is described with a solid black line. Blue and red traces represent the side pathway toward ortho(C2)-product generation and direct N radical attack on 2a, respectively. Energy profile for ortho(C2)-product is only shown in a radical addition step as it has a very similar energy trend with that of p-B'- after radical addition and does not affect the regioselectivity.

To understand the origin of the regioselectivity, a distortion-interaction analysis was conducted, as shown in Fig. 4a, where the pyridinium and the alkyl fragments are calculated at the geometry found in the transition state, but separated from each other. By examining their energies, we can estimate the energy required to distort these molecular components to the structure needed at the transition state and also calculate the interaction energy between these distorted molecular fragments. Note that we use electronic energies for this purpose and the transition state p-B'-TS is found to be 2.7 kcal/mol lower in energy than o-B'-TS, which is slightly more pronounced than 1.3 kcal/mol estimated for the solution phase free energy. Interestingly, the amount of structural distortions that the two reactants must undergo to reach the transition state structures are nearly identical at 6.3 and 6.6 kcal/mol. The interaction energies were found to be –17.8 and –20.7 kcal/mol for the o-B'-TS and p-B'-TS, respectively. Curiously, the lengths of the C–C bonds that are being formed are practically identical at 2.23 and 2.25 Å, which is inconsistent with the interaction energy difference of 2.9 kcal/mol. Further bonding analysis presented in the Supplementary information reveals that the interaction energy difference stems from an additional non-covalent attraction between the partially negatively charged

start a new catalytic cycle. Our calculations indicate that the radical addition step B → C is likely rate-determining and is also responsible for the regiocontrol. Although free energies of two regioisomers p-C and o-C are almost identical at –27.1 and –27.4 kcal/mol, respectively, the transition states p-B'-TS leading to the C4-intermediate p-C is 1.3 kcal/mol lower in energy than the C2-alternative, in good agreement with the experimentally observed regioselectivity.
sulfonyl oxygens and the positively polarized nitrogens of the pyridinium substrate across a distance of 2.98 Å, as illustrated in Fig. 4. This interaction is structurally not possible in o-B-TS.

**Substrate scope studies.** Encouraged by the aforementioned experimental findings and with a solid understanding of the mechanism based on our DFT calculations in hand, we investigated the substrate scope to test the utility and versatility of the current photocatalytic tandem reaction. First, the generality with respect to alkene substrates was investigated, as illustrated in Fig. 5. Various electron-rich alkenes, such as vinyl ether and enamides reacted readily, leading to the formation of β-aminopyridine derivatives with excellent C4-regiocontrol. Aliphatic vinyl ethers with various chain lengths and sizes reacted readily (3a–3e). Substrates bearing polar functionalities, such as hydroxyl and chloro groups were also well-tolerated to provide the desired products in good yield (3f and 3g). We subsequently assessed the applicability of this transformation with respect to the vinyl substrates bearing aryl ethers (3h–3n). For example, the substrates containing naphthyl or coumarin groups could be employed in this transformation to afford the desired products 3k and 3l, although the latter was generated with lower yields. The current protocol can be extended to the functionalization of internal olefins, providing the desired difunctionalized products (3o–3q). It is also noteworthy that the reaction can also be extended to vinyl amides, formamide, and carbamate to yield the desired products (3r–3v). Low reactivity was observed with unactivated alkenes under the standard reaction conditions (see Supplementary Fig. 1). To demonstrate the practical
applicability of this method, we subsequently performed the reaction with alkene 1a and 2a, on the 2.0 mmol scale, and the desired product 3a was formed in 83% yield.

To further test the generality of this reaction, we investigated the scope of reaction with respect to the bifunctional reagents and prepared a series of N-aminopyridinium salts. As summarized in Fig. 6, we observed that substrates bearing electron-rich or electron-deficient groups, such as methyl (4a and 4b), methoxy (4c), and ester (4d) groups on the pyridyl ring successfully afforded the desired products. Concerning the importance of the 2-arylpyridine structural motif in pharmaceutical chemistry and materials science, we next evaluated the scope of the reaction with substrates containing a variety of aryl groups (4e-4g). The reactions of pyridinium substrates bearing methyl, phenyl, methoxy, ester or bromo groups at the C3 positions proceeded well to provide 4h, 4i, 4j, 4k, and 4l. Bicyclic pyridinium substrate was also tolerable to give the desired product 4m. Expanding the scope from the methyl substituent of N-tosylamide to other groups, such as ethyl (4n), \( \text{propyl} (4o) \), trifluoroethyl (4p), or phenyl propyl groups (4q) was also possible, leading to the formation of the corresponding products. Besides, the scope could be expanded to an N-mesyl group, which afforded the desired product in good yield (4r).

To demonstrate the broad synthetic utility of the current method, we assessed the potential of this convenient method for the late-stage modification of seven different classes of biorelevant complex molecules, as highlighted in Fig. 7. Specifically, the reaction of the amino acid derivatives, L-serine, and L-tyrosine under the standard reaction conditions effectively provided the corresponding products 5a and 5b. D-fructopyranose, estrone, and \( \beta \)-citronellol derivatives all underwent aminopyridylation smoothly, affording the desired products 5c, 5d, and 5e. In addition, derivatives of pyriproxyfen and bisacodyl were successfully employed to provide the corresponding products 5f and 5g in moderate to good yield. Therefore, these results highlight the synthetic utility of the current aminopyridylation reactions with respect to the high tolerance of functional groups, such as ester, ketone, amide, acetal, ether, and pyridines in the complex molecules.

Control experiments. Having established that our developed method is generally applicable and broad in scope, we wished to scrutinize the proposed mechanism (see Supplementary Fig. 9). First, kinetic isotope experiments indicated that the deprotonation step is not rate-determining (Fig. 8a). Next, to determine whether the pyridine species generated in situ by single-electron transfer could act as a substrate, mixtures of 2a and 2-\( p \)-methoxyphenyl (PMP)-substituted pyridine were subjected to the standard reaction conditions (Fig. 8b). As anticipated, the
reaction occurred only with the pyridinium salt 2a, whereas pyridine was not involved in the radical trapping step. Stern-Volmer quenching experiments were conducted to reveal that the quenching of the excited state of EY is directly proportional to the concentration of 2a (see Supplementary Fig. 3 and 4). In addition, we measured the cyclic voltammetry of pyridinium salt 2a, and the reduction potential of 2a was ~0.73 V (peak potential vs. Ag/Ag⁺, see Supplementary Fig. 6), indicating that the photocatalytic cycle could operate under oxidative quenching mechanism. The possibility of any formation of the EDA complex could be ruled out by absorption spectra measurements (see Supplementary Fig. 5).

**Discussion**

In summary, we developed a direct 1,2-aminopyridylation of olefins induced by visible light using a variety of N-aminopyridinium salts as efficient bifunctional reagents to give straightforward access to synthetically and biologically relevant β-aminopyridine structural motifs under mild reaction conditions.
In the process, N-aminopyridinium salts serve as both aminating and pyridylating reagents, which directly incorporate vicinal amino and pyridyl groups on the olefins in a controllable and selective manner. Combining experimental and computational methods, a detailed mechanistic understanding of the origin of the regioselectivity in the radical trapping step was obtained. The electrostatic attraction between the pyridinium nitrogen and sulfonyl group of β-aminopyridine directs radical trapping at the C4-position of pyridinium substrates. This strategy provides a convenient and powerful synthetic tool for the alkene aminopyridylation and is well suited for the late-stage modification of complex biorelevant molecules.

**Methods**

**Representative procedure for the aminopyridylation of alkenes.** Reactions were conducted in a test tube (16 mL) sealed with rubber septa. N-protected 1-aminopyridinium tetrafluoroborate (2a) (0.15 mmol), Eosin Y (0.5 mol%), and K2PO4 (0.12 mmol) were combined under N2 atmosphere. To the reaction mixture was added n-butylvinyl ether (1a) (0.1 mmol) in dimethyl sulfoxide (DMSO, 1.0 mL). The sealed test tube was sonicated for 10 s and immediately placed at a temperature of 100 °C. The resulting mixture was stirred at room temperature for 3 h, diluted with ethyl acetate (20 mL). The sealed test tube was sonicated for 10 s and immediately placed at a temperature of 100 °C. The resulting mixture was stirred at room temperature for 3 h, diluted with ethyl acetate and washed with water for 3 times. The organic layer was dried over magnesium sulfate and filtered. The resulting mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (acetone:hexane = 1:4) to obtain the desired product 3a (84%, 30.5 mg) as a colorless oil.

**Data availability**

Experimental procedure and characterization data of new compounds are available within Supplementary Information. Computational details, optimized Cartesian coordinates of all structures, vibrational frequencies, and energy components. This material is available free of charge via the Internet.

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