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Regio- and Diastereoselective Aminopyridylation of Bicyclo[1.1.0]butanes with *N*-Aminopyridinium Ylides Enabled by Photoredox Catalysis

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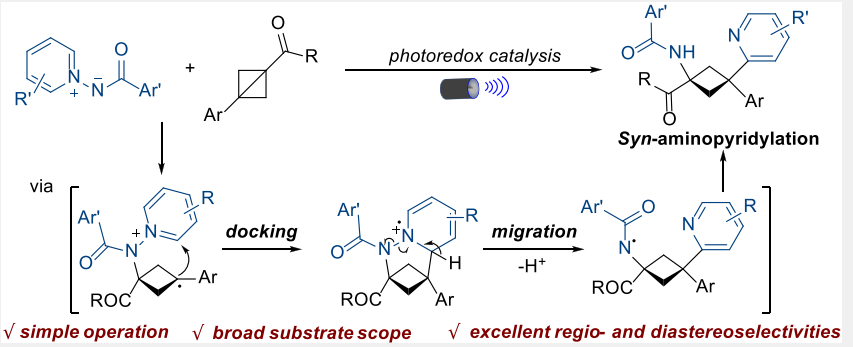

ABSTRACT: Visible-light-mediated functionalization of bicyclo[1.1.0]butanes (BCBs) has been proven to be an efficient way to obtain diverse cyclobutane derivatives. However, achieving diastereoselective control in this field remains challenging. Herein, we reported a mild photoredox-catalyzed aminopyridylation of BCBs with *N*-aminopyridinium ylides, delivering the cyclobutylamine derivatives with excellent regio- and diastereoselectivities. This protocol demonstrated excellent compatibility with a wide range of BCBs and *N*-aminopyridinium ylides, and the value of this approach was highlighted by its application in the preparation of high-value, structurally complex cyclobutane derivatives.

KEYWORDS: *aminopyridylation, excellent regio- and diastereoselectivities, bicyclo[1.1.0]butane, N-aminopyridinium ylide, photoredox-catalysis*

INTRODUCTION

Cyclobutylamine motifs are prevalent in pharmaceuticals and agrochemicals due to their unique biological properties (Figure 1A).[1−3] For instance, apalutamide, an androgen receptor inhibitor, is used in the treatment of prostate cancer.[4] Fluciclovine (18F), a diagnostic agent, is employed in positron emission tomography (PET) imaging,[5] while cyclobutrifluram serves as a multipurpose pesticide, primarily used as a nematocide.[6] Given this importance, there is significant demand for new synthetic methods to obtain diverse cyclobutylamine derivatives.[7−10]

As a complementary approach to conventional [2 + 2] cycloadditions,[11,12] the functionalization of bicyclo[1.1.0]-butanes (BCBs) has emerged an effective strategy for constructing various cyclobutane derivatives.[13−16] Radical-mediated functionalization of BCBs, in particular, has gained considerable attention over the past five years, owing to the availability of various feedstocks and diverse reaction pathways, including Giese additions,[17−19] difunctionalizations,[20−22] and cycloadditions.[23−32]

However, unlike cycloadditions, controlling diastereoselectivity in radical-mediated Giese additions and difunctionalizations of BCBs remains challenging due to the inherent flexibility of the cyclobutane ring (Figure 1B). Most successful examples have relied heavily on steric effects from bulky substrates.[22,33,34]

Recently, Zhu and co-workers introduced a "dock-migration" strategy for radical-mediated selective difunctionalization of alkenes and alkynes.[35−43] This approach involves a newly formed transient radical from radical addition, that undergoes sequential intramolecular radical functional group migration,[44−46] affording difunctionalized products with excellent selectivity. This strategy provides a valuable platform for selective radical-mediated difunctionalization, providing new

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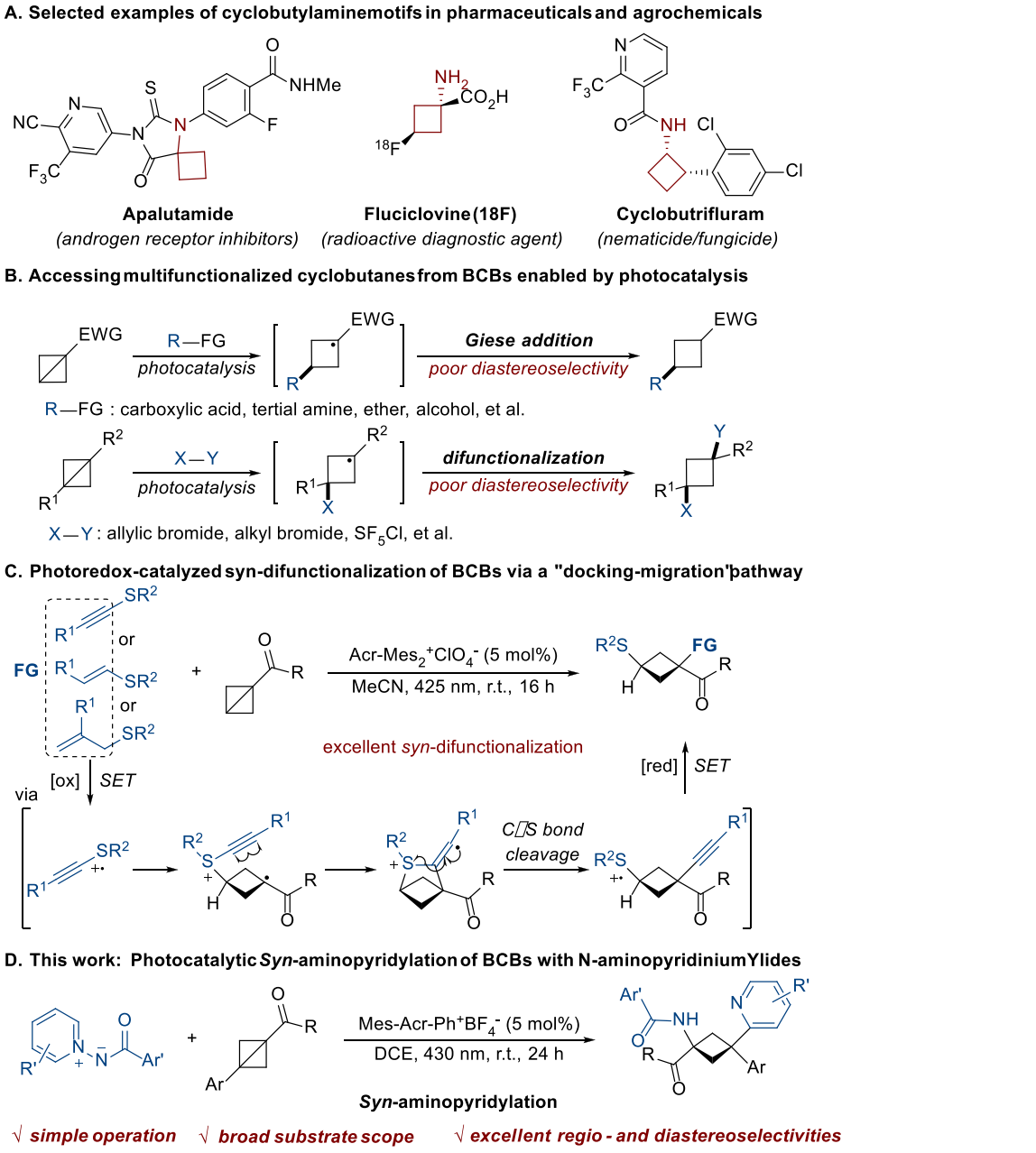

Figure 1. Strategies for syn-difunctionalization of BCBs. r.t.: room temperature.

opportunities to access diverse syn-difunctionalized cyclobutane derivatives through the difunctionalization of BCBs.

In 2024, Glorius et al. demonstrated an efficient photocatalytic syn-difunctionalization of BCBs using this "dock-migration" strategy, wherein thioethers served as bifunctional reagents, delivering cyclobutyl thioethers with excellent diastereoselectivity (Figure 1C).[47,48] Despite these advances, radical-mediated diastereoselective difunctionalization of BCBs that provides more diversely substituted cyclobutane derivatives is still highly sought-after.

Building on our interest in photoinduced selective functionalization of BCBs,[20,49] herein, we report a photoredox-catalyzed protocol for syn-aminopyridylation of BCBs via the "dock-migration" process. By using *N*-aminopyridinium ylides as bifunctional reagents,[50−53] we successfully achieved regio- and diastereoselective difunctionalization of BCBs, offering a novel route to cyclobutylamine derivatives (Figure 1D).

The aminopyridylation reaction was first investigated using acridinium salt **PC1** as the photocatalyst and 3-phenylbicyclo[1.1.0]butane-1-carboxylate **1a** and (4-methoxybenzoyl)(pyridin-1-ium-1-yl)amide **2a** as model substrates. The amide group was exclusively added to the ester side of **1a**, delivering the desired cyclobutylamine product **3** in 8% yield (Table 1, entry 1). Further screening of the photocatalysts revealed that the acridinium salt **PC3** was optimal (entries 2−4), increasing the yield of **3a** to 38%. The reaction was also performed in various solvents, including dichloromethane (DCM), acetone, and acetonitrile (MeCN) (entries 5−9), with 1,2-dichloroethane (DCE) being the most effective. Dimethylformamide (DMF) was found to be unsuitable for this transformation (entry 8). Exploration of light sources indicated that 430 nm LEDs were the optimal light source, affording **3** in 52% isolated yield (entries 9−10). Control

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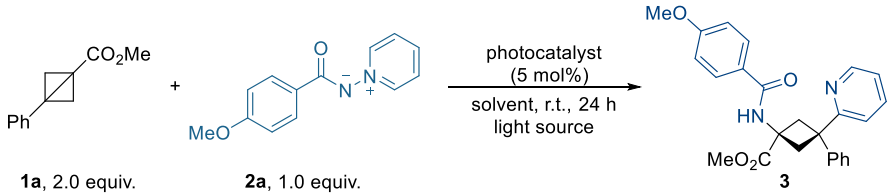
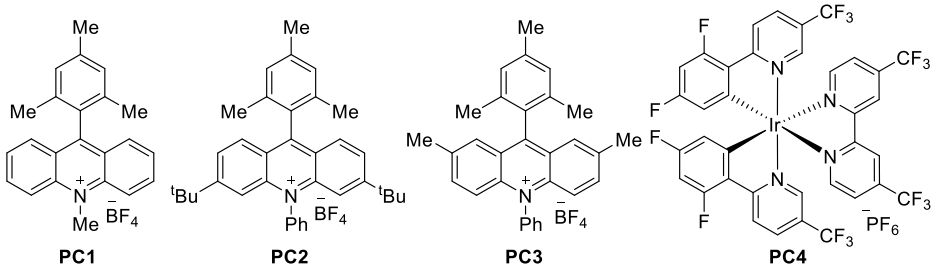
Table 1. Optimization of the Reaction Conditions for Aminopyridylation of BCB 1a and *N*-Aminopyridinium Ylide 2a



entry	photocatalyst	solvent	light source	yield of 3 (%)[a]
1	**PC1**	DCE	475 nm	8
2	**PC2**	DCE	475 nm	24
3	**PC3**	DCE	475 nm	38
4	**PC4**	DCE	475 nm	30
5	**PC3**	DCM	475 nm	35
6	**PC3**	MeCN	475 nm	24
7	**PC3**	acetone	475 nm	15
8	**PC3**	DMF	475 nm	0
9	**PC3**	DCE	430 nm	55 (52)[b]
10	**PC3**	DCE	405 nm	35
11		DCE	430 nm	0
12[c]	**PC3**	DCE	430 nm	0

[a]



The yield of **3** was determined by analysis of the crude ^{1}H NMR spectrum using CH_2Br_2 as an internal standard. [b]Isolated yield. [c]Without light.

experiments confirmed that the reaction did not occur in the absence of either photocatalyst or light (entries 11−12).

With the optimized conditions established, we explored the scope of BCB derivatives (Scheme 1). Esters of BCB, bearing various substituents on the phenyl ring, including methoxy (**4**) and halogen atoms (**5**−**8**), were amenable substrates in this aminopyridylation reaction, giving the corresponding cyclobutylamines in moderate to good yields. The relative configuration of cyclobutylamine **8** was determined by X-ray diffraction (CCDC 2451028). BCBs featuring isopropyl (**9**) and phenyl esters (**10**) also performed well under the optimal conditions. Furthermore, BCB-derived ketones (**11**−**14**) proved to be suitable substrates, delivering the desired products in 52−58% yields.

We next investigated the substrate generality of *N*-aminopyridinium ylides (Scheme 2). Various functional groups, such as phenyl (**15**), ester (**16**), or alkyl (**17**−**19**) groups at the para position of the pyridinium core, were well-tolerated, resulting in the desired cyclobutylamine products in 32−76% yields. When 3-methoxy-1-(4-methoxybenzamido)pyridin-1-ium was employed as a substrate, the reaction primarily occurred at the C2 position of the pyridinium ring, giving product **20** with excellent regioselectivity. Similar regioselectivity has been observed in photocatalytic aminopyridylation of alkenes, as reported by Hong.[50] *N*-Aminopyridinium ylides derived from quinoline (**21**) and isoquinoline (**22**) also reacted smoothly in this protocol.

To demonstrate the synthetic utility of this aminopyridylation protocol (Scheme 3), we subjected cyclobutylamine product **3** to hydrolysis with LiOH, giving the corresponding carboxylic acid **23** in 92% yield. Reduction with $LiAlH_4$ converted compound **3** into desired alcohol analogue **24** with excellent yield. Following Loiseleur's protocol,[54] the cyclobutylamine product **11** was treated with DAST, resulting in the cyclization of an α-acylaminoketones moiety to generate **25** with a 7-oxa-5-azaspiro[3.4]oct-5-ene scaffold in 69% yield.

To gain insight into the reaction mechanism, Stern−Volmer quenching studies were performed (Figures 2A and S6−S9). The results indicated that the excited photocatalyst could be quenched by both BCBs **1a** and *N*-aminopyridinium ylides **2a**. Comparison of the quenching constants revealed that *N*-aminopyridinium ylides **2a** quenched the excited photocatalyst more efficiently. Light on/off experiments suggested that continuous light irradiation was essential for this transformation (Figure S3). In the presence of 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) as a radical scavenge, the aminopyridylation reaction was completely inhibited, and the benzyl radical-TEMPO adduct **26** was detected by HR-MS (Figures 2B and S5).

Based on these observations, we propose the following possible mechanism for the aminopyridylation reaction (Scheme 4). Upon light irradiation, the excited photocatalyst ($E_{1/2(PC/PC^*)}^{red}$ = +2.09 V vs SCE) undergoes single electron reduction by the *N*-aminopyridinium ylides **2a** ($E_{p/2}^{ox}$ = +1.40 V vs SCE, Figure S4),[55,56] generating the *N*-radical intermediate **I**.

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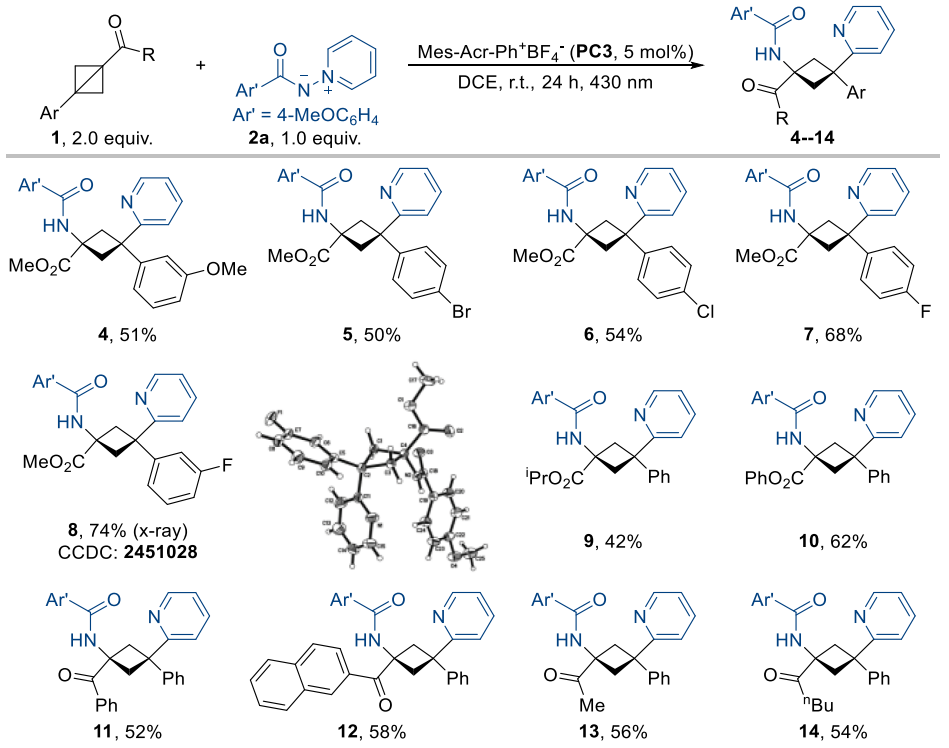
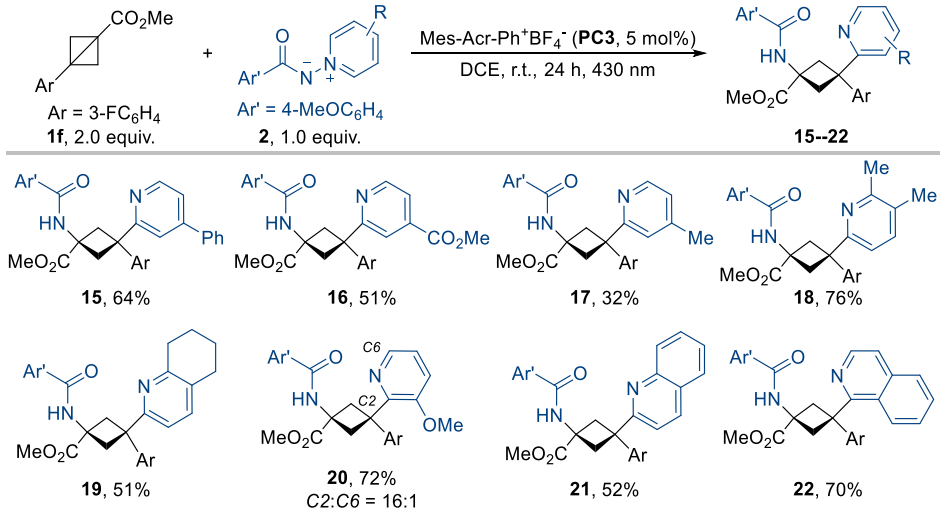
Scheme 1. Substrate Scope of BCBs with *N*-Aminopyridinium Ylide 2a[a]



[a]A mixture of BCB **1** (0.4 mmol), **2a** (0.2 mmol), and **PC3** (0.01 mmol) in anhydrous DCE (2.0 mL) was irradiated at room temperature under a 430 nm LED for 24 h. The yields were isolated yields.

Scheme 2. Substrate Scope of *N*-Aminopyridinium Ylides[a]



[a]A mixture of BCB **1f** (0.4 mmol), *N*-aminopyridinium ylide **2** (0.2 mmol), and **PC3** (0.01 mmol) in anhydrous DCE (2.0 mL) was irradiated at room temperature under a 430 nm LED for 24 h. The yields were isolated yields.

Due to the polarity-match principle,[57] the electrophilic *N*-radical **I** preferentially adds to the ester side of BCB **1a**, forming the nucleophilic benzyl radical intermediate **II**. This intermediate readily undergoes intramolecular radical addition to the electron-deficient pyridinium ring, delivering intermediate **III**. After deprotonation, intermediate **IV** is formed. Driven by rearomatization of the pyridyl ring, intermediate **V** undergoes homolytic N−N bond cleavage to form the thermodynamically favored amidyl radical **V**.[58] Reduction by the radical anion of the photocatalyst and protonation furnish the final product **3**.

CONCLUSION

In summary, an unprecedented syn-aminopyridylation of BCBs with *N*-aminopyridinium ylides, enabled by photoredox catalysis, has been achieved in a mild and step-economical manner. A broad range of BCBs and *N*-aminopyridinium ylides were successfully employed, affording cyclobutylamine derivatives in moderate to good yields with excellent regio- and diastereoselectivities. Preliminary mechanistic studies, including Stern−Volmer quenching, radical-trapping experiments, and

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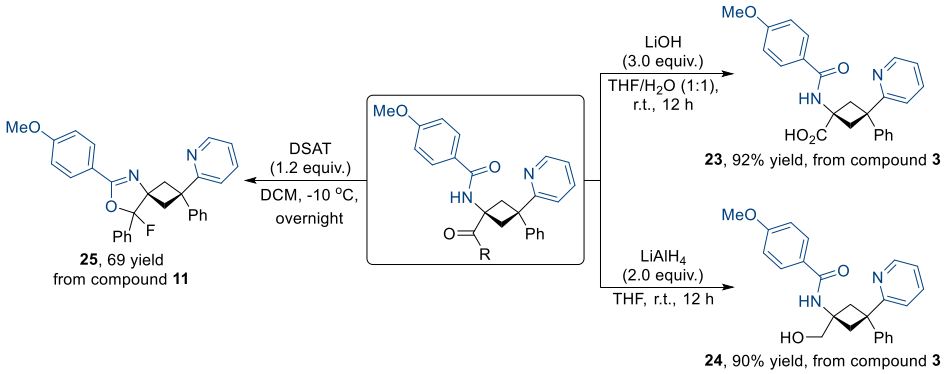
Scheme 3. Synthetic Utility



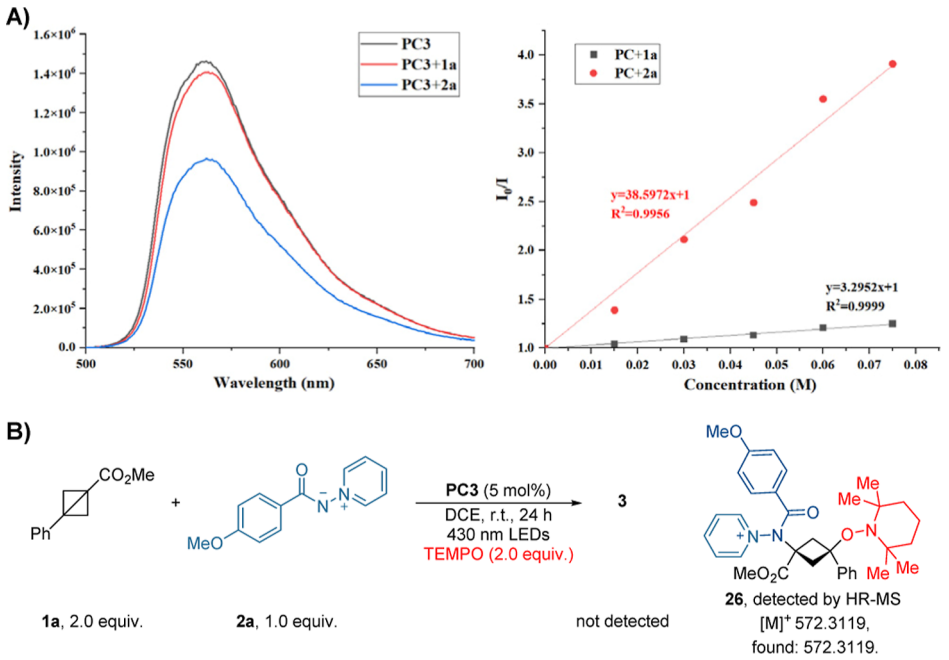
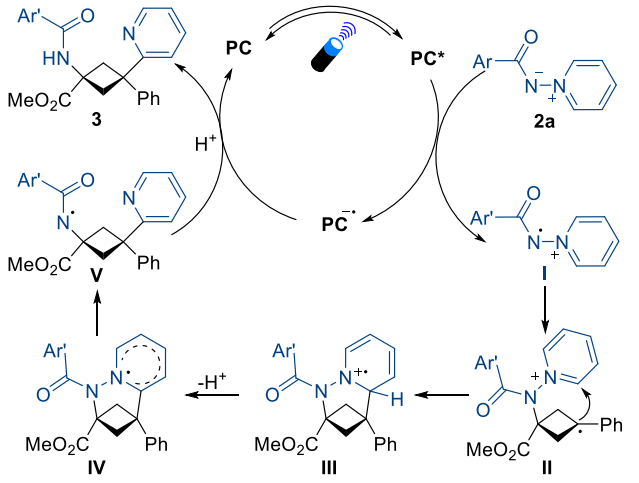


Figure 2. Mechanistic studies. (A) Stern−Volmer fluorescence quenching studies. (B) Radical trapping experiment. [a]Yield calculation was based on **1a**. n.d. = not detected.

Scheme 4. Plausible Mechanisms



cyclic voltammetry (CV) measurements, provide insights into the proposed mechanism of this aminopyridylation reaction.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/prechem.5c00079.

General experimental procedures, tables of reaction optimizations, mechanistic study, and characterization data including ^{1}H and ^{13}C NMR and ^{19}F NMR spectra for all new compounds (PDF)

checkCIF/PLATON report for cyclobutylamine **8** (PDF)

Crystallographic data of cyclobutylamine **8** (CIF)

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Notes

The authors declare no competing financial interest.

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