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# An electron-donor–acceptor complex between two intermediates enables a N–N bond cleavage cascade process to access 2,3-difunctionalized pyridines†

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Chemical transformation triggered by an electron donor–acceptor (EDA) complex without the addition of an exogenous stoichiometric electron donor/acceptor is rare. Herein, we report such a process to access 2,3-difunctionalized pyridines from readily available *N*-aminopyridiniums (**1**) and activated alkenes (**2**) promoted by visible light. This procedure offered multi-substituted pyridines in satisfactory yields at room temperature with broad functional group tolerance. The reaction can be easily performed on a gram scale without the loss of yield. The modification of bioactive molecules including derivatives of clinical drugs and natural products was demonstrated. Mechanistic studies and DFT calculations indicated that the formal [3 + 2] cycloaddition and aza-Michael addition between **1** and **2** generated tetrahydropyrazolo[1,5-*a*]pyridine and a new pyridinium salt, respectively. These two intermediates formed an EDA complex, which under visible-light illumination, triggered the following single electron transfer (SET)/N–N bond cleavage/C–N bond formation cascade process with high atom economy.



## Introduction

Due to exogenous photoredox catalyst-free and environmentally friendly properties, electron donor–acceptor (EDA) complex-triggered bond formation reactions have achieved huge advances in recent years, especially in the construction of challengeable C–C and C–X (N, O, S, P, *etc.*) bonds.[1,2] Among them, *N*-functionalized pyridinium salts,[3] including Katritzky salt,[4] *N*-amidopyridiniums (usually using *N*-sulfonamido-pyridiniums)[5] and *N*-alkoxy pyridiniums,[6] accomplished with their corresponding electron donors, have been extensively used as alkyl, amidyl and alkoxy radical precursors to trigger C–C, C–B or C–S bond formation and regioselective C–H functionalization of pyridines (Schemes 1A and B). However, the addition of an exogenous stoichiometric electron donor and sacrifice of additional groups are still inevitable in those series of reactions, which leaves huge room for the improvement of atom economy. Recently, Su and co-workers reported a unique example where the *in situ*-generated tetrahydroindolizine intermediate,[7] derived from the cycloaddition reaction between *N*-alkylpyridinium salts and α,β-unsaturated compounds, could be used as the electron donor of the EDA complex. Upon irradiating with a 24 W LED, the tetrahydroindolizine intermediate could undergo an intramolecular SET process from the dienamine group (D part)[8] to the benzoyl group (A part), leading to the formation of C2-alkylpyridines with high atom economy (Scheme 1C).

Our research in this area is due to the continuing efforts to exploit mild and efficient protocols for the diversity-oriented transformation of aromatic heterocycles.[9] Recently, our group revealed the regioselective formation of pyrazolo[1,5-*a*]pyridines from *N*-aminopyridinium salts.[9c] Two key features were observed in this protocol: (i) the formal [3 + 2] cycloadditions between *N*-aminopyridinium salts and α,β-unsaturated compounds are reversible, resulting in the cyclized dienamine intermediates (tetrahydro-pyrazolo[1,5-*a*]pyridines) detectable by NMR and HRMS; (ii) exclusive regioselectivity was observed when *N*-aminopyridiniums were substituted at the 3- or 5-position with a strong electron-donating substituent (such as

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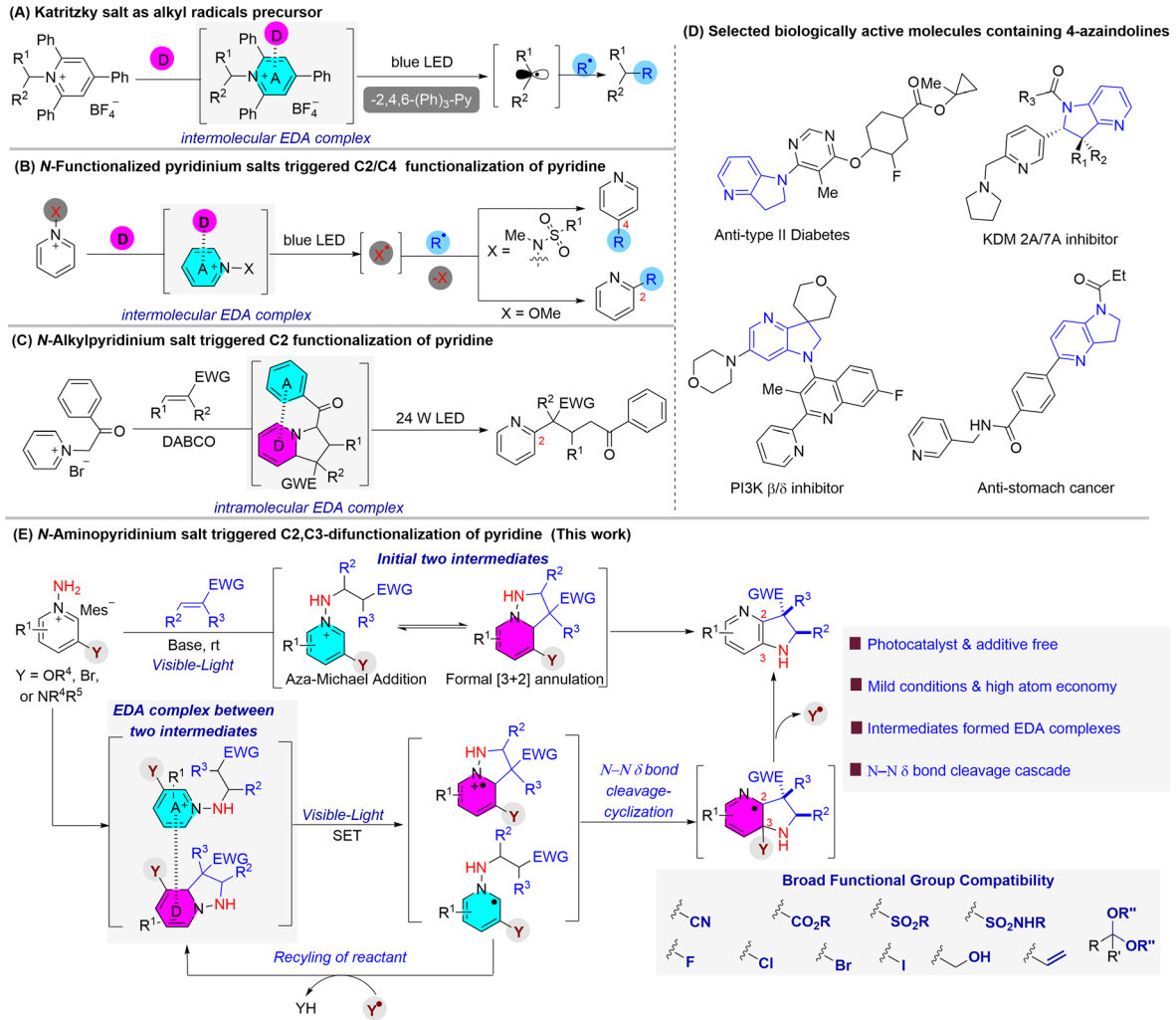



**Scheme 1** Selected examples of regioselective transformation of *N*-functionalized pyridines and biologically active molecules containing 4-azaindolines.

alkoxy or amino groups). These observations plus the successful participation of enamines in EDA complexes fascinated us to explore the further possibility of using tetrahydropyrazolo-[1,5-*a*]pyridine intermediates to realize the multi-functionalization of pyridines through an EDA complex-triggered process. Specifically, we hypothesize that, on behalf of the electron-rich properties, this kind of intermediate could potentially be activated by a visible-light-induced SET process in the presence of an electron-deficient partner, such as the *N*-pyridinium salt. Meanwhile, pre-installation of a readily available electron-donating group may facilitate the cleavage of the N–N bond by enol–keto tautomerization, which would be removed in the subsequent aromatization process. Herein, we report a regioselective [3 + 2] cycloaddition-initiated N–N bond cleavage/N-migration/intramolecular cyclization cascade process, between *N*-aminopyridiniums and α,β-unsaturated compounds, to afford medicinally important 4-azaindolines (Scheme 1D).[10] We found that the initial formal [3 + 2] cycloaddition and the aza-Michael addition reaction produced two intermediates, and these intermediates formed an unprecedented EDA complex which triggered the subsequent process without the need for any additional electron acceptors or photocatalysts, and the reactions could proceed smoothly in the presence of various visible lights including sunlight, white LEDs and fluorescent lamps with similar efficiency. Remarkably, the electron-donating group not only directs regioselectivity and facilitates the cleavage of N–N bonds, but also plays a critical role in reactant recycling, preventing the sacrifice of electron acceptors (Scheme 1E). Most notably, the reaction could be easily performed on a gram scale and is compatible with an array of functional groups including halogen, cyano, ester, free alcohol, alkene, sulphone, and sulfamide. With this simple and easy handling protocol, a wide range of multi-functionalized 4-azaindolines were obtained efficiently from readily available chemical feedstocks under mild conditions and with high atom economy.

## Results and discussion

### Development and optimization of the reaction

Our initial attempt started with the reaction between 3-bromo-5-methoxy-*N*-aminopyridinium salt (**1a**) and acrylonitrile (**2a**). To our surprise, the reaction directly gave **3a** in 93% yield just under the fluorescent lamp (36 W) of a laboratory fume hood, neither adding an exogenous electron-deficient substrate nor using special photochemical reaction apparatus including LED lights. A notable phenomenon of the reaction is that when a base was added to a mixture of pyridinium salt and acrylonitrile in toluene, the heterogeneous reactants simultaneously dissolved and the solution appeared to a marked yellow color, which may be due to the formation of an EDA complex.[11] To prove this, we measured the UV-Vis absorption spectra of the separated reaction constituents **1a**, **2a**, **3a**, DBU, and their mixtures, respectively (Fig. 1, see also Fig. S8 and S9† for more details). A charge-transfer (CT) band[12] was observed in the visible-light region under standard conditions (orange line), while no CT band was detected in the absence of any of the reaction components. It is worth noting that the mixture of DBU and pyridinium salt formed a black suspension in toluene which is not suitable for UV-Vis absorption (see Fig. S10†). These observations suggest the existence of EDA complexes during the process of reaction.

With the initial results in mind, we further explored the reaction conditions (Table 1). We found that increasing the equivalents of acrylonitrile did not reflect obvious changes in the yield (entry 2). However, changing the amount of the base reduced the yield (entry 3). Screening of different bases and solvents indicated that DBU and toluene are the most suitable for this transformation (entries 4–7). Additionally, other electron-donating groups, including ethoxy (entry 8), benzyloxy (entry 9) and dimethylamino groups (entry 10), were also investigated, which gave **3a** in 88%, 91% and 82% yields, respectively. Interestingly, control reactions show that the reaction

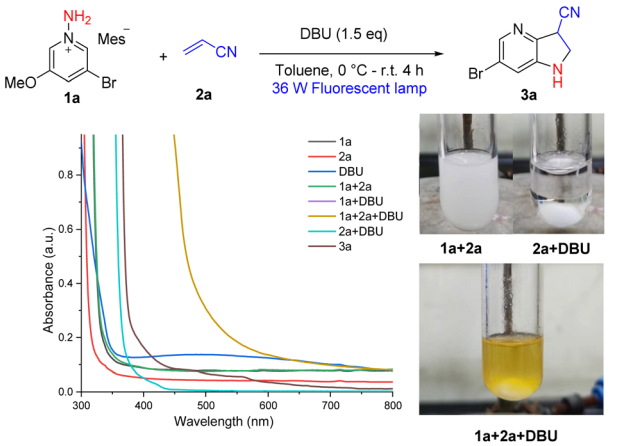
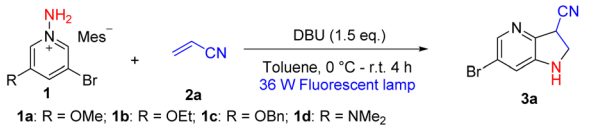



**Fig. 1** UV-Vis absorption spectra of reaction components and the picture of their reactions. Experimental conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), and DBU (0.15 mmol) in toluene (2.0 mL).

**Table 1** Optimization of the reaction conditions[a]




**1a**: R = OMe; **1b**: R = OEt; **1c**: R = OBn; **1d**: R = $NMe_2$

| Entry | Variation from standard conditions | Yield[b] |
|---|---|---|
| 1 | — | 93% |
| 2 | 1.5 eq. of **2a** | 91% |
| 3 | 1.0 eq. of DBU | 62% |
| 4 | $Cs_2CO_3$ instead of DBU | 82% |
| 5 | DIPEA instead of DBU | 85% |
| 6 | DCM instead of toluene | 41% |
| 7 | 1,4-Dioxane instead of toluene | 79% |
| 8 | **1b** instead of **1a** | 88% |
| 9 | **1c** instead of **1a** | 91% |
| 10 | **1d** instead of **1a** | 82% |
| 11 | White LED | 89% |
| 12 | Sunlight | 87% |
| 13 | Blue LED | 75% |
| 14 | In the dark | <5% |

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), and base (0.15 mmol) in solvent (2.0 mL) at 0 °C – rt for 4 h. [b] Isolated yield.

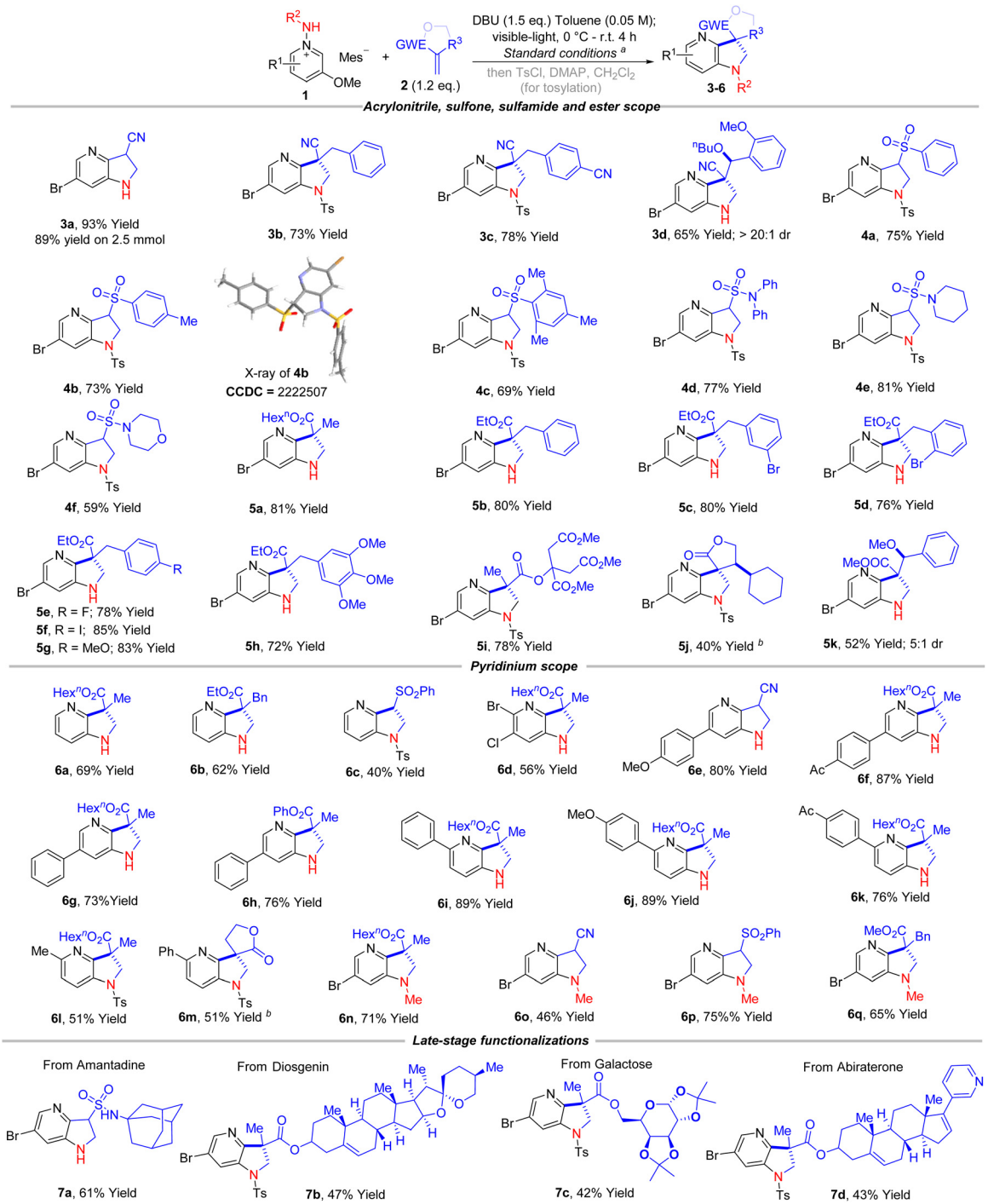
could also smoothly deliver product **3a** in 89% yield under white LED irradiation (entry 11), and 87% yield under sunlight (entry 12). Meanwhile, the same reaction under the irradiation of a blue LED also led to the formation of product **3a** in up to 75% yield (entry 13), while the yield of **3a** was dramatically decreased (<5%) when the reaction was performed in the dark under otherwise identical conditions (entry 14).

### Evaluation of the substrate scope

With the optimal reaction conditions in hand, we then evaluated the substrate scope of this protocol (Scheme 2). 2-Benzylacrylonitrile and 4-(2-cyanoallyl) benzonitrile reacted smoothly and the *N*-tosyl-protected products **3b** and **3c** were isolated in 73% and 78% yield respectively over two steps, due to the stability of the free amine product during purification. Notably, a nitrile derivative from a Morita–Baylis–Hillman reaction was also successfully applied in this protocol and **3d** was generated in 65% yield with excellent diastereoselectivity (>20 : 1 dr). Next, the scope was extended to vinyl-sulfone derivatives under the standard conditions. Phenyl vinyl sulfones, with or without substituent groups, were successfully employed in the protocol and gave the corresponding *N*-tosyl-protected products (**4a–4c**) in satisfactory yields (69%–75%), whose structure was unambiguously confirmed by X-ray analysis of **4b**. To our delight, this strategy also exhibited good tolerance for sulfanylamides, which are found in various on-market medicines, three *N*-tosyl protected products (**4d–4f**) were obtained in moderate to good yields (59%–81% over two steps).

The reaction scope was further examined by employing a wide range of α,β-unsaturated esters. *n*-Hexyl methacrylate worked well under the reaction conditions and gave the



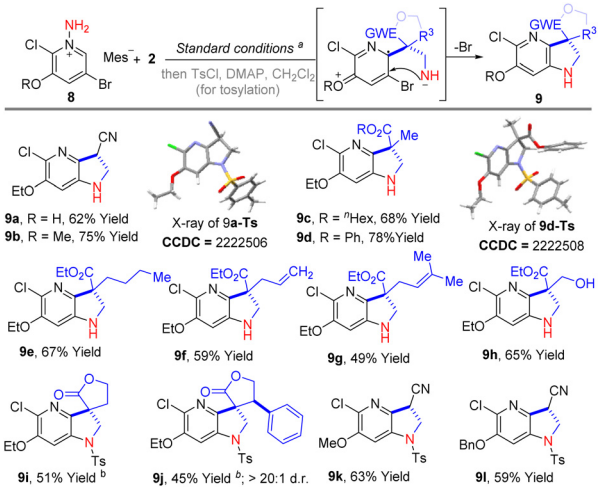

**Scheme 2** Substrate scopes. [a]Standard conditions: 0.1 mmol of **1**, 0.12 mmol of **2**, and 0.15 mmol of DBU in 2 mL of toluene, 0 °C – rt, under the irradiation of a 36 W fluorescent lamp, 4 h; isolated yields are reported; [b]at 50 °C, in 2 mL of 1,4-dioxane, 12 h; isolated yields are reported.

product **5a** in 81% yield. Additionally, α,β-unsaturated esters bearing benzyl groups regardless of their electronic properties were also successfully applied in this protocol and produced the corresponding products (**5b–5h**) in 72%–85% yields. A methyl methacrylate derivative of citric acid delivered the product **5i** in high yield after two steps of transformation. Most notably, substituted α-methylene-γ-butyrolactone, a subunit present in a host of important bioactive molecules,[13] was also reacted well under slightly modified reaction conditions (at 50 °C in 1,4-dioxane), giving the corresponding *N*-tosyl-protected product **5j** in 40% yield as a single diastereoisomer. Besides, Morita–Baylis–Hillman ester was also successfully applied in this protocol and produced **5k** in 52% yield with 5 : 1 diastereoselectivity.

In addition to the 3-bromo-5-methoxypyridinium salts, the scope of the reaction with other pyridinium salts was also evaluated. As expected, 1-amino-3-methoxypyridinium exhibited good tolerance to a variety of α,β-unsaturated compounds, giving products **6a–6c** in satisfactory yields. Additionally, 2,3-disubstituted pyridinium was also suitable for this method and generated **6d** in 56% yield. The modified or unmodified aromatic groups at the C5 or C6 positions of 3-methoxypyridine did not show obvious influence on the yield in our protocol and all test examples delivered the products (**6e–6l**) in satisfactory yields no matter the reaction was with acrylonitrile or methacrylate esters. 3-Methoxy-6-benzyl-*N*-amino-pyridinium was also reacted well with α-methylene-γ-butyrolactone, and *N*-tosylated product **6m** was achieved in 51% yield over two steps, which further verified the generality of this transformation. Besides, 3-bromo-5-methoxy-1-(methylamino)-pyridinium (**1n**) was also suitable for this protocol and reacted smoothly with various activated alkenes including α,β-unsaturated nitriles, esters and sulphones, offering the corresponding 1-*N*-Me-4-azaindolines **6n–6q** in satisfactory to good yields.

To further demonstrate the versatility of our methodology, we explored the late-stage modification of bioactive molecules and carried out the reaction on a gram scale. A vinyl-sulfamide derivative from the first-line medicine Amantadine was encompassed into this strategy, which gave product **7a** in 61% yield. Also, methacrylate ester derivatives from the natural product diosgenin, galactose and the on-market medicine Abiraterone were subjected to the standard reaction conditions, producing the corresponding products (after *N*-tosyl protection) **7b–7d** in around 45% yield. Additionally, gram-scale reactions were also performed, starting from 2.5 mmol of 3-bromo-5-methoxy-1-aminopyridinium salt and 3.0 mmol of acrylonitrile, and **3a** was collected in 89% yield, which would be beneficial for further investigation of biological functions of these compounds.

Notably, in our previous experiments, we have noticed that the regioselective formal [3 + 2] cycloaddition between 3-substituted pyridinium salts and α,β-unsaturated compounds could be switched if a 2,3-di-substituted pyridinium salt was employed.[9c] At the present stage, we were curious if the cyclization was still possible when the 2-position of pyridine was occupied with a substituent. Therefore, 2-chloro-3-ethoxy-5-bromopyridinium salt (**8a**) was subjected to the standard reaction to couple with acrylonitrile and methacrylonitrile. As shown in Scheme 3, the reactions went smoothly and offered products **9a** and **9b** in 62% and 75% isolated yield, respectively. The structure of **9a** was confirmed by single crystal X-ray diffraction analysis of the *N*-tosyl protected derivative (**9a-Ts**). Additionally, phenyl and *n*-hexyl methacrylate were also employed in this transformation, delivering the products **9c** and **9d** in 68% and 78% yield, respectively. Impressively, the alkenyl and hydroxyl groups were also tolerated in this reaction and the corresponding products **9f–9h** were isolated in satisfactory yields (49%–65% yields). Moreover, α-methylene-γ-butyrolactone was also reacted well and produced the




**Scheme 3** Substrate scope of 2-chloride-3-ethoxyl-5-bromopyridinium salt **8**. [a]Standard conditions: 0.1 mmol of **8**, 0.12 mmol of **2**, 0.20 mmol of DBU in 2 mL of toluene, 0 °C – rt, under the irradiation of a 36 W fluorescent lamp, 4 h; isolated yields are reported. Temperature: [b] at 50 °C, in 2 mL of 1,4-dioxane, 12 h; isolated yields are reported.

product (**9i**) in 51% yield after tosylation. A similar process with β-phenyl-substituted α-methylene-γ-butyrolactone gave the product **9j** in 45% yield and higher than 20 : 1 d.r. Besides **8a**, 2-chloro-3-methoxy-5-bromopyridinium salt (**8b**) and 2-chloro-3-benzyloxy-5-bromopyridinium salt (**8c**) were also reacted well and gave tosyl-protected products **9k** and **9l** in 63% and 59% yields, respectively, over two steps.

## Mechanistic investigations

N–N bond cleavage of *N*-amidopyridiniums has been used extensively for C4 selective pyridine C–H functionalizations.[2,3,14] In all cases, it has been well established that a strong electron-withdrawing group such as *N*-sulfonamide or *N*-benzoyl amide is essential to weaken the N–N bond. In certain cases, unselective C3-functionalized pyridines *via* 1,3-migration of *N*-iminopyridiniums were observed as a byproduct.[15,16] Therefore, it appears that the electron-donating group such as OR or $NR_2$ is critical to promote the N–N bond cleavage/*N*-migration cascade process of *N*-aminopyridiniums in our case. To further understand the insight of the reaction mechanism, a series of control experiments were performed (Fig. 2). First, classical radical inhibitors TEMPO and BHT were added respectively to the reaction between **1a** and hexyl methacrylate under the standard reaction conditions. The reactions only resulted in the decomposition of the starting materials and product **5a** was not detected in the reaction mixture, which suggests that the reaction may proceed through a radical pathway (Fig. 2A). To prove the presence of the methoxy radical, methyl phenyl sulfone, its radical trapper,[6] was added to the reaction of **1a** with acrylonitrile under standard conditions, which gave product **3a** in dramatically decreased yield (37%) along with 7% yield of methyl benzenesulfinate **10a**, indicating that the methoxy radical is

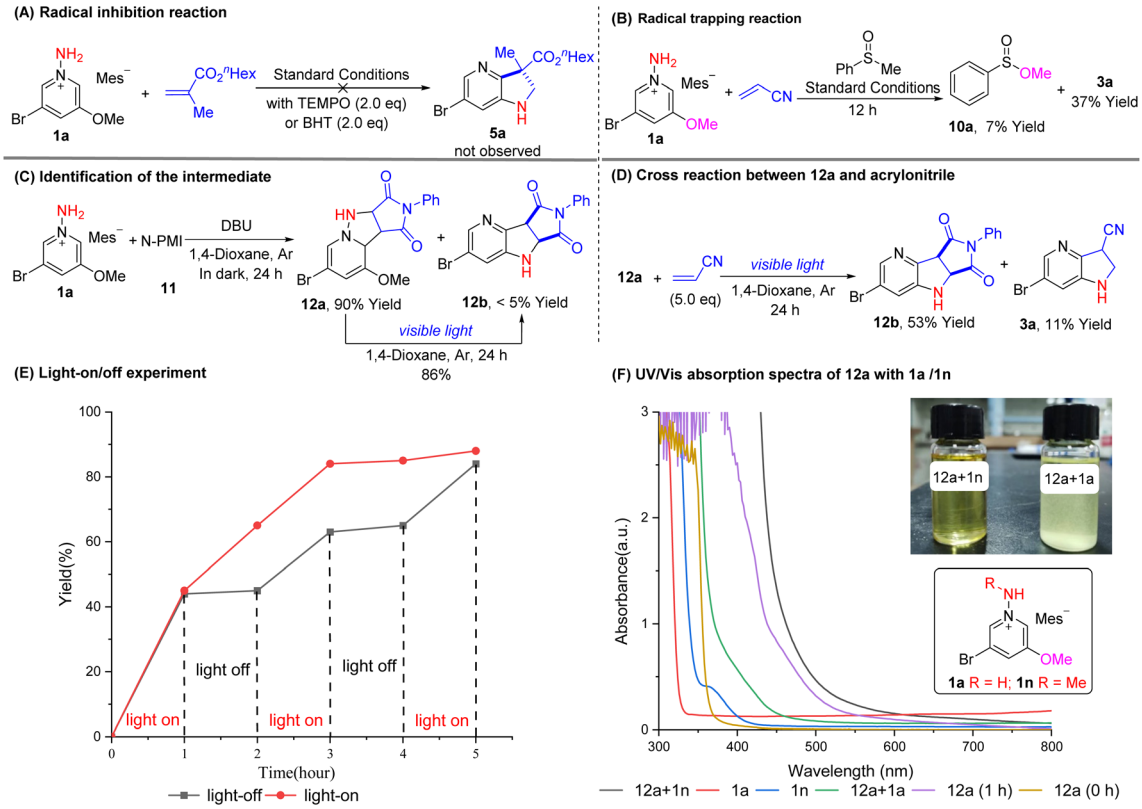
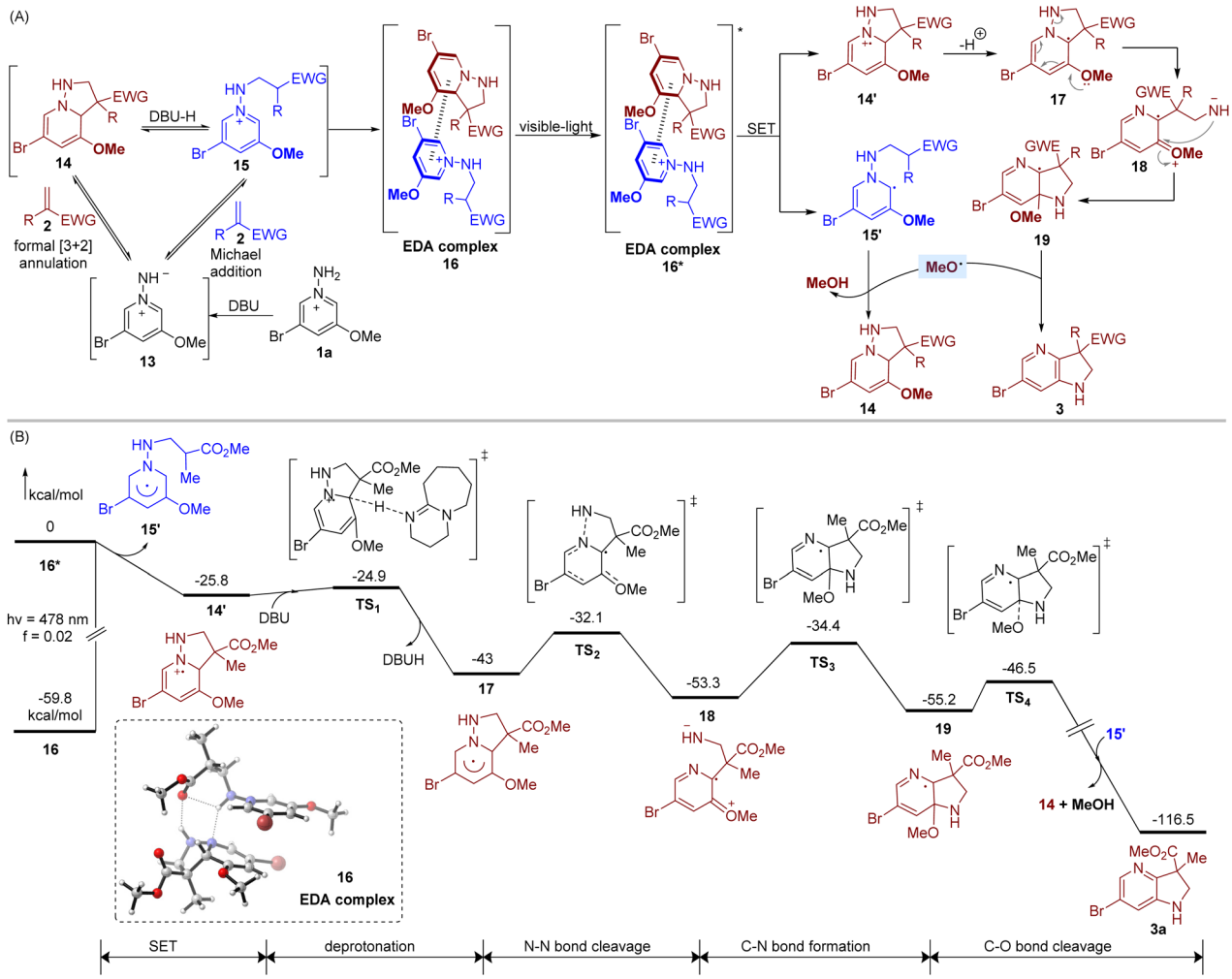



**Fig. 2** Mechanistic study. (A) Radical inhibition reaction. (B) Radical trap reaction. (C) Identification of the intermediate. (D) Cross reaction of **12a** with acrylonitrile. (E) Light-on/off experiment of **1a** (0.05 M), **2a** (0.06 M) and DBU (0.075 M) in toluene. The red line represents the yield of the reaction continuously irradiated with visible-light. The black line represents the yield of reaction under irradiation of visible light in the first, third and fifth hour. (F) UV-VIS absorption spectra of **12a** (0.05 M), **1a** (0.05 M), **1n** (0.05 M) and their mixture (**12a** + **1a** or **12a** + **1n**) in acetonitrile. **1a** was partially dissolved.

crucial for the transformations (Fig. 2B). It is worth noting that during the reaction between 2-chloride-3-ethoxy-5-bromopyridinium salt **8a** and phenyl methacrylate, we also detected the presence of phenyl 3-bromo-2-methylacrylate by LC-MS (see Fig. S18† for more details), which suggests that phenyl methacrylate may capture the bromine radical produced during the reaction.[17] This could also explain why the reaction between **8** and activated alkenes delivered the 4-azaindoline products in lower yields (40%–79%).

Additionally, during the development of the reaction, we discovered that the reaction of pyridinium **1a** and *N*-PMI (**11**) could give a room temperature stable intermediate **12a** (90% isolated yield) under identical conditions but in the dark, with less than 5% yield of 4-azaindoline product **12b** (Fig. 2C). This indicates that the visible light is not essential for the formal [3 + 2] cycloaddition, while it may be critical for the rearrangement from the intermediate to the final product. Furthermore, irradiation of **12a** with visible light in dioxane produced the rearrangement product **12b** in 86% yield, highlighting the necessity of light during the N–N bond cleavage and rearrangement. Also, at the beginning of the conversion of **12a** into **12b**, no obvious CT band was observed, while a clear CT band appeared after the reaction was stirred for 1 h (see Fig. S19†). Besides, re-subjected intermediate **12a** in the presence of acrylonitrile under visible light gave 53% yield of **12b** and 11% yield of **3a** (Fig. 2D), suggesting the reversibility of formal [3 + 2] cycloaddition. To determine whether the reaction involves a radical chain process, a light on–off experiment was performed between **1a** and **2a** under standard conditions (Fig. 2E). The absence of light resulted in no conversion indicating the necessity of continuous light irradiation and a radical chain mechanism is unlikely for this transformation.[18] At this stage, two key information could be obtained from these experiments: (i) the intramolecular EDA complex as in Su's case was not involved in our reactions.[7] (ii) In the solution, **12a** (as the electron donor) and another electron-poor species (as the electron acceptor), generated from a retro-Mannich reaction[19] of **12a** or 3-bromo-5-methoxy-1-aminopyridinium salt (**1a**), may form an EDA complex to trigger the following reaction.

To figure out the potential electron acceptor, we used the 3-bromo-5-methoxy-1-(methylamino)pyridinium salt **1n** to mimic the aza-Michael adduct intermediate, which should have a similar *N*-alkylated structure (such as intermediate **15** in Scheme 4A, *vide infra*) to the species from the retro-Mannich reaction of **12a**, to launch the UV-Vis experiments with **12a**. As shown in Fig. 2F, it was found that when **12a** was




**Scheme 4** (A) Proposed mechanism. (B) DFT calculation. The energies are given in kcal mol$^{-1}$. All the structures were calculated at the (U)B3LYP functional with Grimme's D3(BJ) dispersion correction.

mixed with **1n**, a clear yellow solution was formed immediately along with a significant redshift in the UV-Vis spectrum (black line), which is similar to the reaction in which **12a** was stirred alone in dioxane for 1 hour (purple line). In contrast, there was no noticeable color change and redshift appeared for the mixture of **12a** and **1a** (green line). These results highly suggested that in our case, the entity from aza-Michael addition (or the retro-Mannich reaction after formal [3 + 2] addition) may work as the electron acceptor rather than *N*-aminopyridinium salt itself. Moreover, the Cyclic Voltammetry (CV) experiments of 3-bromo-5-methoxy-1-amino-pyridinium salt (**1a**) and 3-bromo-5-methoxy-1-(methylamino)-pyridinium salt (**1n**), respectively, showed that the irreversible reduction of **1a** and **1n** (see Fig. S16 and S17† for more details). We also detected the conversion of **1n** into 3-bromo-5-methoxypyridine after 2 cycles of CV experiments, which indicated that, after accepting an electron, it would more likely decompose to the corresponding pyridine rather than being oxidized back to the corresponding pyridinium salt **1n**. All taken together, these results suggested that the formal [3 + 2] cycloaddition of *N*-aminopyridiniums and activated alkenes produced tetrahydropyrazolo[1,5-*a*]pyridine derivatives such as **12a**, meanwhile, the retro-Mannich reaction of **12a** or aza-Michael addition of aminopyridiniums and activated alkenes may generate a new *N*-alkylated-amidopyridinium salt which would form an EDA complex with **12a**. In the presence of light, this EDA complex triggered the following process of N–N bond cleavage, which, in turn, led to the formation of an alkoxyl radical (or dimethyl amino radical or bromine radical) keeping the reaction going smoothly.[20]

Based on the above observations, a plausible mechanism for the EDA complexes enabling the intermolecular synthesis of 4-azaindolines was rationalized as shown in Scheme 4A. Initially, *N*-aminopyridinium salt **1** when reacted with the base could form a highly active intermediate *N*-aminopyridine ylide **13**, which would be subsequently trapped by α,β-unsaturated compounds *via* a formal [3 + 2] cycloaddition process to generate tetrahydropyrazolo[1,5-*a*]pyridine **14** (or **12a**). The new pyridinium salt **15** could be obtained by the aza-Michael addition or retro-Mannich reaction of **14**. Then, intermediates **14** and

**15** would form an EDA complex (**16**), which upon irradiation by visible-light generated **16***. Radical cation **14′** and radical **15′** were obtained through a SET process. Deprotonation of **14′** gave a new radical **17**, which would then transform into **18** by imine–enamine tautomerism. Intramolecular re-cyclization of **18** could generate a radical intermediate **19**. The homolytic fission of the C–O bond and aromatization in **19** gave the 4-azaindoline product, along with the release of the methoxy radical.[21] Meanwhile, the methoxy radical would abstract a hydrogen atom from the radical **15′**,[22] which was followed by intramolecular cyclization to form intermediate **14** to re-enter the reaction process. In the whole process, intermediate **14** serves as a formal catalyst promoting the reaction to deliver the desired product. A similar process could also be used to explain the reactions starting from 3-bromo-5-(dimethylamino) pyridinium salt **1d** and 2-chloride-3-ethoxy-5-bromopyridinium salt **8**.

A computational study was then carried out to excavate deeper insight into the mechanism (Scheme 4B). The energy barrier for the formation of tetrahydropyrazolo[1,5-*a*]pyridine **14** *via* formal [3 + 2] annulation, and for the generation of **15** either through Michael addition between **1** and **2** promoted by DBU or through a retro-Mannich reaction of **14** is lower than 20 kcal $mol^{-1}$ supported the ready formation of **14** and **15** at room temperature. Subsequently, the intermediate **15** can be captured by **14** to give the complex **16**, which is exothermic by 1.7 kcal $mol^{-1}$. The excitation energy of complex **16** was also calculated using TD-DFT, and the obtained absorption peak of 478 nm with the oscillator strength of 0.02 is consistent with our experimental result, in which visible-light is used to promote the reaction. The calculation result of complex **16** provides important evidence to support that **16** is the key EDA complex. The SET process then occurs at the excited state from intermediate **14** to **15** of complex **16** to give the radical cation **14′** and radical **15′**. Subsequently deprotonation of **14′** gives radical intermediate **17**, which is exothermic by 17.2 kcal $mol^{-1}$. For **17**, the N–N bond cleavage can occur easily *via* a transition state **TS2** with an energy barrier of 10.9 kcal $mol^{-1}$, to generate intermediate **18**, and this is exothermic by 10.3 kcal $mol^{-1}$. Next, the radical intermediate **19** can be obtained from **18** through a slight exergonic process by overcoming an energy barrier of 18.9 kcal $mol^{-1}$ *via* **TS3**. Finally, product **3** could be formed by homolytic fission of C–O along with the release of the methoxy radical, and this process requires an energy barrier of 8.7 kcal $mol^{-1}$. The dissociative methoxy radical will be captured by **15′** to give MeOH and adduct **14**, which is exothermic by 52 kcal $mol^{-1}$. The computational studies showed that once MeO radical gets close to radical **15′**, the cyclization to form **14** occurred immediately; unfortunately, we were unable to identify a feasible transient state structure for such a process. In addition, the other situations including the intramolecular atom transfer (HAT) in **15′** and the intermolecular single electron transfer process between the MeO radical and **15′**, have been proven unlikely to happen by calculation (see Fig. S21† for details). The computational result shows that before forming the key EDA complex, the overall energy barrier (from **13** to **TS1** in Fig. S20†) is 19.5 kcal $mol^{-1}$, and after SET, the overall energy barrier (from **18** to TS3 in Scheme 4B) is 18.9 kcal $mol^{-1}$. This is also in good accordance with our experimental result, in which all the reactions proceeded smoothly at room temperature.

## Conclusions

In summary, we have developed a visible-light induced intermolecular protocol to access 2,3-difunctionalized pyridines from *N*-aminopyridinium salts and activated alkenes promoted by an *in situ* formed EDA complex under mild conditions. Mechanistic studies and DFT calculations suggested that the two intermediates from the reactants *via* formal [3 + 2] cycloaddition and its ring-opening product (or aza-Michael addition from the reactants) are responsible for EDA complex formation. Besides, the *in situ* generated methoxy or bromine radical plays an important role in the regeneration of the intermediate **14** to maintain the continuous formation of the EDA complex. This unique and straightforward procedure has many advantages such as high atom economy, broad functional group compatibility, mild reaction conditions, easy handling, and photocatalyst- and photoreactor–free conditions, and can be readily performed on a gram scale. The synthetic application was also demonstrated by late-stage modifications of a series of on-market drugs and natural products. Besides, this study also demonstrated how intermediates produced transiently during the reaction can contribute to the formation of photoactive EDA complexes and initiate the subsequent radical process and may open up new avenues for the application of EDA complex photochemistry in synthetic chemistry.

## Author contributions

X. M. conceived the idea and guided the project. Y.-Z. L. carried out reaction condition optimization, substrate screening experiments and mechanistic studies. A. W., Z. S., X. Z., J. Z. and Y. J. performed some of the substrate screening experiments. Y. C. performed the computational studies. X. M. and Y.-Z. L. wrote the manuscript with feedback from other authors.

## Conflicts of interest

The authors declare the following competing interests that one patent has been registered (CN202310032248.5).

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