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π - π Stacking Complex Induces Three-Component Coupling Reactions to Synthesize Functionalized Amines

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Abstract: π - π stacking and ion-pairing interactions induced the generation of α -amino radicals under the irradiation of visible light without the requirement of an expensive photocatalyst. This strategy provided access to the construction of functionalized amines via three-component coupling reactions with broad scopes (we report > 50 examples with an up to 90 % yield). This synthetic pathway also delivered the synthesis of complex functionalized amines with a very high yield. Quantum chemistry Density Functional Theory (DFT) calculations identified the π - π stacked ionic complexes; Time-Dependent DFT simulated the absorption spectra and with the nudged elastic band (NEB) methodology provided a possible interaction/reaction picture of the selected species.

Introduction

Noncovalent interactions (NCIs) such as hydrogen bonding, π -interactions, van der Waals, and Coulombic interactions play a crucial role in enzyme catalysis, supramolecular chemistry, biocatalysis, and organic synthesis.^[1-2] Although NCIs are relatively weak, they still play an essential role in reducing free energy barriers by transition-state stabilization, making the catalytic systems more efficient.^[3] In addition, NCIs have been taken into account in the rational design of catalysts, considering factors such as the orientation, distance, and electronic effects that control or influence the NCIs to achieve high regio- or site-selectivity.^[4-5]

Among all the NCIs, π -interactions, including π - π , lone pair- π , XH- π , and cation/anion- π interactions, have been intensively studied with aromatic functional groups in photochemical synthesis (Figure 1a).^[6-7] In fact, the design of catalysts based on π -interactions has also been achieved; for example, Yoon *et al.* reported one chiral iridium-photosensitizer for the generation of intramolecular [2+2] cycloaddition products (Figure 1b).^[8] In addition, π -interactions also assist the formation of electron donor-acceptor (EDA) and ion-pair charge-transfer (IPCT) complexes, which have been used in photochemical synthesis.^[9-11] These unique adducts showed the potential for activating substrates under the irradiation of visible light. Recently, Bach *et al.* reported that 3-acetoxyquinuclidine could act as the electron donor and form the EDA complex by combining with tetrachlorophthalimide ester, followed by a single electron transfer (SET) process under the irradiation of blue light (Figure 1b).^[12] Later, Melchiorre *et al.* designed radical-based catalytic systems with two EDA complexes involving π - π and anion- π interactions for the generation of alkyl and sulfur-centered radicals (Figure 1b).^[13b,13c] It was demonstrated that the selection of molecules that could form π -interaction complexes enriched the synthetic photochemical approaches and provided new reactivity principles.^[13]

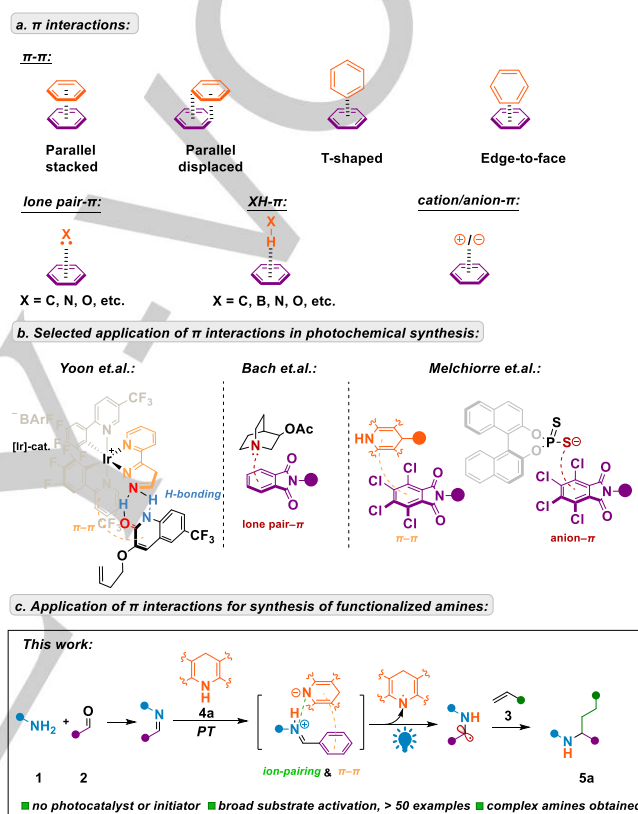


Figure 1. π interactions in photochemical synthesis.

Strategies for the synthesis of functionalized amines have attracted much attention because they are considered as one of the synthetically essential compounds in the areas of pharmaceuticals, natural products, and fine chemicals.^[14-15] To meet these demands, a plethora of procedures, such as C-H bond functionalization, reductive amination, and other techniques, have been developed.^[16-17] In this respect, the generation of α -amino radicals to synthesize functionalized amines has gained tremendous priority.^[18-20] While these radicals can be prepared from amino acids (by releasing CO₂), or directly from an amine substrate,^[21-24] their generation from an imine offers higher scope and versatility for the synthesis of functionalized amines.^[25-29] In general, Hantzsch ester (HE) has been applied as an electron/proton donor to synthesize various organic compounds.^[30] We rationalized that the lone-pair electrons on the aromatic imine nitrogen atom and the π -system of HE ring could establish π interactions, which should be able to facilitate an electron/proton transfer between them under blue light. Considering this possibility, we took the challenge^[31] and

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designed a photochemical system for the formation of α -amino radicals under the irradiation of visible light (**Figure 1c**).

Results and Discussion

At the beginning of this project, we conducted a three-component coupling reaction using *p*-anisidine (**1**), benzaldehyde (**2**) and *n*-butyl acrylate (**3**) in the presence of Hantzsch ester (**4a**) under the irradiation of blue light (**Table S1**) and obtained the Giese-type product butyl 4-((4-methoxyphenyl)amino)-4-phenylbutanoate (**5a**) in 50% yield. To further increase the yield of **5a**, we tried to modify the amount of **3** and **4a**, but these changes did not provide better yields (**Table S1, entries 3-4**). Considering the crucial role of the Hantzsch ester in this reaction, we investigated various HEs: (**Table S1, entries 5-7**).^[28d] among them, only the methoxyethyl-HE **4b** provided the product in 58 % yield, whereas 4-phenyl- and 4-cyclohexyl-substituted HEs did not provide any outcome. Even though the use of DCM as a solvent promoted the *in situ* formation of imine from the corresponding aldehyde and amine, it also promoted reductive amination and oligomerization (**Table S1, 5b, and 5c**) as side products, which were detected by the GC-MS. To avoid by-product formation, we checked the behavior of various solvents, and we found that a mixture of DCM and DMSO (1:1) was the optimal choice for this reaction. Not surprisingly, no product was formed in the absence of HE or light irradiation (**Table S1, entries 10-11**), suggesting that these two ingredients were essential for the whole process. Interestingly, when a pre-formed imine was introduced into the reaction, the yield of **5a** slightly decreased due to the formation of reductive amination products (**Table S1, entries 12**).

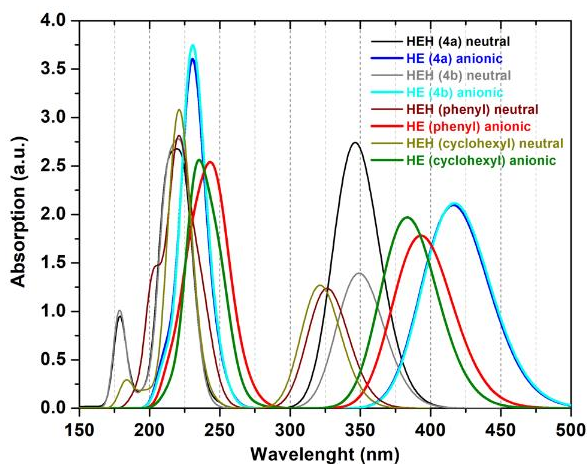


Figure 2. CAM-B3LYP/6-311+G(d,p)/DMSO absorption spectra of the Hantzsch ester structures optimized at the B3LYP/6-311+G(d,p) level in DMSO (artificially broadened with gaussian peaks – HWHH = 0.15 eV).

To explain these unprecedented results at the molecular/atomic/electronic levels, we estimated the UV-vis absorption lengths of the selected HE species in their neutral and anionic forms using quantum chemistry (QC) calculations (**Figure 2**), and we proposed the possible intermediate molecular complexes involving the HE species with a representative imine structure (**Figure 3**). We found, in agreement with experiments, that all the neutral HE species exhibited relatively strong absorption in the near-ultraviolet region (between 300 and 400 nm), as well as their neutral complexes with the selected imine (red curve in **Figure 3**).^[32] Instead, the HE anionic forms extended their absorption bands in the blue part of the spectrum. Thus, we

speculated that, most probably, these were the species activated by the blue LED light that induced an electron transfer between the photoexcited HE and the imine ion, leading to the corresponding radical species.

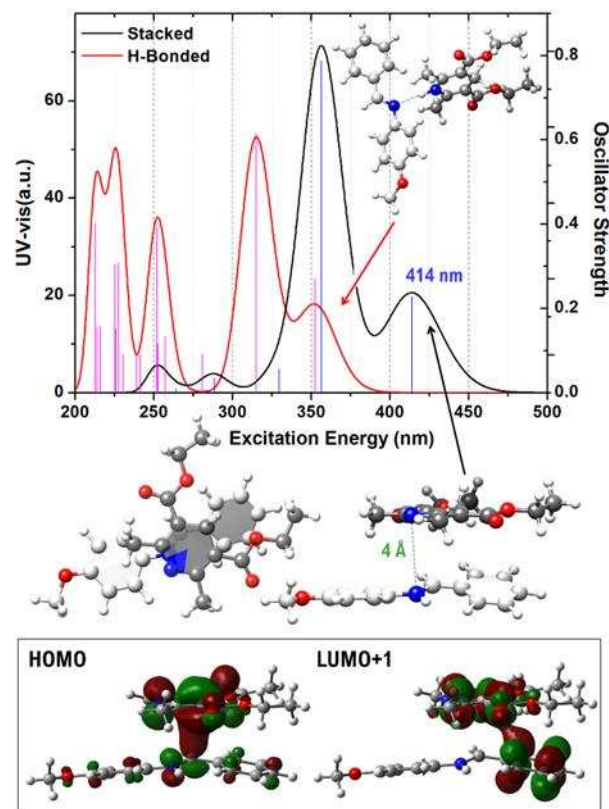


Figure 3. Top. CAM-B3LYP/6-311+G(d,p)/DMSO absorption spectra computed for the stacked complex and T-shaped complexes optimized at the B3LYP/6-311+G(d,p) level in DMSO (artificially broadened with gaussian peaks – HWHH = 0.15 eV). The corresponding geometries are shown in the inset T-shaped) and below the plot (stacked) in two different orientations. Bottom. Representation of the molecular orbitals involved in the bright transition for the stacked complex system (HOMO–LUMO+1 transition).

To check this assumption, we hypothesized the formation of two complexes between the imine and the HE; one was a T-shaped complex (top in **Figure 3**), and another one was a π - π stacked adduct (bottom in **Figure 3**). The QC calculations predicted the T-shaped complex to have a dipole moment of about 7 Debye, and a distance between the nitrogen atoms of 3.11 Å. Compared to the T-shaped complex, the stacked complex with a dipole moment of about 16 Debye was an ionic pair, in which the HE had already released its H(N) hydrogen. The ionic pair was linked by a π -system with a distance between the nitrogen atoms of approximately 4 Å. The calculated energy difference of - 8.5 kcal/mol between the π - π stacked ionic complex and the sum of the energy of the isolated species validated the stability of this particular assembly (bottom in **Figure 3**). From a computational point of view, this complex was a stable minimum energy configuration but could not be experimentally detected.^[33]

Based on the formation of the π - π stacked complex, we speculated that a radical catalysis pathway could be initiated by a blue-light activated intermolecular single-electron transfer (SET) from the HE reductant to the electrophilic iminium ion. Such a process took place in the intermediate ion-pair charge-transfer complex shown in **Figure 3** (black line) and **Figure S12**.

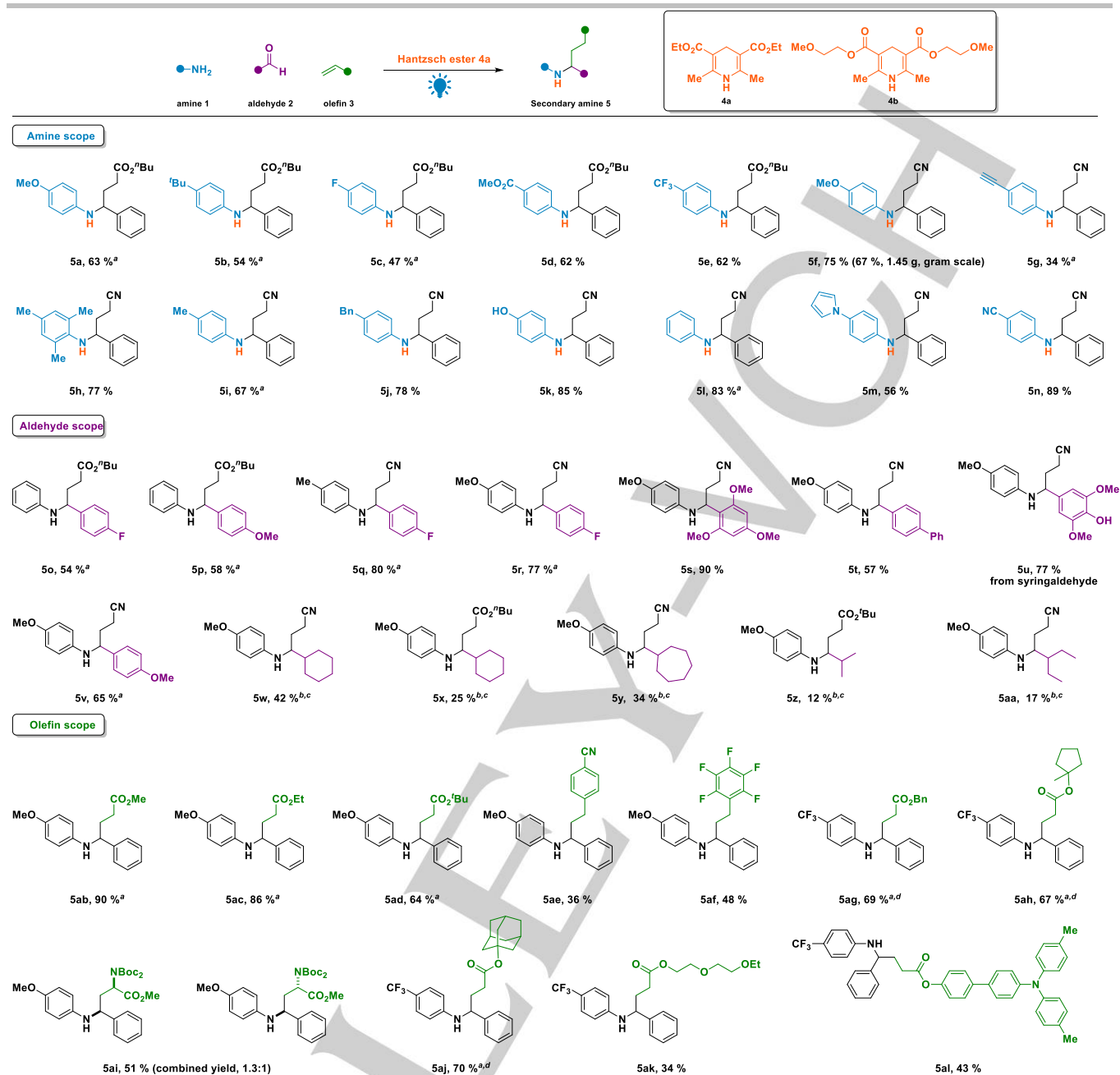


Figure 4. Scope of amines, aldehydes and olefins. Standard reaction conditions: amines (0.2 mmol), aldehyde (0.2 mmol), olefin (0.4 mmol), **4a** (0.3 mmol), DCM:DMSO (1:1, 0.2 M), 24 W blue LED (456 nm), 4Å MS, 24 h; **4b** (0.3 mmol); ^aamines (0.2 mmol), aldehyde (0.4 mmol), olefin (0.4 mmol); ^badditional 10 mol% acetic acid; ^cpre-formed imine.

Considering these suggestions, we evaluated the scope of our three-component coupling reaction (Figure 4). To our delight, various electron-rich and electron-poor aniline derivatives (**5a-5e**) reacted smoothly, providing the desired products in moderate to good yields. It is worth noting that the products formed by electron-rich substituted anilines and *n*-butyl acrylate were not stable; instead, they readily formed the substituted pyrrolidones via intramolecular cyclization.^[29a,34] To avoid this cyclization reaction, acrylonitrile was selected as model olefin to investigate the scope further. Indeed, the presence of acrylonitrile improved the yield of the corresponding noncyclic amines, and diverse classes of anilines (**5f-5n**) were efficiently transformed to the desired secondary amines in moderate to excellent yields (up to 89 %).

Intrigued by these results, we examined the scope of different aldehydes under the model reaction conditions. As expected, benzaldehydes containing electron-donating groups such as methoxy, phenyl, and hydroxyl groups and weak electron-deficient groups such as fluorine (**5o-5r**) performed well under the applied reaction conditions. To intensify the scope of this reaction, we examined unactivated aldehydes, particularly aliphatic and alicyclic aldehydes, as the coupling partners. However, that led to the unstable alkyl imines by reacting with the amines present in the reaction.^[27b] It is well known that the formation of alkyl imines is complex, and they can be obtained only by adding a catalytic amount of acetic acid.^[28c] The addition of acetic acid not only promoted the formation of imine but also assisted the formation of the corresponding iminium salts, which, due to their less negative reduction potential, facilitated the reduction by the HE.^[15a,35] Following this strategy, the aldehydes of cyclohexane and cycloheptane worked smoothly without forming side products via

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the ring-opening, albeit in decreased yields of ca. 40 %. Similarly, aliphatic aldehydes also reacted with acrylates to provide **5z** and **5aa**.

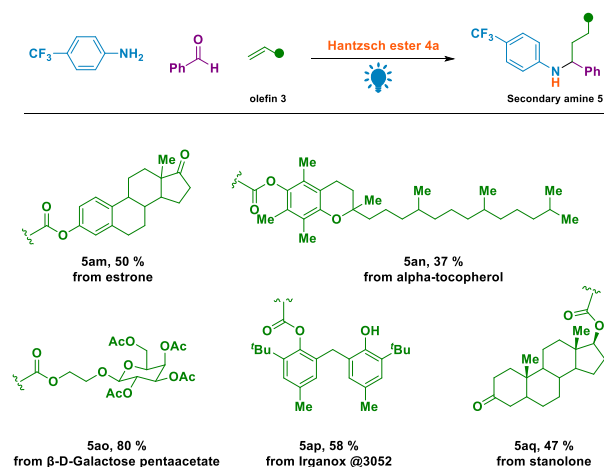


Figure 5. Scope of complex olefins. Standard reaction conditions: amines (0.2 mmol), aldehyde (0.2 mmol), olefin (0.24 mmol), **4a** (0.3 mmol), DCM:DMSO (1:1, 0.2 M), 24 W blue LED (456 nm), 4Å MS, 24 h.

Further diversification of this concept was achieved by varying the olefins under the model reaction conditions. Our results suggested that this three-component coupling reaction could be efficiently carried out in the presence of electron-deficient alkenes. In fact, the performance of alkenes was related to their electrophilicity (E): for example, methyl acrylate (**5ab**, $E = -18.84$) and ethyl acrylate (**5ac**, $E = -19.07$) exhibited higher yields than *tert*-butyl acrylate (**5ad**, $E = -20.22$) due to the less negative electrophilicity.^[36] Acrylonitrile ($E = -19.05$) was expected to be a more suitable coupling candidate due to its very close electrophilicity of the ethyl acrylate. However, ca. 20% lower yield of the resulting product was obtained due to the oligomerization in radical reaction.^[28c] Furthermore, 4-vinylbenzonitrile and 2,3,4,5,6-pentafluorostyrene were viable alkenes to deliver the corresponding secondary amines (**5ae-5af**). We could also observe that various acrylates from natural products such as estrone, α -tocopherol, *etc.*, provided complex secondary amine products in moderate to good yields (**5am-5aq**). These results demonstrated the strong potential of this methodology for the synthesis of complex secondary amines *via* three-component coupling reactions (**Figure 5**).

The formation of complex amines *via* three-component reactions intrigued us to achieve cyclic amines *via* intramolecular C-C bond formation reactions. For this purpose, under the model reaction conditions, α,β -unsaturated ester-tethered benzaldehydes were investigated to assess 1-aminoindanes, which can be used as intermediates for the construction of pharmaceutical compounds.^[29d] Indeed, the reaction system was effective in providing *trans*-1-aminoindanes in moderate yields with both electron-rich and -deficient aniline derivatives (**Figure 6, 7a-7f**). According to the substrate scope, we observed that if the nucleophilicity of α -amino radicals matched well with the electrophilicity of olefins, better yields of coupling products could be obtained. In comparison with amines, methyl acrylate ($E = -18.84$) had less negative electrophilicity than *tert*-butyl acrylate ($E = -20.22$), and the former reacted more smoothly with electron-rich functionalized amines (**7a** and **7d**). Then, we compared the action of two acrylates, namely methyl and *tert*-butyl acrylates. These showed different trends: methyl acrylate preferred reacting with electron-rich functionalized amines (see yields for **7a-7c**),

whereas *tert*-butyl acrylate preferred reacting with the electron-deficient functionalized amines (see corresponding yields in **7d-7f**).

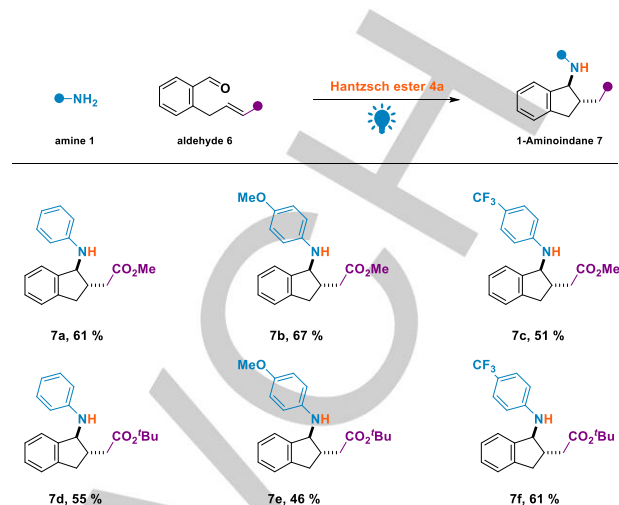


Figure 6. Scope of complex olefins. Standard reaction conditions: amines **1** (0.2 mmol), aldehyde **6** (0.2 mmol), **4a** (0.3 mmol), DCM:DMSO (1:1, 0.2 M), 24 W blue LED (456 nm), 4Å MS, 24 h.

To simulate these cyclization reactions, we used QC models and managed to identify possible minimum-energy paths (MEPs) and activation energies (transition states-TS) in line with the experimental yield. As already done in other studies,^[37] we used the nudged elastic band (NEB) methodology (See SI 1.5.2), and we found that all the energy barriers were connected to the concomitant hydrogen transfer from HE to the reactant, and the C-C bond formation (cyclization reactions, **Figures S13-S14**), were relatively low (at most 10 kcal/mol, **Table S5**) and in agreement with the experimental yield.

After achieving the scope of this reaction and considering all the results of the QC calculations, we propose the mechanism shown in **Figure 7** for our three-component coupling reaction. Briefly, at first, the Hantzsch ester (**I**) and *in-situ*-generated imine (**II**) formed the π - π stacked ionic complex (**III**), followed by the proton transfer (PT). Upon the irradiation of blue light (456 nm), an electron transfer process occurred to provide α -amino radical (**VI**) and Hantzsch ester intermediate (**IV**). α -Amino radical (**VI**) further reacted with the polarity-matched olefin to deliver the open-shell intermediate (**VII**), which abstracted an atom of H(D) from (**IV**) to provide the final product (**VIII**) and Hantzsch pyridine (**V**).

We measured the UV-absorption bands of both the imine substrate and the Hantzsch ester to confirm the existence of π - π stacked complex **III**, (**Figure S2**). The absorption band of their mixture did not display any shift. In addition, cyclic voltammetry (CV) titration has been carried out to detect the transient complex. When HE **4a** added in solution of model imine (10 mM), new peak has shown and the current of new peak was linearly increased with increasing concentration of HE **4a** (**Figure S10**). At last, we carried out the model reaction under green light (550 nm) to find the proof for **III**. Although the desired product **VIII** was not obtained, we obtained the direct hydrogenation product **IX** in 44 % yield (7 % yield under dark, see SI 1.4.3). Since **I** and **II** cannot be directly excited by green light, along with the CV titration we can speculate that a π - π stacking complex between **I** and **II** was present.

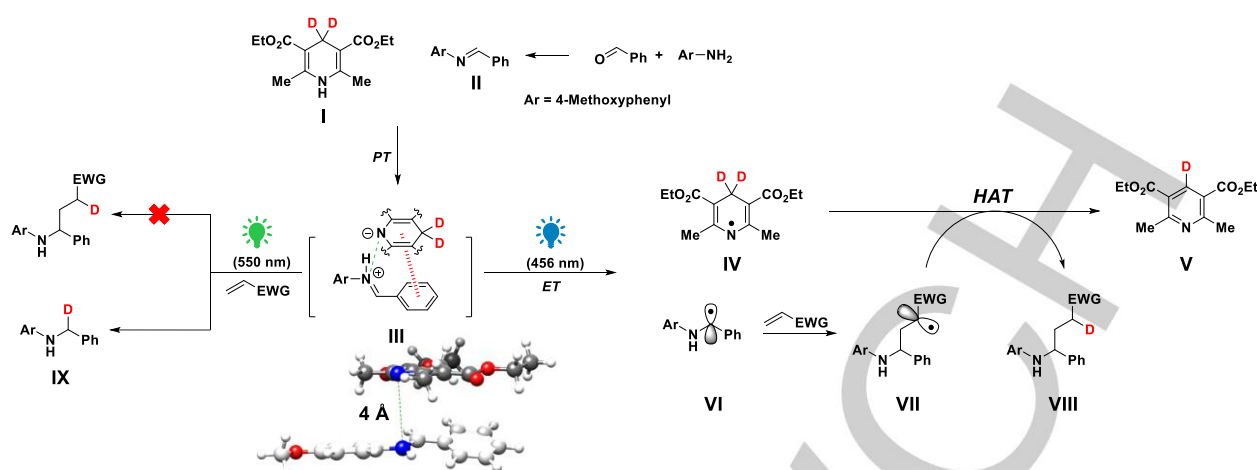


Figure 7. Proposed mechanism for three-component coupling reactions.

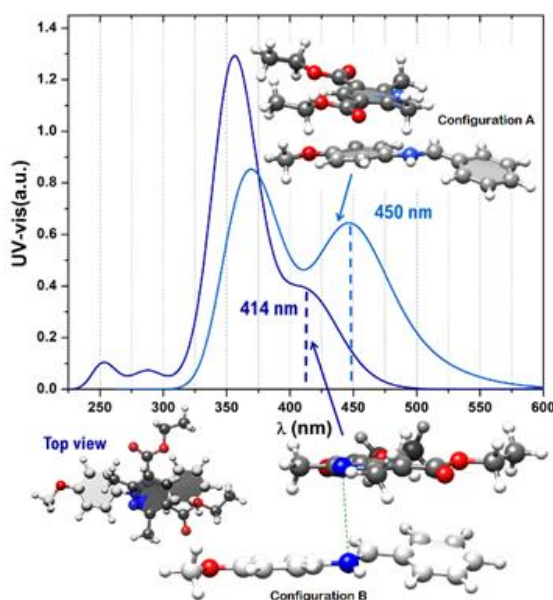


Figure 8. CAM-B3LYP/6-311+G(d,p) absorption spectrum of the stacked-rings ionic complexes of an iminium cation and **4a** anions optimized at the B3LYP/6-311+G(d,p) level in solution. In the geometry corresponding to the light blue curve, the Hantzsch ester has already released one of its H(C) (configuration A), whereas, in the other configuration below the plot, the H(N) was released (configuration B).

Among the ionic complexes identified through QC calculations, two promising configurations, presenting UV-vis spectra in agreement with the experiments, are shown in **Figure 8**. Only configuration B could be stabilized, as demonstrated by the labeling experiment (**Figure 9, B-C**). On the contrary, configuration A consisting of an HE that had lost one of its H(C) which was stacked on the iminium ion, could not be stabilized and evolved towards a final configuration made of neutral species. We could speculate that, most probably, **III** (configuration B) is the species activated by blue light that induces an electron transfer to obtain the corresponding radical species.

Furthermore, Stern-Volmer fluorescence quenching experiments revealed that the Hantzsch ester was quenched neither by the aldehyde nor by the amine but rather by the imine **II** (**Figure S1**). In fact, the fluorescence intensity decreased with the increase of imine concentration, while only slight changes were observed for aldehyde and amine. In order to prove the generation of **VI** in the system, the model reaction was further carried out without the presence of *n*-butyl acrylate, and the dimer of **II** was observed

(**Figure 9A**). Furthermore, we expected the presence of a HAT process between **IV** and **VII** to provide product **VIII**. Hence, labeling reactions were carried out with deuterated-Hantzsch esters (**4c** and **4d**). As shown in **Figure 9**, **5s** was formed in dramatically decreased yield, and no deuterated product was observed. This was due to the fact that N-D bond was not stable and was easily exchanged with a hydrogen atom (**Figure 9B**). In contrast, **5s-D** was successfully obtained in slightly decreased yield, and no H/D exchange occurred since only the deuterated product was detected (**Figure 9C**). To further verify the HAT, process, an intermolecular competition reaction was carried out and 55% combined yield of **5s** and **5s-D** was obtained; the ratio of **5s** and **5s-D** was 9:1 (**Figure 9D**). This intermolecular competition reaction suggested that this procedure was going *via*

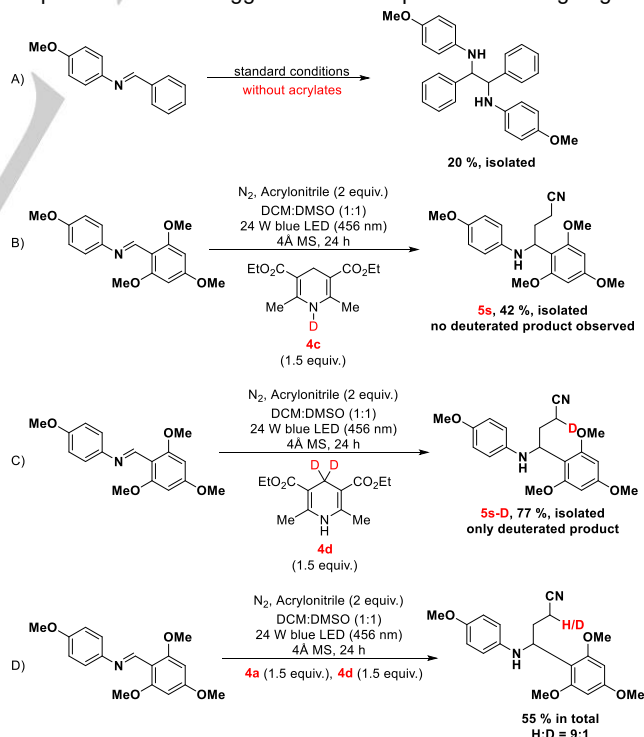


Figure 9. Control experiments and labeling reactions.

a HAT pathway.^[38] *N*-methyl Hantzsch ester (**4e**) was also examined under standard reaction conditions, and only a trace amount of the product was obtained. As expected, deuterated solvents had no apparent effect on the product (see **SI 1.4.3**).

Conclusion

We have explored a novel visible-light-induced procedure for the reductive generation of synthetically important α -amino radicals via a π - π stacked ionic complex. Notably, multiple π interactions stabilized the reactive intermediate, and neither photocatalysts nor initiators were required in this Giese-type three-component coupling system. A wide range of amines, aldehydes, and olefins displayed reactivity. We believe this protocol could find more opportunities for synthesizing underexplored amines in both academic and industrial branches of organic synthesis.

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Keywords: noncovalent interactions • ionic complexes • α -amino radicals • visible light

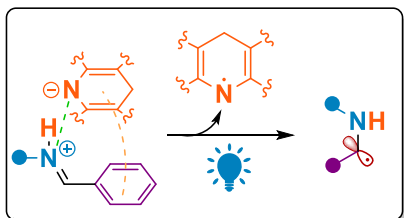
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Π - Π Stacking Complex Induces Three-Component Coupling Reactions to Synthesize Functionalized Amines

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This article describes a novel visible-light-induced strategy for the reductive generation of synthetically important α -amino radicals *via* a π - π stacked ionic complex. Multiple π interactions stabilized the reactive intermediate, and neither a photocatalyst nor an initiator was required. This synthetic pathway delivered the synthesis of complex functionalized amines with a very high yield.

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