Thiol-mediated α-amino radical formation via visible-light-activated ion-pair charge-transfer complexes

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Abstract: Visible-light-activated electron donor-acceptor complexes offer distinct reaction pathways for the synthesis of complex molecules under mild conditions. Herein, we report a method for the reductive generation of α-amino radicals via the reaction of a visible-light-activated ion-pair charge-transfer complex formed between an in situ-generated alkyl-iminium ion and a thiophenolate. This distinct activation mode is demonstrated through the development of a multicomponent coupling reaction to form substituted aminomethyl-cyclopentanes from secondary amines, cyclopropyl aldehydes and alkenes. The operationally straightforward transformation displays broad scope and provides a means to generate cyclic amine-containing scaffolds from readily available feedstocks.

The exploitation of α-amino radicals has been dramatically advanced by the advent of visible-light (VL)-photoredox catalysis.[1,2] Four distinct activation modes have been identified for the generation of this nucleophilic species, which have made the deployment of α-amino radicals a useful tactic in complex molecule synthesis (Figure-1A). Most common among these strategies are single-electron oxidation pathways that convert *N*-aryl tertiary alkylamines to the corresponding α-amino radical (α-AR) and permit a variety of couplings with suitable acceptors.[3] Direct hydrogen atom abstraction methods have also been developed using more versatile carbamate-derived alkylamines.[4] However, despite their efficacy, oxidative- and many of the direct hydrogen-atom abstraction methods display selectivity issues when there are two similar C–H bonds next to the directing nitrogen atom that leads to mixtures of regioisomers, with notable exceptions.[4b-c] As a means to obviate the selectivity issues, oxidative fragmentation of substrates adorned with pre-installed functionality (such as carboxylic acids, silane-derivatives or BF_3K salts) adjacent to an *N*-aryl or *N*-carbamate-derived alkylamine motif can be used for regiospecific α-AR formation.[5] Finally, single-electron reduction of imines or iminium ions provides a means for regiospecific generation of an α-AR. The apparent simplicity of this approach is often disguised by functional group requirements on the amine and carbonyl components that are needed to overcome intrinsically high reduction potentials of imines.[6] This is particularly notable in all-alkyl systems required to form α-ARs that are unbiased by activating groups where reduction potentials often lie between –1.8 and –3.0 V, making them out of reach for all but the most powerful visible-light activated reducing photocatalysts.[7] That said, the convergent and regiospecific nature of α-AR formation via single-electron reduction of imines makes the development of new methods for their generation an important goal in chemical synthesis.[6c]

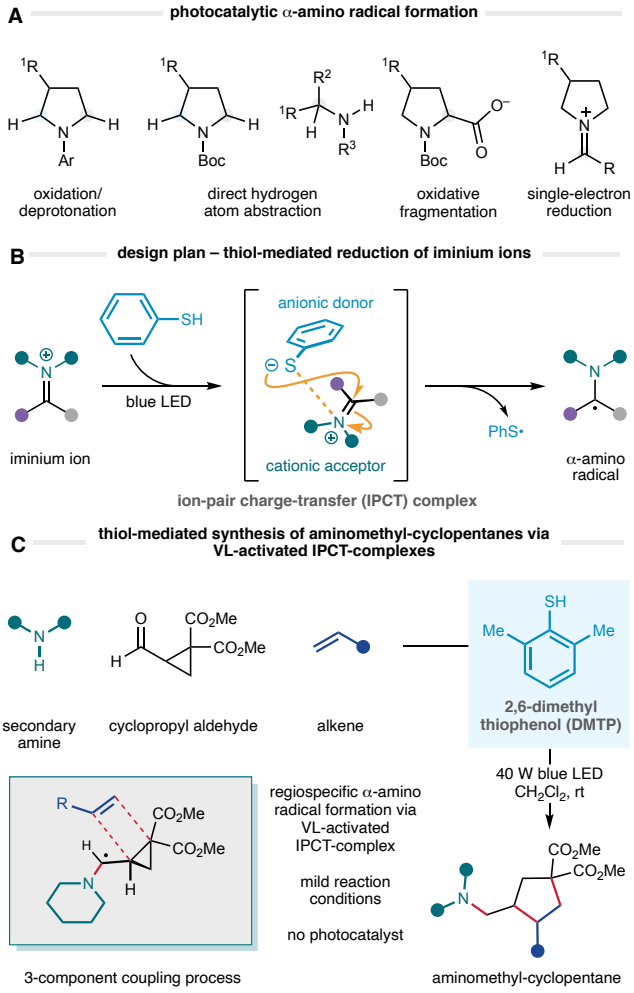


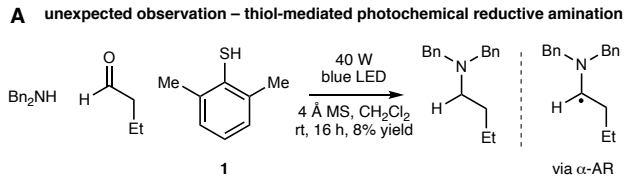
Figure-1. Design plan for the generation and reaction of α-

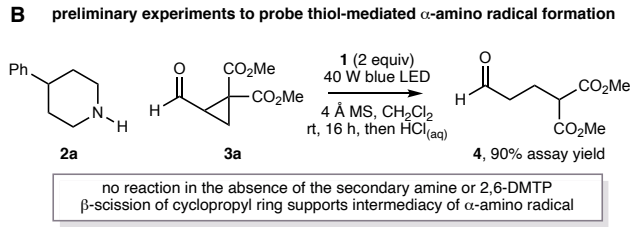
ARs via thiol-mediated, VL-activation of ion-pair charge-transfer complexes

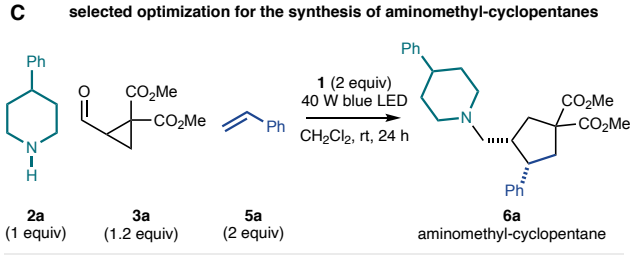
As part of our continued efforts towards platforms for the reductive generation and subsequent exploitation of α-ARs derived from alkyl-iminium ions,[6c-f] we considered that the challenges posed by high reduction potentials might be circumvented by a method based on an intracomplex single-electron transfer (SET) step between an electron-rich 'reductant' and electrophilic iminium ion by way of an electron donor-acceptor-(EDA) or ion-pair charge-transfer (IPCT)-complex.[8] While highly conjugated iminium ions have been shown to participate in reactions through VL-activated EDA-complexes,[9a] there are no examples of alkyl-iminium ions reacting through these intermediates to the best of our knowledge.[9b-c] Herein, we report the successful realization of a distinct reductive process for the generation of α-ARs from iminium ions via the action of a simple thiophenol and VL-irradiation (Figure-1B). This activation mode is harnessed through a transformation that combines a secondary-amine, a cyclopropyl-aldehyde and an alkene to form aminomethyl-cyclopentanes (Figure-1C).

Based on the seminal studies by Kochi,[10a,b] Gilmour[10c] and Yu[10d] in examining the EDA-based reactivity of highly-conjugated iminium ions with pyruvate anions, we set about exploring the feasibility of alkyl α-AR formation via a VL-activated IPCT-complex. Importantly, Miyake and co-workers showed that EDA-complexes involving thiophenolates were shown to undergo SET with difficult-to-reduce bromoarenes (E_{red} ~ −2.0 V),[11] which possess similar reduction potentials to alkyl iminium ions. Inspired by this, we found that irradiating a dichloromethane solution of dibenzylamine, butyraldehyde and 2,6-dimethylthiophenol (**1**) in the presence of 4 Å molecular sieves (MS) with a 40 W blue LED Kessil lamp, formed *N*,*N*-dibenzyl-propylamine in an assay yield of 8%, reflecting a formal reductive amination through the corresponding α-AR (Figure-2A). The low yield of this reaction was attributed to rapid back electron-transfer from the α-AR to the concurrently formed thiyl-radical, which would reform the ground state of the IPCT-complex. To avoid this unproductive quenching process, we engineered the iminium system by using an aldehyde substituted with an adjacent cyclopropane (**3a**); α-AR formation would drive a rapid β-scission to form a stable electrophilic malonyl-radical less likely to undergo back electron-transfer. Testing the reaction with **3a** and secondary-amine-**1a** under the same reaction conditions revealed a 90% assay yield (65% yield of isolated product) of aldehyde-**4** (Figure-2B). No reaction was observed in the absence of secondary amine or thiol-**1**, supporting our proposed pathway involving β-scission of a cyclopropyl-derived α-AR intermediate. Interestingly, 34% assay yield of **4** was observed when the reaction was carried out in the dark at 25 ˚C, suggesting a background thermal activation of the proposed IPCT-complex (cf. 90% with visible-light irradiation[12]).[13] The aldehyde functionality is formed after hydrolysis of the corresponding enamine, which results from the β-scission step; hydrogen atom transfer is assumed to take place from excess thiol to the malonyl-radical. Notably, this mild reductive process is facilitated in the absence of a classical reducing agent.

Based on these preliminary results, we extrapolated the hypothesis towards a plan for the multicomponent synthesis of substituted aminomethyl-cyclopentanes from secondary-amines, cyclopropyl-aldehydes and alkenes by way of a [3c+2c]-type annulation pathway (Figures-1C & 2C)[14]. The reduction of an in situ-generated α-AR would trigger β-scission of the cyclopropane, π-addition to the alkene and ring closure to the cyclopentane. The resulting cyclic C(sp^3)-rich amine scaffolds, displaying versatile polar functionality, could serve as attractive fragments for the design of pharmaceutical or agrochemical candidates.[15] Based on this, and our initial observations, we began by exploring a variety of reaction parameters that may influence the target process.[12] Our initial hit reaction found that the combination of amine-**2a** and aldehyde-**3a** (1.2 equiv) with 2 equivalents of alkene-**5a** and thiophenol-**1** gave a 99% conversion to cyclopentane-**6a**, with 9:1 *syn*- selectivity, after irradiation of a dichloromethane solution for 24 h (Figure 2C, entry 1).







entry	thiol	assay yield[a]
1	2,6-dimethylthiophenol	99
2	thiophenol	34
3	4-methylthiophenol	19
4	3,5-dimethylthiophenol	31
5	2,4,6-trimethylthiophenol	64
6	4-nitrothiophenol	0
7	dodecanethiol	0
8	methyl thioglycolate	0
9	*N*-acetyl cysteine	0

[a]Determined using ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

Figure-2. Discovery of thiol-mediated, VL-activated synthesis of aminomethyl-cyclopentanes.

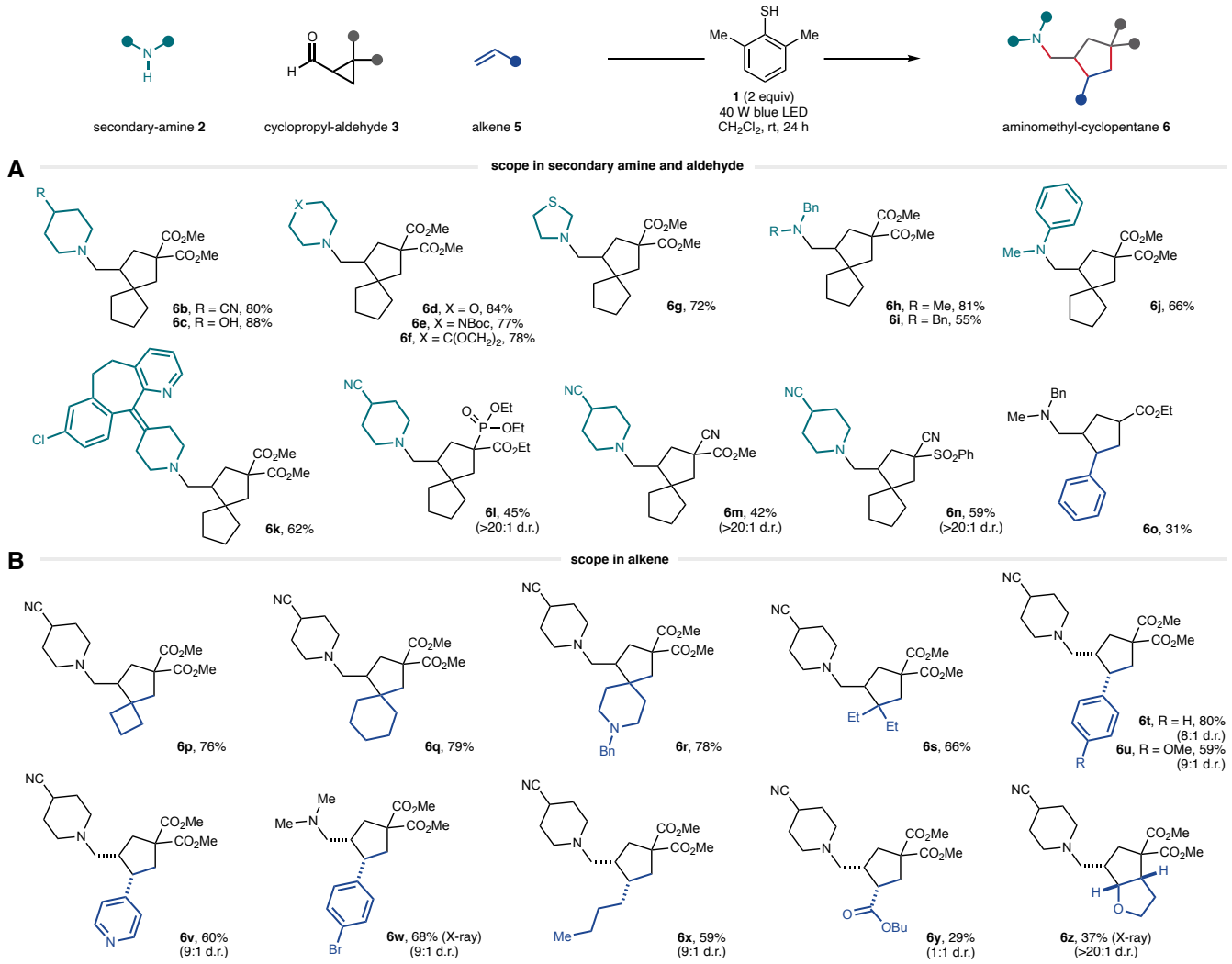


Figure-3. Scope of the multicomponent process for the synthesis of aminomethyl-cyclopentanes. Yields and d.r. of isolated material.

The use of less hindered thiophenols resulted in lower conversion to the product, presumably due to the facile formation of the corresponding *N,S*-hemiaminal (*vide infra*) (entries 2-5). Additionally, no reaction was observed with electron-deficient aryl thiols or any of the alkyl-thiols that were tested (entries 6-9).

We found that a range of alkylamines coupled well with methylene cyclopentane (as a representative alkene) and cyclopropyl-aldehyde-**3** (Figure-3A). For example, reaction of saturated heterocyclic amines displaying versatile functionalities produced the corresponding aminomethyl-cyclopentanes in excellent yields (**6b**-**g**). Acyclic secondary amines, including *N,N*-dialkyl- and *N*-alkyl-aniline derivatives, effectively generated carbocycles **6h**-**j**. A secondary alkylamine-derived from a pharmaceutical fragment (**6k**) was also an excellent substrate, demonstrating the tolerance of the reaction towards diverse functional groups. We were pleased to find that, in addition to geminal ester substituted cyclopropyl-aldehyde **3a**, other functional groups including phosphonates (**6l**), nitriles (**6m**), and sulfones (**6n**) were found to be competent substrates in the multicomponent reaction providing the highly functionalized products in reasonable yields. Even a monosubstituted ester cyclopropyl-aldehyde afforded the corresponding aminomethyl-cyclopetane **6o**, albeit in modest yield as a mixture of diastereomers.

Next, a selection of alkenes that could be deployed in the multicomponent process was explored (Figure-3B). A series of cyclic and acyclic 1,1-disubstituted alkenes worked well in combination with 4-cyanopiperidine and aldehyde-**3a** (to give **6p**-**s**); the deployment of a piperidine-derived alkene is noteworthy as the C(sp^3)-rich spirocycle-**6r**, containing numerous orthogonal functionalities and polar motifs,[16] could be an attractive fragment for pharmaceutical scaffolds. A series of styrenes and vinyl-heteroarenes also performed well and resulted in substituted 2-(hetero)aryl-aminomethyl-cyclopentanes (9:1 dr, *syn*:*anti*, **6t**-**y**). Remarkably, 1-hexene worked well in the reaction to generate the alkyl-substituted cyclopentane-**6x** in 9:1 dr. The reaction with *n*-butyl acrylate proceeded in modest yield to form cyclopentane-**6y** as a 1:1 mixture of diastereomers. Finally, 2,3-dihydrofuran was a good substrate and formed substituted 2-oxabicyclo[3.3.0]octane-**6z** as a single diastereomer. Ketones did not react.

To probe the process through which the α-AR is formed, a number of mechanistic experiments were conducted. Firstly, we found that the reaction proceeded in the

presence of long-pass filters designed to block light below wavelengths of 420 nm (83% yield) & 455 nm (64% yield), indicating the pathway operates well within the range of the VL-spectrum (≥400 nm). A reaction without VL-irradiation between piperidine, aldehyde-**3a** and thiophenol-**1** gave quantitative conversion to *N,S*-hemiaminal-**7** (Figure-4A). While the facile formation of a stable *N,S*-hemiaminal is a possible thermodynamic sink for the reaction, nitrogen-driven α-elimination would form the iminium-acceptor and thiolate-donor (Figure-4B). Moreover, the enhanced reactivity observed using sterically hindered thiophenols supports this assertion as they would destabilize *N,S*-hemiaminal-**7**. Furthermore, electron-deficient thiophenols did not form the product (Figure-2C), presumably reflecting a larger HOMO-LUMO gap in the corresponding IPCT-complex (**int-I**). UV/vis spectra were measured for mixtures of various reaction components in combination with *N,S*-hemiaminal-**7** but, unfortunately, no absorbances above 370 nm were observed. The lack of a diagnostic absorbance to support the putative IPCT-complex is attributed to the relative stability of **7**, which may mean that only very small concentrations of **int-I** are present in solution, beyond the detection limit of the spectrometer. Accordingly, we considered other mechanisms for the formation of the α-AR under these conditions, which included direct *N,S*-hemiaminal excitation,[17a] disulfide energy-transfer,[17b-d] homolytic substitution with a thiyl-radical[17c,e,f] and photoinduced thiol-excitation, but these pathways were ruled out after further studies.[12]

Instead, computational studies were explored to garner support for the single-electron transfer within the VL-activated IPCT-complex **int-I**. Calculation of the Gibbs energy profile for the key species showed *N,S*-hemiaminal-**7** with ΔG of –19.5 kcal mol^{-1} compared to the discrete iminium and thiophenolate ions (Figure-4B). Importantly, the energy of the **int-I** was calculated to be –7.8 kcal mol^{-1} lower in energy than the separated ions, suggesting stabilizing interactions are operational in this intermediate.[18] The calculated energetic stability of **7** relative to **int-I** (ΔG= –11.7 kcal mol^{-1}) indicates a low equilibrium concentration of the IPCT-complex, which could account for the negligible empirical absorbance profile observed in the visible region of the UV/vis spectrum of the reaction mixture. Time-dependent density functional theory (TD-DFT) calculations on *N,S*-hemiaminal-**7** predicted an electronic transition at 239 nm,[12] which matched the observation in the UV/vis spectrum of an absorbance at 237 nm. Further DFT calculations revealed the iminium ion adopts a co-planar geometry to the thiophenolate, with interatomic distances between N and S atoms calculated at 3.63 Å and C1(aryl) and C(iminium) atoms calculated at 3.13 Å (Figure-4C). The distance between the C1(aryl) and C(iminium) is less than the typical Van der Waals distance for aromatic molecules and is consistent with the interplanar separation observed in charge-transfer complexes.[19] TD-DFT calculations conducted on IPCT-complex-**int-I** predicted λ_{max} of 458 nm, which corresponds to an electron-transfer between the HOMO and LUMO components (Figure-4D). Orbital visualization showed that the HOMO is comprised of the thiophenolate π-contributions and the LUMO is made up of contributions from the π* of the C=N bond in the iminium ion. This suggests that at 458 nm, **int-I** can undergo excitation leading to intermolecular SET between the thiophenolate and the iminium ion and formation of an α-AR and the corresponding thiyl-radical (as shown in Figure-4B).

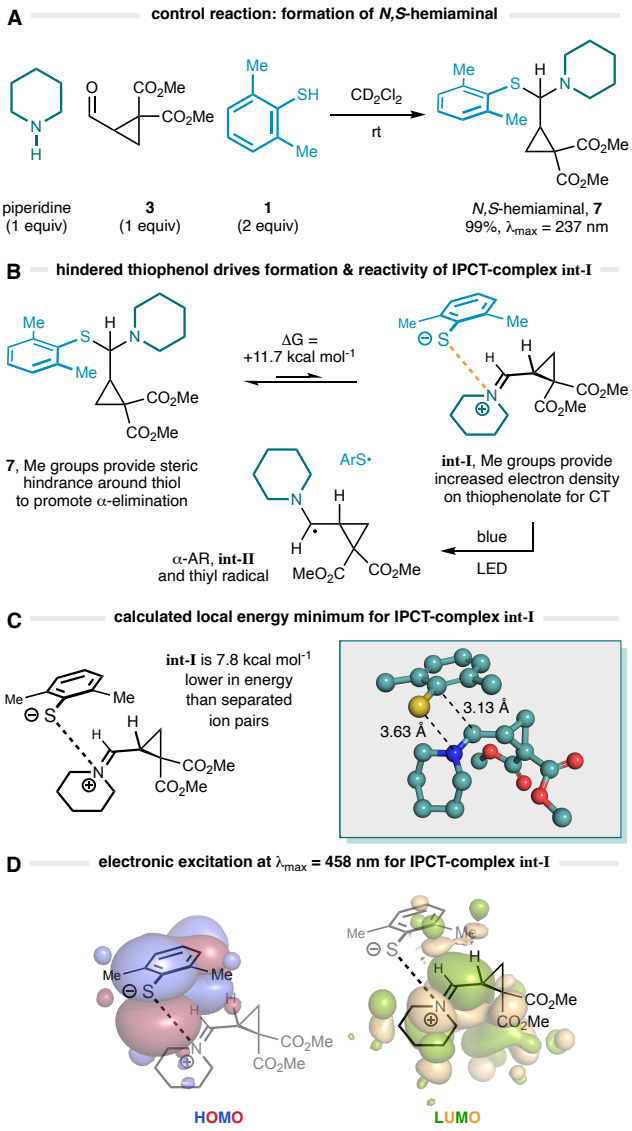


Figure-4. Preliminary mechanistic and computational studies.[18] TD-DFT calculations were conducted on optimized **int-I**, at the CAM-B3LYP/6-311+G(d,p) level.[20]

As a result of both experimental and computational lines of investigation, we propose a pathway to cyclopentane-**6** beginning with condensation of amine, aldehyde, and thiol to form *N,S*-hemiaminal-**7**, followed by nitrogen-driven α-elimination of the thiolate to form the iminium/thiophenolate ion-pair (Figure-5). VL-activation of this species would lead to SET in IPCT-complex-**int-I** from the thiophenolate donor to the iminium acceptor, forming α-AR-**int-II**. β-Scission of the cyclopropyl ring in **int-II** leads to an enamine displaying stabilized radical-**int-III**, which undergoes addition to the alkene and forms corresponding radical-**int-IV**. 5-*Exo*-trig cyclization of radical-**int-IV** onto the enamine forms exocyclic α-aminomethyl-radical-**int-V**, which undergoes hydrogen atom transfer with excess thiophenol to form the aminomethyl-cyclopentane-**6**. The *syn*-selectivity is assumed to arise through the minimization of

interactions within an envelope-type transition state during 5-*exo*-trig ring-closure.[21]

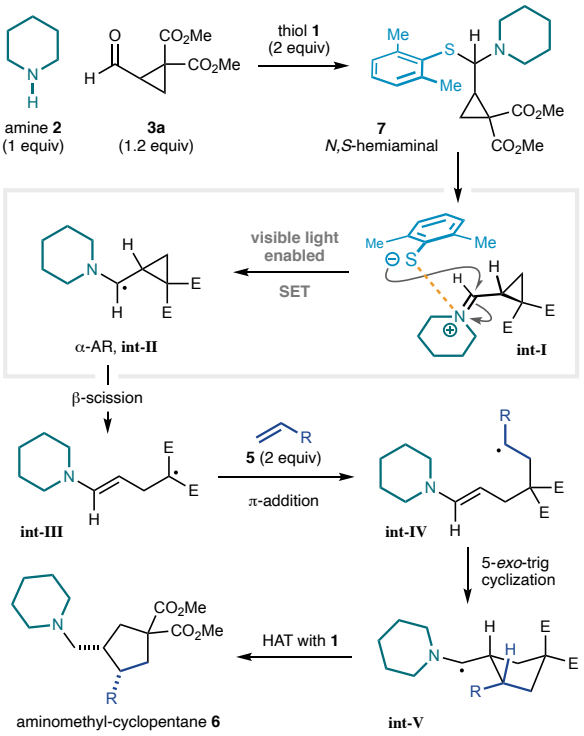


Figure-5. Proposed mechanistic pathway for VL & thiophenol-mediated synthesis of aminomethyl-cyclopentanes.

In summary, we have developed a novel process for the formation of α-ARs via VL-activation of an IPCT-complex formed between an in situ-generated alkyl-iminium ion and thiophenolate. While the thiolate component of the IPCT-complex is responsible for the iminium reduction step, it is not incorporated into the product. Computational support for SET within this complex provides a basic understanding of the reaction pathway. We believe the resulting multicomponent reaction to produce substituted aminomethyl-cyclopentanes demonstrates a practical, operationally straightforward, and photocatalyst-free process that will not only provide streamlined access to new complex amine products but will also provide complementary means to perform α-amino radical-based transformations. Further exploration of this activation mode will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization (PDF).
X-ray data for **6w**, **6z** (CIF).

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

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