

## Photoinduced Acylations Via Azonium-Promoted Intermolecular Hydrogen Atom Transfer

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**ABSTRACT:** Photoinduced hydrogen atom transfer (HAT) has been developed as a powerful tool to generate synthetically valuable radical species. The direct photoexcitation of ketones has been known to promote HAT or to generate acyl radicals through Norrish-type pathways, but these modalities remain severely limited by radical side reactions. We report herein a catalyst- and transition metal-free method for the acylation of C–H bonds that leverages the unique properties of stable, isolable acyl azonium species. Specifically, acyl azonium salts are shown to undergo an intermolecular and regioselective HAT upon LED irradiation with a range of substrates bearing active C–H bonds followed by C–C bond formation to afford ketones. Experimental and computational studies support photoexcitation of the acyl azonium followed by facile intersystem crossing to access triplet diradical species that promote selective HAT and radical–radical cross-coupling.

The power of light-driven chemical transformations has captured the attention of synthetic chemists for over a century. Some of the earliest examples of organic photochemistry include the photoreduction of ketones, first reported in 1885 by Klinger, Ciamician, and Silber.<sup>1</sup> It was observed that the exposure of an ethereal solution of an aromatic ketone to sunlight slowly formed the reduced alcohol. Since then, countless photochemical transformations of ketones have been developed. Notable early innovations include the discovery of Norrish-type photochemistry, wherein excitation to the triplet diradical state of ketones leads to rapid and uncontrolled fragmentation, abstraction, and coupling reactions. Norrish II and Norrish-Yang reactivities stem from initial intramolecular hydrogen atom transfer (HAT) and have found various synthetic applications,<sup>2–7</sup> including natural product total synthesis.<sup>8,9</sup> Norrish Type I chemistry, on the other hand, is the direct generation of an acyl and alkyl radical by ketone irradiation (Figure 1A).<sup>2,10,11</sup> Despite presenting an attractive solution to the generation of valuable radical species, this subset of photochemistry remains far less developed than its counterparts, primarily due to the uncontrolled reactivity of its initial radical products.<sup>12–14</sup> As such, strategies that could provide more controlled outcomes from Norrish-type processes would enable powerful new synthetic tools.

HAT has gained significant attention as a powerful bond-forming strategy in the past decade. Direct abstraction of hydrogen atoms offers a unique regio- and chemoselectivity compared to other methods of radical generation and avoids the need for prefunctionalized redox-active precursors. Many groups have developed methodologies that use HAT to generate radical fragments, often employing a cocatalyst that can abstract a hydrogen atom when activated.<sup>15–22</sup>

Similarly, triplet state ketone-induced HAT has been employed in catalytic transformations on its own<sup>23–29</sup> as well as in conjunction with transition metal catalysis.<sup>30</sup> In these

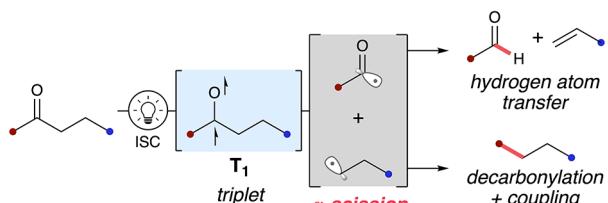
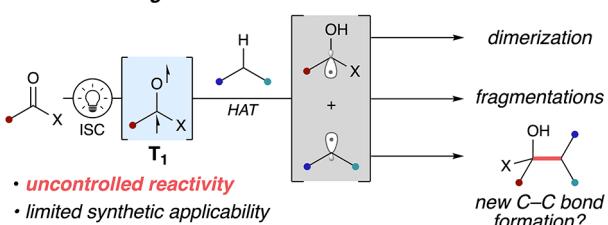
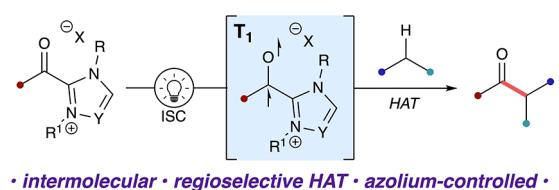
cases, however, the ketyl radical generated upon HAT is *not* incorporated into the final product.

We envisioned that a union of these two modes of photochemical reactivity could enable a catalyst-free transformation that directly links ketones with activated C–H bonds (Figure 1B). A combination of triplet state ketone-driven intermolecular HAT with Norrish-Yang-like radical–radical coupling would provide a new strategy for C–C bond formation. However, as demonstrated by several prior attempts, this combined intermolecular HAT/coupling suffers from several issues associated with Norrish I chemistry, including dimerization, fragmentation, and undesired secondary HAT between the newly generated radical pair.<sup>13,14,31</sup> Recent reports by our group, Hopkinson, and others on single-electron N-heterocyclic carbene catalysis highlight the utility of radical azonium species as stabilized acyl radical surrogates.<sup>32–49</sup> Due presumably to their persistence, these radical species have been shown to avoid common radical side reactivity in favor of selective radical–radical cross coupling. We hypothesized that utilizing an acyl azonium as a triplet ketone reagent would enable our desired HAT/coupling reaction manifold (Figure 1C). Our reaction design then consists of irradiation of the target substrate with an acyl azonium. After excitation, acyl azoniums can readily undergo intersystem crossing to access triplet diradical species.<sup>50</sup> Subsequent HAT from a coupling partner generates a pair of radicals, which, due to the unique reactivity of the acyl azonium

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**A. Norrish I Photochemistry****B. Reaction Design****C. This work**

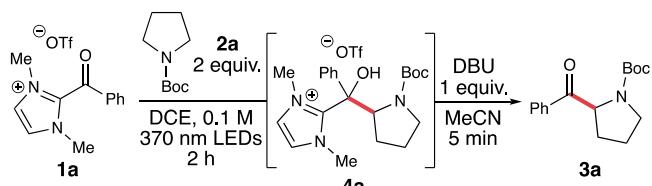
• intermolecular • regioselective HAT • azonium-controlled •

**Figure 1.** (A) Norrish I photochemistry and selected products; (B) design and challenges of intermolecular triplet ketone HAT; (C) effective HAT acylation is achieved by leveraging acyl azonium triplet reactivity.

radical, could then selectively cross-couple to provide a masked ketone. Finally, the desired acylated product could be readily liberated by the addition of base.<sup>51–53</sup>

We began exploration and optimization of this triplet acylation strategy with stable benzoyl azonium **1a** and N-Boc-pyrrolidine **2a**. Irradiation of a 0.1 molar solution of acyl azonium in 1,2-dichloroethane (DCE) with two equivalents of carbamate provided the desired ketone product **3a** in 35% yield after base-mediated deprotection (Table 1, entry 1). Notably, no di- or polyacylated products were detected, which we hypothesize originates from the cationic character of intermediate **4a**, preventing further HAT from acyl azonium **1a**.

**Table 1. Optimization of Reaction Conditions**



| entry # | deviation from standard          | yield <b>3a</b> (%) <sup>a</sup> |
|---------|----------------------------------|----------------------------------|
| 1       | none                             | 35                               |
| 2       | MeCN instead of DCE              | 15                               |
| 3       | PhCF <sub>3</sub> instead of DCE | 28                               |
| 4       | 0.2 M instead of 0.1 M           | 27                               |
| 5       | 0.025 M instead of 0.1 M         | 49                               |
| 6       | 3 equiv. of <b>2a</b> , 0.025 M  | 58                               |
| 7       | 3 equiv. of <b>2a</b> , 8.33 mM  | 67 <sup>b</sup>                  |

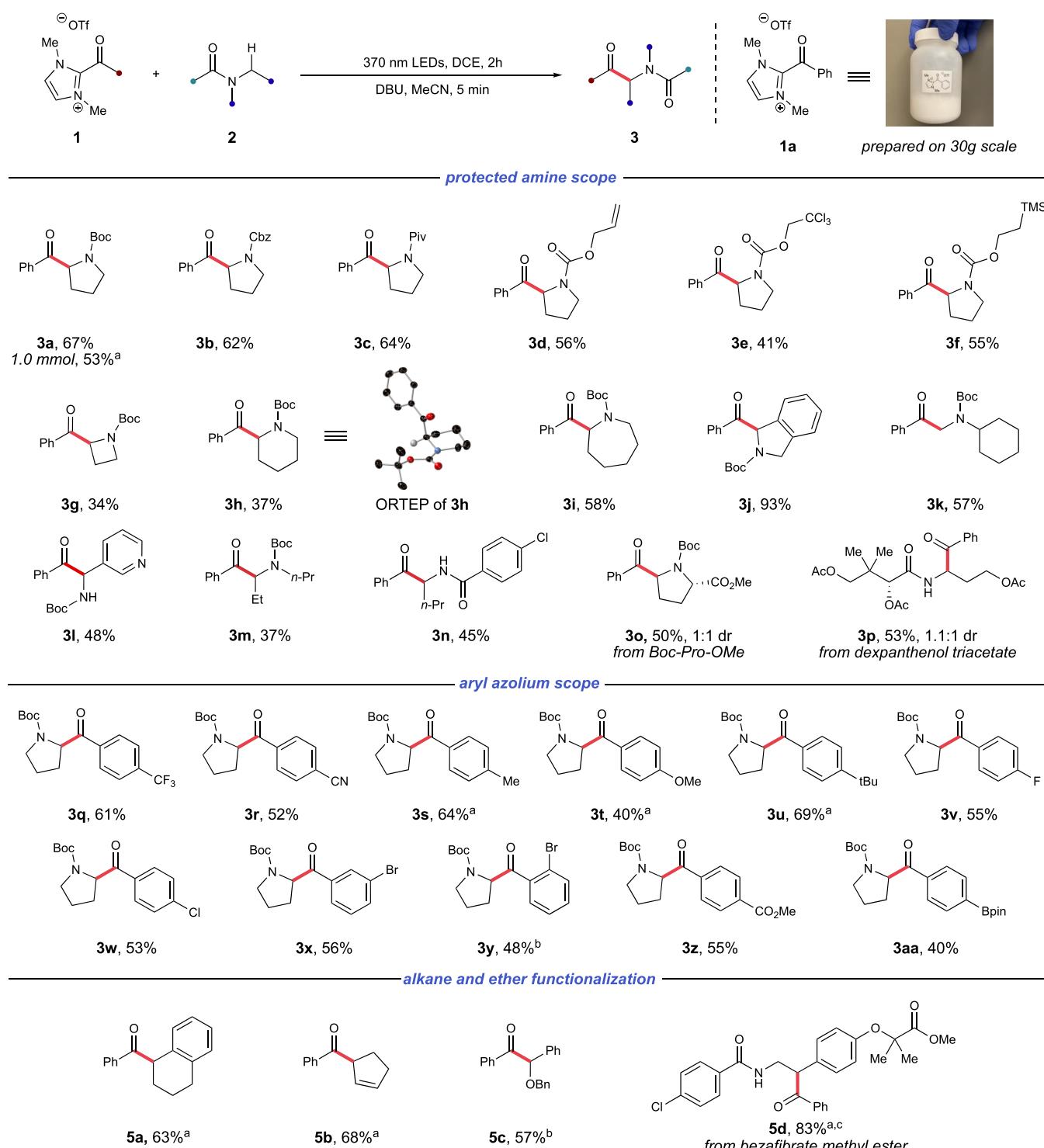
<sup>a</sup>yield determined by <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as a standard. <sup>b</sup>Isolated yield.

due to Coulombic repulsion. The investigation of other solvents, including acetonitrile and trifluorotoluene, did not lead to improvements in reaction efficiency (Table 1, entries 2 and 3). A screen of reaction concentrations demonstrated a correlation between yield and dilution, with lower concentrations providing higher yields of ketone **3a** (Table 1, entries 4 and 5). Further increases in yield were achieved by increasing the loading of carbamate **2a** and further decreasing the concentration (Table 1, entries 6 and 7), which we hypothesize minimizes side reactivity between the transient  $\alpha$ -amino radicals. This high dilution, while optimal for certain substrates, proved unnecessary across the whole scope (*vide infra*).

These reaction conditions were then employed to prepare a variety of  $\alpha$ -amino ketones. It is worth noting acyl azonium salts such as **1a** can be prepared on multigram scale. Products **3b** and **3c** bearing benzyl carbamate and pivalate protecting groups, respectively, were prepared in good yields (Table 2). More complex carbamates were also tolerated under the reaction conditions without significant loss of yield (**3d**–**3f**). Beyond pyrrolidine-based scaffolds, ketones containing Boc-protected azetidine, piperidine, and azepane were prepared in moderate yields (**3g**–**3i**). Additionally, isoindoline ketone **3j** was prepared in excellent yield. Linear amine-derived substrates were tolerated, and the corresponding ketones isolated in moderate-to-good yields (**3k**–**3n**). Finally, under these conditions, Boc-protected L-proline methyl ester and protected B<sub>5</sub> provitamin dexamphenol triacetate were successfully and selectively acylated (**3o** and **3p**), demonstrating the utility of this methodology for the late-stage functionalization of high-value structures. Diastereoselectivity, however, remains a challenge for radical acylations and radical–radical couplings.<sup>54–56</sup>

The scope of aryl acyl azoniums compatible with this methodology was also investigated. Electron-withdrawing substituents (**3q**–**3r**) and electron-donating substituents (**3s**–**3u**) were tolerated, providing the corresponding ketones in moderate-to-good yields. Halogenated acyl azoniums were also successfully employed in the acylation, affording para-, meta-, and ortho- substituted aryl ketones (**3v**–**3y**). Acyl azoniums bearing functional handles for further diversification were tolerated, providing methyl (**3z**) and pinacol boronic (**3aa**) ester-containing ketones. Notably, these substrates and/or products would be problematic to access with traditional anionic chemistry (e.g., Weinreb amide). Acyl azoniums derived from saturated carboxylic acids or certain heterocycles are not productive or high yielding in these coupling processes (see Supporting Information page S29).

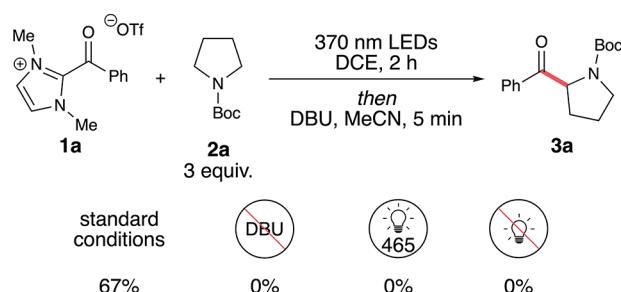
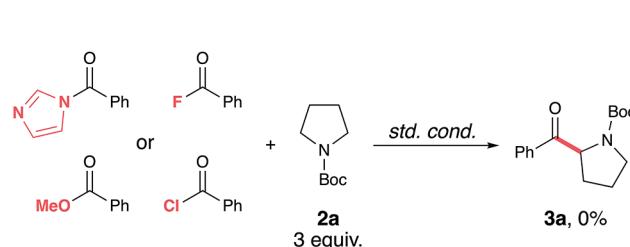
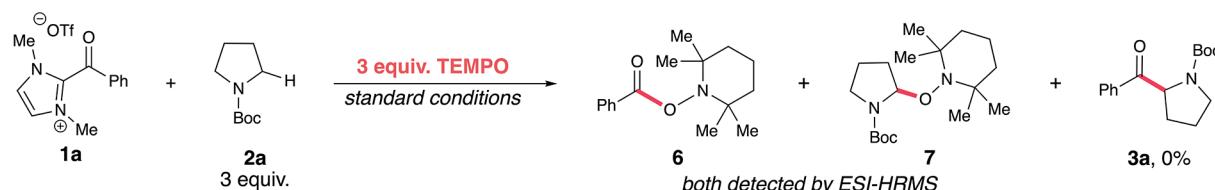
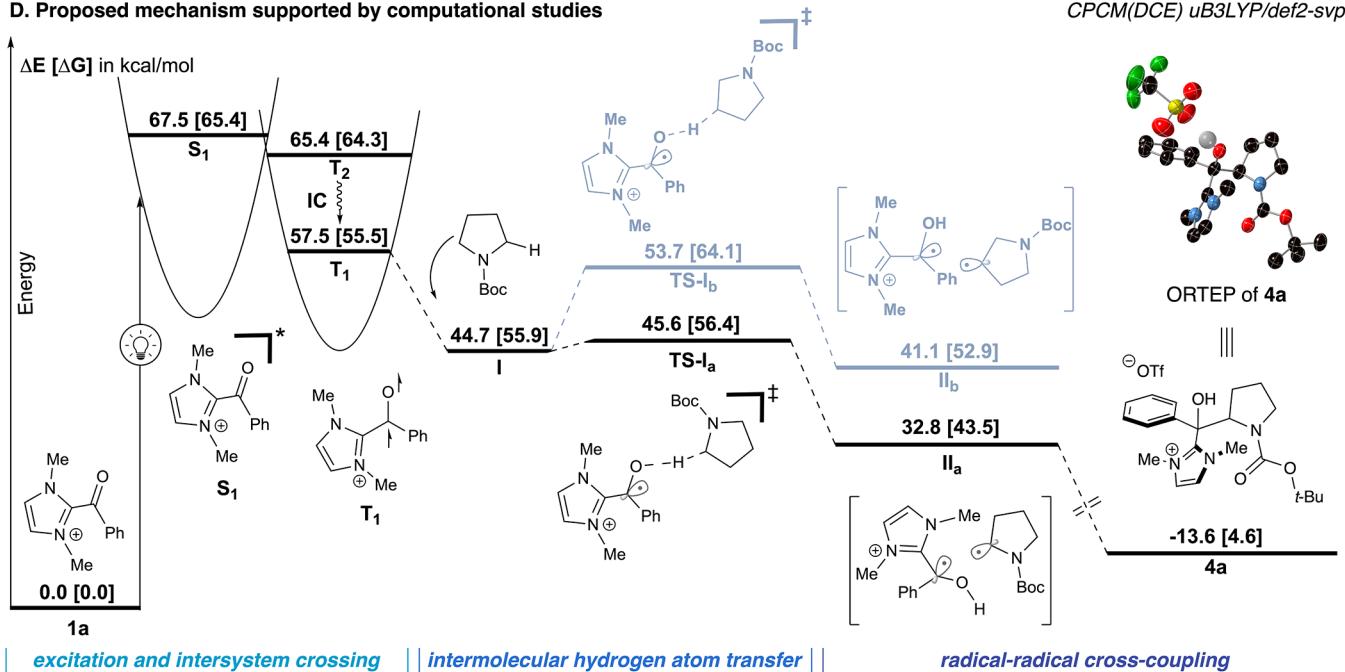
We also investigated the photoinduced hydrogen atom abstraction/acylation of substrates beyond carbamates and amides. Based on their relative C–H bond strength<sup>57,58</sup> as well as prior reports,<sup>26,59–62</sup> we anticipated being able to functionalize benzylic, allylic, and  $\alpha$ -oxo C–H bonds. We were delighted to find that our methodology successfully acylated tetralin, cyclopentene, and dibenzyl ether, providing the corresponding ketones (**5a**–**5c**) without further optimization. This expands the utility of the methodology by synthesizing benzylic ketones,  $\beta,\gamma$ -unsaturated ketones, and glycolic acid derivatives. Interestingly, applying our methodology to the methyl ester of lipid-lowering agent bezafibrate yielded the benzylic ketone **5d** in excellent yield instead of the  $\alpha$ -amido ketone.

**Table 2. Substrate Scope of Triplet Azolium Acylation<sup>d</sup>**

<sup>a</sup>Reaction performed at 0.05 M. <sup>b</sup>Reaction performed at 0.025 M. <sup>c</sup>Reaction performed with 0.1 mmol of azolium. <sup>d</sup>Isolated yields are reported. Reaction conditions: acyl azolium (0.2 mmol, 1.0 equiv), coupling partner (0.6 mmol, 3.0 equiv), 1,2-dichloroethane (8.33 mM), 370 nm LEDs, RT, 2 h.

Several mechanistic studies were performed to elucidate the nature of the triplet acyl azolium acylation. Control experiments employing 465 nm LEDs or omitting irradiation provided none of the desired ketone after basic workup, strongly suggesting that excitation of the acyl azolium is key to the transformation (Scheme 1A). UV-vis spectroscopic studies

confirmed that the acyl azolium does not absorb above 400 nm (see the Supporting Information page S32). Additionally, we were able to verify no change in UV-vis absorption profile occurs when combining acyl azolium **1a** and N-Boc-pyrrolidine **2a**, eliminating the possibility of the formation of an electron donor–acceptor complex (see the Supporting Information

**Scheme 1.** Mechanistic Studies, Density Functional Theory Calculations, and Proposed Reaction Pathway**A. Control experiments****B. Acyl electrophile experiments****C. TEMPO radical trapping experiment****D. Proposed mechanism supported by computational studies**

page S35).<sup>63–65</sup> One additional control reaction omitting the addition of DBU led to none of the desired product per NMR spectroscopic or LC-MS analysis (Scheme 1A), further supporting the presence of an intermediate that liberates the desired ketone upon workup. Experiments substituting acyl azolium **1a** with other commonly employed acyl electrophiles did not provide any ketone **3a** after workup, suggesting the acylation reactivity is unique to the acyl azolium (Scheme 1B). We hypothesize that acyl azolium **1a** enables access to singlet excited state **S<sub>1</sub>** under UVA irradiation. UV-vis studies and computational studies of the other acyl electrophiles support a high energy requirement for excitation (see the Supporting Information pages S33–34 and S37). A TEMPO-trapping experiment was conducted by adding three equivalents of TEMPO to the standard reaction (Scheme 1C). TEMPO adducts of the acyl azolium (**6**) and of N-Boc-pyrrolidine (**7**)

were detected by ESI-HRMS, strongly supporting the intermediacy of the two radical fragments. Direct TEMPO trapping of the azolium-derived radical has not been observed in the literature, likely due to the rapid collapse of the hemiketal structure produced. This observation is in line with previous acyl azolium methodology.<sup>66–68</sup> Additionally, ketone **3a** was not detected after basic workup of the reaction mixture, indicative of a radical acylation process inhibited by TEMPO (Scheme 1C).

To further explore the proposed mechanism, we turned to dispersion-corrected density functional theory (DFT) calculations (Scheme 1D, see the Supporting Information for additional details). As previously reported,<sup>69</sup> acyl azolium **1a** is calculated to reach the singlet excited state **S<sub>1</sub>** under violet or UVA irradiation. Time-dependent density functional theory (TD-DFT) calculations at the UB3LYP-D3/Def2-SVP-

CPCM(DCE) level were used to study the excited state pathways (**Scheme 1D**) which show that  $S_1$  can undergo a favorable intersystem crossing to the second triplet ( $T_2$ ) excited state ( $\Delta\Delta E = 1.8$  kcal/mol),<sup>70</sup> which can then rapidly undergo internal conversion to the lowest energy triplet excited state  $T_1$ . To investigate the factors controlling selectivity in the HAT step, we explored all possible sites for HAT (see the Supporting Information page S36). Notably, analysis of the optimized  $T_1$  structure indicated that spin density was primarily located on the oxygen atom, consistent with selective O–H bond formation (vs C–H) in the HAT step (*vide supra*). Consistent with the observed high regioselectivity of acylation, the hydrogen atom abstraction from the  $\alpha$ -amino C–H bond of the N-Boc-pyrrolidine takes place through a small energy barrier (TS- $I_a$ ,  $\Delta G^\ddagger = 0.5$  kcal/mol; with respect to complexed intermediate **I**), compared to a much higher (8.2 kcal/mol) barrier for HAT at the  $\beta$ -position (TS- $I_b$ ). This energy difference and corresponding selectivity aligns with literature reports of polarity-matched and mismatched HAT kinetics<sup>71–74</sup> and reflects the relative stabilities of the formed radical pairs ( $\text{II}_b$  vs  $\text{II}_a$ ). In addition, we also considered the possibility of the carbonyl carbon in  $T_1$  promoting the HAT step. However, as expected, high energy barriers were calculated for this path ( $\Delta G^\ddagger > 17.0$  kcal/mol) making it unfeasible. Thus, this pathway was not considered further (see the Supporting Information, Figure S1). Finally, from in-cage radical pair  $\text{II}_a$ , radical–radical cross coupling can proceed rapidly to produce tertiary alcohol **4a**, which was unambiguously characterized by XRD of a crystal grown prior to workup to form **3a**.

In summary, we have developed a photoinduced direct acylation of activated C–H bonds with stable acyl azonium salts. This process does not require any catalyst and leverages the apparent unique reactivity of acyl azonium triplet excited states. With simple irradiation, the acyl azonium can readily access a triplet diradical, which undergoes highly regioselective hydrogen atom transfer and subsequent radical–radical coupling to deliver a tetrahedral intermediate. This azonium alcohol is then cleanly converted to the desired ketone by simple treatment of the reaction with mild base. Overall, this redox-neutral process delivers valuable acylated materials from simple chemical starting materials and enables the late-stage functionalization of complex bioactive structures. Further investigations exploring the utility of azonium triplet excited states as unique intermediates and their propensity to prevent traditional Norrish reactivity limitations in synthesis are underway.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c12845>.

General information, experimental procedures, characterization of compounds, UV/vis experiments, DFT calculations, and XRD data ([PDF](#))

### Accession Codes

CCDC 2195739–2195740 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS

HAT, hydrogen atom transfer; DCE, 1,2-dichloroethane; LED, light emitting diode; NMR, nuclear magnetic resonance; LC-MS, liquid chromatography mass spectrometry; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; ESI-HRMS, electrospray ionization high resolution mass spectrometry; UVA, ultraviolet A; DFT, density functional theory; TD-DFT, time-dependent density functional theory; XRD, X-ray diffraction; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene

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