

Photoinduced Acylations Via Azolium-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 azolium species. Specifically, acyl azolium 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 azolium 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 photo-reduction of ketones, first reported in 1885 by Klinger, Ciamician, and Silber.¹ 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,^{2–7} including natural product total synthesis.^{8,9} Norrish Type I chemistry, on the other hand, is the direct generation of an acyl and alkyl radical by ketone irradiation (Fig. 1A).^{2,10,11} 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.^{12–14} 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 co-catalyst that can abstract a hydrogen atom when activated.^{15–22} Similarly, triplet state ketone-induced HAT has been employed in

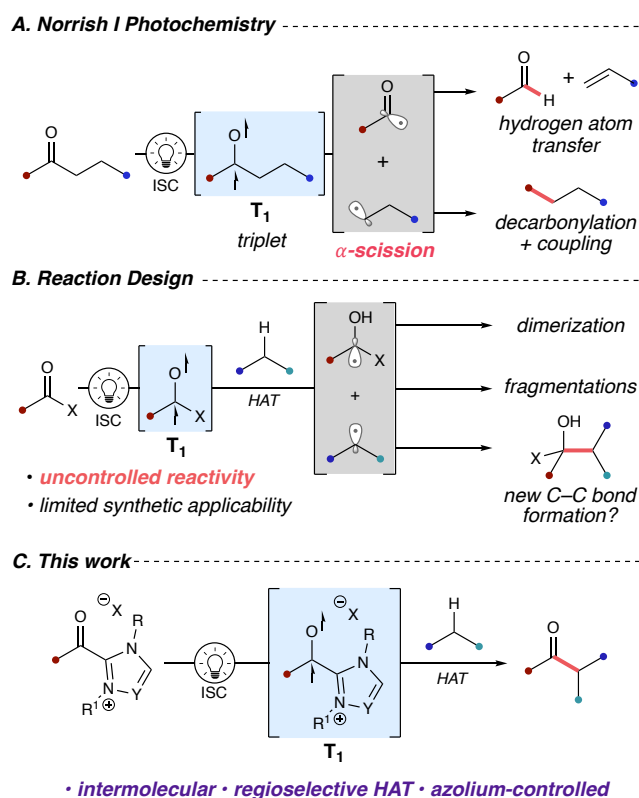


Figure 1. (A) Norrish I photochemistry and selected products (B) Design and challenges of intermolecular triplet ketone HAT (C) Effective HAT acylation is achieved by leveraging acyl azolium triplet reactivity.

catalytic transformations on its own^{23–29} as well as in conjunction with transition metal catalysis.³⁰ In these cases, however, the ketyl radical generated upon HAT is *not* incorporated into the final product.

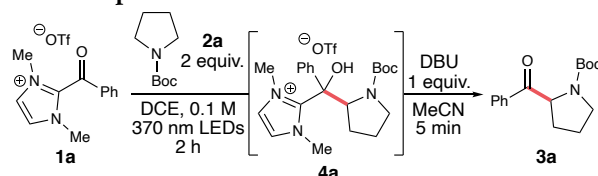
We envisioned that a union of these two modes of photochemical reactivity could enable a catalyst-free transformation that directly links ketones with activated C–H bonds (Fig. 1B). A combination of triplet state ketone-driven intermolecular HAT with Norrish I-like radical-radical coupling would provide 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.^{13,14,31} Recent reports by our group, Hopkinson, and others on single-electron N-heterocyclic carbene catalysis highlight the utility of radical azolium species as stabilized acyl radical surrogates.^{32–49} 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 azolium as a triplet ketone reagent would enable our desired HAT/coupling reaction manifold (Fig. 1C). Our reaction design then consists of irradiation of the target substrate with an acyl azolium. After excitation, acyl azoliums can readily undergo intersystem crossing to access triplet diradical species.⁵⁰ Subsequent HAT from a coupling partner generates a pair of radicals, which, due to the unique reactivity of the acyl azolium radical, could then selectively cross-couple to provide a masked ketone. Finally, the desired acylated product could be liberated instantaneously by addition of base.^{51–53}

We began exploration and optimization of this triplet acylation strategy with stable benzoyl azolium **1a** and N-Boc-pyrrolidine **2a**. Thus, irradiation of a 0.1 molar solution of acyl azolium 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 azolium **1a** 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 α -amino radicals.

These reaction conditions were then employed to prepare a variety of α -amino ketones. Notably, acyl azolium 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 B₅ provitamin

dexpanthenol triacetate were successfully and selectively acylated (**3o** & **3p**), demonstrating the utility of this methodology for the late-stage functionalization of high-value structures.

Table 1. Optimization of Reaction Conditions.



entry #	deviation from standard	yield 3a (%) ^a
1	none	35
2	MeCN instead of DCE	15
3	PhCF ₃ 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. 2a , 0.025 M	58
7	3 equiv. 2a , 8.33 mM	67 ^b

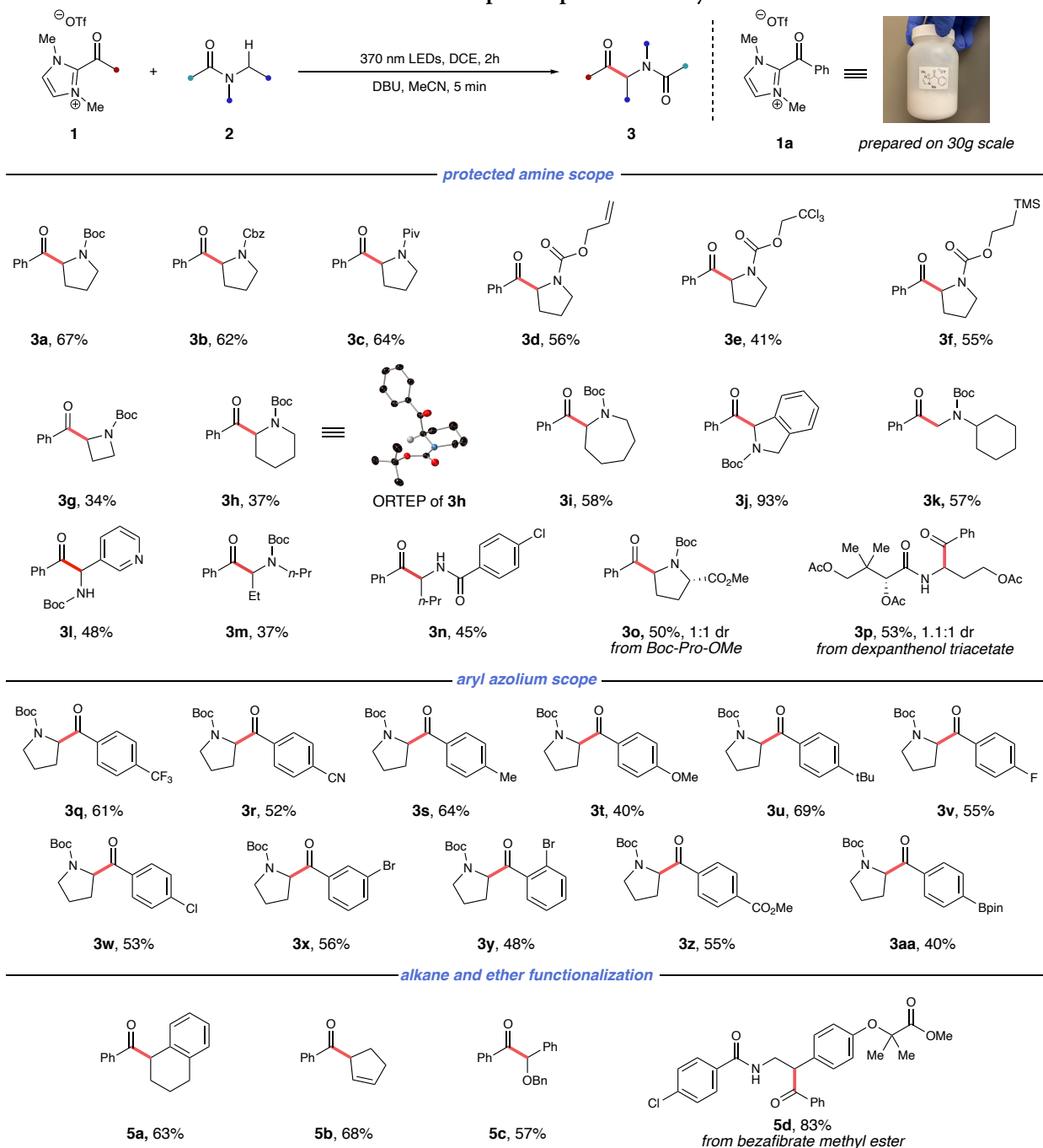
^ayield determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as a standard. ^bIsolated yield.

The scope of aryl acyl azoliums 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 azoliums were also successfully employed in the acylation, affording para-, meta-, and ortho- substituted aryl ketones (**3v** – **3y**). Acyl azoliums bearing functional handles for further diversification were tolerated, providing methyl (**3z**) and pinacol boronic ester-containing (**3aa**) ketones. Currently, acyl azoliums derived from saturated carboxylic acids (e.g., hydrocinnamic acid) are not productive in these coupling processes and we are actively investigating the expansion of scope to engage these potential substrates.

We also investigated the photoinduced hydrogen atom abstraction/acylation of substrates beyond carbamates and amides. Based on their relative C–H bond strength^{54,55} as well as prior reports,^{26,56–59} we anticipated being able to functionalize benzylic, allylic, and α -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, β,γ -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 α -amido ketone.

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 Supporting Information page S30). 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 Supporting Information page S31).^{60–62} 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

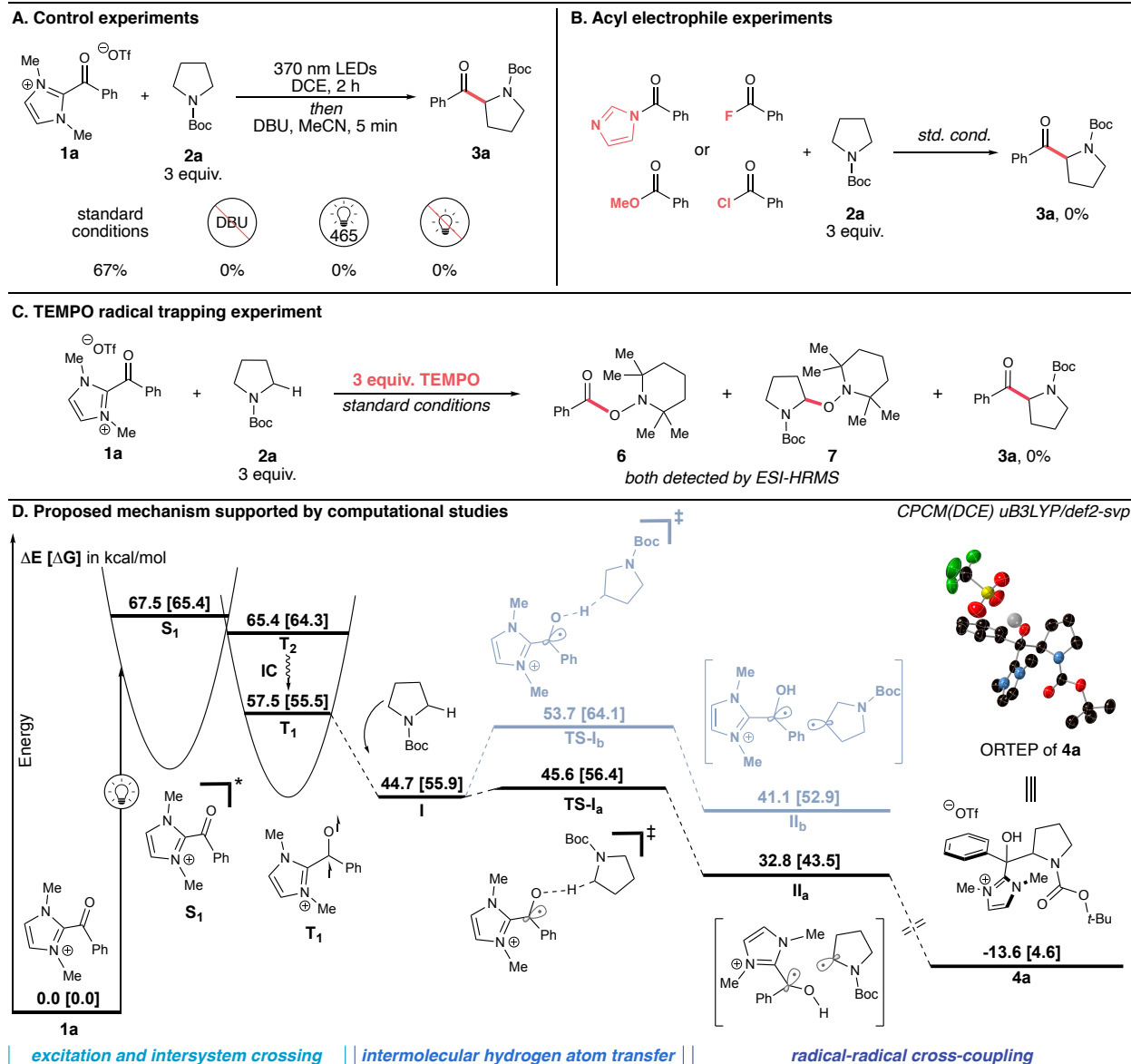
Table 2. Substrate Scope of Triplet Azolium Acylation



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). 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. 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 Supporting Information for additional details). As previously reported,⁶³ acyl azolium **1a** is calculated to reach the singlet excited state **S**₁ under violet or UVA irradiation. Time-dependent density functional theory (TD-DFT) calculations at the B3LYP-D3/Def2-SVP-CPCM 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),⁶⁴ which can then rapidly undergo internal conversion to the lowest energy

Scheme 1: Mechanistic Studies, Density Functional Theory Calculations, and Proposed Reaction Pathway



triplet excited state **T**₁. To investigate the factors controlling selectivity in the HAT step, we explored all possible sites for HAT (See Supporting Information page S32). 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 α-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 β-position (**TS-I**_b). This energy difference and corresponding selectivity aligns with literature reports of polarity-matched and mismatched HAT kinetics^{65–68} and reflects the relative stabilities of the formed radical pairs (**II**_a vs. **II**_b). 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 Supporting Information, Figure S1). Finally, from in-cage radical

pair **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 azolium salts. This process does not require any catalyst and leverages the apparent unique reactivity of acyl azolium triplet excited states. With simple irradiation, the acyl azolium can readily access a triplet diradical, which undergoes highly regioselective hydrogen atom transfer and subsequent radical-radical coupling to deliver a tetrahedral intermediate. This azolium 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 azolium triplet excited states as unique intermediates and their propensity to prevent traditional Norrish reactivity limitations in synthesis are underway.

ASSOCIATED CONTENT

Supporting Information

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

General information, experimental procedures, characterization of compounds, UV/Vis experiments, DFT calculations, and XRD data. (PDF).

Crystallographic files (CIF).

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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.

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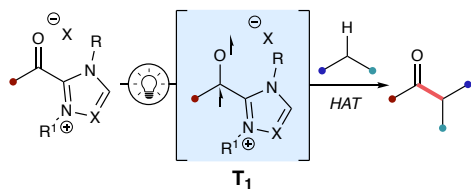
ABBREVIATIONS

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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