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Letter

Cross-Dehydrogenative Coupling of Strong $C(sp^3)-H$ with *N*-Heteroarenes through Visible-Light-Induced Energy Transfer

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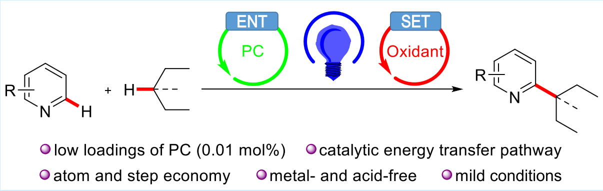
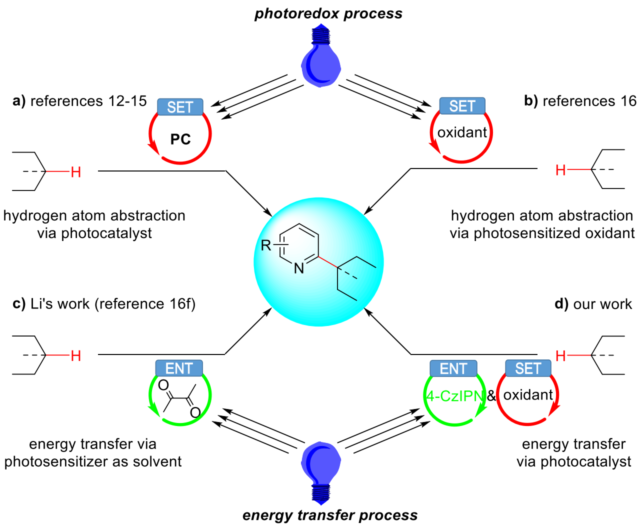
ABSTRACT: The sustainable cross-dehydrogenative coupling of strong $C(sp^3)-H$ with *N*-heteroarenes has been developed using an efficient organic photocatalyst. It features atomic- and step-economy, and acid-free conditions. Mechanism studies suggest a previous elusive energy transfer pathway from photocatalyst to *N*-heteroarenes and oxidants.



The heteroarenes, especially *N*-heteroarenes, are important and ubiquitous structural motifs in pharmaceuticals, natural products, and ligand scaffolds.[1] Minisci-type C−H functionalization of electron-deficient *N*-heteroarenes via alkyl radicals offers efficient methods for synthesis of complex alkyl substituted *N*-heteroarenes. However, the harsh conditions of classical Minisci reaction limit its scope.[2] With the emerging of visible light mediated photoredox catalysis, its environmental benign features and mild conditions stimulate the development of several elegant photocatalytic Minisci reactions which bear extensive substrate scope, and enable late-stage functionalization.[3] Diverse alkyl radical sources such as carboxylic acids,[4] alkyl halides,[5] boronic acid and derivatives,[6] sulfonates,[7] activated esters,[8] alcohols[9] and aldehydes[10] can successfully afford corresponding alkylated *N*-heteroarenes under this low energy consumption mode. Alternatively, owing to the natural abundance of alkyl structures and the greatest atom and step economy of direct alkyl radical generation via hydrogen atom abstraction from alkanes,[11] cross-dehydrogenative coupling (CDC) between alkanes and arenes is the most desirable.

Since Macmillan reported $C(sp^3)-H$ arylation of ethers using iridium photocatalyst,[12] Ir, Ru, Cu, and several organic photocatalysts have been employed to undergo single electron transfer reduction of oxidants, which promoted hydrogen atom abstraction from *N*-protected secondary amines,[13] remote site of free alcohols,[14] and even alkanes (Scheme 1a).[15] Decatungstate photocatalysts were reported as photo sensitized catalytic hydrogen atom abstractor for alkanes.[15b] Additionally, selectfluor, phenyliodine bis(trifluoroacetate) and diacetyl have been introduced as stoichiometric photosensitized hydrogen atom abstractor, realizing elegant catalyst-free Minisci reactions (Scheme 1b).[16] Besides these impressive advances, complementary energy transfer strategy has seldom been reported. Recently, Li and co-workers disclosed that diacetyl as a stoichiometric photosensitizer would undergo an energy transfer process, producing oxy radical (Scheme 1c).[16f] Owing to high lifetime and excellent energy transfer quantum efficiency of their triplet state,[17] we envisioned that the organic light-emitting diode (OLED) materials would be suitable catalysts for catalytic energy transfer photoredox Minisci reactions. Herein, we reported an efficient CDC type Minisci reaction under an acid-free condition (Scheme 1d). It undergoes an energy transfer pathway enabled by using OLED materials as energy transfer catalyst for both *N*-heteroarenes and oxidants, and allows coupling between

Scheme 1. Visible-Light-Mediated CDC Minisci Reactions



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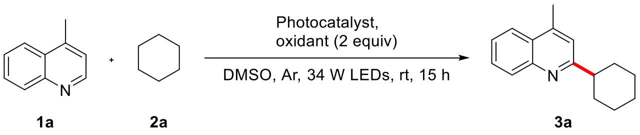
diverse C(sp^3)−H and *N*-heteroarenes using inexpensive inorganic oxidants.

2,4,5,6-Tetra(9H-carbazol-9-yl)isophthalonitrile (4-CzIPN), an important organic light-emitting diodes material with thermally activated delayed fluorescence, has emerged as a remarkable organic photocatalyst.[18] Since Zhang's dual catalytic C(sp^3)−C(sp^2) cross-coupling reaction, numerous reports have disclosed for the use of 4-CzIPN in photoredox catalysis process, including decarboxylative reactions,[18a] C−H activation,[19] etc.[20] Given the high energy of its triplet state (59.6 kcal/mol),[21] we envisioned that 4-CzIPN would be a potential energy transfer catalyst to replace diacetyl for activation of peroxides (average O−O bond energy:45 kcal/mol).[22] Thus, 4-CzIPN was selected as a catalyst for energy transfer and our initial study was conducted by reacting lepidine **1a** with cyclohexane **2a** at room temperature under the irradiation of 34 W 390 nm LED (Kessil, PR160,390 nm). Gratifyingly, 82% yield of **3a** was observed in the presence of $(NH_4)S_2O_8$ as oxidant after tedious optimization (Table 1, entry 1). To verify the energy transfer pathway, the addition of anthracene, a common triplet state quencher (ET = 42.6 kcal/mol),[23] completely shut down the transformation (entry 2), implying that the photocatalyst would enhance the efficiency for homolytic cleavage of O−O bond via triplet energy transfer. Replacement of 4-CzIPN with previous reported catalyst for energy transfer process, such as $Ir(ppy)_3$,[24a] Ir(dF-$Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$,[24b] $Ru(bpy)_3Cl_2{\cdot}6H_2O$,[24c] Eosin Y,[24d] and Rose Bengal,[24e] led to the decreasing yield (entries 3−7), which can be attributed to the appropriate energy transfer capacity of 4-CzIPN.[21,25] Furthermore, the yield of **3a** significantly decreased in absence of 4-CzIPN, illustrating the crucial role of 4-CzIPN (entry 8). Notably, reducing the catalyst loading to 0.01 mol % maintained the reaction efficiency, demonstrating the high energy transfer capacity of 4-CzIPN (entry 9). A thorough screening of diverse oxidants revealed that an inexpensive inorganic peroxides, $(NH_4)_2S_2O_8$, provided **3a** with best outcome (entries 1 vs 10−14). Surprisingly, other than previous reports, the addition of strong acid (trifluoroacetic acid) decreased the reactivity (entry 15). Further investigation of acidic conditions revealed that the addition of acid in our Minisci reaction system is not essential (entries 15−16). To test the influence of pH in the reaction, we monitored the pH during the reaction and found that the pH before the reaction is 6.8 and the pH after the reaction is 6.0. Besides, addition of base under standard conditions resulted in slight decrease yield (73% with 4 equiv of Cs_2CO_3, 78% with 4 equiv of 2,4,6-Collidine), supporting that the acidity is not crucial to enhance the electrophilicity of *N*-heteroarenes in this process (see the Supporting Information (SI), Table S4).

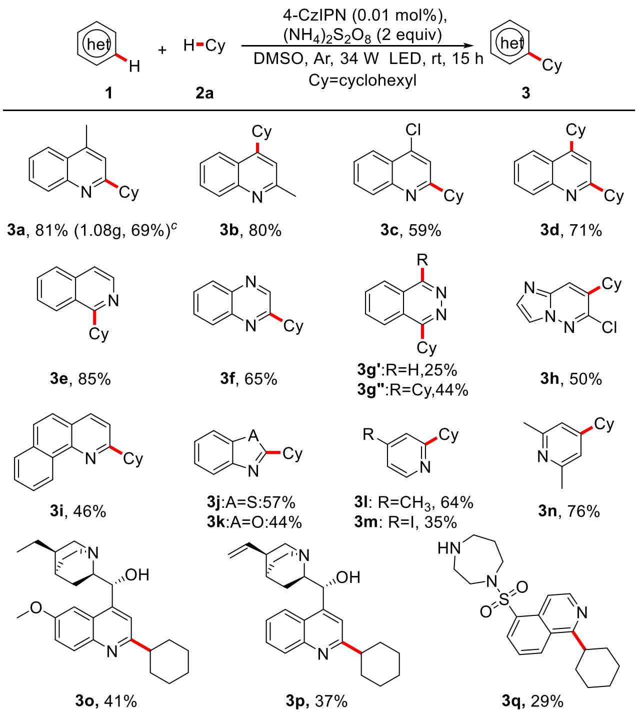
Table 1. Optimization of the Reaction Conditions[a]



entry	photocatalyst	oxidant	yield (%)[b]
1	4-CzIPN	$(NH_4)_2S_2O_8$	82
2[c]	4-CzIPN	$(NH_4)_2S_2O_8$	ND
3	$Ir(ppy)_3$	$(NH_4)_2S_2O_8$	22
4	$Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$	$(NH_4)_2S_2O_8$	77
5	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	$(NH_4)_2S_2O_8$	17
6	Eosin Y	$(NH_4)_2S_2O_8$	15
7	Rose Bengal	$(NH_4)_2S_2O_8$	6
8	−	$(NH_4)_2S_2O_8$	30
9[d]	4-CzIPN	$(NH_4)_2S_2O_8$	81
10	4-CzIPN	$Na_2S_2O_8$	29
11	4-CzIPN	$K_2S_2O_8$	31
12	4-CzIPN	TBHP	trace
13	4-CzIPN	DTBP	trace
14	4-CzIPN	PIFA	ND
15[e]	4-CzIPN	$(NH_4)_2S_2O_8$	39
16[f]	4-CzIPN	$(NH_4)_2S_2O_8$	80

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 mL), photocatalyst (0.5 mol %), oxidant (2 equiv), and DMSO (1.8 mL) under an argon atmosphere. [b]Isolated yields. [c]1 equiv of anthracene was added. [d]0.01 mol % photocatalyst. [e]Trifluoroacetic acid was added. [f]Acetic acid was added. DMSO = dimethyl sulfoxide. TBHP = 1,1-dimethylethyl-hydroperoxide, DTBP = di-*tert*-butyl peroxide. PIFA = phenyl-l3-iodanediyl bis(2,2,2-trifluoroacetate).

Scheme 2. Substrate Scope of *N*-Heteroarenes[a,b]

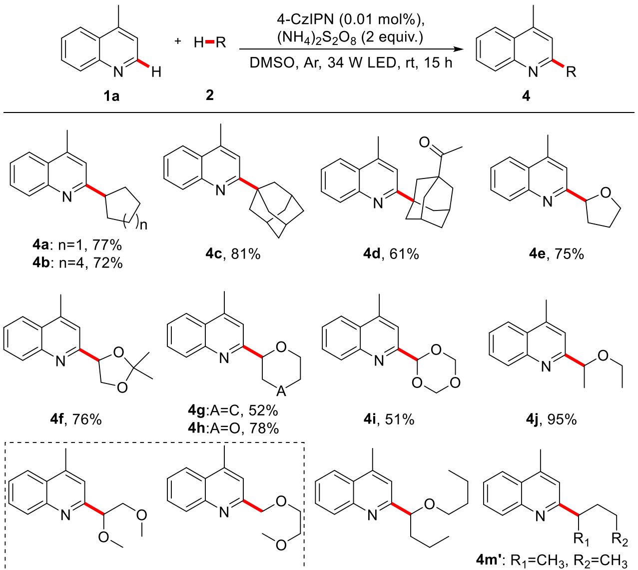


[a]Reaction conditions: **1** (0.1 mmol), **2a** (2 mL.), 4-CzIPN (0.01 mol %), $(NH_4)_2S_2O_8$ (2 equiv), and DMSO (1.8 mL) under blue LED irradiation under argon atmosphere for 15 h. [b]Isolated yield of the product. [c]**3a** (7 mmol), **2a** (140 mL), and DMSO (126 mL) was used.

With the optimal conditions in hand, we explored the reactivity of diverse *N*-heteroarenes (Scheme 2). Substituted quinolones were readily alkylated at the most electrophilic position with **2a** in moderate to good yields (**3a**−**3c**). Comparing electron deficient and electron neutral substrates, the former (**3c**) gave inferior yields as similar trends in most previous literatures.[4b,c,15gh] Quinoline only afforded dialkylated product **3d** in 71% yield. Moreover, other medicinal related *N*-heteroarenes including isoquinoline, quinoxaline, phthalazine and 6-chloroimidazo[1,2- b]pyridazine were viable substrates with good selectivities (**3e**−**3h**). Previous uninvestigated benzo[h]quinolone afforded only C2 product **3i**. Five membered fused heteroarenes are amenable to the alkylation as well (**3j**−**3k**). Further extension to challenging pyridine derivatives gave monoalkylated products **3l**−**3n** in regioselective manner. To prove the robustness of this protocol, we applied this protocol to late-stage functionalization of agrochemical and pharmaceutical agents. Hydroquinine, cinchonine and fasudil underwent this CDC alkylation process smoothly, providing **3o**, **3p** and **3q** in 41%, 37% and 29% yields, respectively. Furthermore, a gram-scaled reaction by reacting 1.0 g of **1a** (7 mmol) with cyclohexane afforded **3a** (1.08 g) in 69% yield with 27% recovery of **1a**.

Next, diverse C(sp^3)−H sources were subjected to the standard conditions (Scheme 3). Cycloalkanes underwent the Minisci reaction smoothly with **1a**, providing **4a** and **4b**. Given that the rigid caged structure of adamantane leads to an increased 3 °C−H bond dissociation energy (BDE) of 99 kcal/mol over the 2° C−H BDE of 96 kcal/mol,[26] it is unexpected to observed that the CDC process occurred at 3° C−H bond of both adamantane and adamantanyl ketone in a regioselective manner (**4c** and **4d**). Compared to the recent works,[27] it demonstrates that our visible light catalytic system would be an alternative inexpensive strategy for selective functionalization of adamantane derivatives, the unique structure and chemical properties of which have led to many applications in nanoscale frameworks, optical materials, and clinically approved drugs (e.g., memantine, antidementia).[28] Further extension of this protocol to ethers also gave desired products **4e**−**4l** in moderate to excellent yields. Notably, *s*-trioxane failed to react with **1a** under acid conditions (Table 1, entries 15−16) owing to its instability in the presence of acids. In the case of 1, 2-dimethoxy ethane the arylation takes place at two positions, viz., methylene C−H and methoxy C−H, to give isomers **4k′** and **4k″** were in a total yield of 63%, in a ratio of 2:1. Alkylation of linear alkanes only occurred at the methylene group, providing products **4m′** and **4m″** in a ratio of 5:4.

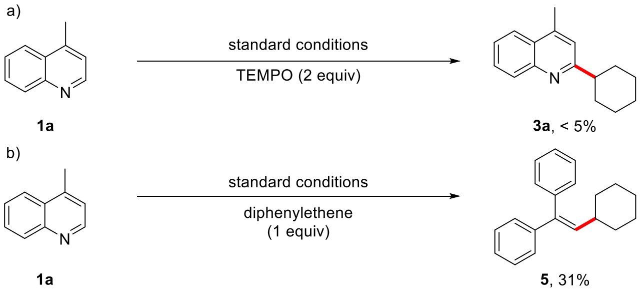
Scheme 3. Substrate Scope of Diverse C(sp^3)−H Sources[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (2 mL.), 4-CzIPN (0.01 mol %), $(NH_4)_2S_2O_8$ (2 equiv), and DMSO (1.8 mL) under blue LED irradiation under argon atmosphere for 15 h. [b]Isolated yield of the product.

To gain insight into the reaction mechanism, we conducted a series of experiments. First, a light on/off experiment demonstrated that the transformation needed continuous irradiation of visible light (see the SI, Scheme S1). The radical scavenger, 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), inhibited the alkylation process and allowed more than 95% recovery of the starting materials, implying a single electron transfer (SET) process (Scheme 4). Radical capture reaction with diphenylethene revealed the generation of cyclohexyl radical during the process (Scheme 4).

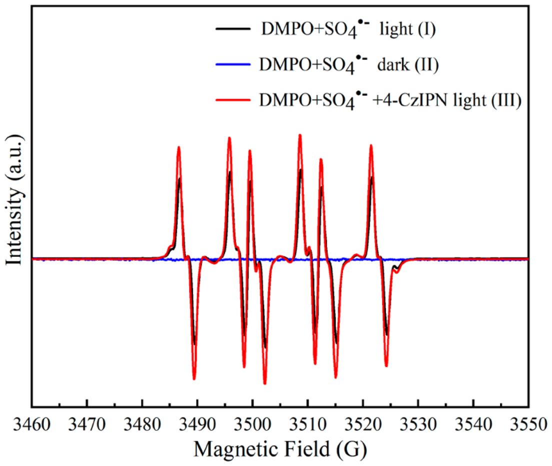
Scheme 4. Cyclohexyl Radical Capture Experiments



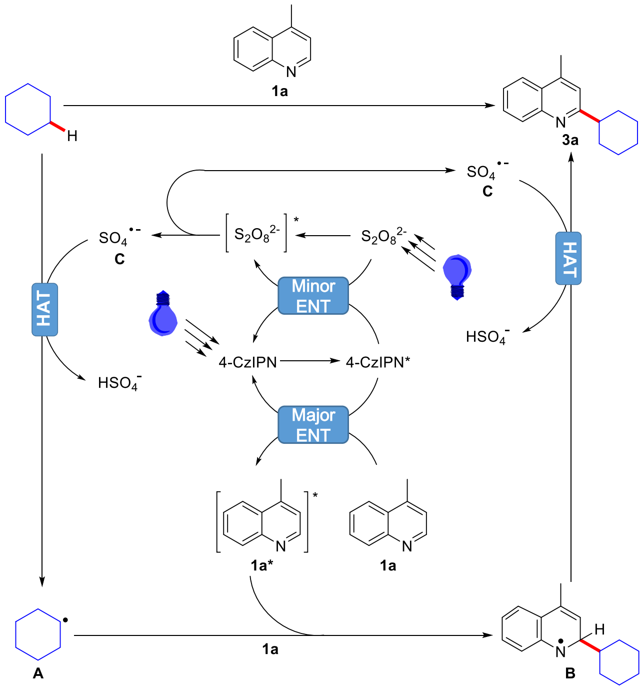
Furthermore, the reaction vanished in the absence of oxidants even with larger loadings of photocatalyst (see the SI, Table S2, entry 2). However, the Minisci reaction of **1a** and **2a** resulted in successful alkylation of **1a** (Table 1, entry 8). These results together with the inhibition test by anthracene (Table 1, entry 2) imply that 4-CzIPN is an energy transfer catalyst rather than a photoredox catalyst for the redox process and hydrogen abstraction. This hypothesis is further confirmed by the redox potential of **B** and 4-CzIPN. As the reaction undergoes acid-free conditions, the intermediates and plausible pathway would be distinct from the previous reports.[24b24c] In a previous reported mechanism, **B** is normally protonated for a further redox process owing to an acid additive. However, in this acid-free conditions, in either the photoredox catalysis pathway or energy transfer routine, **B** is in its neutral form. The oxidation potential of **B** can be estimated using literature data ($E_{p/2}^{red}$ = −1.19 V vs SCE).[29] The lower reduction potential of 4-CzIPN ($E_{p/2}^{red}$ = −1.22 V vs SCE) over the complex **B** suggests that the oxidation of radical **B** to produce **3a** with 4-CzIPN is thermodynamically unfavorable. Additionally, given the common O−O bond energy of 45 kcal/mol,[25] the energy of the triplet state of *4-CzIPN (ET > 59 kcal/mol)[21] is sufficient for homolytic cleavage of the O−O bond in persulfate *via* energy transfer, and the resulting sulfate radical would be the hydrogen abstractor for alkanes [$O_3SO{-}H^-$ BDE = 105.0 kcal mol^{-1} versus C(sp^3)−H of cyclohexane BDE = 100.0 kcal mol^{-1}].[30]

On the other hand, we conducted a series electron paramagnetic resonance experiments between persulfate and 4-CzIPN including $(NH_4)_2S_2O_8$/5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) under irradiation (I), $(NH_4)_2S_2O_8$/DMPO without irr-adiation (II) and $(NH_4)_2S_2O_8$/DMPO/4-CzIPN under irradiation (III) (Scheme 5). DMPO trapped sulfate radical signals (DMPO−$SO_4^{\bullet-}$ with hyperfine splitting constants of α_N = 13.2 G, α_H = 9.6 G, α_H = 1.48 G, and α_H = 0.78 G)[31] appeared in both I and III, while the signal vanished without irradiation (II). These results suggest the

Scheme 5. Electron Paramagnetic Resonance Experiments



Scheme 6. Proposed Reaction Pathway



irradiation is crucial for generation of the sulfate radical. In comparison with I, addition of 4-CzIPN to the mixture of $(NH_4)_2S_2O_8$ and DMPO (III) afforded only slightly enhanced characteristic signals of DMPO−$SO_4^{\bullet-}$ and no other signals of SET products from 4-CzIPN was detected, indicating the interaction between 4-CzIPN and persulfate is mainly an energy transfer process rather than an SET pathway. Besides, Stern−Volmer experiments showed that $(NH_4)_2S_2O_8$ and lepidine **1a** can quench 4-CzIPN independently (Schemes S8 and S10), indicating two plausible energy transfer pathways for 4-CzIPN. When both S−V experiments are compared, the slope of the quenching curves between 4-CzIPN and lepidine (0.28) is significantly larger than that of $(NH_4)_2S_2O_8$ (0.038) and the quenching with lepidine occurred at a rather lower concentration (0.2 mM) than that of persulfate (2 mM). These results suggest the energy transfer between 4-CzIPN and lepidine is more effective and a major energy transfer route for 4-CzIPN, which provides another plausible energy transfer route from catalyst to heteroarenes and an alternative activation mode for **1a** instead of acid addition.

Additionally, prominent primary kinetic isotope effects (KIE) were observed through both the intermolecular and parallel competition with a KIE factor of 6.1 and 6.8, respectively, suggesting that the C−H activation is the rate-determining step (see SI, Schemes S4 and S5).[32]

Based on previous literature,[16f,g,17a] and our results, a plausible mechanism for the CDC reaction through a photocatalytic energy transfer pathway has been proposed (Scheme 6). Initially, a minor energy transfer from the excited state of photocatalyst (4-CzIPN*) to $(NH_4)_2S_2O_8$ together with direct irradiation of $(NH_4)_2S_2O_8$ results in homolysis of peroxydisulfate into 2 equiv of the sulfate radical **C**. **C** abstracts a hydrogen atom from the cyclohexane to form the cyclohexyl radical **A**. Meanwhile, 4-CzIPN* undergoes an energy transfer path to generate **1a***, which reacts with **A** to form intermediate adduct radical **B**. Finally, sulfate radical **C** abstracts a hydrogen atom from the radical **B**, affording the CDC product **3a**.

In summary, we have developed a visible-light-induced energy transfer strategy using catalytic organic photosensitizers for CDC-type Minisci reactions. These acid-free Minisci reactions bear high atom and step economy and good functional group compatibility and require low loadings of catalyst. Mechanistic investigation suggests that the photocatalyst in the reaction would likely undergo an energy transfer pathway to mainly activate *N*-heteroarenes to enhance the radical trapping. These results would inspire further exploration of photocatalytic transformations via triplet energy transfer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02912.

Experimental details, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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