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Letter

Photoredox-Catalyzed α-C(sp^3)−H Activation of Unprotected Secondary Amines: Facile Access to 1,4-Dicarbonyl Compounds

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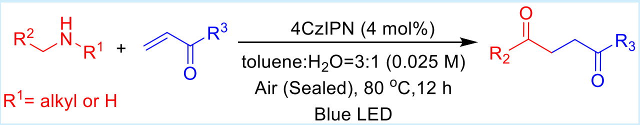
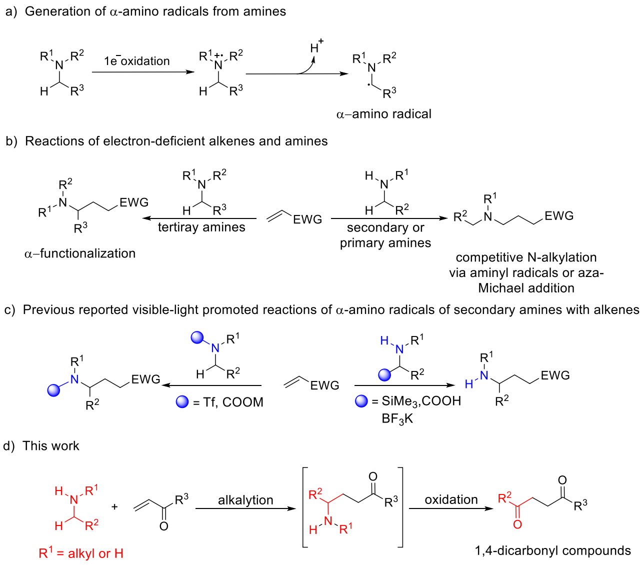
ABSTRACT: A photoredox-catalyzed α-C(sp^3)−H activation approach of unprotected secondary amines is reported. Such transformations provide facile access to various 1,4-dicarbonyl compounds using readily available amines and α,β-unsaturated compounds as feedstocks under air conditions. The substrate scope of this method is broad, and a wide array of functional groups are tolerated.



Photoredox-catalyzed functionalization of the α-C(sp^3)−H bond of amines through highly reactive α-amino radical intermediates has received considerable attention as an efficient and straightforward way to construct C−C bonds.[1] One particularly intriguing transformation is the visible-light-mediated addition of α-amino radicals to electron-deficient alkenes to provide γ-aminocarbonyl or other useful skeletons.[1d] However, the reported approaches are mainly limited to tertiary amine derivates due to the easy formation of α-amino radicals by the single electron oxidation (Scheme 1a).[2] Competitive *N*-alkylation products were usually observed for unprotected primary and secondary amines, due to the generation of aminyl radicals[3] or direct aza-Michael addition (Scheme 1b).[4] In 1994, Das and co-workers[5] reported the addition of α-amino radicals from primary and secondary amines to α,β-unsaturated esters under irradiation of a 450 W medium pressure mercury lamp. Nevertheless, only limited substrates gave desired products in low conversions and yields. To realize the α-C(sp^3)−H alkylation of primary and secondary amines, methods employing amines with preinstalled cleavable groups at the α-position[6] and protected groups[7] were developed (Scheme 1c). Recently, Cresswell and co-workers reported an elegant C−H alkylation of unmasked α-tertiary primary amine through the combination of photoredox and hydrogen-atom-transfer catalysis.[8] However, direct radical addition of unprotected secondary amines to electron-deficient akenes remains a challenge.

Scheme 1. α-C(sp^3)−H Alkylation of Amines via α-Amino Radical Intermediates



1,4-Dicarbonyl compounds are useful synthetic intermediates in organic synthesis.[9] Although tremendous efforts have been made to construct these skeletons, greener and efficient methods are still desirable.[10] Visible-light-induced oxidative C−N bond cleavage of amines to produce carbonyl compounds through iminium ion intermediates has been disclosed.[11] In this regard, we envisioned that γ-aminocarbonyl compounds generated from the addition of α-amino radicals to α,β-unsaturated esters could be oxidized to 1,4-dicarbonyl compounds under photoredox conditions. Thus, the radical addition process may be promoted by introducing external oxidants to transfer γ-aminocarbonyl products to 1,4-dicarbonyl compounds (Scheme 1d). To this end, the oxidation of initial primary and secondary amines to iminium ions ought to be avoided. Herein, we described here the successful realization of tandem addition of α-amino radicals derived from unprotected primary and secondary amines to

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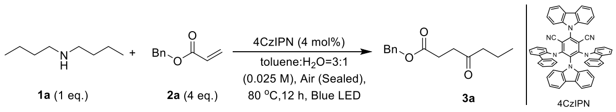
α,β-unsaturated esters and oxidation of γ-aminocarbonyl intermediates providing 1,4-dicarbonyl compounds using oxygen as the oxidant under photoredox conditions.

We initially carried out the transformation using dibutylamine (**1a**) and benzyl acrylate (**2a**) as substrates under blue LED irradiation. After extensive investigation (Scheme 2), we found that using 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN, 4 mol %) as the photoredox catalyst in the mixture solution of toluene and H_2O (3:1) under an air (sealed) atmosphere at 80 °C provided the optimal result, affording benzyl 4-oxoheptanoate (**3a**) in 82% yield (entry 1). No product was obtained employing $Ru(bpy)_3(PF_6)_2$ as the photocatalyst (entry 2). And using $Ir[df(CF_3)ppy]_2(dtbbpy)PF_6$ instead of 4CzIPN afforded a lower yield (entry 3). Using toluene as the solvent gave **3a** in 30% yield indicating that the addition of H_2O is essential (entry 4). Switching the reaction solvent from toluene/H_2O to CH_3CN/H_2O and CH_2Cl_2/H_2O delivered products in decreased yield (entries 5 and 6). When the concentration of **1a** was increased from 0.025 to 0.05 M, the yield of product **3a** decreased to 10% (entry 7). Subsequently, using 1 equiv of K_2CO_3 or Cs_2CO_3 as the additive resulted in lower yields (entries 8 and 9). When the reaction was carried out using 2 equiv of **2a** or at lower temperature, a lower yield was obtained (entries 10 and 11). Notably, the product **3a** was afforded in only 28% yield employing O_2 instead of air, suggesting that the amount of O_2 is of importance in this system. We reasoned that excessive oxygen may lead to C−N bond cleavage of **1a**. The control experiments indicated that photocatalyst and light irradiation are both critical for the reaction (entries 13 and 14).

Scheme 2. Reaction Optimization[a]

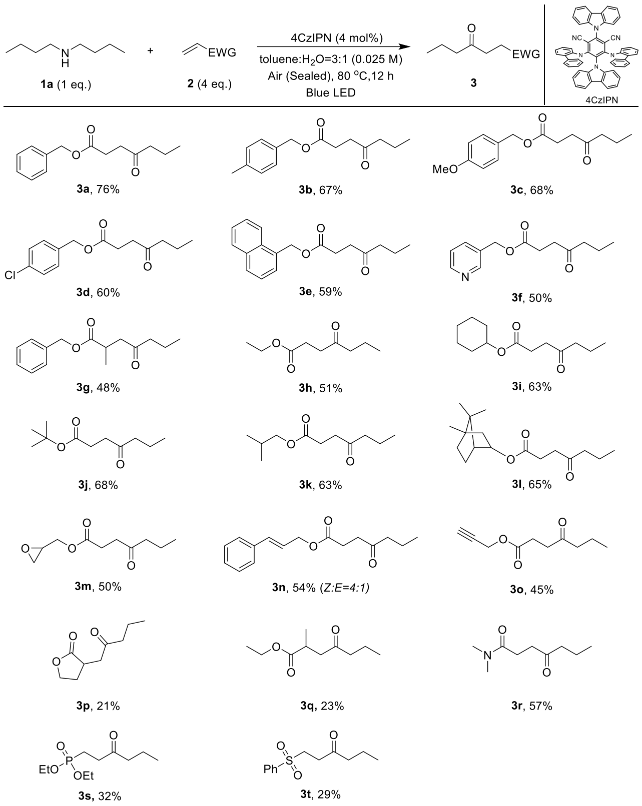


entry	deviation	Yield[b] (%)
1	none	82 (76[c])
2	$Ru(bpy)_3(PF_6)_2$ instead of 4CzIPN	0
3	$Ir[df(CF_3)ppy]_2(dtbbpy)PF_6$ instead of 4CzIPN	26
4	toluene as the solvent	30
5	CH_3CN/H_2O (3:1) as the solvent	66
6	CH_2Cl_2/H_2O (3:1) as the solvent	55
7	0.05 M instead of 0.025 M	10
8	K_2CO_3 as the additive	68
9	Cs_2CO_3 as the additive	46
10	using 2 eq. **2a**	45
11	40 °C instead of 80 °C	56
12	O_2 instead of air	28
13	Without 4CzIPN	0
14	Without light	0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.4 mmol), 4CzIPN (4 mol %), toluene:H_2O (3 mL/1 mL), blue LED, Air (Sealed), 80 °C, 12 h. [b] Yields determined by ^1H NMR spectroscopy using trimethoxybenzene as an internal standard. [c] Isolated yield.

With the optimal conditions in hand, the substrate scope of alkenes was investigated (Scheme 3). As shown in Scheme 3, benzyl acrylates bearing different functional groups on aromatic rings were effective to afford products in good yields (**3b**−**3d**). Naphthalen-1-ylmethyl acrylate (**3e**) and pyridin-3-ylmethyl acrylate (**3f**) were also accommodated. In addition, the 1,1-disubstituted acrylates could be used to deliver product **3g** in 48% yield and **3q** in 23% yield. Moreover, simple alkyl acrylates were suitable substrates (**3h**−**3l**), and functional groups such as epoxide (**3m**), alkenes (**3n**), and alkynes (**3o**) moieties were tolerated. Lactones (**3p**) were compatible affording the corresponding products in moderate yield. Intriguingly, acrylamide (**3r**), vinylphosphonate (**3s**), and vinylsulfone (**3t**) underwent the reaction smoothly to deliver desired products.

Scheme 3. Substrate Scope of Alkenes[a]

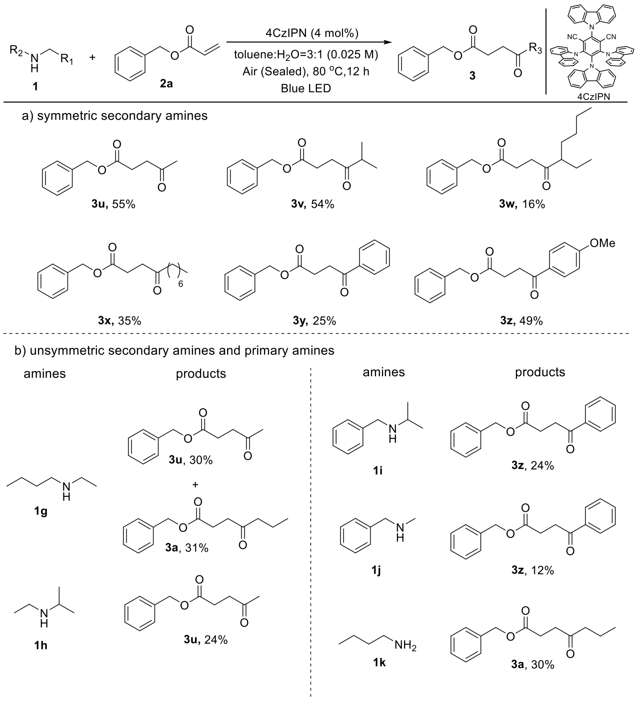


[a] The standard reaction condition, isolated yields.

We next investigated the substrate scope of amines with benzyl acrylate as the partner (Scheme 4). As shown in Scheme 4, employing symmetric aliphatic secondary amines, such as diethylamine, diisobutylamine, bis(2-ethylhexyl)amine, dioctylamine, dibenzylamine, and bis(4-methoxybenzyl)amine, gave desired products in moderate to good yields (**3u**−**3z**). The mixture of **3u** and **3a** was obtained employing *N*-ethylbutan-1-amine as the substrate, due to the existence of two reactive α positions. Interestingly, using isopropyl (**1h** and **1i**) or methyl (**1j**) substituted amines, the reaction proceeded with good regioselectivity. We reasoned that steric hindrance of isopropyl and instability of methyl radical may suppress the alkylation of the corresponding α-C(sp^3)−H site. Finally, a primary amine (**1k**) was subjected to the reaction providing corresponding product **3a** in a 30% yield, demonstrating the broad substrates scope of the system.

Various control experiments were conducted to understand the reaction mechanism. Based on the result of Stern−Volmer quenching studies, the excited photocatalyst [$E_{1/2}$(*P/P$^-$) = +1.35 V vs SCE in MeCN][12] could be quenched by dibutylamine (E_p = 1.09 V vs SCE in MeCN, Figure S3).

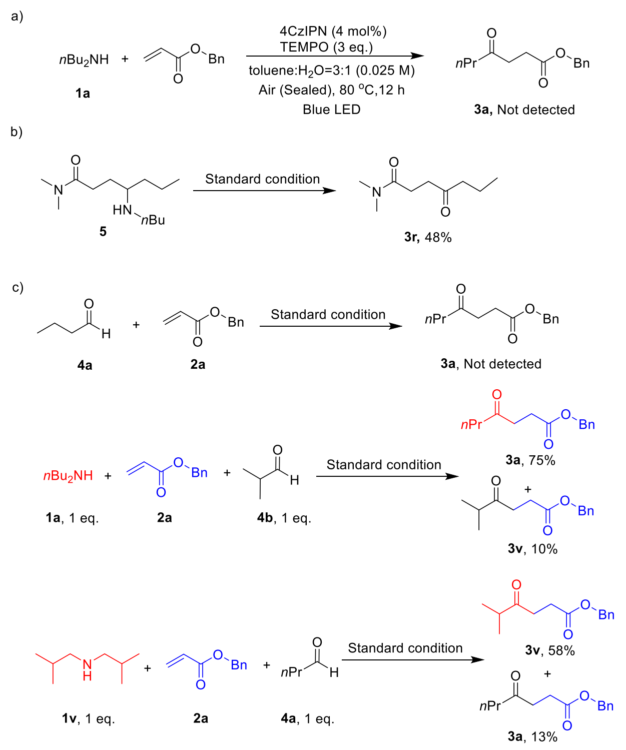
Scheme 4. (a) Scope of Symmetric Secondary Amines; (b) Scope of Unsymmetric Secondary Amines and Primary Amines[a]



[a]The standard reaction condition, isolated yields.

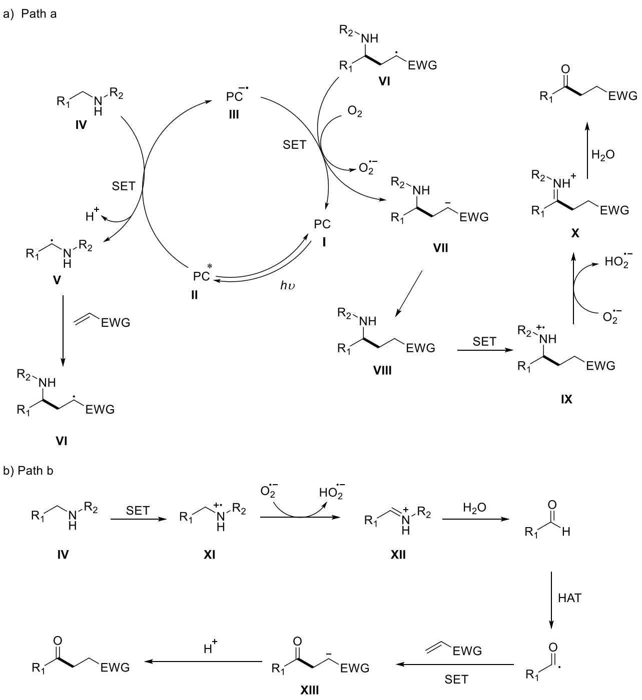
The formation of **3a** was completely inhibited using TEMPO as the additive, suggesting that radical intermediates were generated during the transformation (Scheme 5a). The postulated intermediate 4-(butylamino)-*N*,*N*-dimethylheptanamide (**5**) was synthesized and subjected to the standard conditions, giving desired 1,4-dicarbonyl compounds (**3r**) in 48% yield (Scheme 5b). Secondary and primary amines could be oxidized easily to generate aldehydes in the presence of oxidants under photoredox conditions.[11] And the addition of acyl radical from aldehydes to electron-deficient alkenes has been developed.[13] Performing the reaction of **1a** in the presence of aldehydes (**4b**) under standard reaction conditions afforded **3a** and **3v** in 75% and 10% yields, respectively (Scheme 5c). Conversely, adding **4a** to the reaction of **1v** afforded **3v** and **3a** in 58% and 13% yields (Scheme 5c). The results of these two crossover experiments suggested that aldehydes derived from direct oxidation of started amines may contribute to the formation of 1,4-dicarbonyl compounds. However, according to the ratios of **3a** and **3v**, the reaction mainly went through *γ*-aminocarbonyl intermediates, rather than aldehydes. In addition, **3a** was not obtained when we used the butyraldehyde (**4a**) as the substrate instead of dibutylamine, indicating that the addition of the aldehydes to alkenes could not occur without the amines (Scheme 5c).

Scheme 5. Control Experiments



Based on the aforementioned control experiments, we propose a plausible mechanism for the transformation of unprotected primary and secondary amines to 1,4-dicarbonyl compounds under photoredox conditions (Scheme 6). The exited-state 4CzIPN (**II**) can be reduced by the amine (**IV**) to afford the *α*-amino radical (**V**). Addition of **V** to the electron-deficient alkene gives rise to a radical adduct (**VI**). Subsequent reduction of adduct (**VI**) and protonation of **VII** affords the *γ*-aminocarbonyl intermediate (**VIII**) which can be oxidized to generate (**IX**). Oxygen in the system can also oxidize **III** to **I** and deliver oxygen radical anion species. Hydrogen atom transfer from **IX** to oxygen radical anion provides an iminium ion (**X**). Finally, hydrolysis of **X** occurs to furnish the 1,4-dicarbonyl compound. The direct oxidation of started amines to aldehydes and subsequent radical addition of acyl radical

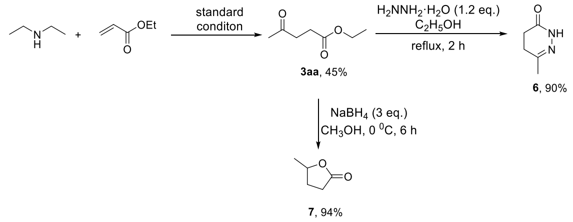
Scheme 6. Proposed Mechanism



from aldehydes to electron-deficient alkenes may be the minor pathway of the process (Scheme 6b).

To demonstrate the importance and utility of this method, transformations of ethyl 4-oxopentanoate (**3aa**) to 4,5-dihydropyridazin-3(2*H*)-one (**6**) and 5-methyldihydrofuran-2(3*H*)-one (**7**) were conducted, giving desired products in good yields (Scheme 7).

Scheme 7. Transformations of 1,4-Dicarbonyl Compounds



In summary, we have developed a visible-light-driven $C(sp^3)$−H activation strategy to realize direct radical addition of unprotected secondary and primary amines to electron-deficient alkenes. This work represents a rare example of visible-light-promoted direct functionalization of α-$C(sp^3)$−H of unmasked secondary amines. This protocol provides a novel access to important 1,4-dicarbonyl compounds. Moreover, the substrate scope of this method is broad and a wide array of functional groups are tolerated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02571.

Experimental procedures, detailed mechanistic studies, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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