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Research Article

Carbene-Catalyzed Alkylation of Carboxylic Esters via Direct Photoexcitation of Acyl Azolium Intermediates

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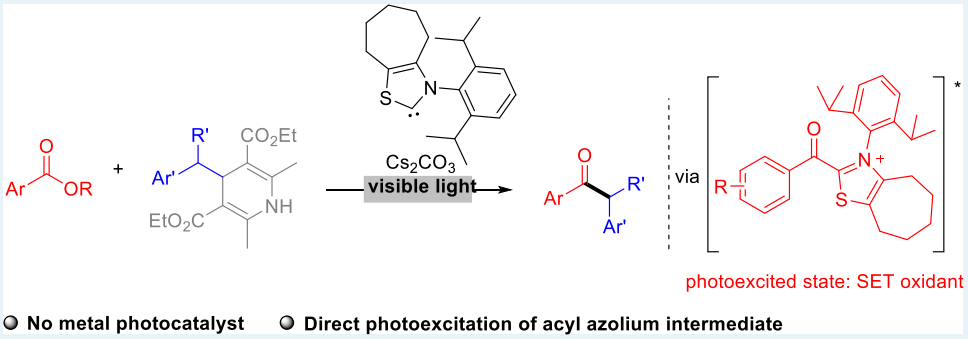

ABSTRACT: A carbene-catalyzed reductive coupling reaction of carboxylic esters and substituted Hantzsch esters is disclosed. Key steps of this reaction include one-electron reduction of a carbene catalyst-bound acyl azolium intermediate to generate the corresponding radical intermediate for subsequent alkylation reactions. The reaction is promoted by irradiation with visible light without the involvement of transition-metal photocatalysts. Mechanistic studies suggest that direct photoexcitation of the in situ formed acyl azolium intermediate is likely responsible for this light-induced one-electron-reduction process. Photoexcitation converts the acyl azolium intermediate to a single-electron oxidant, enabling single-electron oxidation of Hantzsch esters to generate radical intermediates. Our reactions work well for a broad range of aryl carboxylic ester and Hantzsch ester substrates. Sophisticated structures, including those present in medicines, can be incorporated into ketone molecules using our approach via very mild conditions that tolerate various functional groups.

KEYWORDS: *N-heterocyclic carbene, reductive-radical-coupling reaction, acyl azolium, photocatalyst-free, ketone synthesis*

Carboxylic esters and related carbonyl compounds are basic building blocks and ubiquitous functional groups in natural and non-natural molecules. The use of N-heterocyclic carbenes (NHCs) as organic catalysts has been proved effective in activating this class of molecules for diverse transformations.[1] Traditionally, NHC-catalyzed reactions are designed based (or assumed to be based) on electron-pair transfers as the key reaction steps.[1] In recent years, single-electron-transfer radical reactions mediated by NHCs have received increasing attention, in part, due to their potential to cover a broader range of substrates including otherwise inert molecules.[2] Till this point, the reported NHC-mediated radical reactions are mainly based on single-electron oxidation of aldehyde-derived Breslow acyl anion intermediates for further reactions, as developed by Scheidt,[3] Studer,[4] our own laboratory,[5] Rovis,[6] Sun,[7] Ye,[8] Ohmiya,[9] and a few others[10] (Figure 1a). In contrast, single-electron reduction of NHC-bound azolium ester intermediates for radical reactions remains less explored. (Figure 1a). Recently, Scheidt reported NHC-mediated photoredox coupling of acyl imidazoles and Hantzsch esters to form ketones in the presence of an Ir(III) catalyst (Figure 1b).[11] Key steps in Scheidt's approach involved an Ir(III) complex photocatalyst and light-promoted generation of alkyl radical intermediates from the Hantzsch ester substrates and single-electron reduction of the acyl azolium intermediate to form acyl azolium radical intermediates enabled by the in situ-generated Ir(II) complex (Figure 1b). Around the same period, Studer reported NHC-mediated three-component coupling of acyl fluorides, alkenes, and Langlois reagent, in which the iridium photocatalyst-mediated one-electron reduction of the NHC-bound acyl azolium intermediate was postulated as a key step (Figure 1b).[11b]

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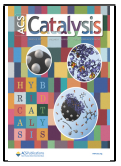

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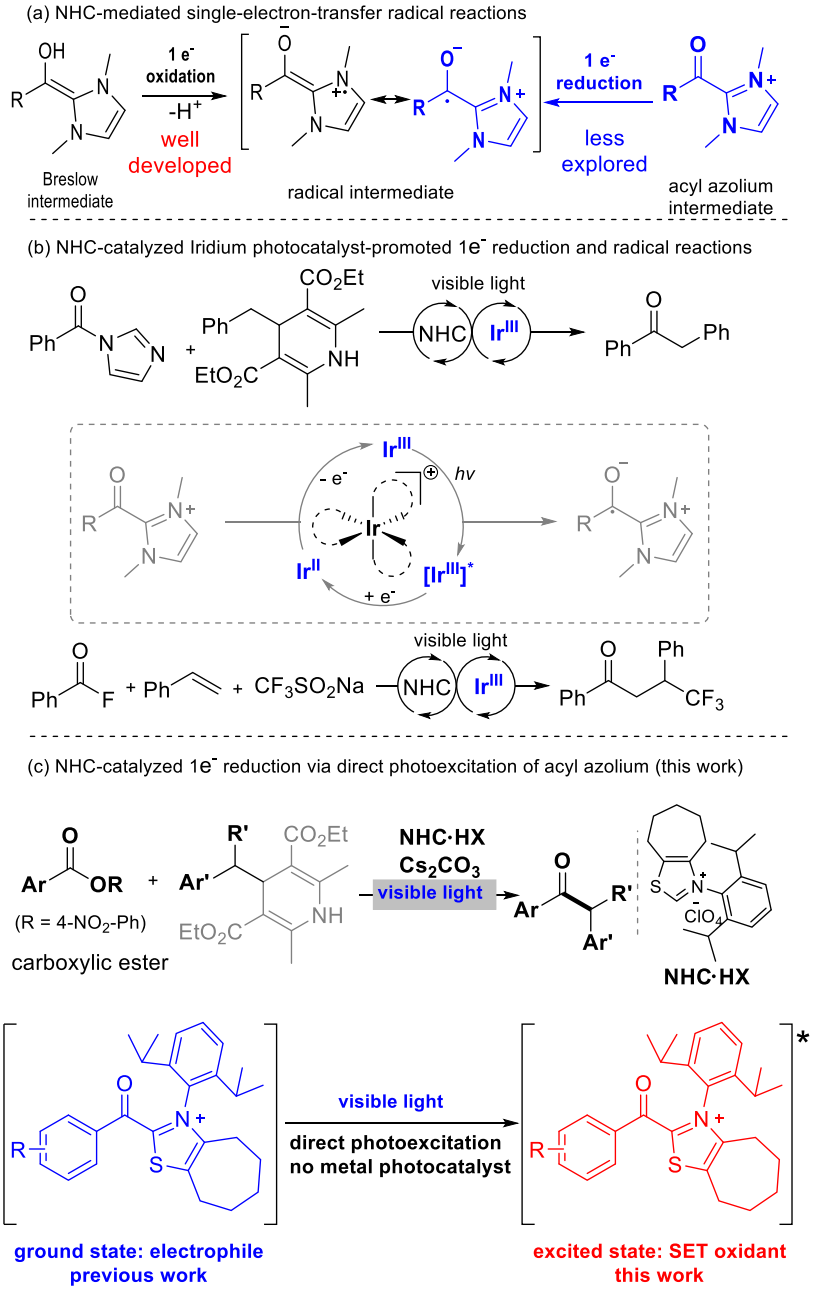

Figure 1. Approaches of NHC-mediated radical reactions.

Our entry to this objective of one-electron reduction of an NHC-bound acyl azolium intermediate (Figure 1a, right part) was, in part, inspired by the tremendous success in the area of light-induced photocatalyst-free reactions that proceed via electron donor–acceptor (EDA) complex pathways[12,13] or direct photoexcitation of organic molecules/intermediates.[14] In particular, direct photoexcitation can convert organic molecules/intermediates to the corresponding single-electron-transfer reductants or oxidants. For example, Melchiorre and coworkers reported direct photoexcitation of an electron-deficient iminium ion for enantioselective β-alkylation of enals, in which the excited state of the iminium ion acts as a strong oxidant that removes an electron from Hantzsch ester.[14d] The excited states of electron-rich imines, Hantzsch esters, and alkylborates have also been utilized as single-electron reductants by the Melchiorre[14] and Ohmiya group.[14i]

As important intermediates in NHC catalysis, acyl azolium intermediates have found wide application in catalytic organic reactions.[1] Here, we disclose that under the influence of visible light and the NHC catalyst, aryl carboxylic esters can couple with Hantzsch esters to form ketone products (Figure 1c). Unlike the studies from Scheidt[11a] and Studer,[11b] our reaction proceeds without the involvement of iridium or other metal complexes as the photoredox catalysts. Mechanistic studies suggest that direct photoexcitation of an electron-deficient acyl azolium intermediate is likely responsible for its one-electron reduction to generate the corresponding radical intermediate. Specifically, photoexcitation converts the acyl azolium intermediate to its excited state and thus acts as a single-electron oxidant to trigger the single-electron-transfer process with the electron-rich Hantzsch ester substrate.

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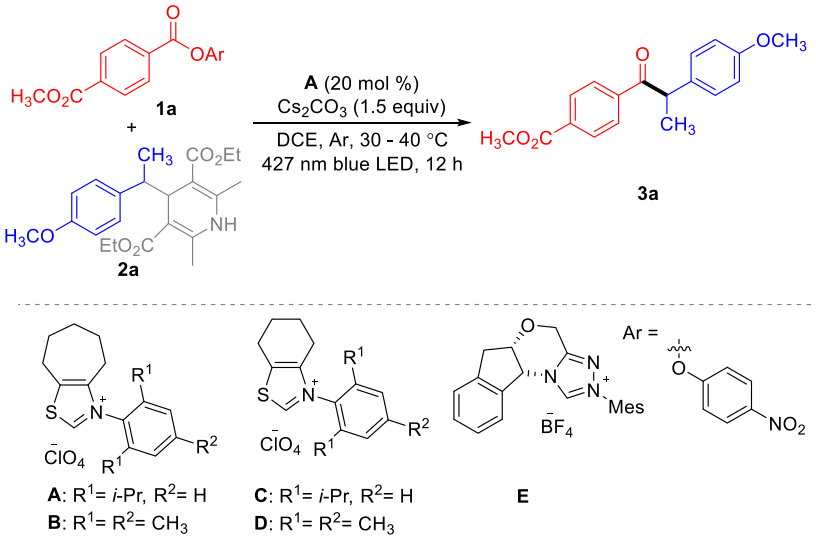
Table 1. Condition Optimization[a]



entry	variation from standard conditions	yield [%][b]
1	none	70 (68)[c]
2	0.2 equiv Cs_2CO_3	0
3	0.5 equiv Cs_2CO_3	22
4	K_2CO_3, Li_2CO_3, and Na_2CO_3 instead of Cs_2CO_3	0−trace
5	K_2CO_3, Li_2CO_3, Na_2CO_3, and CH_3CN as a solvent	2−30
6	K_2CO_3 and acetone as a solvent	16
7	DBU, DMAP, DIPEA, and DABCO instead of Cs_2CO_3	0
8	*t*-BuONa instead of Cs_2CO_3	14
9	**B** instead of **A**	32
10	**C** instead of **A**	40
11	**D** instead of **A**	24
12	**E** instead of **A**	trace
13	440, 456, and 467 nm instead of 427 nm	66−69
14	400 nm instead of 427 nm	0
15	without the NHC catalyst	0
16	without light irradiation (in dark), rt	0
17	without light irradiation (in dark), 80 °C	0

[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), **A** (20 mol %), and Cs_2CO_3 (1.5 equiv) in DCE (1.5 mL), blue LED (Kessil PR160 series, λ_{max} = 427 nm), Ar, 30−40 °C, and 12 h. [b]Nuclear magnetic resonance (NMR) yield using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield is shown in parentheses.

We started to search for suitable radical coupling conditions using 4-nitrophenyl carboxylic ester (**1a**),[15] a readily available and stable acyl azolium precursor, and Hantzsch ester (**2a**)[16] as the model substrate to form ketone product **3a** (Table 1). One acceptable condition that led to the formation of **3a** in 68% yield involved the use of azolium **A**[9,16] as the NHC precatalyst (20 mol %), Cs_2CO_3 as a base (150 mol %), and blue light-emitting diode (LED) (λ_{max} = 427 nm) as the visible-light source (entry 1). The amount of Cs_2CO_3 was found to be important, as decreasing its loading from 150 to 20 or 50 mol % led to dramatic losses on reaction yields (entries 2 and 3). Under the condition with 1,2-dichloroethane (DCE) as the solvent, the use of K_2CO_3, Li_2CO_3, or Na_2CO_3 as the carbonate sources led to little formation of the ketone product, presumably due to the low solubilities of these bases in DCE (entry 4). The desired radical coupling reaction under these carbonates could be partially restored when DCE was replaced by CH_3CN or acetone as the solvent (entries 5 and 6). Replacing the carbonates with organic bases [such as 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 4-Dimethylaminopyridine (DMAP), N, N-Diisopropylethylamine (DIPEA), and Triethylenediamine (DABCO)] led to no formation of **3a** (entry 7). The use of *t*-BuONa as the base gave **3a** in 14% yield (entry 8). The steric and electronic natures of the NHC catalysts have a clear influence on the reaction outcomes (entries 9−12).[9] Additionally, the influence of the illumination wavelength was explored. The reactions, under irradiation of different sources of visible light (λ_{max} = 440, 456, and 467 nm) gave similar yields with that at 427 nm (entry 13). In contrast, LEDs (λ_{max} = 400 nm) resulted in no product (entry 14). No coupling reactions were observed in the absence of light or the NHC precatalyst (entries 15−17).

With optimized conditions in hand, we set out to investigate the generality of this NHC-catalyzed light-induced alkylation reaction (Tables 2 and 3).

We first evaluated the scope of 4-nitrophenyl carboxylic esters (Table 2). Various substituents on the aryl ring of the ester substrates, such as halogen atoms (**3b**−**3e**), trifluoromethyl (**3h**), and cyano (**3f**) units, were all tolerated to give the corresponding ketone products with moderate to good yields. It is worth noting that due to the mild coupling conditions, functional groups (such as esters and ketone

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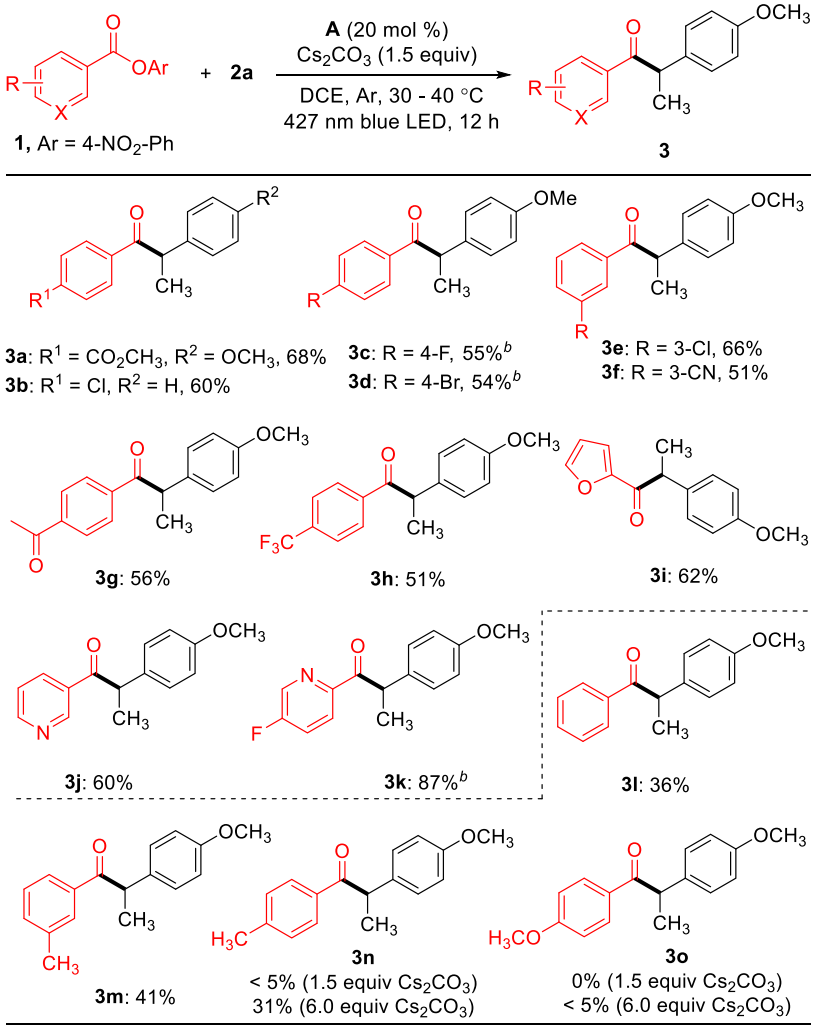
Table 2. Scope of Carboxylic Esters[a]



[a]Reaction conditions: **2** (0.1−0.2 mmol), **1** (2.0 equiv), **A** (20 mol %), and Cs_2CO_3 (1.5 equiv) in 1,2-dichloroethane (1.5 mL), blue LED (Kessil PR160 series, λ_{max} = 427 nm), Ar atmosphere, 30−40 °C, and 12 h. [b]4.0 equiv of Cs_2CO_3 was used.

moieties) typically incompatible with a traditional ketone synthesis method such as Grignard reactions were well tolerated in our approach (**3a** and **3g**). Heteroaryl carboxylic esters were effective substrates as well (**3i**−**3k**). The electronic property and the substitution patterns of the substituents on a benzene ring have a considerable influence on the reaction outcomes. The use of benzoic ester (with an unsubstituted benzene ring) could give the corresponding ketone product **3l** in an encouraging yield. Placing a methyl substituent on the *meta*-carbon of the benzene ring led to **3m** with 41% yield. However, when the electron-releasing methyl substituent was placed on the *para*-carbon of the benzene ring of the ester (**3n**), a sharp drop in the reaction yield (<5%) was observed with the use of the standard condition (1.5 equiv of Cs_2CO_3). To our delight, the yield could be improved to 31% yield when a large excess of Cs_2CO_3 (6.0 equiv) was used. The reason regarding the beneficial effects from excess Cs_2CO_3 remains unclear at this point. Replacing the methyl substituent with a stronger electron-releasing methoxyl (CH_3O−) unit led to nearly a complete loss of the radical coupling reactions even in the presence of 6 equiv of Cs_2CO_3 (**3o**).

We then examined the scope of the 4-substituted Hantzsch esters using **1a** as a model ester substrate (Table 3). Various substituents on a benzene ring were tolerated to give the corresponding ketone products with moderate to good yields, regardless of their electronic nature (**4a**−**4f**). The substituent on the *meta* position of the benzene ring was also tolerated, giving the ketone product with moderate yield (**4g**). The methyl group of **2a** could be replaced with other alkyl substituents such as an ethyl (**4h**) or *n*-butyl (**4i**) unit without affecting the reaction yield. Replacing the methyl group of **2a** with a phenyl unit led to a dropped yield (**4j**). The phenyl group of **2a** could be switched into a 2-naphthalene group to give **4k** with 63% yield. Additionally, cyclic alkyl units such as cyclohexyl and cyclopentyl could also be installed to the Hantzsch esters to give the corresponding ketone products with moderate to high yields (**4l** and **4m**). It should be noted that alkenes and primary alkyl halides were well tolerated under our conditions, affording the ketone products (**4a** and **4n**) bearing readily transferrable functional groups. Substrates bearing alkyl substituents other than a benzyl moiety are incompatible with this method, presumably due to the stability of the corresponding radicals.

Our protocol could also be used to install functional groups to complex molecules (Table 4). For example, probenecid is a medicine for the treatment of psoriasis, acne, and photo-

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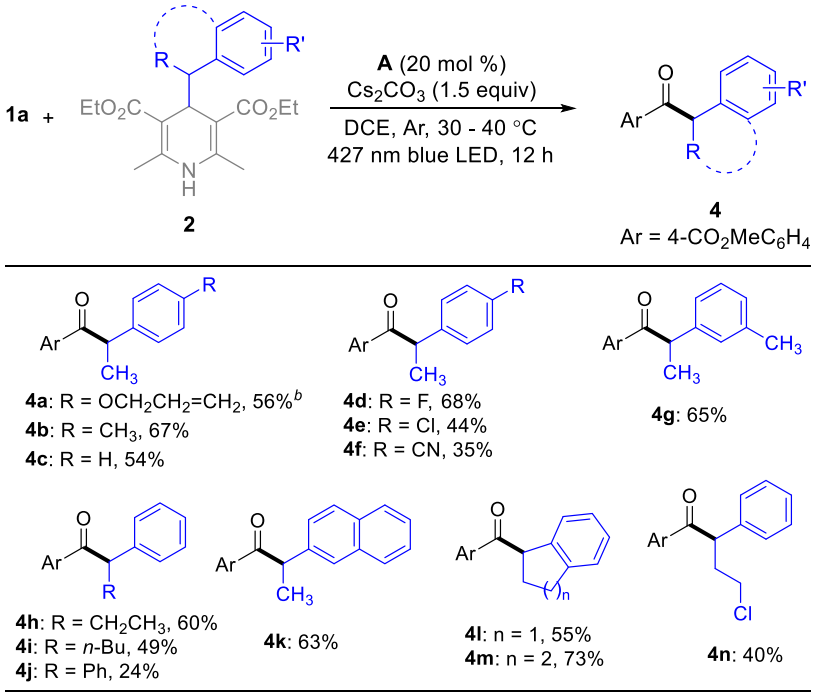
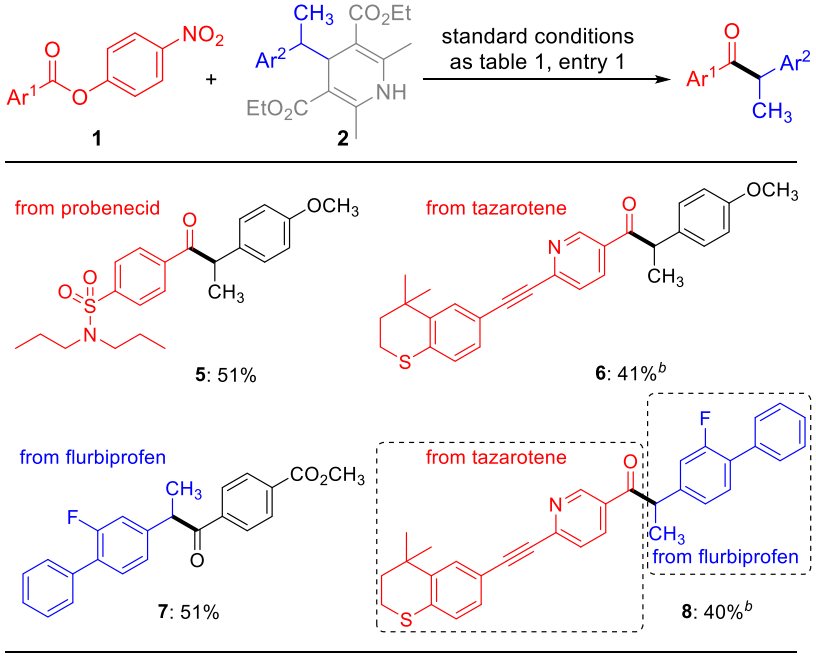
Table 3. Scope of 4-Substituted Hantzsch Esters[a]



[a]Reaction conditions: **2** (0.1−0.2 mmol), **1** (2.0 equiv), **A** (20 mol %), and Cs_2CO_3 (1.5 equiv) in 1,2-dichloroethane (1.5 mL), blue LED (Kessil PR160 series, λ_{max} = 427 nm), Ar atmosphere, 30−40 °C, and 12 h. [b]6.0 equiv of Cs_2CO_3 was used.

Table 4. Coupling of Medicinal Fragments[a]



[a]Reaction conditions: **2** (0.05−0.2 mmol), **1** (2.0 equiv), **A** (20 mol %), and Cs_2CO_3 (1.5 equiv) in 1,2-dichloroethane (1.5 mL), blue LED (Kessil PR160 series, λ_{max} = 427 nm), Ar atmosphere, 30−40 °C, and 12 h. [b]6.0 equiv of Cs_2CO_3 was used.

damage. The ester of probenecid could be readily converted to the corresponding ketone product (**5**) using our method. Similar transformations could be performed for many other drugs (such as tazarotene) containing carboxylic acids or their derivatives to give various ketone adducts (**6**). The drug molecules (such as flurbiprofen) may also be incorporated into the Hantzsch ester substrate and thus be transferred to the corresponding ketone adduct (**7**). Our method also allows for direct coupling of two medicinal fragments to form a new ketone entity that may show alternative activities. Here, we showed that the carboxylic ester from tazarotene could couple with Hantzsch ester bearing the key fragment of flurbiprofen (**8**). This study indicates that our method can likely be used to readily assemble complex molecules.

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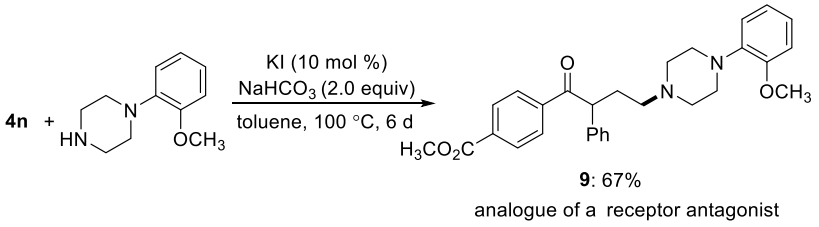
Scheme 1. Synthetic Transformation of Our Ketone Product



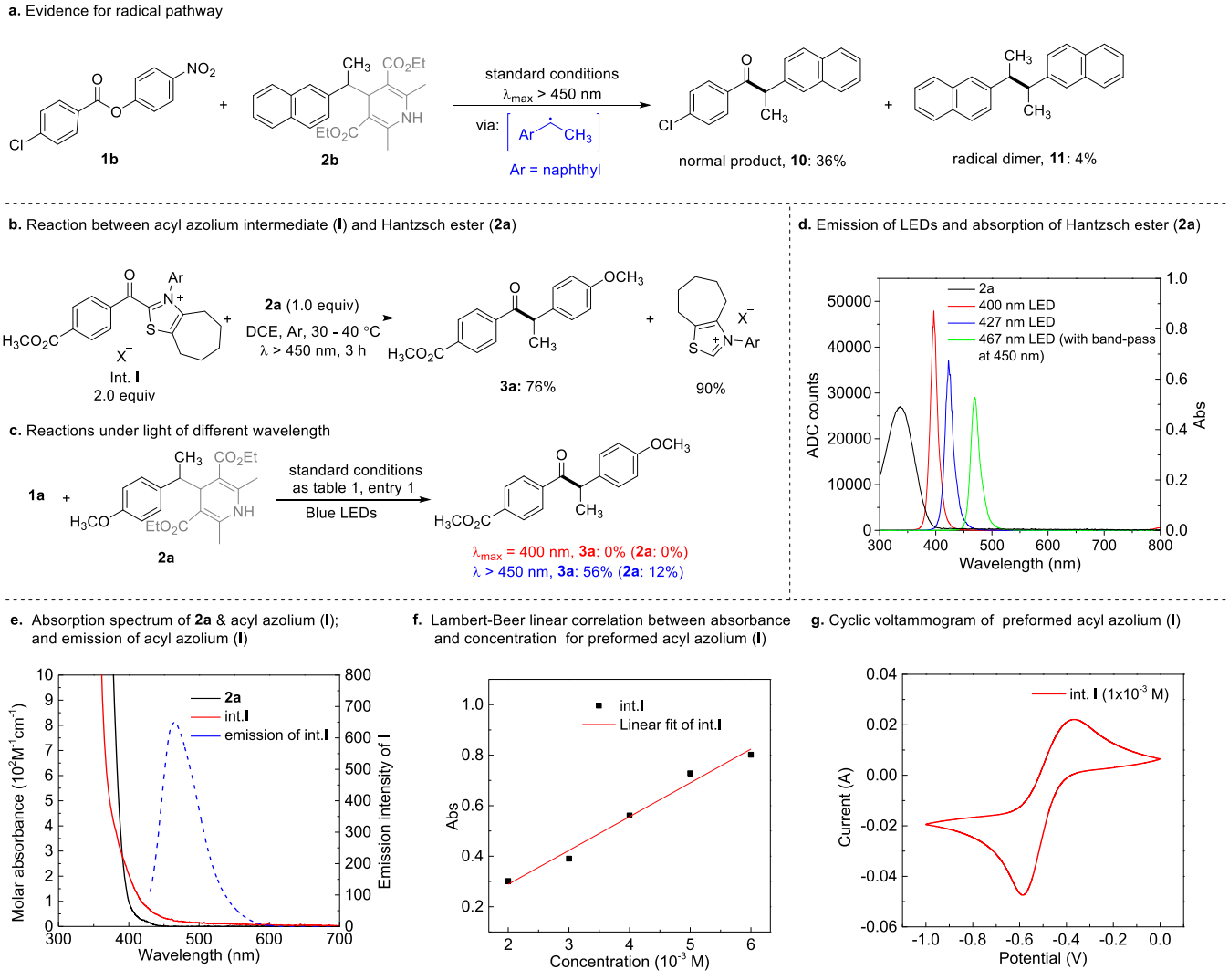


Figure 2. (a) LEDs of 467 nm with a band pass at 450 nm were used; (b) acyl azolium intermediate (**I**) was prepared using the corresponding acyl chloride and NaH, see the Supporting Information for details; (c) LEDs of 400 and 467 nm (with a band pass at 450 nm) were used, respectively; (d) UV−vis absorption spectra of **2a** (10^{-4} M in DCE, black line) and emission spectra of LEDs (red, blue and green lines); (e) UV−vis absorption spectra of acyl azolium **I** (10^{-3} M in DCE, red line) and **2a** (10^{-3} M in DCE, black line). Fluorescence spectrum of acyl azolium **I** (10^{-3} M in DCE, blue line); (f) Lambert−Beer linear correlation experiments, see the Supporting Information for details; and (g) cyclic voltammograms of the preformed acyl azolium intermediate **I** (0.001 M) in [0.1 M] $TBAPF_6$ in CH_3CN. Sweep rate: 100 mV/s. A Pt electrode was used as a working electrode, a calomel electrode as a reference electrode, and a Pt wire as an auxiliary electrode.

The ketone product from our catalytic reaction can undergo further transformations to prepare bioactive molecules. For example, product **4n** was transformed to an analogue of a serotonin $5HT_{1A}$ receptor antagonist[17] (**9**) in one step with 67% yield (Scheme 1).

Multiple experiments were conducted to gain insight into the reaction mechanism. When carboxylic ester **1b** was employed to react with Hantzsch ester **2b**, the desired ketone (**10**) was generated in 36% yield. A small amount of dimerization adduct (**11**, Figure 2a) was formed from self-coupling of the Hantzsch ester-derived radical intermediate, suggesting that our reaction proceeds through a radical pathway. Considering the ability of carbonate[18] and Hantzsch ester[13i,l] to form an electron donor−acceptor (EDA) complex with electron-deficient aromatic rings, we first proposed that an EDA complex between acyl azolium (**I**) and carbonate anion

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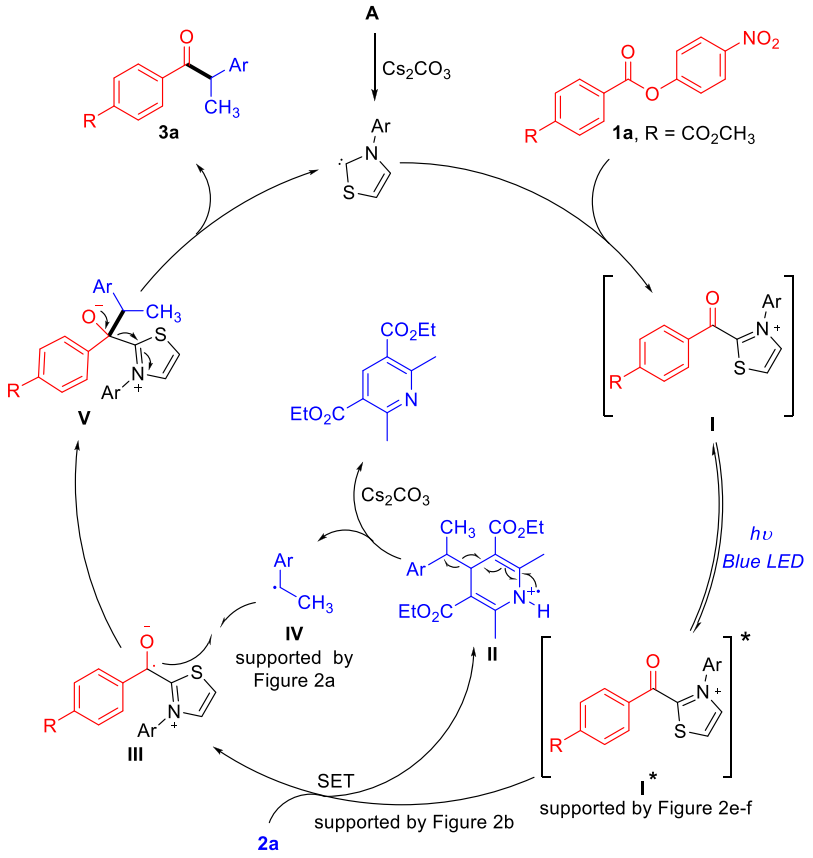
Scheme 2. Plausible Reaction Pathway



or Hantzsch ester is responsible for this radical reaction. However, direct irradiation of a solution of preformed acyl azolium (**I**) and Hantzsch ester (**2a**) in DCE under the light of λ > 450 nm without the presence of Cs_2CO_3 (Figure 2b) resulted in 76% yield of the desired product (**3a**) with 90% of the NHC precatalyst recovered. Further UV−vis absorption experiments showed that no EDA complex was formed between acyl azolium (I) and Hantzsch ester (see Figure S10 for details). These results exclude the possible pathway via an EDA complex involving Cs_2CO_3 or Hantzsch ester (**2a**). Instead, the results point toward a reaction pathway with direct photoexcitation of acyl azolium (**I**) or Hantzsch ester (**2a**).

We next performed experiments to exclude photoexcitation of Hantzsch ester (**2a**) as the driving force for our reaction. Hantzsch ester (**2a**) can be excited (to behave as reductant) under the light of a shorter wavelength (around 400 nm).[14h] However, it has little absorption at the visible-light region (λ > 420 nm).[14g] This was further confirmed by the emission spectra of LEDs and the absorption spectrum of **2a** (Figure 2d). However, our reaction works well (Figure 2c) under the irradiation of long-wavelength visible lights (λ > 450 nm), where Hantzsch ester has no absorption (Figure 2d, green line).[19] In contrast, using LEDs of λ_{max} = 400 nm, with the emission region overlapping lightly with the strong absorption region of **2a** (Figure 2d, black and red lines), did not result in radical coupling product (**3a**). Under this condition (λ_{max} = 400 nm), **2a** decomposed completely to form the corresponding pyridine and alkane (Figure 2c). These results (Figure 2c) suggest that direct excitation of the Hantzsch ester was not responsible for the radical coupling reactions.

We then turn our attention to investigate the photophysical behaviors of preformed acyl azolium intermediate (**I**) to evaluate the feasibility of its direct photoexcitation. The UV−vis absorption spectrum of acyl azolium (**I**) revealed a significant absorption of visible light, and the tail wavelength reached over 520 nm (Figure 2e, red line). The absorption spectra of preformed **I** were measured at different concentrations in DCE. The absorbances showed a typical Lambert−Beer linear correlation with the concentrations (Figure 2f). The corresponding emission spectrum of **I** upon excitation at 400 nm was also recorded (Figure 2e, a blue dotted line). A cyclic voltammetry experiment was used to measure the redox potential of ground state of **I** (Figure 2g). The cyclic voltammogram of preformed intermediate **I** (as a solution in MeCN) features a reversible peak at $E_{1/2}$ = −0.48 V vs a saturated calomel electrode (SCE), which could be attributed to the redox couple of acyl azolium (**I**) and its reduced radical intermediate.[20] With the UV−vis, fluorescence, and cyclic voltammetry data in hand, the excited state potential of **I** was estimated to be +1.9 V vs SCE (see the Supporting Information for details).[21] This redox potential (+1.9 V) is higher than that of the Hantzsch ester (**2a**, E_{ox} = +1.1 V vs SCE, see Figure S8 for details), indicating that thermodynamically single-electron-transfer (SET) oxidation of **2a** by **I** (at its excited state) is feasible.

To provide further evidence in supporting the photoexcitation of acyl azolium (**I**), we conducted the Stern−Volmer quenching experiments. *N*-Methyl-*N*-((trimethylsilyl)methyl)-aniline (E_{ox} = +0.62 V vs SCE, see Figure S9 for details), which cannot react with the ground state of acyl azolium **I** ($E_{1/2}$ = −0.48 V vs SCE), was chosen as the quenching agent.[22] It was

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found that *N*-methyl-*N*-((trimethylsilyl)methyl)aniline could effectively quench the emission of **I** (see Figure S9 for details), supporting that the acyl azolium **I** at its excited state can behave as an effective oxidant.

Based on the results from the mechanistic studies above, a plausible reaction pathway is proposed (Scheme 2). The reaction starts with addition of an NHC catalyst to the carboxylic ester (**1a**) to generate an electron-deficient acyl azolium intermediate **I**.[15] Photoexcitation converts intermediate **I** to its electronically excited state (**I***) that can act as a single-electron oxidant ($E_{1/2}$ = +1.9 V vs SCE). A subsequent single-electron transfer between electron-rich Hantzsch ester (**2a**, E_{red} = +1.1 V vs SCE) and the excited acyl azolium (**I***) leads to a Hantzsch ester-derived radical cation **II** and an NHC-bound radical intermediate **III**. This radical cation (**II**) undergoes a homolytic C−C bond cleavage to generate an alkyl radical intermediate **IV**. Subsequent radical coupling between the alkyl radical (**IV**) and the NHC-bound radical (**III**) intermediate eventually affords the desired ketone product (**3a**) and regenerates the carbene catalyst.

In conclusion, we have developed NHC-catalyzed light-induced alkylation of aryl carboxylic esters with 4-substituted Hantzsch esters. A transition-metal photocatalyst is not involved in the photopromoted process. Instead, the direct excitation of an acyl azolium intermediate contributes to a visible-light-induced one-electron-transfer process that reduces an acyl azolium intermediate to the corresponding radical species for subsequent coupling reactions. The reaction conditions are very mild and various functional groups are well tolerated. Sophisticated ketone products, including those bearing one or two medicinal fragments, can be readily prepared. Our study provides a new approach in NHC-catalyzed reductive-radical-coupling reactions. Additional mechanistic studies, including density functional theory (DFT) calculation, are in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00165.

Experimental procedures, analytical and spectroscopic data for new compounds, and copies of NMR (PDF)

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Notes

The authors declare no competing financial interest.

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