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Visible light-assisted organocatalytic α-acyloxylation of ketones using carboxylic acids and *N*-halosuccinimides

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The α-acyloxylcarbonyl motif can be found in many important pharmaceuticals and biologically active natural products and their derivatives. In this manuscript, the direct synthesis of α-acyloxylketones from ketones and readily available carboxylic acids was realized using a photo-assisted halogen bond-mediated organocatalytic α-acyloxylation reaction. The desired α-acyloxylation products were obtained in good to high yields.

The α-acyloxylketone motif can be found in many important pharmaceuticals and biologically active natural products and their derivatives, such as Valrubicin, Aranidipine, and Taxol.[1] Moreover, α-acyloxylketones are also very useful starting materials in organic synthesis.[2] Because of their relevance in medicinal and synthetic chemistry, many methods have developed for the synthesis of α-acyloxylketones.[3]

Nevertheless, among these reported methods, only a few are using the readily available carboxylic acids directly as the acyloxylation reagents. In this regard, Ishihara and coworkers[4a] developed the first direct α-acyloxylation of carbonyl compounds with carboxylic acids using the combination of TBAI and TBHP.[4] Later, Xu and coworkers reported the direct α-acyloxylation of acetone with carboxylic acids using the combination of $KI/K_2S_2O_8$.[1b] Most recently, Zhang and coworkers also developed a direct α-acyloxylation method for ketones with carboxylic acids using KI/1,2-dibromoethane.[3] Meanwhile, organocatalytic methods have also been developed for the asymmetric synthesis of α-acyloxylketones or -aldehydes.[5,6] However, since most of these methods are based on the oxidation of the enamine intermediates by diacyl peroxides, carboxylic acids cannot be used as the α-acyloxylation reagent.[5] Only Jørgensen and coworkers have reported an asymmetric α-acyloxylation of α-branched aldehydes directly using carboxylic acids via the oxidation of the enamine intermediates with Ag_2CO_3.[6]

Halogen bonding, the noncovalent interaction of Lewis bases with an electron-deficient region of halogen substituents, has received dramatic increase of interest in the past two decades due to its wide applications in crystal engineering, anion recognition, and drug design.[7] Most recently, its potential in catalysis and organic synthesis has also been recognized.[7c,8] When a halogen bond complex is placed under visible light irradiation, an electron transfer between the Lewis base and the halogenated compound happens, and the radical species thus generated can be utilized for developing novel synthetic methodologies.[8c] For example, Yajima and coworkers reported the use of halogen bond complexes between enamines and perfluoroalkyl iodides for the visible light-induced alkylation and atom transfer radical addition (ATRA) reactions.[9] While the halogen bonding between *N*-halosuccinimides and amines, imines, or nitrogen-containing heterocycles are well known,[10] the halogen bond complexes between enamines and *N*-halosuccinimides have been rarely studied. To our knowledge, only Guha and Sekar have mentioned the halogen bonding between an enamine and *N*-bromosuccinimide (NBS) in their proposed mechanism.[11] Most recently, Li and coworkers reported a photo-assisted C-H amination mediated by *N*-iodosuccinimide (NIS) via the halogen bonding with sulfonamides.[12] Inspired by these few reports, we reasoned that the halogen bonding between an enamine and *N*-halosuccinimides could be employed for the organocatalyzed photo-assisted halogenation of ketones (such as compound **6** in Table 1). Nevertheless, when we conducted the proposed reaction with NBS under the irradiation of blue light, the α-benzoyloxylation product **5a** (Table 1) was obtained instead, which was a reaction product of the cocatalyst benzoic acid. This reaction offers a direct α-acyloxylation of cyclohexanone with carboxylic acids. Herein we wish to report the first visible-light assisted organocatalytic direct α-acyloxylation of ketones with carboxylic acids involving the halogen bond between the enamine and *N*-halosuccinimides.

As the results in Table 1 show, when the proposed α-bromination reaction of cyclohexanone (**1a**) was conducted in chlorobenzene at 70 ˚C using NBS (**3a**) as the brominating agent under the catalysis of pyrrolidine (**4a**) and benzoic acid (**2a**) and the irradiation of blue LED lights (460 nm, 2×36 W), the expected α-bromination product **6** was not obtained, instead, the α-acyloxylation product **5a** was obtained in 7% yield (entry

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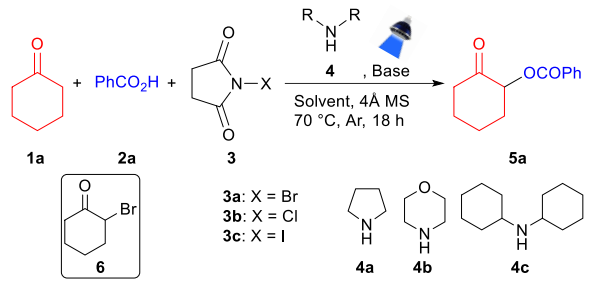
Table 1. Optimization of the reaction conditions[a]



Entry	**1a** (equiv.)	**3** (equiv.)	**4** (equiv.)	Na_2CO_3 (equiv.)	yield (%)[b]
1[c]	10.0	**a** (1.5)	**a** (1.0)	---	7
2[d]	10.0	**a** (1.5)	**a** (1.0)	0.5	45
3[d]	10.0	**a** (1.5)	---	0.5	---
4[d]	10.0	---	**a** (1.0)	0.5	---
5[d,e]	10.0	**a** (1.5)	**a** (1.0)	0.5	trace
6	10.0	**a** (1.5)	**a** (1.0)	1.0	71
7	10.0	**b** (1.5)	**a** (1.0)	1.0	35
8	10.0	**c** (1.5)	**a** (1.0)	1.0	79
9	3.0	c (1.1)	a (0.2)	1.0	87
10	3.0	**c** (1.1)	**a** (0.2)	1.0[f]	50
11	3.0	**c** (1.1)	**a** (0.2)	1.0[g]	21
12	3.0	**c** (1.1)	**b** (0.2)	1.0	25
13	3.0	**c** (1.1)	**c** (0.2)	1.0	trace
14[h]	3.0	**c** (1.1)	**a** (0.2)	1.0	65
15[i]	3.0	**c** (1.1)	**a** (0.2)	1.0	59
16[j]	3.0	**c** (1.1)	**a** (0.2)	1.0	50
17[k]	3.0	**c** (1.1)	**a** (0.2)	1.0	67
18[l]	3.0	**c** (1.1)	**a** (0.2)	1.0	67
19[m]	3.0	**c** (1.1)	**a** (0.2)	1.0	54
20[n]	3.0	**c** (1.1)	**a** (0.2)	1.0	15
21[o]	3.0	**c** (1.1)	**a** (0.2)	1.0	24

[a]Unless otherwise indicated, all reactions were carried out using cyclohexanone (**1a**, 3.0 mmol), benzoic acid (**2a**, 1.0 mmol), NIS (**3c**, 1.1 mmol), Na_2CO_3 (1.0 mmol), 4 ÅMS (100.0 mg), and pyrrolidine (**4a**, 0.20 mmol, 20.0 mol %) in chlorobenzene (5.0 mL) under argon at 70 °C with the irradiation of two 36 W blue LED (460 nm) for 18 h. [b]Yield of the isolated product **5a** after column chromatography. [c]Reaction was performed with cyclohexanone (**1a**, 1.0 mmol), NBS (**3a**, 0.15 mmol), and benzoic acid (**2a**, 0.10 mmol), pyrrolidine (**4a**, 0.10 mmol), and without 4 ÅMS at 80 °C overnight. [d]The reaction time was 2 h. [e]Conducted without Blue-LED. [f]K_2CO_3 was used as the base. [g]Cs_2CO_3 was used as the base. [h]Conducted in benzene. [i]Conducted in THF. [j]Conducted in $CHCl_3$. [k]Conducted in CH_3CN. [l]Conducted in EtOAc. [m]Conducted in DMF. [n]Conducted at rt. [o]Conducted under air.

1). Formation of **5a** suggests the involvement of benzoic acid (**2a**) in this reaction, a cocatalyst used for the formation of the enamine intermediate. This reaction provides a direct α-acyloxylation of ketone using the readily available carboxylic acid as the acyloxylation agent. Nevertheless, the yield of **5a** was very low and our attempts to increase the yield of **5a** by simply increasing the loading of **2a** failed and, therefore, the reaction conditions were very carefully optimized. It was found that the yield of **5a** could be improved to 45% by employing excessive cyclohexanone (**1a**, 10.0 equiv.), 1 equiv. of pyrrolidine (**4a**), 4 Å molecular sieves, and a base additive (Na_2CO_3, entry 2). In contrast, control reactions conducted without either pyrrolidine (**4a**), NBS (**3a**), or light yielded no desired product (entries 3-5). These results indicate that all these three parameters are essential to the α-acyloxylation reaction. The yield of **5a** could be further improved to 71% by employing 1.0 equiv. of Na_2CO_3 and prolonging the reaction time to 18 h (entry 6). Using *N*-chlorosuccinimide (NCS, **3b**) instead of NBS (**3a**) led to a dramatic decrease of the yield of **5a** (to 35%, entry 7). In contrast, using NIS (**3c**) instead of NBS (**3a**), the yield of **5a** was slightly increased to 79% (entry 8). The observed yield trend agrees well with the expected halogen bonding strength between the *N*-halosuccinimides and the enamine. Further optimizations with NIS (**3c**) revealed that the highest yield of **5a** (87%) could be obtained with the use of a slight excess of cyclohexanone (**1a**) and NIS (**3c**) (3.0 and 1.1 equiv., respectively) and a catalytic amount of pyrrolidine (**4a**, 20 mol %) (entry 9). Using other base additives, such as K_2CO_3, and Cs_2CO_3 (entries 10-11), other amine catalysts, such as **4b** and **4c** (entries 12-13), or other organic solvents, such as benzene, THF, chloroform, acetonitrile, ethyl acetate, and DMF (entries 14-19), all led to lower yields of **5a**. Moreover, conducting the reaction at room temperature (entry 20) or under air (entry 21) also led to lower yields of **5a**. Thus, the best conditions for this reaction are those listed in entry 9.

Once the reaction conditions are optimized, the scope of this direct α-acyloxylation reaction were investigated under the optimized reaction conditions. As the results in Table 2 show, besides benzoic acid, substituted benzoic acids can be used in this reaction to yield the desired α-acyloxylation products in good yields (**5b**-**5k**), and the electronic effects of the substituent has almost no effects on this reaction (**5b**-**5i**). In addition, the position of the substituent on the phenyl ring has no effects on this reaction, either (**5i**-**5k**). 2-Naphthoic acid is also an excellent substrate for this reaction, which gives **5l** in a high yield. Among the heterocyclic carboxylic acids screened, no desired product could be obtained from picolinic acid (**5m**), but the expected product of coumalic acid (**5n**) was obtained in a good yield. These two results suggest that the failure of picolinic acid might be due to its pyridine heterocycle, which is also known to form halogen bond with NIS.[10b] Besides those of aryl carboxylic acids, the expected products of aliphatic carboxylic acids, such as, pivalic acid (**5o**), 5-phenylvaleric acid (**5p**), and acetic acid (**5q**), were also obtained in good yields. Moreover, *trans*-cinnamic acid and abietic acid also gave the corresponding products in good to high yields (**5r** and **5s**). Besides cyclohexanone, acetone is also a good substrate for this reaction and good yields were obtained for the expected products of benzoic acid (**5t**) and *N*-Boc-protected proline (**5u**). When an α-branched aldehyde was employed, the formation of product **5v** was be observed in the crude NMR, together some unidentified products, but could not be isolated. Nevertheless, no desired product was obtained from cyclopentanone, cycloheptanone, or benzylacetone, and α-unbranched aldehydes gave only the aldol condensation products (data not shown). To show the synthetic utility of this reaction, a gram-scale synthesis of **5a** was conducted, a good yield of 74% was obtained (Table 2).

To understand the reaction mechanism, some additional reactions were conducted (Scheme 1). When the preformed enamine **7** was employed as the substrate under the optimized

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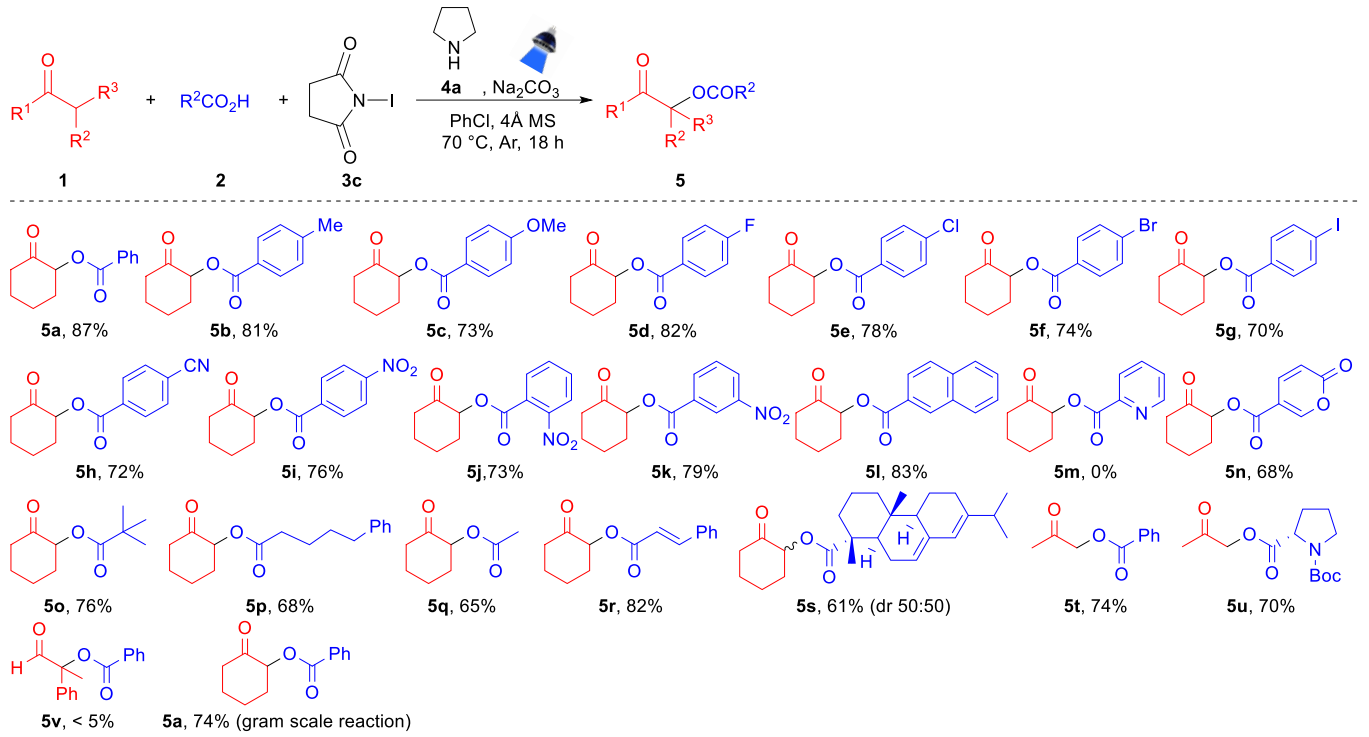
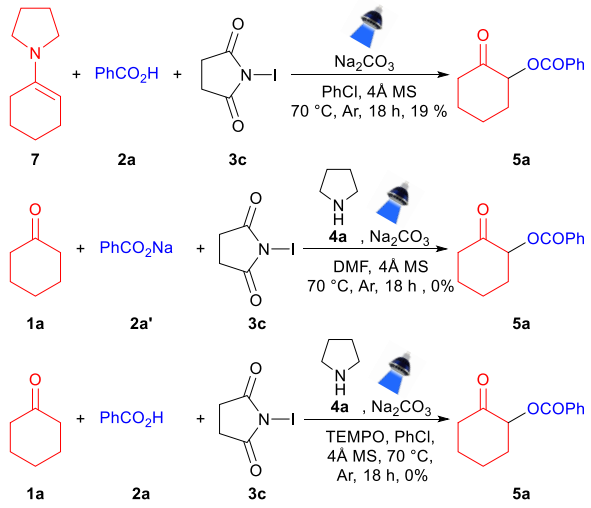
Table 2. Substrate scope of the light-assisted organocatalytic α-acyloxylation reaction[a]

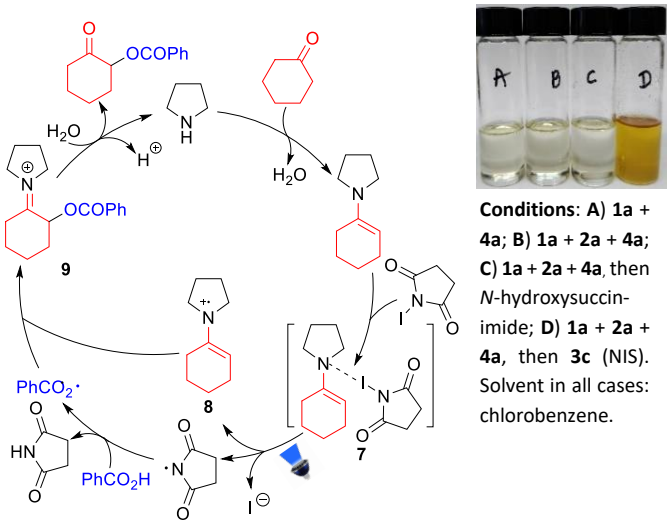


[a]Unless otherwise indicated, all reactions were carried out using ketone (**1**, 3.0 mmol), carboxylic acid (**2**, 1.0 mmol), NIS (**3c**, 1.1 mmol), Na_2CO_3 (1.0 mmol), 4 Å MS (100.0 mg), and pyrrolidine (**4a**, 0.20 mmol, 20.0 mol %) in chlorobenzene (5.0 mL) under argon at 70 ˚C with the irradiation of two 36 W blue LED (460 nm) for 18 h.



Scheme 1. Control reactions with enamine, sodium benzoate, and TEMPO.

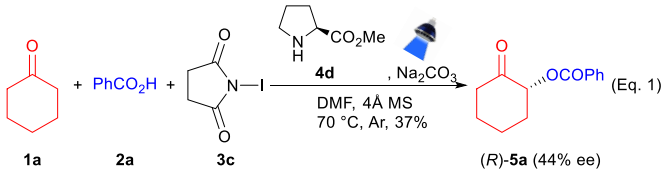
reaction conditions, the desired product **5a** was also obtained, but in a much lower yield of 19% (top equation).[13] Product **5a** could be obtained in good yields from both chlorobenzene and DMF using benzoic acid (**2a**) as the acyloxylating reagent (Table 1, entries 9 and 19). However, when sodium benzoate (**2a'**) was used as the substrate in DMF, the desired product **5a** was not obtained (middle equation). This negative result renders the involvement of a carbocation mechanism[1b] or an S_N2 mechanism via the intermediacy of 2-iodocyclohexanone in this reaction[3] very unlikely. When NIS (**3c**) was added to the mixture of cyclohexanone (**1a**), pyrrolidine (**4a**), and benzoic acid (**2a**), a dark yellow solution formed immediately (vial **D**, Scheme 3). In contrast, adding *N*-hydroxysuccinimide, which is incapable of halogen bonding, to the same mixture showed no such color change (vial **C**, Scheme 2). These observations support the proposed halogen bonding between the enamine and NIS. Based on these results, the following mechanism is proposed [Scheme 2 (left side)]:[14] The cyclohexanone enamine forms an EDA complex[15] (**7**) with NIS via halogen bonding. Under the blue light irradiation, the electron transfer between the enamine and NIS leads to the formation of the enamine cation radical **8** and a succinimidyl radical. A HAT reaction between benzoic acid and the succinimidyl radical generates the benzoyloxyl radical,



Conditions: **A**) **1a** + **4a**; **B**) **1a** + **2a** + **4a**; **C**) **1a** + **2a** + **4a**, then *N*-hydroxysuccinimide; **D**) **1a** + **2a** + **4a**, then **3c** (NIS). Solvent in all cases: chlorobenzene.

Scheme 2. Proposed reaction mechanism and images showing the formation of halogen-bonded complex (yellow).

which reacts with **8** to give the iminium intermediate **9**. The hydrolysis of **9** yields the expected product and completes the organocatalytic cycle. As a support of the proposed radical mechanism, adding TEMPO to the reaction mixture under the optimized conditions completely suppressed the formation of **5a** (Scheme 1, bottom equation). In addition, the presence of oxygen also suppresses the formation of **5a** (Table 1, entry 21). Based on the proposed mechanism, if a chiral amine catalyst is applied, potential asymmetric induction can be achieved in the reaction product. Indeed, when catalyst **4d** was used, product (*R*)-**5a** was obtained in 37% yield and 44% ee (Eq. 1).



In summary, we have developed a photo-assisted halogen bond-mediated direct α-acyloxylation method for the synthesis of α-acyloxylated ketones using readily available carboxylic acids as the α-acyloxylating reagents. The corresponding products were obtained in good to high yields. An enantioselective version of this reaction is currently under development, and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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13 Using pure enamine will result in quick generation of the enamine cation radical **8** and a succinimidyl radical (see the proposed mechanism), which will lead to side products if the subsequent steps of the reaction are slow.

14 Alternatively, the electron transfer can form an iodine radical and a succinimide anion, and then the HAT can be achieved by the iodine radical. For a discussion on alternative mechanisms, please see the Supporting Information.

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