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N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Synthesis of δ-Ketocarbonyls

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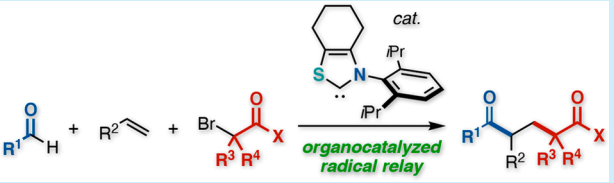
ABSTRACT: An NHC-catalyzed radical relay enabled the vicinal alkylacylation of alkenes using aldehydes and tertiary α-bromo esters as a versatile route to δ-keto esters bearing an all-carbon quaternary center at the position α to the ester. The protocol was applicable to the reaction of tertiary α-bromoamides to afford δ-keto amides. This protocol enabled the conversion of readily available starting materials to congested and functionalized δ-ketocarbonyls in a single step without using transition metals.



δ-Keto esters are valuable synthetic intermediates that can be easily derivatized to form lactones and lactams through reductive functionalization. Lewis acid-mediated conjugate addition of ketene silyl acetals to vinyl ketones is well-known as the conventional and direct approach to δ-keto esters (Figure 1A).[1] Nevertheless, the reaction using α,α-disubsti-

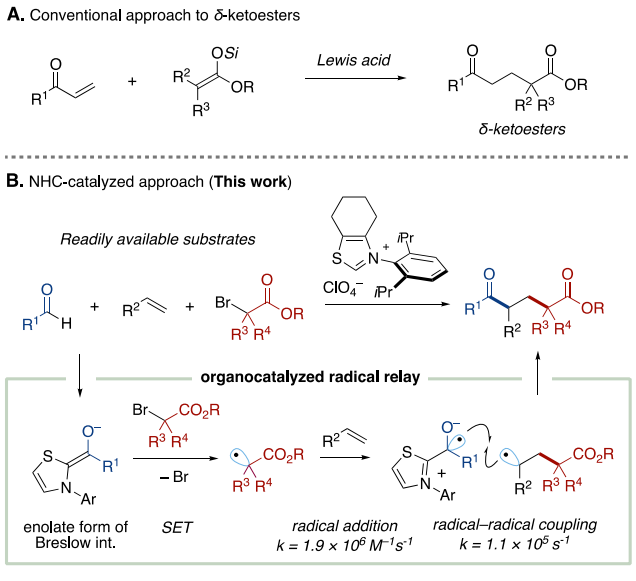


Figure 1. Synthetic approaches to δ-keto esters.

tuted silyl ketene acetals for the synthesis of δ-keto esters bearing an all-carbon quaternary center at the position α to the ester is still limited because of the steric repulsion that occurs in the carbon−carbon bond-formation step. In this case, catalytic or stoichiometric amounts of specific Lewis acids and additives are required. Recently, Dai and co-workers demonstrated the alternative approach to δ-keto esters bearing an α-quaternary center through a copper-catalyzed ring-opening reaction of cyclopropanols with tertiary α-bromo esters.[2] These methods are useful for the preparation of δ-keto esters bearing an α-quaternary center but have some limitations due to the cumbersome preparation of substrates.

Earlier, we demonstrated that an N-heterocyclic carbene (NHC)-catalyzed[3] radical relay enables vicinal alkylacylation of alkenes using aldehydes and tertiary alkyl carboxylic acid-derived redox-active esters to produce complex ketones.[4b] A tertiary alkyl group and acyl group could be introduced to carbon−carbon double bonds. This reaction is initiated by single electron transfer (SET) from an enolate form of the Breslow intermediate to a redox-active ester to produce a persistent Breslow intermediate-derived radical and a transient alkyl radical.[4,5] Subsequently, the radical addition of the resultant alkyl radical to styrene ($k = 1.3 \times 10^5$ M^{-1} s^{-1})[6] occurs preferentially before the competing radical−radical coupling ($k = 1.1 \times 10^5$ s^{-1}). Then, the elongated radical couples with the Breslow intermediate-derived radical to afford the three-component coupling product. Following this, we questioned whether this protocol could be applied to the synthesis of δ-keto esters using α-bromo esters instead of redox-active esters (Figure 1B). α-Bromo esters are known to be reduced by tetrakis(dimethylamino)ethylene (TDAE) (E°_{ox} = −0.78 V vs SCE in MeCN)[7a] to generate the corresponding α-alkoxycarbonylakyl radicals.[7b] The rate of addition of the α-alkoxycarbonylalkyl radical to styrene (1.9×10^6 M^{-1} s^{-1})[5] is higher than that of a tertiary alkyl radical to styrene ($k = 1.3 \times$

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10^5 M^{-1} s^{-1}). These features would meet the requirement that the α-bromo ester could participate in the NHC-catalyzed radical relay.

Herein we report NHC-catalyzed vicinal alkylacylation of alkenes using aldehydes and tertiary α-bromo esters as a versatile and efficient route to δ-keto esters bearing an all-carbon quaternary center at the position α to the ester. Tertiary α-bromo amides were also utilized as the coupling partner for the synthesis of δ-keto amides. This protocol allowed for the direct synthesis of congested and functionalized α-bromocarbonyls from readily available starting materials under transition-metal-free conditions.

After the survey of reaction conditions based on our previous report for the vicinal alkylacylation of alkenes using aldehydes and redox-active esters,[4] we found that the reaction of benzaldehyde (**1a**) (0.2 mmol), styrene (**2a**) (0.4 mmol) and α-bromo ester **3a** (0.3 mmol) occurred in the presence of a catalytic amount of *N*-2,6-diisopropylphenyl-substituted six-membered-ring-fused thiazolium salt **N1**[8] (5 mol %) as the NHC precursor and a stoichiometric amount of Cs_2CO_3 (0.22 mmol) in DCM solvent at 60 °C to afford the three-component coupling product, δ-keto ester **4aaa**, in 74% yield with a small amount of **5aa** arising from two-component coupling between **1a** and **3a** (Table 1, entry 1).

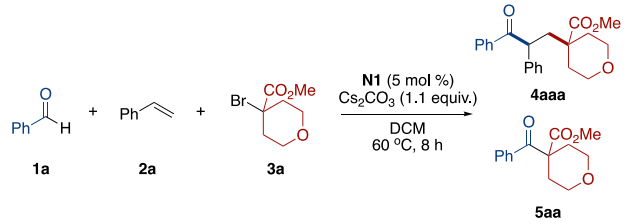
The effect of the carbene catalyst was evaluated (Table 1, entries 2−6). **N2** possessing a seven-membered-ring backbone and **N3** possessing a dimethyl backbone also exhibited comparable reactivities and chemoselectivities (entries 2 and 3). Although sterically less hindered **N4** having an *N*-mesityl group gave improved chemoselectivity, the product yield of **4aaa** was decreased (entry 4). Other NHCs having triazolium and imidazolium cores did not give either the desired product or the two-component coupling product (entries 5 and 6).

The choice of base and solvent was critical to obtain high chemoselectivity (entries 7−11). The use of K_2CO_3 instead of Cs_2CO_3 inverted the major product to the two-component coupling product **5aa** (entry 7). DBU, known as a common organic strong base, also gave **5aa** preferentially (entry 8). With highly polar solvents such as DMSO and MeCN, the formation of δ-keto ester **4aaa** was inhibited (entries 9 and 10). In contrast to these results, the use of THF as the solvent preferred to give **4aaa** over **5aa** (entry 11).

With the optimal reaction conditions in hand, we explored the scope of each carbon fragment. First, a variety of aldehydes were evaluated (Scheme 1, top). Aromatic aldehydes having electron-rich or electron-deficient groups at the *para* position could participate as acyl donors in this NHC-catalyzed three-component coupling (**4baa**−**4faa**). It is noteworthy that C(sp^2)−halogen bonds, which are known to be reactive toward oxidative addition in transition-metal catalysis, were totally compatible (**4gaa**−**4iaa**). A substituent at the *meta* position of benzaldehyde was also tolerated (**4jaa**). Various heteroaromatic or ring-conjugated aldehydes were found to be suitable coupling partners (**4kaa**−**4naa**). Although some reports described that α-alkoxycarbonylalkyl radicals derived from α-bromo esters couple with electron-rich heteroaromatics,[9] the related products were not observed in this NHC-catalyzed reaction. The present reaction conditions did not allow aliphatic aldehydes to be used as substrates (data not shown).

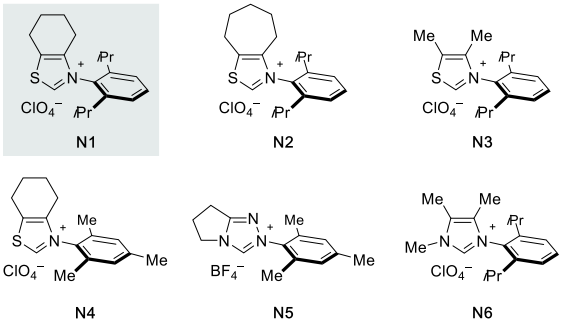
Next, the scope of tertiary α-bromo esters was examined (Scheme 1, middle). An acyclic tertiary fragment could be introduced to the product (**4aab** and **4aac**). Various cyclic

Table 1. Screening of Conditions for Coupling between 1a, 2a, and 3a[a]



entry	change from standard conditions	yield of **4aaa** (%)[b]	yield of **5aa** (%)[b]
1	none	74	22
2	**N2** instead of **N1**	60	20
3	**N3** instead of **N1**	64	24
4	**N4** instead of **N1**	45	6
5	**N5** instead of **N1**	0	0
6	**N6** instead of **N1**	1	0
7	K_2CO_3 instead of Cs_2CO_3	26	56
8	DBU instead of Cs_2CO_3	14	67
9	DMSO instead of DCM	31	64
10	MeCN instead of DCM	22	63
11	THF instead of Cs_2CO_3	55	14

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), **N1** (5 mol %), Cs_2CO_3 (0.22 mmol), DCM (400 μL), 60 °C, 8 h. [b]^{1}H NMR yields based on **1a**.



carbon scaffolds at the α-position of the ester were tolerated (**4aad**−**4aag**). These products are expected to provide the unique spiro-lactones. In addition to α-bromo esters, this protocol permitted the use of α-bromo amides to produce δ-keto amides. Dimethylamine, morpholine, and tetrahydroisoquinoline were shown to be representative examples of tertiary amide substrates (**4aah**−**4aaj**). An anilide having a proton did not inhibit the reaction (**4aak**). The synthetic utility of this protocol was demonstrated by the functionalization of α-amino acid- or dipeptide-derived α-bromo amides (**4aal** and **4aam**). Although secondary and primary α-bromocarbonyls were tested, these did not give the desired coupling products (data not shown).

A wide range of vinyl arenes were tested (Scheme 1, bottom). Electron-donating groups such as 3,5-dimethyl, *p*-methoxy, and *p*-benzyloxy substituents on the aromatic ring gave the desired δ-keto esters in good yields (**4aba**−**4ada**). A halogen substituent remained untouched (**4aea**). 1,3-Benzodioxole, thiophene, and naphthalene were efficiently incorporated at the α-position of the ketone moiety (**4afa**−**4aha**). On the other hand, when aliphatic alkenes were subjected to the reaction conditions, formation of the three-component coupling products was not observed (data not shown).

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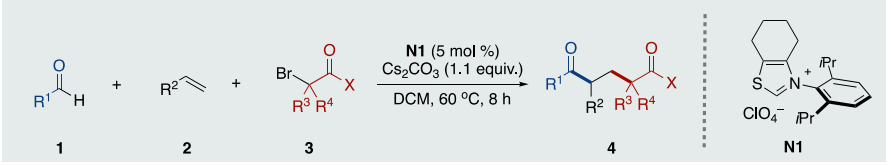
Scheme 1. Substrate Scope[a]

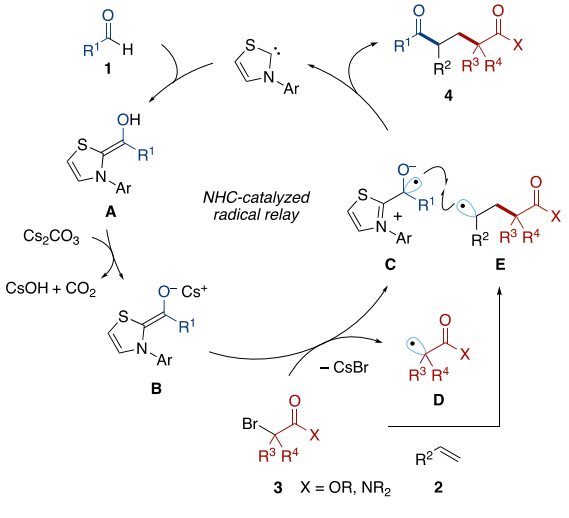


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.3 mmol), **N1** (5 mol %), Cs_2CO_3 (0.22 mmol), DCM (400 μL), 60 °C, 8 h. [b]**N1** (10 mol %) was used. [c]**2a** (0.6 mmol) was used. [d]MeCN (400 μL) was used instead of DCM.

As discussed above, the present reaction proceeds through a radical relay mechanism involving the NHC organocatalyst (Scheme 2). The catalytic cycle is initiated by the formation of a neutral Breslow intermediate (**A**) arising from the reaction between **1** and the NHC. Subsequently, deprotonation of the enol OH in **A** by cesium carbonate produces the highly reducing enolate form of the Breslow intermediate (**B**) (E°_{ox} = −0.95 to − 0.97 V vs SCE in MeCN).[10] SET from enolate **B** to **3** produces a ketyl radical (**C**) and an alkyl radical (**D**), respectively. After addition of the resultant tertiary alkyl radical **D** to styrene **2** to form secondary benzylic radical **E**, radical−radical coupling between **C** and **E** followed by elimination liberates the desired coupling product **4** and regenerates the NHC for the next catalytic cycle.

In summary, we have developed an NHC-catalyzed radical relay enabling the vicinal alkylacylation of alkenes using aldehydes and tertiary α-bromocarbonyls, forging two C−C bonds in a single step. The protocol provides a versatile and efficient approach to congested and functionalized δ-

Scheme 2. Possible Pathway



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ketocarbonyls such as δ-keto esters and δ-keto amides bearing an α-all-carbon quaternary center.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01199.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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