Communication

N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes

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N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes

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Supporting Information Placeholder

ABSTRACT: The *N*-heterocyclic carbene-catalyzed radical relay enables the vicinal alkylacylation of styrenes, acrylates and acrylonitrile using aldehydes and tertiary alkyl carboxylic acid-derived redox-active esters. This protocol introduces tertiary alkyl groups and acyl groups to C–C double bonds with complete regioselectivity to produce functionalized ketone derivatives. The radical relay mechanism involves single electron transfer from the enolate form of a Breslow intermediate and radical addition of the resultant alkyl radical to the alkene followed by radical–radical coupling.

Vicinal dicarbofunctionalization of widely available alkenes, which results in simultaneous formation of two C–C bonds, is an attractive and efficient method for the synthesis of complex carbon frameworks.[1] This method relies heavily on the use of transition-metal catalysts. However, transition-metal-catalyzed vicinal alkylcarbofunctionalization of alkenes, installing a sp^3-alkyl group and another carbon group into the substrate, is challenging because *in situ* generated alkyl metal intermediates can undergo potential side reactions such as β-H elimination and isomerization. The radical relay strategy has been known to overcome such problems.[2,3] This process involves single electron transfer (SET) from an organometal intermediate (R^1–TM^A) to an alkyl electrophile and radical addition of the resultant alkyl radical to an alkene followed by radical recombination (Figure 1A). Recently, a visible light-mediated catalyzed radical relay has been introduced as a new approach for the vicinal alkylcarbofunctionalization of alkenes.[4]

Earlier, we developed the *N*-heterocyclic carbene (NHC)-based radical catalysis that enabled the decarboxylative coupling of aryl aldehydes and tertiary alkyl carboxylic acid-derived redox active esters.[5,6] The reaction pathway involves SET from the enolate form of a Breslow intermediate, derived from the aldehyde, NHC and a base, to a redox ester followed by recombination of the resultant radical pair to form a carbon–carbon bond. This finding prompted us to consider whether such NHC catalysis could enable the vicinal alkylcarbofunctionalization of alkenes through a radical relay mechanism involving SET from the enolate form and radical addition of the resultant alkyl radical to an alkene followed by radical–radical coupling (Figure 1B). Based on the NHC-catalyzed radical ring-closing experiment in our previous study,[5] we estimated that the rate of radical–radical coupling between the Breslow-derived ketyl radical and a tertiary alkyl radical was equal to that of 5-exo-radical cyclization (1.1×10^5 s^{-1}).[7] This process is slower than addition of a tertiary alkyl radical to an alkene such as styrene (1.3×10^5 s^{-1}) or acrylate (1.1×10^6 s^{-1}).[8] Thus, the radical addition/radical–radical coupling pathway as shown in Figure 1B would be kinetically feasible.

Herein, we report an unprecedented radical relay by organocatalysis, reminiscent of that by transition-metal catalysis or photoredox catalysis. The NHC catalysis allows for vicinal alkylacylation of styrenes, acylates and acrylonitriles using aldehydes and tertiary alkyl carboxylic acid-derived redox-active esters.[9] This protocol could introduce tertiary alkyl groups and acyl groups into C–C double bonds with complete regioselectivity to produce functionalized ketone derivatives. Notably, the protocol does not require metals, additional reagents (oxidant, reductant) or light.

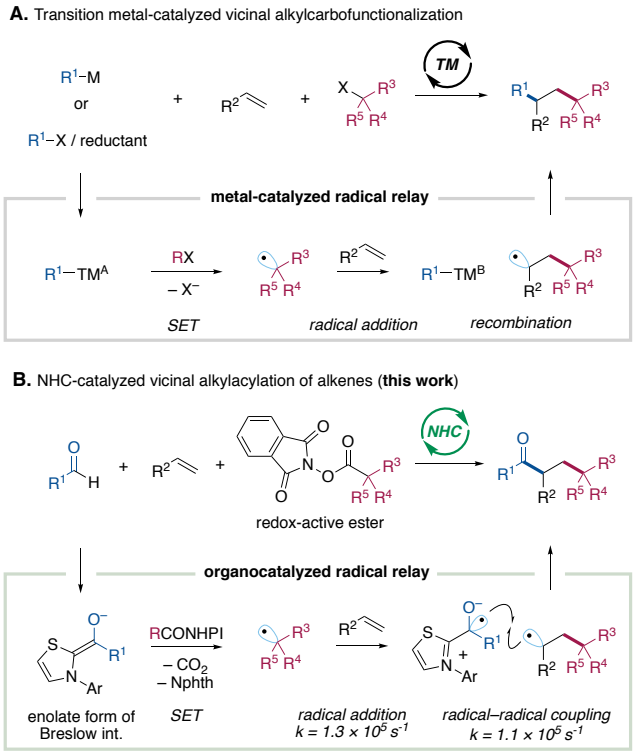


Figure 1. Radical relay strategies for vicinal alkylcarbofunctionalization of alkenes

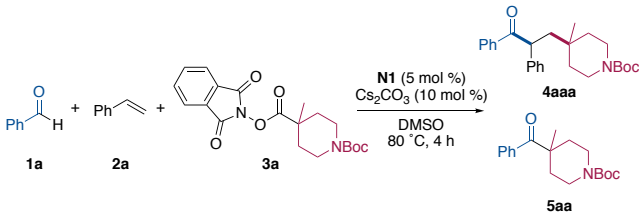
Upon exploring the various reaction parameters based on our earlier investigations on the NHC-catalyzed decarboxylative coupling of aryl aldehydes and alkyl carboxylic acid-derived redox active esters,[5] we found that the reaction using benzaldehyde (**1a**) (0.2 mmol), styrene (**2a**) (0.4 mmol) and *N*-(acyloxy)phthalimide

3a (0.3 mmol) occurred in the presence of catalytic amounts of the *N*-2,6-diisopropylphenyl-substituted six-membered ring fused thiazolium salt **N1**[6,10] (5 mol %) as the NHC precursor and Cs_2CO_3 (10 mol %) in DMSO at 80 °C to afford the three-component alkylacylation product (**4aaa**) in 84% yield (Table 1, entry 1). The acyl and tertiary alkyl moieties were introduced at the α and β carbons of styrene, respectively, with complete regioselectivity. A small amount of the expected side product, **5aa** derived from the NHC-catalyzed two-component coupling of **1a** and **3a**, was observed.

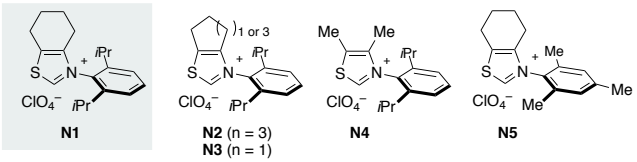
The steric and electronic natures of the NHC catalyst had marked influence on the reactivity (Table 1, entries 2–5). Using **N2** possessing a 7-membered backbone, which exhibited high performance in the previously reported two-component coupling,[5] resulted in a decrease in the product yield of **4aaa** (entry 2). **N3** having a 5-membered backbone did not show substrate conversion (entry 3). The use of a dimethyl backbone instead of the cyclohexane backbone in **N1** diminished the product yield (entry 4). Changing the substituent on the nitrogen in NHC to a smaller mesityl group caused a significant decrease in the reactivity (entry 5). Other NHCs having triazolium, imidazolium or oxazolium structures were ineffective (data not shown).

The choice of base was also critical for this reaction (Table 1, entries 6–8). As shown above, cesium carbonate was found to be best. The reaction proceeded less effectively when cesium carbonate was replaced with potassium carbonate (entry 6). The use of strong organic bases such as DBU and TMG showed low reaction efficiencies (entries 7 and 8).

Table 1. Screening of catalysts and bases for reaction of **1a**, **2a** and **3a**[a]



entry	Change from standard conditions	Yield of **4aaa** (%)[b]	Yield of **5aa** (%)[b]
1	none	84 (84)	13
2	**N2** instead of **N1**	76	15
3	**N3** instead of **N1**	0	0
4	**N4** instead of **N1**	52	16
5	**N5** instead of **N1**	11	3
6	K_2CO_3 instead of Cs_2CO_3	74	17
7	DBU instead of Cs_2CO_3	55	14
8	TMG instead of Cs_2CO_3	47	9

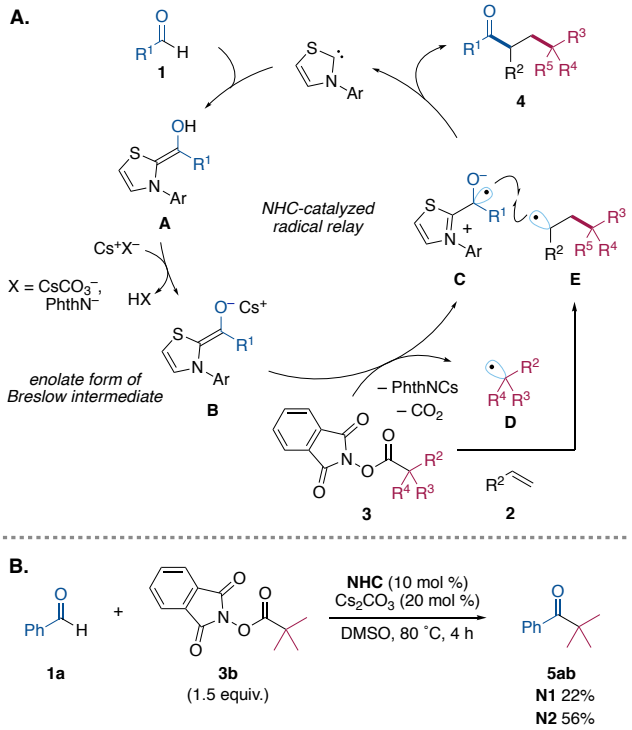


[a] Reaction was carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), NHC (0.01 mmol), and Cs_2CO_3 (0.02 mmol) in DMSO (0.4 mL) at 80 °C for 4 h. [b] ^{1}H NMR yield based on **1a**. DMSO = dimethylsulfoxide. DBU = 1,8-diazabicyclo[5.4.0]-7-undecene. TMG = 1,1,3,3-tetramethylguanidine.

The generality of the NHC-catalyzed three-component alkylacylation was evaluated by exploring different substrates. Various aryl aldehydes were subjected to the reaction (Table 2, top). Neither electron-rich nor electron-deficient functional groups in the aromatic ring affected the reactivity (**4baa**–**4faa**). The reaction was compatible with halogen substituents, which can be utilized for further derivatizations (**4gaa**–**4iaa**). Although a substituent at the meta position of benzaldehyde was tolerated (**4jaa**), *o*-substituted aryl aldehyde completely inhibited the reaction (data not shown). Electron-rich and electron-deficient heteroaromatic rings such as pyridine, thiophene and benzofuran participated in the reaction (**4kaa**–**mlaa**). 2-Naphthaldehyde was a suitable substrate (**4naa**). The use of aliphatic aldehyde as a coupling partner resulted in no product formation (data not shown).

The range of tertiary alkyl carboxylic acid derived redox esters is shown in Table 2, middle. The use of pivalic acid or 2-methyl-2-phenylpropanoic acid gave high product yields (**4aab** and **4aac**). Various tertiary carboxylic acids bearing a ring system engaged in the alkylacylation. For example, 3-, 5- or 6-membered rings were tolerated (**4aad**–**4aaf**). Adamantyl and bicyclo[2,2,2]octyl groups were introduced efficiently (**4aag** and **4aah**). Benzoate and THP groups remained untouched under the reaction conditions (**4aai** and **4aaj**). The reaction using *α*-oxy or *α*-amino carboxylic acids occurred to afford the corresponding ketones (**4aak**–**4aam**). This reaction could be applied to the late-stage functionalization of pharmaceutical drugs such as bezafibrate and gemfibrozil with excellent yields (**4aan** and **4aao**). Unfortunately, primary and secondary redox active esters were not compatible in this reaction (data not shown).

Table 2, bottom summarizes the results of the reactions of various alkenes under the NHC catalyst system.[11] Functional groups such as methoxy, benzyl ether, bromo and acetal substituents were tolerated in the aromatic ring of the vinyl arenes (**4aca**–**4afa**). Naphthyl and thiophene-substituted alkene substrates were also suitable (**4aga** and **4aha**). Notably, Michael acceptors such as acylate and acrylonitrile participated in the reaction (**4aia** and **4aja**). The acyl and tertiary alkyl groups were delivered to the α and β carbons of the acylate and acrylonitrile with complete regioselectivity.

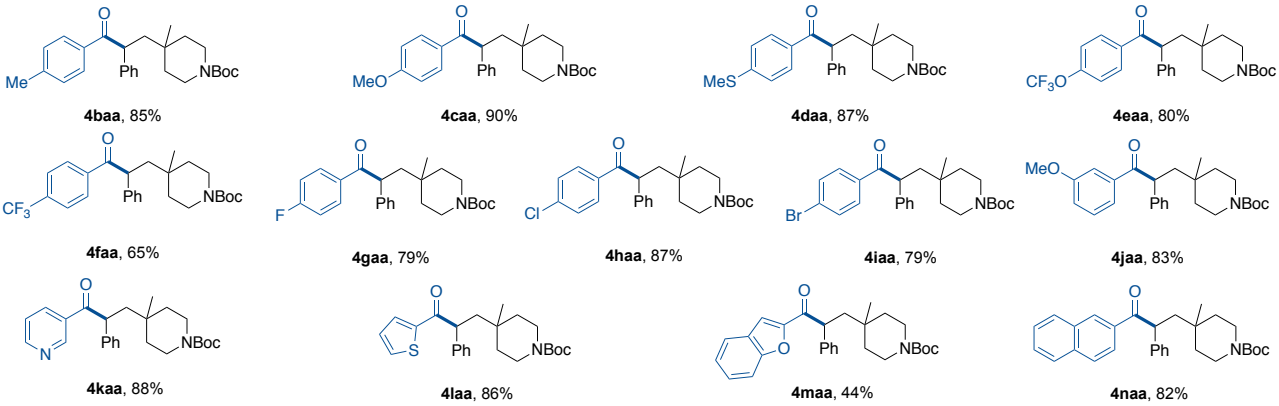


Scheme 1. Mechanistic considerations

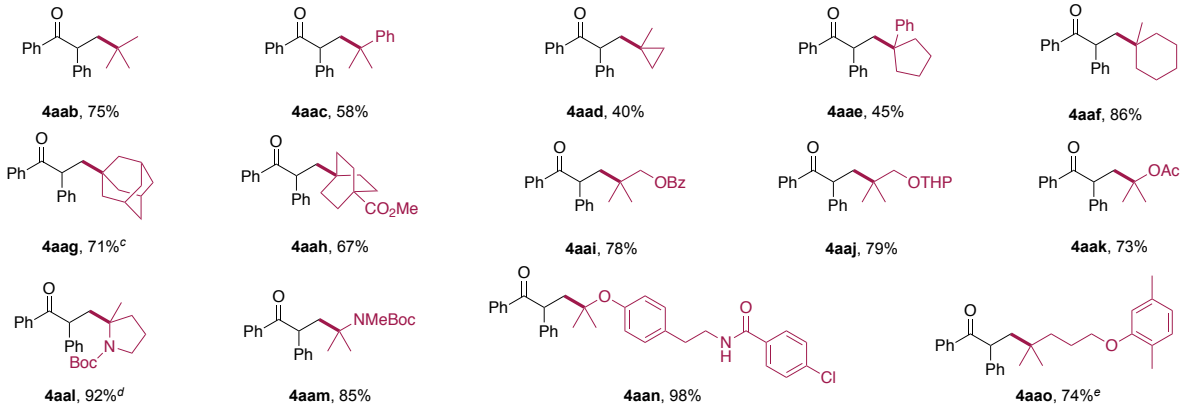
We proposed the NHC-catalyzed radical relay mechanism for the vicinal alkylacylation of alkene **2** using aldehyde **1** and redox ester **3** as depicted in Scheme 1A. The initial reaction between **1** and NHC forms a neutral Breslow intermediate (**A**). Next, deprotonation of the enol OH in **A** by cesium carbonate generates the high reducing enolate form of the Breslow intermediate (**B**) (E^0_{ox} = –0.95 ~ –0.97 V vs. SCE in MeCN).[12] Subsequently, the single electron transfer event between the enolate **B** and **3** provides a ketyl radical (**C**) and an alkyl radical (**D**), respectively. After addition of the resultant tertiary alkyl radical **D** to alkene **2** forming secondary radical **E**, the radical–radical coupling between **C** and **E** followed by elimination releases the alkylacylation product **4** and regenerates NHC for the next catalytic cycle.[13]

Table 2. Substrate scope[a,b]

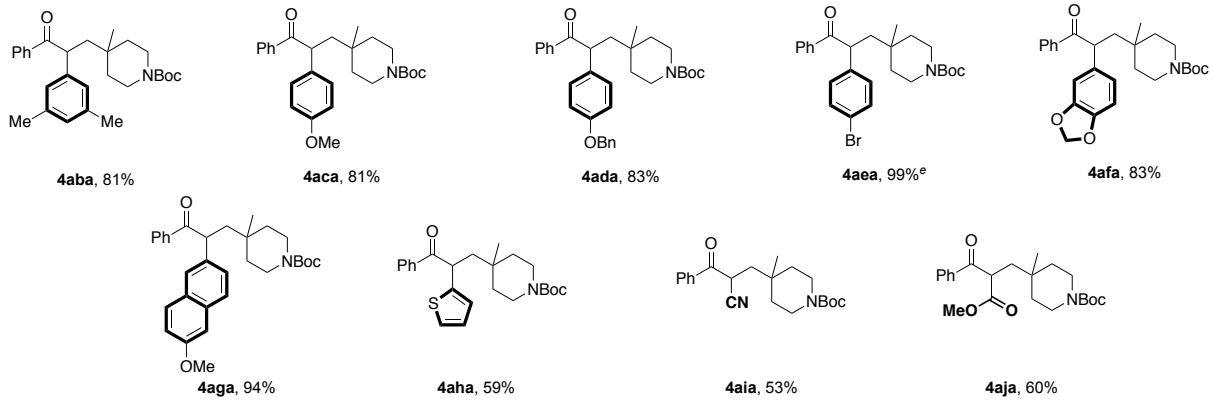
Scope of Aldehydes



Scope of Redox-Active Esters



Scope of Alkenes



[a] Reaction was carried out with aldehyde **1** (0.2 mmol), alkene **2** (0.4 mmol), redox-active ester **3** (0.3 mmol), **N1** (0.01 mmol), and Cs_2CO_3 (0.02 mmol) in DMSO (0.4 mL) at 80 °C for 4 h. [b] A small amount of two-component coupling product **5** was observed. [c] **N1** (0.02 mmol) and Cs_2CO_3 (0.04 mmol) were used. [d] Diastereomeric ratio is 1:1. [e] Isolated as the corresponding alcohol (see Supporting Information).

To gain insight into the effect of the NHC catalyst, we conducted two-component couplings between aldehyde **1a** and redox ester **3b** using six- and seven-membered ring fused thiazolium salts **N1** and **N2** (Scheme 1B). The six-membered **N1** was less effective than the seven-membered **N2** in terms of product yield of **5ab**. This might be due to the slow radical–radical coupling of the **N1**-derived ketyl radical and the tertiary alkyl radical. This is consistent with the experimental observations that **N1** has higher chemoselectivity than **N2** (**4aaa**/**5aa**) in the three-component coupling (see Table 1, entries 1 and 2).[14]

In summary, we demonstrated the NHC organocatalyzed vicinal alkylacylation of styrenes, acylates and acrylonitrile using simple aldehydes and tertiary alkyl carboxylic acid-derived redox-active esters to produce functionalized ketone derivatives. The reaction proceeds through a radical relay mechanism, in which the NHC organocatalyst precisely controls SET, radical addition and radical–radical coupling. Our NHC-based radical catalysis presents a new platform for C–C bond formation in organic synthesis. Studies on the asymmetric version of this alkylacylation (see Supporting Information) and mechanistic investigations aided by theoretical calculations are currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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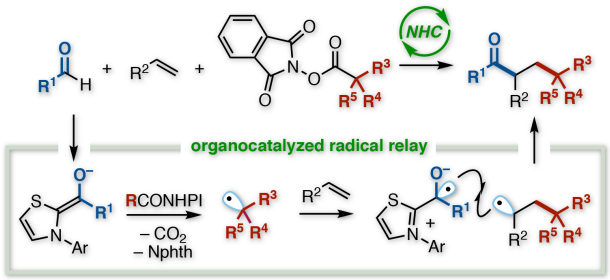
(13) The further addition of benzyl radical **E** to alkene **2** was not detected. This would be due to the slower rate of addition of benzyl radical to styrene (1.1×10^3 s^{-1}, see ref 8) than that of radical–radical coupling between **C** and **E** (1.1×10^5 s^{-1}) (see Scheme 1A).

(14) Further information on the effect of NHC catalyst is available in Supporting Information.


NHC
organocatalyzed radical relay
RCONHPI
– CO2
– Nphth