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# N-Heterocyclic carbene-catalyzed radical ring-opening acylation of oxime esters with aldehydes†

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A cross-coupling of cycloketone oxime esters with aldehydes catalyzed by N-heterocyclic carbenes *via* a radical pathway was established. This modular protocol features easy operation, no external oxidants or reductants, and a broad functional group compatibility. The merit of this method was showcased by late-stage modification of complicated aldehydes derived from the medical intermediate pregnenolone and natural product diacetone-D-glucose.

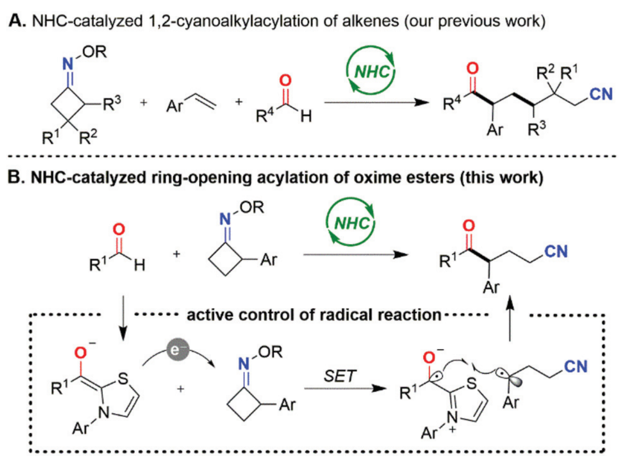


## Introduction

Owing to their unique nucleophilicity and Lewis basicity, N-heterocyclic carbenes (NHCs) have arisen as prominent organocatalysts with wide applications in chemical synthesis.[1] Commonly, NHC-catalyzed transformations proceed by the generation of Breslow,[2] π-extended Breslow[3] or acyl azolium intermediates[4] in electron-pair-transfer pathways. In contrast, the emerging realm of NHC catalyzed single-electron-transfer (SET) reactions still remains underdeveloped,[5] but has opened new avenues for developing novel catalytic modes and promising synthetic strategies.[6] Thus, the development of novel reaction types *via* radical NHC catalysis is highly desirable.

Since the pioneering disclosure of the reducing ability of the enolate form of the Breslow intermediate by the Fukuzumi group,[7] elegant radical transformations mediated by NHCs have been reported by Scheidt,[8] Studer,[9] Rovis,[10] Chi,[11] Ye,[12] Ohmiya,[13] and other groups.[14] Recently, we also developed a regioselective, intermolecular 1,2-cyanoalkylacylation of alkenes with oxime esters[15] and aldehydes by NHC organocatalysis (Scheme 1A).[16] A SET from the enolate form of the Breslow intermediate to a cyclobutanone oxime ester occurs to give a persistent aldehyde-derived ketyl radical and a transient primary cyanoalkyl radical after radical transposition *via* C–C bond cleavage. Radical addition of the primary cyanoalkyl radical to styrene occurs preferentially to lead to the more stable benzyl radical, which then engages in radical–radical cross-coupling with the persistent ketyl radical to afford the three-component coupling product.

Enlightened by this finding, we surmised that if the cycloketone oxime esters themselves can form the more stable benzyl radicals, the direct radical cross-coupling of aldehydes with such cycloketone oxime esters might be realized. Herein, we report an NHC-catalyzed radical ring-opening acylation of oxime esters with aldehydes under transition-metal-free and redox-neutral conditions, granting a straightforward, flexible access to ketonitrile structures (Scheme 1B). It is noteworthy that the products are a class of versatile building blocks.




Scheme 1 Synthetic strategy.

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## Results and discussion

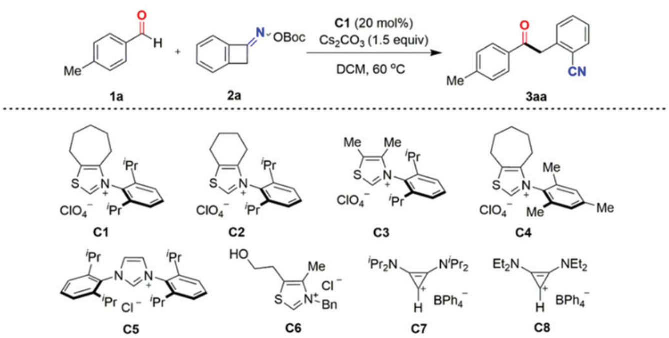
At the outset, 4-methylbenzaldehyde **1a** and *O*-(*tert*-butoxycarbonyl) oxime **2a** were chosen as model substrates to investigate the ring-opening acylation of oxime esters in the presence of the carbene precursor. Indeed, in our most recent work,[16] the two-component cross-coupling of an oxime and an aldehyde was observed;[17] thus a brief optimization of the carbene catalyst, solvent, and base led to the identification of optimal conditions, which involved the use of the *N*-2,6-diisopropylphenyl-substituted cycloheptane-fused thiazolium precatalyst **C1** (20 mol%), dichloromethane (DCM), and cesium carbonate to furnish the two-component coupling product ketonitrile **3aa** in 95% yield (Table 1, entry 1).

It was found that both the backbone architecture and the *N*-aryl substituent of the thiazolium salts played a significant role in reaction efficiency (Table 1, entries 2–5). Employing 10 mol% carbene precursor **C**, such as the six-membered-ring thiazolium salt bearing *N*-2,6-diisopropylphenyl-substituent **C2** (entry 3), or the thiazolium salt with an acyclic backbone **C3** (entry 4), or the seven-membered-ring thiazolium salt bearing an *N*-mesityl-substituent **C4** (entry 5) resulted in reduced yields. The sterically demanding *N*-2,6-diisopropylphenyl group and a cycloheptane backbone were identified as the optimum structure (entry 2). Increasing the precatalyst **C1** loading to 20 mol% further boosted the product yield (entry 1). On the other hand, the commercially available imidazolium- and thiazolium-type NHC precatalysts **C5** and **C6** were quite ineffective in this transformation (entries 6 and 7), as were non-heterocyclic-based carbenes derived from bis(amino) cyclopropenium salts[18] **C7** and **C8** (entries 8 and 9).

The solvent had a profound effect on the reaction, as other solvents including 1,2-dichloroethane (DCE), acetonitrile (MeCN), tetrahydrofuran (THF), and dimethyl sulfoxide (DMSO) were found to be unsuitable for this ring-opening acylation transformation (Table 1, entries 10–13). The choice of the base also proved to be the key. $K_2CO_3$ gave **3aa** in a comparable yield to $Cs_2CO_3$, whereas the use of other bases such as $Na_2CO_3$, DBU, or TMG instead of $Cs_2CO_3$ all led to a stark decrease in yield (entries 14–17). Control experiments revealed that the NHC catalyst and base were necessary for the success of this ring-opening acylation of oxime esters.

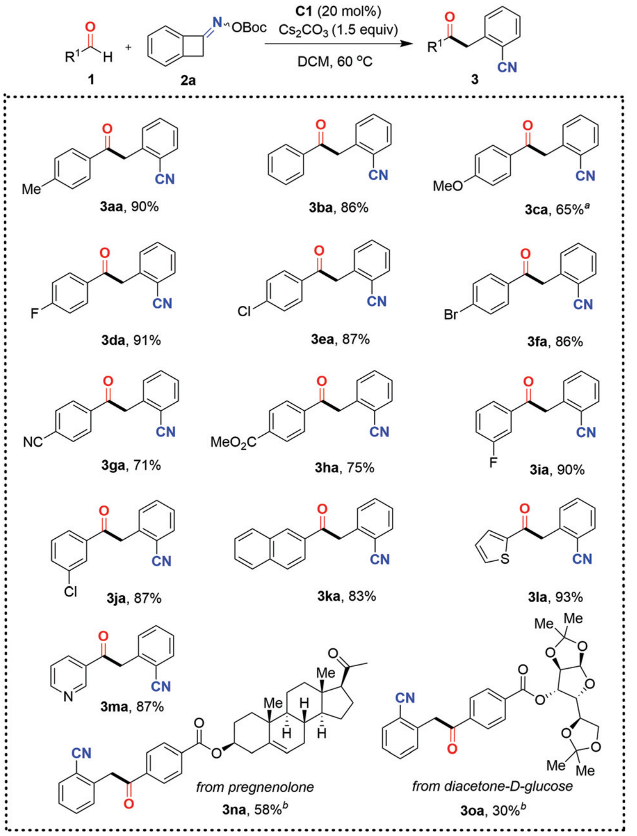
With the optimal reaction conditions in hand, the scope and limitations of this ring-opening acylation of oxime esters were investigated (Schemes 2 and 3). The initial focus was on assessing aldehyde diversity. As shown in Scheme 2, the C–C bond cleavage of benzocyclobutenone-derived oxime ester occurred with complete regioselectivity to form the more stable benzyl radical to engage in the reaction. When benzaldehyde **1b** was subjected to the standard conditions, the ketonitrile **3ba** was obtained in 86% yield. Benzaldehydes **1c–1h** bearing a gamut of pendant functionalities at the *para* position, such as ether (**3ca**), halides (**3da–3fa**), cyano group (**3ga**), and ester (**3ha**), were well accommodated, giving access to the corresponding coupling products **3ca–3ha** with yields ranging from 65% to 91%. Relatively lower reactivity was observed for 4-methoxybenzaldehyde **1c**, indicating that the introduction of a strong electron-donating group onto the aryl ring of the aldehyde might be detrimental for the aldehyde-derived Breslow radical intermediate to undergo radical–radical coupling with the benzyl radical. Although a substituent at the *para* and *meta* positions of the aryl aldehyde was tolerated (**3ea** and **3ja**), *o*-substituted benzaldehyde completely inhibited the reaction (data not shown). 2-Naphthaldehyde proved to be a viable coupling partner in this reaction manifold, affording the expected product **3ka** in 83% yield. Furthermore, aldehydes containing electron-rich and electron-deficient heteroaromatic rings such as thiophene and pyridine can also be used, as exemplified by **3la** and **3ma**. As a current limitation, aliphatic aldehydes are not competent as acyl donors in this reaction. This may be attributed to the instability (short lifetime) of the aliphatic aldehyde-derived Breslow radical intermediate. Although cinnamaldehyde was also attempted, no products were observed. Finally, this organocatalytic approach was further applied to the late-stage modification of complex mole-

**Table 1** Optimization of the reaction conditions[a]

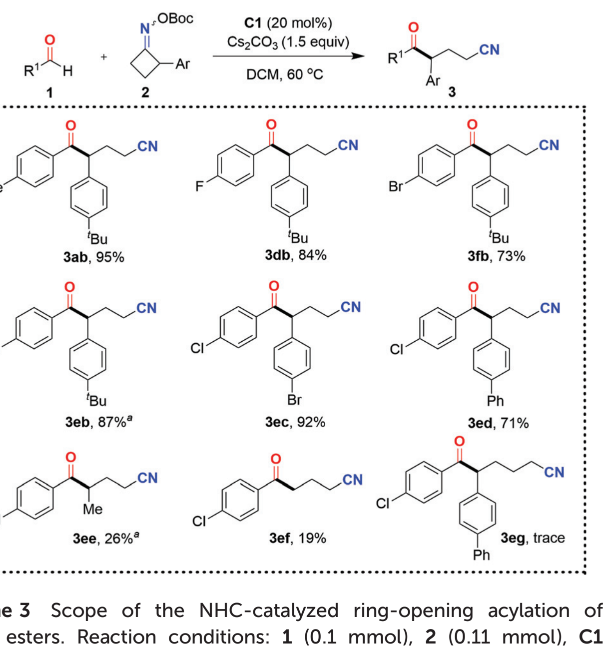



| Entry | Deviation from standard conditions | Yield[b] (**3aa**, %) |
|---|---|---|
| 1 | None | 95 |
| 2 | Using 10 mol% **C1** | 66 |
| 3[c] | **C2** instead of **C1** | 53 |
| 4[c] | **C3** instead of **C1** | 40 |
| 5[c] | **C4** instead of **C1** | 30 |
| 6[c] | **C5** instead of **C1** | 1 |
| 7[c] | **C6** instead of **C1** | 0 |
| 8[c] | **C7** instead of **C1** | 0 |
| 9[c] | **C8** instead of **C1** | 0 |
| 10 | DCE instead of DCM | 12 |
| 11 | MeCN instead of DCM | 1 |
| 12 | THF instead of DCM | 3 |
| 13 | DMSO instead of DCM | 0 |
| 14 | $Na_2CO_3$ instead of $Cs_2CO_3$ | 6 |
| 15 | $K_2CO_3$ instead of $Cs_2CO_3$ | 93 |
| 16 | DBU instead of $Cs_2CO_3$ | 10 |
| 17 | TMG instead of $Cs_2CO_3$ | 43 |
| 18 | No NHC catalyst | 0 |
| 19 | No base | 0 |

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), **C1** (20 mol%), and $Cs_2CO_3$ (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar. [b] Yield determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Using 10 mol% **C**. Boc = *tert*-butyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]-7-undecene, and TMG = 1,1,3,3-tetramethylguanidine.




**Scheme 2** Scope with respect to aldehydes. Standard reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), **C1** (20 mol%), and $Cs_2CO_3$ (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar; isolated yields based on **1** are given. [a] Using 40 mol% **C1**. [b] Using 30 mol% **C1**.



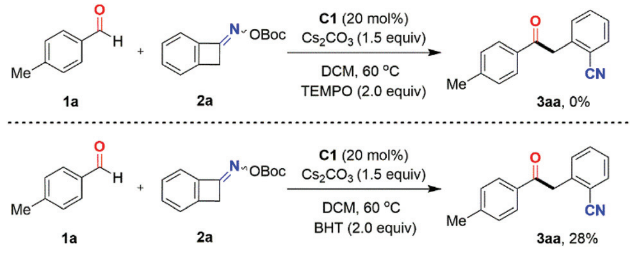

**Scheme 3** Scope of the NHC-catalyzed ring-opening acylation of oxime esters. Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), **C1** (20 mol%), and $Cs_2CO_3$ (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar; isolated yields based on **1** are given. [a] 0.2 mmol scale.

cules. For example, complex aldehyde derivatives of pregnenolone and diacetone-D-glucose were apt to give serviceable yields of the coupling products **3na** and **3oa**. It is noteworthy that the thus obtained ketonitrile products **3** could be further converted to biologically active CWJ-a-5 analogues according to a reported procedure.[19]

Our attention then turned to evaluating the scope of cycloketone oxime esters. Gratifyingly, the range of cycloketone oxime esters was not restricted to the benzocyclobutenone-derived oxime ester **2a**, and could also encompass α-aryl-substituted cyclobutanone-derived oxime esters (Scheme 3). The cyclobutanone oxime esters **2** with substituents such as tertiary butyl (**2b**), bromide (**2c**), and phenyl (**2d**) groups at the *para*-position of the aromatic ring reacted smoothly with 4-chlorobenzaldehyde **3e**, affording the corresponding products δ-keto nitriles (**3eb**, **3ec**, and **3ed**) with yields ranging from 71% to 92%. On the downside, the reaction performed poorly with the α-methyl-substituted cyclobutanone-derived oxime ester **2e** and non-substituted cyclobutanone-derived oxime ester **2f**, presumably due to the instability of the generated secondary or primary radical in comparison with the benzyl radical. The less-strained, five-membered cycloketone oxime ester **2g** was nonproductive under the present organocatalytic conditions. Only a trace amount of the target product **3eg** was detected by HRMS.

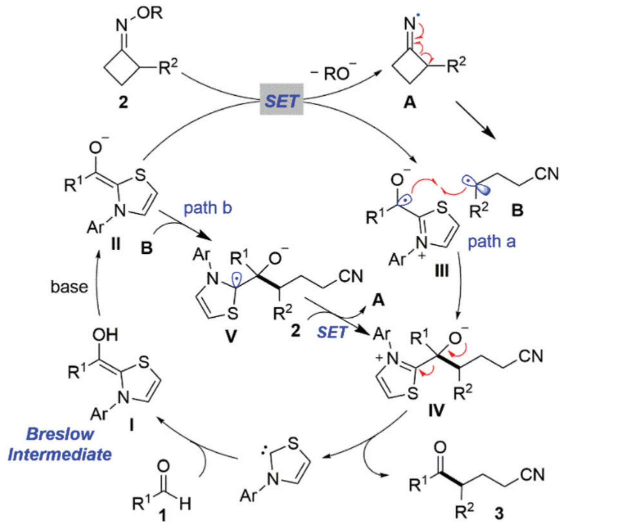
To shed light on the tentative reaction mechanism, a preliminary mechanistic investigation was performed (Scheme 4). In the presence of 2.0 equivalents of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the standard reaction of 4-methylbenzaldehyde **1a** and *O*-(*tert*-butoxycarbonyl) oxime **2a** was totally inhibited. Furthermore, 4-methylbenzaldehyde **1a** was reacted with *O*-(*tert*-butoxycarbonyl) oxime **2a** under standard conditions in the presence of 2.0 equivalents of the radical scavenger 2,6-*di*-*tert*-butyl-4-methylphenol (BHT), affording the two-component coupling product **3aa** in only 28% yield. This result indicated the radical nature of this transformation.

On the basis of the above experimental results and the literature,[13a,16] a tentative mechanism for the NHC-catalyzed ring-opening acylation of oxime esters is illustrated in Scheme 5. First, NHC reacts with the aldehyde **1** to give the corresponding Breslow intermediate **I**. Next, the enolate form of the Breslow intermediate **II** would be generated by deprotonation in the presence of a base and induce the SET event




**Scheme 4** Mechanistic investigations.




**Scheme 5** Proposed mechanism for the NHC-catalyzed ring-opening acylation of oxime esters.

between the enolate **II** and cyclobutanone oxime ester **2**, affording a persistent ketyl radical **III** and an iminyl radical **A**, respectively. Subsequent regioselective ring-opening of **A** *via* C–C bond β-cleavage forms the benzyl radical **B**. Intermediates **III** and **B** would undergo radical–radical cross-coupling to furnish the intermediate **IV** (path a).[20] Alternatively, another addition of the benzyl radical **B** to the enolate form of the Breslow intermediate **II** might occur, giving a plausible NHC-bound radical intermediate **V**. SET from the intermediate **V** to oxime ester **2** would ensue to form the intermediate **IV** and a new iminyl radical **A**, respectively (path b). Currently, we cannot exclude either pathway. Ultimately, the species **IV** would undergo facile elimination to deliver the target product ketonitrile **3** and release the NHC, thereby closing this catalytic redox-neutral cycle.

## Experimental

### General procedure for ring-opening acylation of oxime esters

A flame-dried 10 mL resealable screw-cap Schlenk tube containing a magnetic stirring bar was charged with the aldehyde **1** (0.1 mmol, 1.0 equiv.), oxime ester **2** (0.12 mmol, 1.2 equiv.), NHC precursor C1 (8.3 mg, 0.02 mmol, 0.2 equiv.), $Cs_2CO_3$ (48.9 mg, 0.15 mmol, 1.5 equiv.), and anhydrous DCM (1.0 mL) under an argon atmosphere. The reaction mixture was stirred in a preheated 60 °C oil bath for 12 h. After that, the mixture was concentrated under reduced pressure. The resulting crude product was purified by silica gel flash column chromatography to give the corresponding products **3aa–3ef**.

## Conclusions

In summary, we have developed an emerging NHC-catalyzed radical cross-coupling of cycloketone oxime esters with readily available aldehydes. By using an *N*-2,6-diisopropylphenyl-substituted cycloheptane-fused thiazolium salt as the NHC precatalyst, the cyanoalkyl or 2-cyanobenzyl from the cycloketone oxime esters and the acyl from the aldehydes were docked efficiently, giving access to ketonitriles in moderate to good yields. The aromatic nitriles can be used to construct a compound library of topoisomerase I inhibitor CWJ-a-5 analogues. This protocol features easy operation, with no need for external oxidants, reductants or transition-metal catalysts, and a good functional group tolerance. The compatibility of substrate scope covers benzocyclobutenone oxime esters, α-aryl-substituted cyclobutenone oxime esters, and aromatic aldehydes. Complicated aldehydes derived from the medical intermediate pregnenolone and natural product diacetone-D-glucose also proved to be viable coupling partners, affording the corresponding coupling products in synthetically useful yields. Mechanistic studies indicated that a radical pathway was involved. This work further enriches the types of radical reactions catalyzed by NHC.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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