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N-Heterocyclic Carbene/Magnesium Cocatalyzed Radical Relay Assembly of Aliphatic Keto Nitriles

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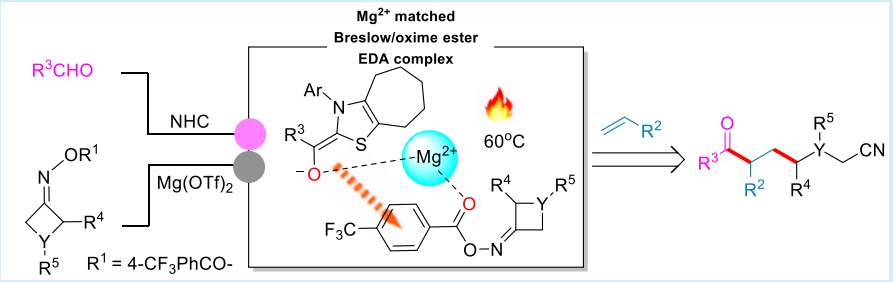

ABSTRACT: An unprecedented N-heterocyclic carbene and magnesium cocatalyzed three-component acylcyanoalkylation of alkenes with cycloketone oxime esters and aldehydes is presented. This method displayed good scope generality, providing a transition-metal- and photoredox-free pathway to access various multifunctionalized aliphatic keto nitrile structures under mild reaction conditions. Moreover, this strategy is supposed to follow a radical relay mechanism via a single electron transfer event of a Mg/matched Breslow intermediate/oxime ester electron-donating acceptor (EDA) complex.

Aliphatic compounds bearing multiple functional groups represent key structures in many chemical frontier fields. For example, they are the basic skeletons for dual target inhibitors,[1] the chemical linkers for surfactants or polymers,[2] and the connectors for supported catalysts[3] (Scheme 1a). The traditional synthesis of such compounds usually required the installation of each functional group in sequence, resulting in extra workloads such as protection/deprotection procedures, selectivity issues, and workup problems.

Multicomponent reactions (MCRs) have been recognized as powerful tools to provide straightforward access to various complex structures.[4] Among them, the intermolecular dicarbofunctionalization of olefins, installing an sp^3-alkyl group and another carbon group into the substrates, represents one of the most efficient MCR strategies to enable the streamlined construction of aliphatic frameworks in a single step.[5] Regularly, transition metal (TM) catalysis,[6] especially Pd[7] and more recently Ni catalysis,[8] have been successfully applied to these transformations (Scheme 1b). However, the in situ-generated alkylmetal intermediates may undergo potential side reactions such as β-H elimination and isomerization. Despite the significant progress in TM-catalyzed reactions, catalytic transition-metal-free dicarbofunctionalization, especially acylalkylation of alkenes, remains highly desired.

N-Heterocyclic carbenes (NHCs) have emerged as leading organocatalysts, especially for the characteristic ability to access umpolung reactivity of diverse aldehydes.[9] In recent years, NHC-catalyzed reactions via a radical process have evoked great interest among organic chemists.[10] However, there are limited NHC-catalyzed radical relay reactions for $C(sp^3)-C$ bond formation via olefin dicarbofunctionalization (Scheme 1b).[11] Therefore, further discovery of novel radical relay matched substrate pairs and reaction systems for $C(sp^3)-C$ bond formation via olefin dicarbofunctionalization is in high demand. To the best of our knowledge, three-component acylcyanoalkylation of olefins has not been reported to date. We noticed that cycloketone oxime esters are useful and versatile intermediates in organic synthesis that serve as the feedstock for the synthesis of functionalized nitriles via the formation of nitrile alkyl radicals under TM catalysis or photoredox conditions.[12] Thus, in principle, the incorporation of cyclobutanone oxime esters with alkenes and aldehydes under NHC catalysis might enable the olefin acylcyanoalkylation reaction to afford diverse structurally interesting aliphatic keto nitriles via the electron-donating acceptor (EDA) strategy (Scheme 1c). In particular, the newly formed keto nitriles can allow various further transformations that would be useful in synthetic and medicinal chemistry.

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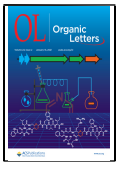

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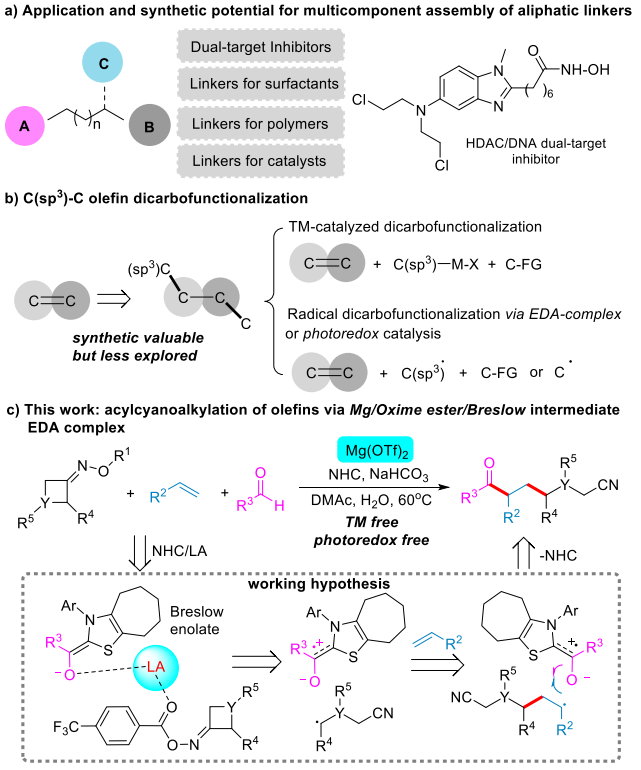
Scheme 1. Overview of Dicarbofunctionalization of Olefins and Our Working Hypothesis



However, it was found that the reductive potentials of cyclobutanone oxime esters were around −1.6 V vs SCE in MeCN,[12d] while the reductive potentials of enolates (deprotonation of the Breslow intermediates) were around −0.95 to −0.97 V vs SCE in MeCN.[13] It seems that the enolates might not attain sufficient reductive potential for the cyclic oxime esters. Since NHC/Lewis acid (LA) cocatalysis[14] has been widely used to enable numerous unconventional transformations, we assumed that the electron transfer of this theoretically mismatched species might occur with the assistance of a Lewis acid. Herein we present a magnesium-promoted NHC-catalyzed radical relay protocol to patch up the potential gap between cycloketone oxime esters, aldehydes, and alkenes, providing facile access to functionalized aliphatic keto nitriles (Scheme 1c).

To start this work, cyclobutanone oxime ester **1a**, styrene (**2a**), and 4-chlorobenzaldehyde (**3a**) were used as the model substrates (Figure 1). No product was observed in the absence of NHC catalyst **A** (Figure 1, line 1). The presence of $Mg(OTf)_2$ was also crucial to this MCR reaction, as otherwise a low yield was observed (Figure 1, line 2). $La(OTf)_3$ could slightly enhance the reaction yield to 23% (Figure 1, line 3), while other tested Lewis acids led to no acceleration (Table S3). To our interest, the water content (2.0 equiv, 4600 ppm; Table S5) was found to be another key factor for the success of this reaction because using a super-dry solvent along with molecular sieves (300 ppm; Table S5) or adding more water (i.e., 20 equiv) always gave inferior results (Figure 1, lines 4 and 5). Water may act as the activator for oxime esters,[15] and meanwhile, $Mg(OTf)_2$ is prone to absorb moisture to form the hydrated magnesium salt, which may affect the reactivity of magnesium ions in organic solvent. Further screening of the bases identified the weak base $NaHCO_3$ as the optimal one,

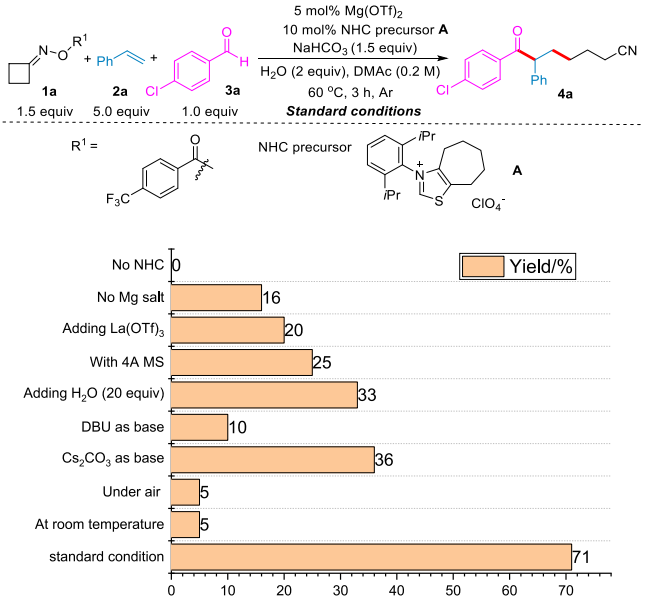


Figure 1. Modifications of the conditions for NHC-catalyzed radical relay acylcyanoalkylation of alkenes. Isolated yields are based on **3a**.

and poor conversions were observed for both strong organic and inorganic bases (Figure 1, lines 6 and 7). Additionally, conducting the reaction under air or at room temperature was found to be ineffective (Figure 1, lines 8 and 9). Finally, the standard conditions were identified as those resulting in 71% isolated yield (Figure 1, lines 8 and 9, and Tables S1−S5).

With the optimized conditions in hand, the substrate scope was then investigated. The reactions of diverse olefins **2** with **1a** and **3a** were initially tested (Scheme 2). Excess olefins were usually required to reach the best yields because of their high volatility. Overall, substituted styrenes showed good tolerance, with isolated yields ranging from 54% to 85% (**4b−o**). Particularly, the reactions of sterically hindered 2-substituted styrenes and 1-vinylnaphthalene proceeded smoothly to give the corresponding products **4n−p** in moderate yields. The reaction of 4-vinylpyridine was also found to be feasible, although with a slightly decreased yield (**4q**). Notably, the intermolecular olefin acylalkylation has seldom been applied to activated olefins such as acrylates because Michael addition side reactions were prone to occur. Gratifyingly, the desired products **4r−t** were obtained in moderate yields for several acrylates under 20 mol % NHC catalysis. However, phenyl acrylate was not suitable for this protocol with low reaction conversion, which might be explained by the lower reactivity resulting from its conjugated structure and electronic effect (**4u**). It was noteworthy that an acrylate bearing a perfluorocarbon chain was also applicable to this method, although with a lower yield. The obtained product **4v** might have potential applications in fluorine chemistry.[16] To further demonstrate the utility of this protocol, some presynthesized olefins bearing natural or bioactive fragments such as cholesterol and estrone were then screened. To our delight, they produced the desired products **4w** and **4x** in 28% and 60% yield, respectively.

Subsequently, the generality of aryl aldehydes was investigated (Scheme 3). The substituents of the aryl aldehydes were found to have a great impact on the reaction yield. The yields varied widely from 41% to 73% (**5a−n**), perhaps as a result of the varied reactivity and redox potential

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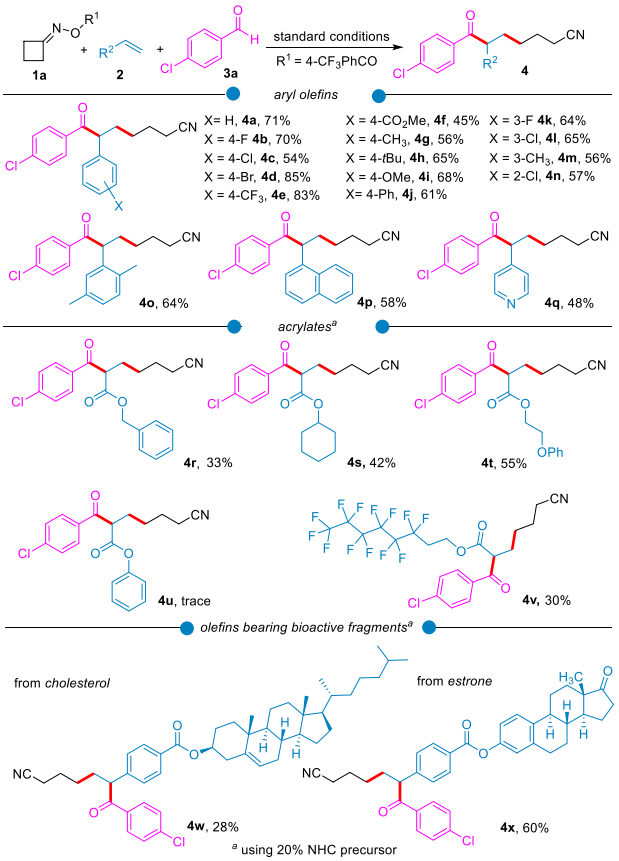
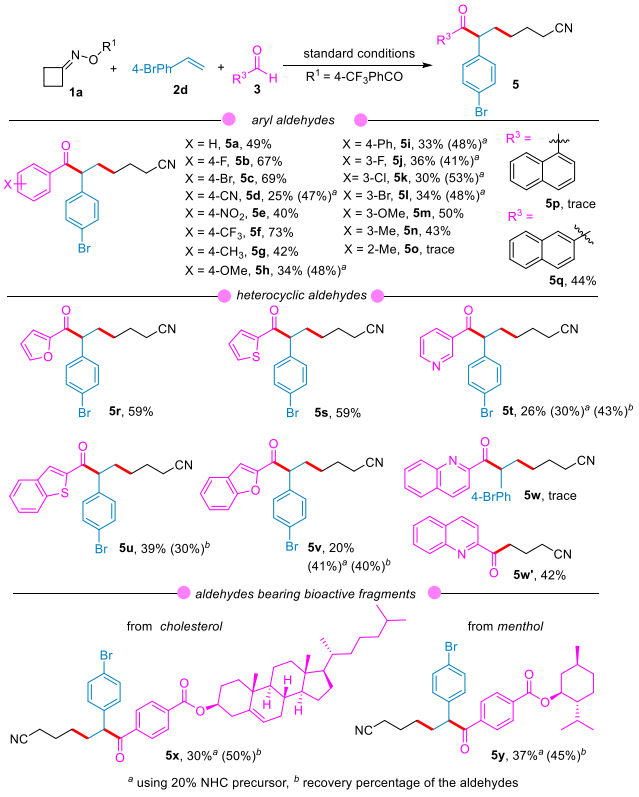
Scheme 2. Substrate Scope of Diverse Olefins



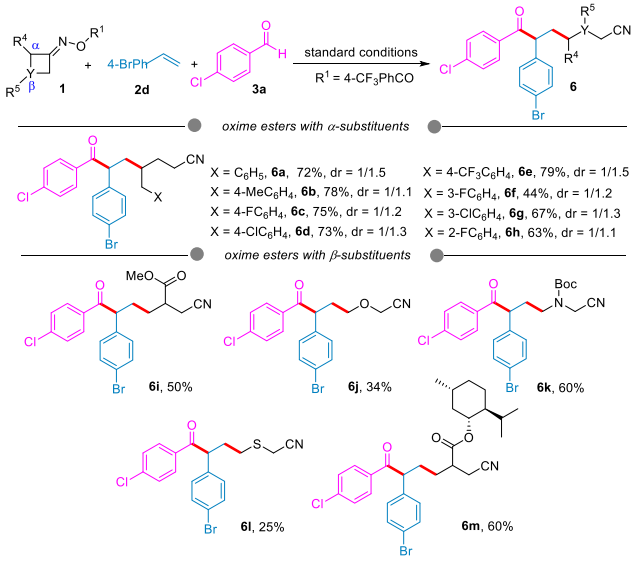
Scheme 3. Substrate Scope of Diverse Aryl Aldehydes



of the Breslow intermediates generated via the combination of aryl aldehydes with the NHC. Overall, some of the *para*-substituted benzaldehydes gave superior yields compared with those bearing *meta* substituents (**5a**–**c** and **5f** vs **5j**–**n**). In some cases, increasing the NHC precatalyst loading slightly enhanced the reaction yields (**5d** and **5h**–**l**). The more sterically hindered 2-methylbenzaldehyde and 1-naphthaldehyde were inapplicable to this protocol (**5o** and **5p**), while the less sterically hindered 2-naphthaldehyde was tolerated to afford product **5q** in 44% yield. Next, several representative heterocyclic aromatic aldehydes were examined. The reactions of 2-furyl and 2-thienyl aldehydes proceeded smoothly to afford the desired products **5r** and **5s**, both in 59% yield. Decreased yields were obtained with nicotinaldehyde, benzo[*b*]thiophene-2-carbaldehyde, and benzofuran-2-carbaldehyde (**5t**–**v**) because of poor conversion of the aldehyde substrates. However, in the case of quinoline-2-carbaldehyde, the undesired compound **5w′** derived from the two-component coupling of the oxime ester with the aldehyde was obtained as the major product. Moreover, aldehydes bearing bioactive fragments were found to be suitable for this transformation. Products **5x** and **5y** were obtained in lower yields because of poor conversion of the aldehydes even when a higher catalyst loading (20 mol %) was applied.

Next, we turned our attention to the scope of oxime esters (Scheme 4). Cyclobutanone oxime esters bearing substituted

Scheme 4. Substrate Scope of Cycloketone Oxime Esters



benzyl groups at the α-position (**6a**–**h**) were well-tolerated under the optimal conditions, affording the corresponding aliphatic keto nitriles in satisfactory yields but with poor diastereoselectivity. α-Substituted cyclobutanone oxime esters always exhibited excellent regioselectivity due to the tendency to form more stable alkyl radicals. Besides α-substituted cyclobutanone oxime esters, several other representative β-substituted cycloketone oxime esters were also checked. To our delight, β-methoxycarbonyl-substituted oxime ester, oxetan-3-one oxime ester, and *N*-Boc-azetidin-3-one oxime were also applicable under the optimal conditions, affording products **6i**, **6j**, and **6k**, respectively. Notably, the difficulty of isolating the above products from the reaction mixture might have a certain influence on the reaction yield. However, the

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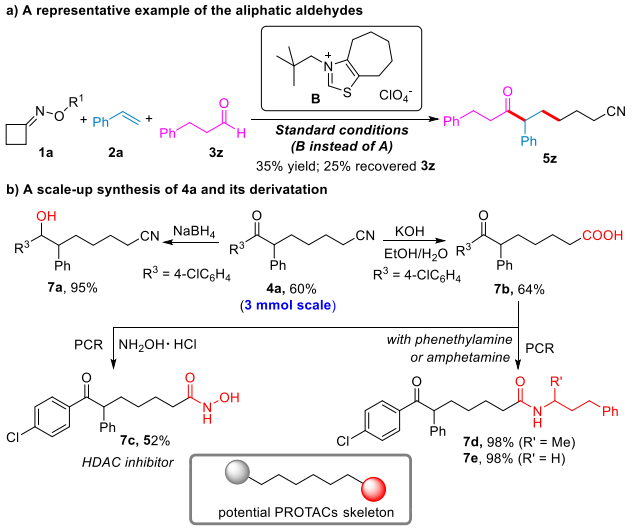
coupling of thietan-3-one oxime ester led to a significantly decreased yield because of the complexity of the reaction (**6l**). It is noteworthy that the reaction of the oxime ester bearing a menthol fragment worked equally well to introduce the aliphatic chain with four functional groups in a single step (**6m**).

After exploring the substrate scope, we also tested the feasibility of the reaction of a representative aliphatic aldehyde **3z** (Scheme 5a). Gratifyingly, the reaction of aldehyde **3z** with

Scheme 5. Synthetic Applications



1a and **2a** was also able to form the desired product **5z**, although in a lower yield, under the catalysis of the unique NHC precursor **B** reported by Ohmiya's group.[17] Since keto-alkylated nitriles represent a class of important synthetic intermediates,[18] investigation of the scaled-up reaction and downstream applications using product **4a** as the starting material were then conducted (Scheme 5b). The reaction on a 3 mmol scale under the standard conditions gave rise to product **4a** with a slightly decreased yield (60%). Reduction of **4a** with $NaBH_4$ afforded alcohol **7a** in 95% yield. **4a** could be also smoothly hydrolyzed to carboxylic acid **7b** in a moderate yield, which had the potential for late-stage assembly of medicinal molecules, such as the PROTACs and dual-target inhibitors. In this case, late-stage decoration of **7b** with NH_2OH using a peptide coupling reagent (PCR) led to HDAC inhibitor skeleton **7c**.[19] Alternatively, the amidation of acid **7b** with amphetamine or phenethylamine afforded potential PROTACs frameworks **7d** and **7e** in high yields.[20] The above-developed methods demonstrated a great potential for further medicinal and biochemical uses.

Several control experiments were then carried out to clarify the possible mechanism (Figure 2 and Scheme 6). An "on−off" experiment was conducted with a model reaction via intermittent heating (Figure 2). The reaction mixture was heated to 60 °C for 20 min, and then heating was stopped for another 20 min. Subsequently, this progression was repeated for two cycles. As expected, the reaction proceeded faster during the heating period and slowed down without heating. The heat input might be the driving force to accelerate the single electron transfer (SET) in the Mg/oxime ester/Breslow intermediate EDA complex. However, it was found that in the absence of **2a**, the two-component reaction between substrates

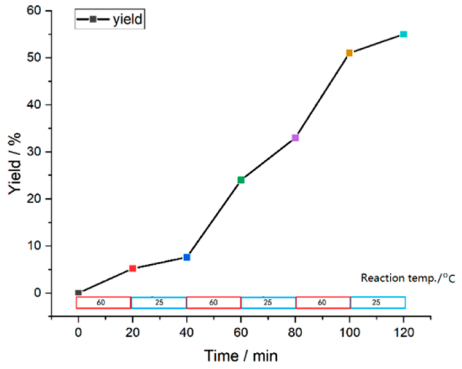
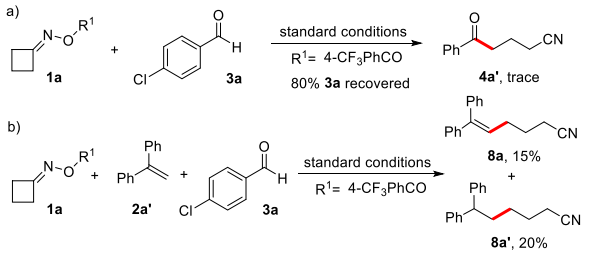


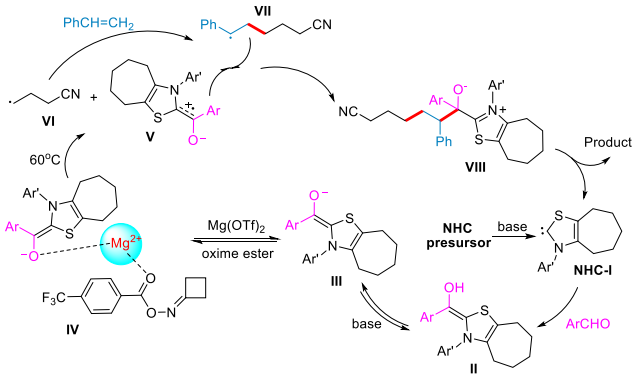
Figure 2. "On−off" experiment: tracking of the yields for different reaction times with heating turned on or off every 20 min. All of the yields were determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard.

Scheme 6. Control Experiments



1a and **3a** did not perform well (Scheme 6a), and only a trace amount of product **4a′** was observed along with a large quantity of recovered aldehyde **3a**. Additionally, the desired three-component product was not observed when **2a** was replaced with 1,1-diphenylethene (**2a′**). Instead, a mixture of two-component coupling products **8a** and **8a′** was obtained (Scheme 6b). Therefore, the role of styrene in this reaction system was to capture nitrile alkyl radical **IV** to form the more stable benzyl radical (intermediate **VII** in Scheme 7).

Scheme 7. Proposed Mechanism



However, in the case of **2a′**, the more sterically hindered tertiary benzyl radical generated upon the combination of the nitrile alkyl radical with **2a′** may block the further interaction with the Breslow enolate radical intermediate **V** in Scheme 7. Thus, this "matched" radical reactivity might be another important factor for the success of this reaction.

Finally, a proposed radical−radical coupling mechanism based on the experimental results and the literature is

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illustrated in Scheme 7.[13,21] Initially, the deprotonated Breslow intermediate **III** is formed through combination of the aldehyde and NHC-**I** under basic conditions. As mentioned above, the Breslow enolate may not have enough reductive potential to reduce the oxime esters. Therefore, $Mg(OTf)_2$ is supposed to have an important interaction with the cyclobutanone oxime ester and enolate **III** to produce sandwich-type complex **IV**.[14,22] Next, the thermally controlled SET event between the enolate and cyclobutanone oxime ester provides NHC-bound radical **V** and nitrile alkyl radical **VI**, respectively.[23] The nitrile alkyl radical is quickly captured by an olefin, forming the more stable benzyl radical **VII**. Subsequent radical−radical coupling between **VII** and **V** affords intermediate **VIII**, which is further transformed to the final product with the regeneration of the NHC for the next catalytic cycle.

In summary, we have described an NHC/Mg-cocatalyzed olefin acylcyanoalkylation protocol to access structurally diverse multifunctionalized aliphatic nitrile molecules. The proposed Mg/cycloketone oxime ester/Breslow intermediate EDA complex might account for the observed reactivity. Moreover, given the simple reaction manipulation, freedom from transition metal and photoredox catalysts, and wide substrates generality, the developed protocol might have widespread use in the fields of molecule assembly, PROTACs, and dual target inhibitor library synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03883.

General information, experimental procedures, compound characterizations, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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