OL Organic Letters

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Organocatalytic Three-Component 1,2-Cyanoalkylacylation of Alkenes via Radical Relay

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03907 Read Online

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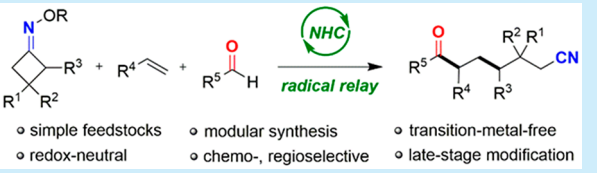
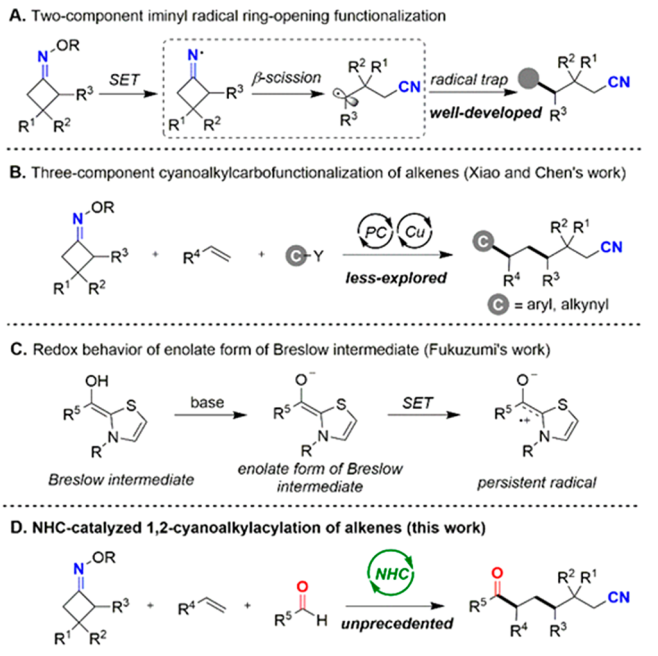
ABSTRACT: Here, we report an unprecedented regioselective, intermolecular 1,2-cyanoalkylacylation of feedstock alkenes with readily available oxime esters and aldehydes by *N*-heterocyclic carbene (NHC) organocatalysis. The crux of this success is the exquisite control over the radical relay process by an NHC organocatalyst. This protocol offers a general platform for diversity-oriented synthesis of valuable ketonitriles under mild, transition-metal-free, and redox-neutral conditions and highlights its potential in the late-stage functionalization of pharmaceutical architectures and natural products.



The direct transformation of commodity chemicals into value-added products plays a vital role in chemical synthesis. Multicomponent reactions, a powerful method to accomplish this goal, enable a rapid buildup of molecular complexity and diversity through simultaneously coupling three or more starting materials.[1] An attractive subset of these reactions is three-component vicinal dicarbofunctionalization of simple feedstock alkenes, which forges two consecutive carbon−carbon (C−C) bonds across the π-systems in one pass and would allow for a rapid influx of carbon frameworks' complexity.[2] Recently, considerable progress has been achieved within this domain via transition-metal catalysis or metal-laphotoredox catalysis.[2−4] Radical relay in this context has arisen as a prominent strategy to add a challenging sp^3-hybridized carbon component onto the alkene through a single-electron transfer (SET)-mediated pathway, retarding problematic side reactions inherent to the two-electron character of the traditional transmetalation.[5] Notwithstanding, the types of carbon-based coupling partners are still limited and a fully organocatalytic version of this dicarbofunctionalization reaction remains elusive.

Owing to their unique reactivity profile, iminyl radicals have emerged as versatile reactive intermediates with wide applications in synthetic organic chemistry.[6] Stimulated by the seminal work of Zard,[7] readily available cycloketone oxime derivatives have recently been harnessed as precursors of iminyl radicals by reductive or oxidative SET. Such reactive open-shell nitrogen-centered radicals are susceptible to undergoing a β-scission process,[6a] providing translocated carbon-centered radicals (cyanoalkyl radicals), which can further be trapped by a portfolio of synthetically useful radical acceptors (Scheme 1A). Following this line, a range of impressive transformations have been developed to install valuable cyanoalkyl components onto structurally diverse molecules.[6d,8−10] Most of these dedicated efforts, however, were somewhat limited to the two-component mode, enabling the formation of one single C−C or C−heteroatom linkage

Scheme 1. Motivation and Synthetic Strategy



Received: November 25, 2020

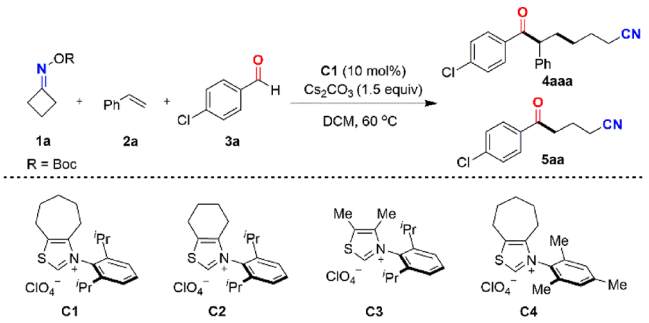
(Scheme 1A). In contrast, three-component intermolecular cyanoalkylcarbofunctionalization of alkenes, which would efficiently forge two C−C bonds and rapidly achieve high levels of molecular complexity, remains challenging and more underdeveloped. One prominent challenge is an unwanted competitive two-component reaction. Recently, elegant works from the group of Xiao and Chen revealed the viability of 1,2-cyanoalkylaryllation[11] and 1,2-cyanoalkylalkynylation[12] of alkenes through a photoinduced, copper-catalyzed radical relay (Scheme 1B). Nevertheless, vicinal cyanoalkylacylation of alkenes, to the best of our knowledge, is still unexplored to date. Given the ubiquity and paramount importance of carbonyl group in almost every facet of chemical science,[13] as well as the prevalence of cyanoalkyl moieties in many natural products and pharmaceuticals,[14] an efficient and modular method for 1,2-cyanoalkylacylation of alkenes would be highly desirable.

Enlightened by recent striking radical transformations mediated by *N*-heterocyclic carbene (NHC),[15−17] we envisioned that the merging of iminyl radical chemistry with NHC organocatalysis might provide a new opportunity for accomplishment of vicinal cyanoalkylacylation of alkenes with widely available aldehydes. In this regard, we became intrigued by the reducing enolate form of Breslow intermediate, which can form a persistent radical intermediate through single-electron oxidation as reported in the pioneering studies of Fukuzumi group (Scheme 1C).[18] Building on this knowledge, recently, the Ohmiya group used redox-active carboxylic esters as SET oxidants to fulfill the 1,2-alkylacylation of alkenes via NHC-catalyzed radical relay.[19] Prompted by this elegant study, fluoroalkyl reagents[20] and Katritzky pyridinium salts[21] were subsequently identified as viable SET oxidants by other groups. Despite these venerable advances, in contrast to NHC-enabled electron-pair-transfer reactions,[22] the realm of NHC catalyzed radical transformations is still in its infancy,[15b] especially with respect to vicinal alkene dicarbofunctionalization. Herein, we report an unprecedented protocol for the intermolecular radical 1,2-cyanoalkylacylation of alkenes with oxime esters and aldehydes through NHC organocatalysis in a completely regioselective fashion (Scheme 1D). This modular method grants a rapid, flexible access to densely functionalized versatile ketonitrile architectures under mild, transition-metal-free, and redox-neutral conditions.

Our investigations commenced by reacting *O*-(*tert*-butoxycarbonyl) oxime **1a** with styrene **2a** and 4-chlorobenzaldehyde **3a** in the presence of the NHC catalyst. An abbreviated outline of optimization studies is provided in Table 1. In its optimal manifestation, a 79% yield of the three-component coupling product, ζ-keto nitrile **4aaa**, was obtained from **1a** (0.15 mmol), **2a** (0.2 mmol), and **3a** (0.1 mmol) using 1.5 equiv of Cs_2CO_3 in concert with the *N*-2,6-diisopropylphenyl-substituted cycloheptane-fused thiazolium precatalyst **C1** (10 mol %) in DCM at 60 °C (entry 1). The acyl and γ-cyanoalkyl fragments were incorporated into the α and β positions of styrene, respectively, in an exclusively regioselective fashion. A small quantity of the byproduct **5aa** was observed due to the competitive two-component cross-coupling of **1a** and **3a**.

The screening of NHC catalysts unveiled that both the backbone and the *N*-substituent of the NHC precursors were essential for the reaction efficiency (Table 1, entries 2−4). The reaction saw an obvious decrease in yield when conducted using NHC precursors possessing a cyclohexane or dimethyl backbone or a smaller *N*-mesityl group. Switching the R group

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	yield (**4aaa**, %)[b]	yield (**5aa**, %)[b]
1	none	79	14
2	**C2** instead of **C1**	56	10
3	**C3** instead of **C1**	55	11
4	**C4** instead of **C1**	45	15
5	**1a′** (R = 4-$CF_3C_6H_4CO$) instead of **1a**	64	18
6	**1a″** (R = C_6F_5CO) instead of **1a**	40	15
7	using Li_2CO_3, Na_2CO_3, K_2CO_3, or K_3PO_4	<15	<5
8	DBU instead of Cs_2CO_3	10	0
9	NEt_3 instead of Cs_2CO_3	32	9
10	NMM instead of Cs_2CO_3	10	0
11	using pyridine or 2,6-lutidine	0	0
12	1.0 equiv of Cs_2CO_3	48	10
13	ratio of **1a**:**2a**:**3a** = 2:2:1	56	18
14	ratio of **1a**:**2a**:**3a** = 1.2:2:1	62	14
15	ratio of **1a**:**2a**:**3a** = 1.5:1.5:1	42	18
16	no NHC catalyst	0	0
17	no base	0	0

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.2 mmol), **3a** (0.1 mmol), **C1** (10 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 ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Boc = *tert*-butyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]-7-undecene. NMM = *N*-methylmorpholine.

of *O*-acyl oxime from Boc to 4-(trifluoromethyl)benzoyl or perfluorobenzoyl rendered an erosion in the reactivity (entries 5 and 6). The specific identity of the base proved critical (entries 7−11), as did the choice of the solvent system (see the Supporting Information for details). Attempts to reduce the equivalent of Cs_2CO_3 employed led to lower yields (entry 12). Further refinement of the molar ratio of **1a** and **2a** to **3a** did not boost the product yield (entries 13−15). As speculated, control studies confirmed that the NHC catalyst and base were indispensable to this vicinal alkene dicarbofunctionalization reaction (entries 16 and 17).

With an optimized set of conditions established, the scope of this NHC organocatalytic three-component cyanoalkylacylation of alkenes was then explored (Scheme 2). The initial focus was on evaluating alkene diversity. Aside from **2a**, vinyl arenes bearing either electron-withdrawing or -donating substituents on the phenyl ring could all engage in this dicarbofunctionalization reaction and furnish the desired ζ-keto nitriles in moderate to good yields (**4aba**−**4aga**). Chloro-substituents at the *meta*- and *ortho*-position of styrene were well tolerated under the standard conditions (**4afa** and **4aga**). Naphthyl-, thiophene-, and pyridine-substituted olefins also proved to be competent coupling partners (**2h**−**2k**) for the facile assembly

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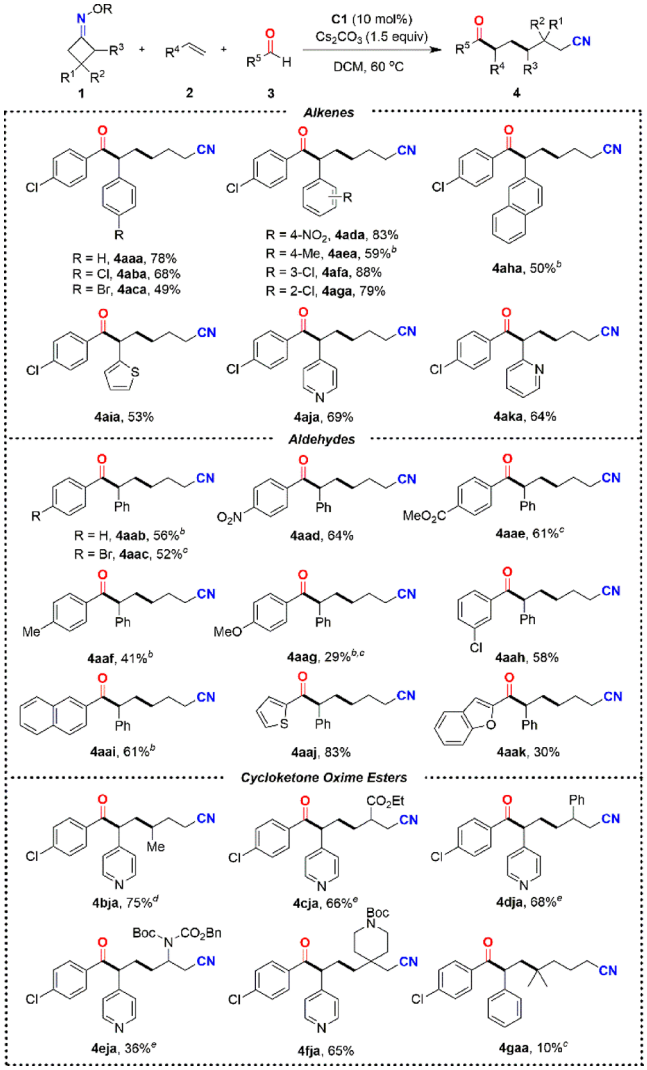
Scheme 2. Scope of the NHC-Catalyzed Three-Component Cyanoalkylacylation of Alkenes[a]



[a]Standard reaction conditions: **1** (0.3 mmol), **2** (0.4 mmol), **3** (0.2 mmol), **C1** (10 mol %), and Cs_2CO_3 (0.3 mmol) in DCM (2.0 mL) at 60 °C for 12 h under Ar; isolated yields based on **3** are given. [b]Oxime ester **1a′** instead. [c]Using 20 mol % **C1**. [d]Diastereomeric ratio is 2.5:1 determined by ^{1}H NMR analysis. [e]Diastereomeric ratio is 1:1 determined by ^{1}H NMR analysis.

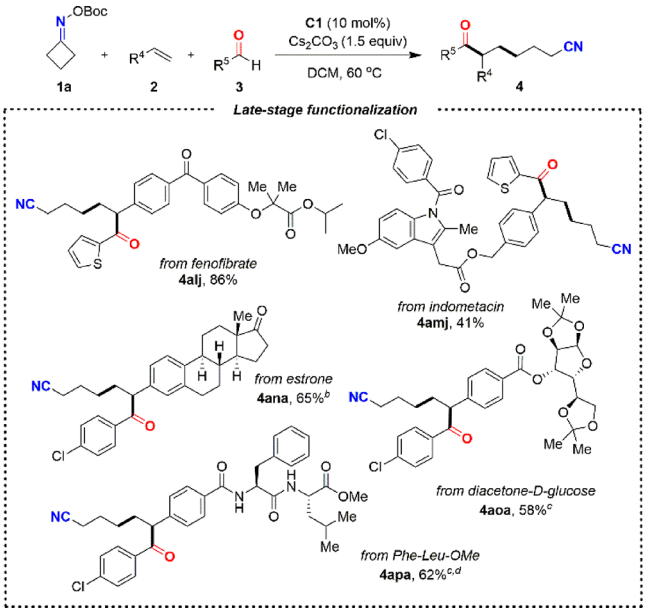
of ζ-keto nitriles **4aha**–**4aka** with yields ranging from 50% to 69%. To showcase the scalability of this method, a 6.0 mmol scale reaction of **3a** was conducted, and the target product **4aaa** could be furnished in 56% yield on a 1.05 g scale, albeit with a higher catalyst loading.[23] However, the present catalytic system is nonproductive for aliphatic alkenes.

Next, the amenability toward aldehydes was examined. A multitude of pendant functionalities in the aromatic aldehydes, encompassing halides (**4aac** and **4aah**), nitro group (**4aad**), ester (**4aae**), and ether (**4aag**), were left unscathed. Electronic effects can be observed for *para*-substituted aromatic aldehydes (**4aad** vs **4aag**). 2-Naphthaldehyde featuring an aromatic fused ring can also be enlisted (**4aai**). Furthermore, heteroaromatic rings such as thiophene and benzofuran were tolerated in the dicarbofunctionalization process, as exemplified by **4aaj** and **4aak**. Unfortunately, attempts to leverage aliphatic aldehydes as acyl donors were met with failure.

Finally, the scope of cycloketone oxime esters was assessed.[24] Nonsymmetrical cyclobutanone oxime ester **1b** furnished the desired product **4bja** in 75% yield, where C–C bond cleavage occurred at the sterically more demanding site with complete selectivity. On the other hand, the monosubstituted, symmetrical cyclobutanone oxime esters with functionalities including ester (**1c**), phenyl (**1d**), and carbamate (**1e**) smoothly reacted, providing synthetically useful quantities of the corresponding products (**4cja**, **4dja**, and **4eja**). In the case of 3,3-disubstituted *O*-acyl oxime ester **1f** bearing a Boc-protected medicinally prevalent piperidine core, the three-component cyanoalkylacylation product **4fja** was obtained in 65% yield. However, less-strained *O*-acyl oximes such as **1g** derived from cyclopentanone did not function well, giving the target product **4gaa** in low yield.

The merit of this organocatalytic protocol was further magnified by late-stage functionalization of drug derivatives and natural products (Scheme 3). A derivative of fenofibrate **2l**

Scheme 3. Late-Stage Functionalization of Drug Derivatives and Natural Products[a]



[a]Conditions as Table 1, entry 1; 0.1 mmol scale; isolated yields based on **3** are given. [b]Diastereomeric ratio is 17:1 determined by ^{1}H NMR analysis. [c]Diastereomeric ratio is 1:1 determined by ^{1}H NMR analysis. [d]Using 20 mol % **C1**.

bearing a pendent alkene was amenable to cyanoalkylacylation under the standard reaction conditions, affording the drug-like compound **4alj** in good yield. A vinylarene installed on the skeleton of a well-known nonsteroidal anti-inflammatory drug, indomethacin, reacted smoothly with oxime ester **1a** and aldehyde **3j** to give the target product **4amj** in useful yield. Beyond these drug-like molecules, derivatives of estrone **2n**, carbohydrate **2o**, and peptide **2p** bearing functionalities such as ketone, ester, acetal, and amide were also apt to furnish good yields of the cyanoalkylacylated products (**4ana**, **4aoa**, and **4apa**), which would be otherwise difficult to prepare by other methods. As such, this modular approach shows promise in accelerating drug discovery.

To shed light on the putative reaction pathway, several mechanistic experiments were conducted (Scheme 4). In the

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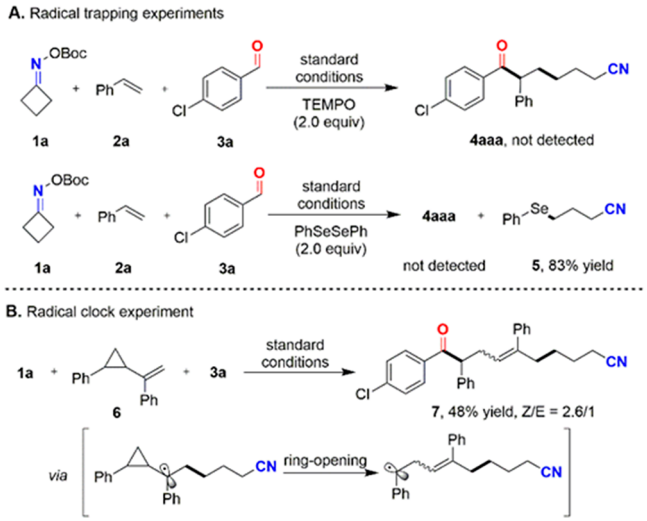
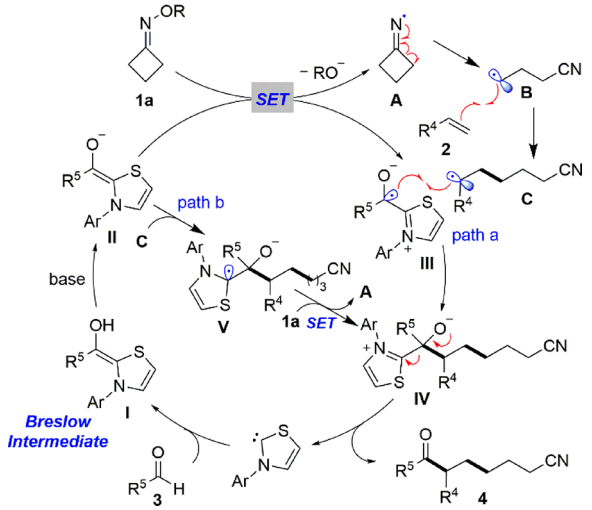
Scheme 4. Mechanistic Investigations



presence of 2.0 equiv of radical traps TEMPO or PhSeSePh, the standard reaction of **1a**, **2a**, and **3a** was completely inhibited (Scheme 4A). Notably, the radical-trapping product PhSe-$(CH_2)_3$CN (**5**) was isolated in 83% yield. This is indicative of the intermediacy of a cyanoalkyl radical in this transformation. Furthermore, the radical clock reaction with vinyl cyclopropane **6** under the standard conditions furnished the rearranged coupling product **7** in 48% yield, which is in agreement with a radical relay pathway (Scheme 4B).

Based on the experimental results aforementioned, a mechanistic rationale for this 1,2-cyanoalkylacylation of alkenes via NHC organocatalyzed radical relay is outlined in Scheme 5. Initially, NHC combines with the aldehyde **3** to

Scheme 5. Proposed Catalytic Cycle for the NHC-Catalyzed Cyanoalkylacylation of Alkenes



afford a neutral Breslow intermediate **I**. Then, the enolate form of the Breslow intermediate **II**, produced by deprotonation, would act as a competent single-electron reductant and undergo facile SET with cyclobutanone oxime ester **1a**. This process results in the formation of a persistent aldehyde-derived ketyl radical **III** and a cyclic iminyl radical **A**, respectively. Subsequent fast ring opening of **A** via homolytic C−C single bond cleavage generates the translocated cyanoalkyl radical **B**, which can further add onto alkene **2** to render the secondary radical **C**. In the next step, the resultant radical **C** undergoes radical−radical cross-coupling with the persistent ketyl radical **III**,[19,20a,25] giving the species **IV** (path a). Finally, the intermediate **IV** would engage in facile elimination to furnish the desired ketonitrile product **4** and regenerate the NHC, thereby completing this organocatalytic cycle. On the other hand, radical **C** might undergo addition to the enolate form of the Breslow intermediate **II** to form another possible NHC-bound radical intermediate **V**. Then, SET from intermediate **V** to **1a** produces intermediate **IV** and a new radical **A**, respectively (path b).[26]

In conclusion, we have developed an intermolecular, three-component 1,2-cyanoalkylacylation of alkenes with easily accessible oxime esters and aldehydes enabled by NHC organocatalysis. This emerging modular protocol enjoys mild, redox-neutral, and transition-metal-free conditions, exhibits broad compatibility of substrate scope and functional groups, and highlights its potential in the late-stage diversification of pharmaceutical architectures and natural products. The NHC organocatalyst gives exquisite control over the radical relay pathway involving reductive generation of iminyl radicals/radical transposition by C−C bond cleavage/radical addition/radical−radical cross-coupling sequence, thus enabling regioselective formation of $C(sp^3)$−$C(sp^3)$ and $C(sp^3)$−$C(sp^2)$ bonds in a single step. This work not only offers a general method for the efficient and flexible assembly of diversely functionalized valuable ketonitriles from simple building blocks but also expands the repertoire of NHC catalyzed radical-mediated alkene dicarbofunctionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03907.

Experimental details and spectral data (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c03907
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The support of this work by the National Natural Science Foundation of China (U1463201 and 21522604), the National Key Research and Development Program of China (2017YFC1104802), the Natural Science Foundation of Jiangsu Province, China (BK20150031), the Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), and the Top-Notch Academic Programs Project of Jiangsu Higher Education Institutions (TAPP) is gratefully acknowledged.

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(26) We gratefully acknowledge a reviewer for pointing out this possibility.

https://dx.doi.org/10.1021/acs.orglett.0c03907
Org. Lett. XXXX, XXX, XXX−XXX