ACS Catalysis

pubs.acs.org/acscatalysis Letter

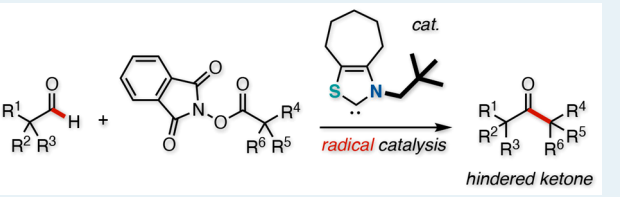
Direct Synthesis of Dialkyl Ketones from Aliphatic Aldehydes through Radical *N*-Heterocyclic Carbene Catalysis

Yuki Kakeno, Mayu Kusakabe, Kazunori Nagao,* and Hirohisa Ohmiya*

Cite This: *ACS Catal.* 2020, 10, 8524−8529 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A designed thiazolium-type *N*-heterocyclic carbene (NHC) catalyst having an *N*-neopentyl group and seven-membered backbone structure was achieved through the use of aliphatic aldehydes as acyl donors in the decarboxylative radical coupling with aliphatic carboxylic acid derived-redox active esters. The NHC catalyst also enabled the vicinal alkylacylation of vinyl arenes using aliphatic aldehydes and redox-active esters through a radical relay mechanism. These reactions provided the synthetic route to sterically hindered dialkyl ketones.



KEYWORDS: *N-heterocyclic carbene, organocatalysis, radical, aldehydes, dialkyl ketones*

Dialkyl ketones are one of the fundamental and essential class of organic molecules. These compounds are found in many pharmaceutical and bioactive molecules. In addition, they are recognized as versatile synthetic precursors of valuable functional groups, such as alcohols and amines. The conventional synthetic approach to dialkyl ketones from aliphatic aldehydes is the nucleophilic addition of aliphatic organometallic reagents followed by oxidation (Scheme 1A). On the other hand, the direct synthesis of dialkyl ketones from aliphatic aldehydes are also demonstrated, even though such a process is difficult and less mature at present. This process using aliphatic aldehydes as carbonyl sources would be useful, in terms of their availability and inexpensiveness. Specifically, *N*-heterocyclic carbene (NHC)-catalyzed Stetter and benzoin condensation reactions using aliphatic aldehydes could provide the dialkyl ketones.[1,2] The hydroacylation of alkenes using transition-metal catalyst[3] or hydrogen atom transfer (HAT) catalyst[4,5] is known as a high atom-economical method. The direct methods exhibited high functional group compatibility. However, the fragility to steric bulkiness limited the scope and the complexity of dialkyl ketone products.

Recently, we developed the direct synthesis of alkyl aryl ketones from aromatic aldehydes using aliphatic carboxylic acid derived-redox active esters and NHC catalyst under mild conditions (Scheme 1B).[6] This protocol allowed the use of secondary and tertiary alkyl carboxylic acid-derived redox-active ester to produce sterically hindered alkyl aryl ketones. The reaction involves a single electron transfer (SET) from the enolate form of the Breslow intermediate, which is derived from aldehyde and NHC in the presence of base, to redox active ester, followed by radical−radical coupling between the resultant Breslow intermediate-derived radical and alkyl radical (Scheme 1B).[6,7] However, the useable aldehydes have been limited to aromatic aldehydes. Thus, aliphatic aldehydes did not give dialkyl ketones at all under the optimized conditions using a thiazolium salt (**N1**)[8] possessing an *N*-2,6-diisopropylphenyl substituent and seven-membered backbone structure as the NHC precursor (Scheme 1B). To expand the substrate scope, we thought that redesign of the NHC catalyst would be required.

Herein, we report that the design of NHC catalyst enabled the use of aliphatic aldehydes for the radical reactions involving the Breslow intermediate-derived radical species. A thiazolium-type NHC having an *N*-neopentyl group and seven-membered backbone structure was effective. The catalyst system provided a synthetic approach to sterically hindered dialkyl ketones from aliphatic aldehydes in a single step.

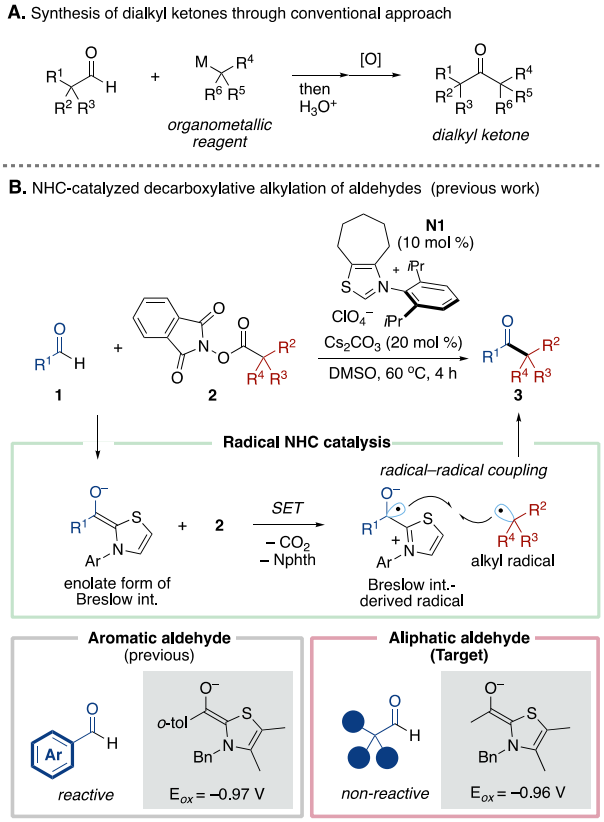
Fukuzumi and co-workers studied the redox properties of the enolate form of Breslow intermediates that are prepared from aldehydes and thiazolium-type NHC in the presence of a strong base.[9] The enolate forms of Breslow intermediates derived from aliphatic aldehyde have reduction potentials comparable to the one derived from aromatic aldehyde (E_{ox} = −0.96 V for acetaldehyde and E_{ox} = −0.97 V for *o*-tolualdehyde) (Scheme 1B). Thus, the SET process mediated by the aliphatic aldehyde-derived Breslow intermediate would be feasible.

Next, the stoichiometric reaction using a silylated thiazolium aliphatic alcohol **4a**, which is known to act as a Breslow intermediate equivalent with treatment of TBAF, was

Received: June 30, 2020
Revised: July 14, 2020

https://dx.doi.org/10.1021/acscatal.0c02849
ACS Catal. 2020, 10, 8524−8529

Scheme 1. Direct Synthesis of Ketones from Aldehydes through NHC-Catalyzed Radical Reactions

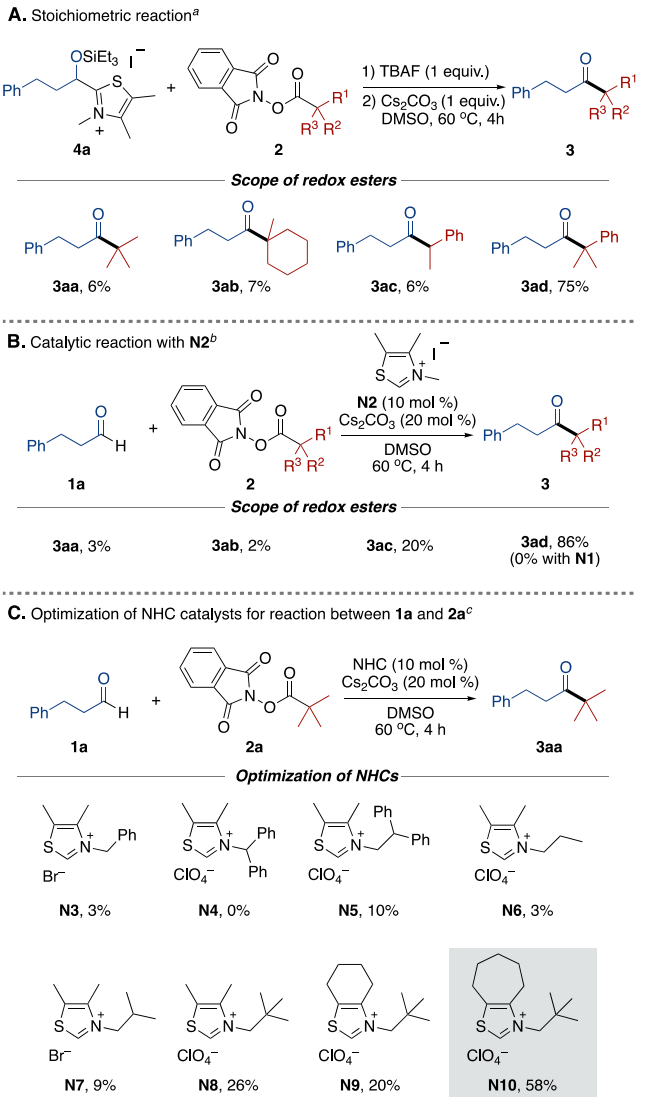


conducted (Table 1A).[10] Specifically, the reaction between **4a** and pivalic acid derived-redox active ester **2a** using stoichiometric amounts of TBAF and Cs_2CO_3 for generating the enolate form of the Breslow intermediate afforded the desired dialkyl ketone **3aa** in 6% yield.[11] Three additional redox active esters containing tertiary or benzyl substituents were examined (**3ab**–**3ad**). Tertiary benzylic redox active ester **2d** produced a highly stabilized benzyl radical coupled with **4a** in an exceptionally high yield.

Encouraged by the results of the stoichiometric experiments described in Table 1A, the catalytic reactions of 3-phenylpropionaldehyde (**1a**) and **2a**–**2d** with 2,4,5-trimethyl thiazolium salt **N2** were conducted (Table 1B). The enolate form of the Breslow intermediate derived from **N2** would be same as that derived from **4a**. The reaction with **2a** gave the desired coupling product **3aa**, although the yield was low. The product yield of **3ab** diminished under the catalytic conditions (7% to 2%; see Table 1B vs Table 1A). On the other hand, the improvement of the product yield was observed in the case of **2c**. As with the stoichiometric reaction, the high reactivity was observed when **2d** was used as a substrate. Interestingly, using the *N*-2,6-diisopropylphenyl-substituted **N1** instead of **N2** did not afford the product at all. In our previous study using **N1**,[6a] we assumed that the reason why aliphatic aldehydes were ineffective was attributed to the instability of the Breslow intermediate-derived radical. However, these results (**N2** vs **N1**) using **2d** suggested that the cause seems to be the steric environment on the radical–radical coupling process.

Based on the preliminary experiments in Tables 1A and 1B, we envisioned that the improvement of reaction efficiency for aliphatic aldehydes would be solved by the tuning the steric

Table 1. Design of NHC Catalyst for Aliphatic Aldehydes



[a]Reaction was performed with **4a** (0.2 mmol), **2** (0.2 mmol), and TBAF (0.2 mmol) in DMSO (0.4 mL) at 25 °C for 10 min. Then, Cs_2CO_3 (0.2 mmol) was added and stirred at 60 °C for 4 h. ^{1}H NMR yield. [b]Reaction was performed with **1a** (0.3 mmol), **2** (0.2 mmol), **N2** (0.02 mmol), and Cs_2CO_3 (0.04 mmol) in DMSO (0.4 mL) at 60 °C for 4 h. ^{1}H NMR yield based on **2**. [c]Reaction was performed with **1a** (0.3 mmol), **2a** (0.2 mmol), **N3**–**N10** (0.02 mmol), and Cs_2CO_3 (0.04 mmol) in DMSO (0.4 mL) at 60 °C for 4 h. ^{1}H NMR yield based on **2a**.

environment of carbene. To find the effective NHC catalyst quickly, the *N*-substituent was evaluated with thiazolium salt having a dimethyl backbone (Table 1C, **N3**–**N10**). The reaction with *N*-benzyl thiazolium salt resulted in the slight product formation (**N3**). The introduction of a diphenylmethyl substituent did not give the product (**N4**). Interestingly, putting a single methylene unit into **N4** resulted in the desired product formation with 10% yield (**N5**). A propyl substituent (**N6**) was comparable with **N3**. The *N*-isobutyl-substituted **N7** showed comparable reactivity. After screening of other sterically hindered groups, *N*-neopentyl-substituted thiazolium salt was found to be effective (**N8**). Subsequently, the backbone structure of thiazole ring was evaluated (**N9** and **N10**). **N10** bearing a seven-membered backbone dramatically

https://dx.doi.org/10.1021/acscatal.0c02849
ACS Catal. 2020, 10, 8524–8529

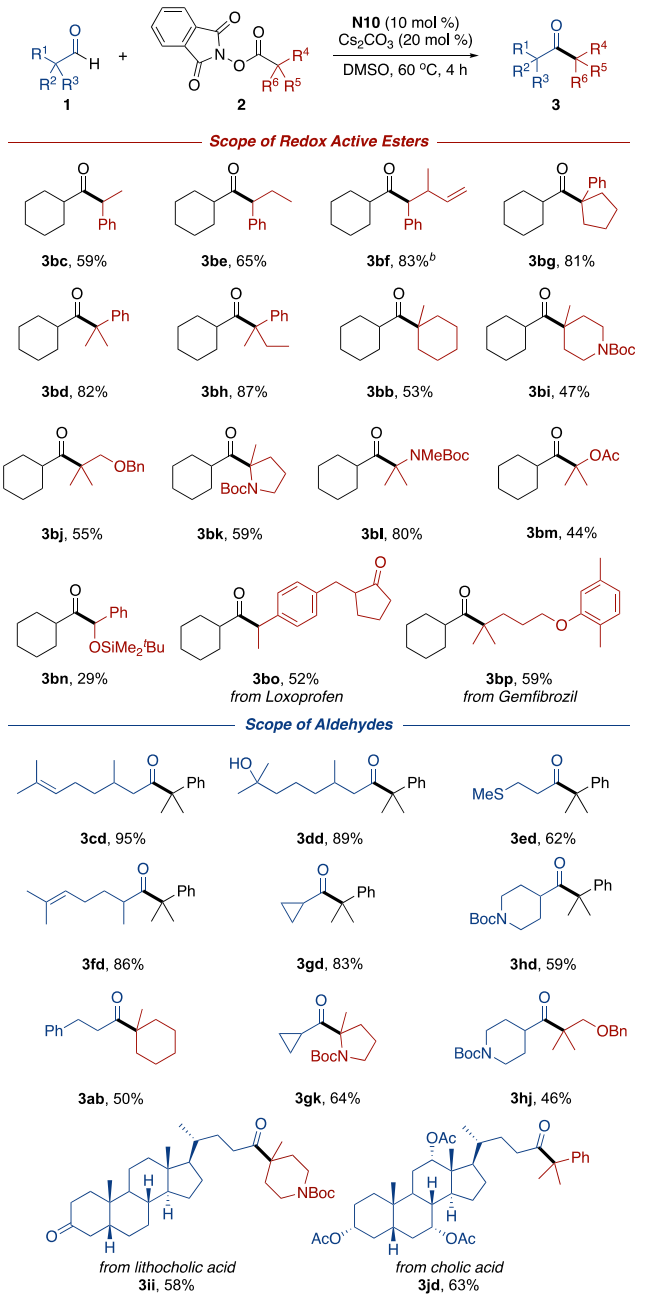
increased the product yield.[12,13] As observed in our previous report, triazolium- and imidazolium-type NHCs did not afford any products (data not shown).[6a,b] The control experiments revealed that both NHC and the Cs_2CO_3 base were essential for this reaction (data not shown).

In the radical NHC catalysis, the bulky N-substituents would not only secure the persistent nature[14] of the Breslow intermediate-derived radical but also prohibit the possible side reactions between nucleophilic species generated in situ from NHC and the ester moiety in **2**. However, the sterically demanding N-substituents such as 2,6-disopropylphenyl (**N1**) or diphenylmethyl (**N4**) groups in close proximity to the carbene center were not suitable in the case of aliphatic aldehyde substrates (see Table 1C). These N-substituents would lead to unsuccessful radical−radical coupling, because the Breslow intermediate-derived radical from aliphatic aldehyde would be more three-dimensionally congested than that from aromatic aldehyde, because of the sp^3 nature of α-carbon. As a result, *N*-neopentyl-substituted **N10**, in which steric hindrance is introduced at some distance from the carbene center, rather than within a proximity, might be effective both for the radical−radical coupling and the suppression of side reactions.

This protocol under the **N10** catalyst system was useful to construct the sterically hindered dialkyl ketones bearing secondary or tertiary alkyl substituents (Table 2). In the top portion of Table 2, various redox active esters were examined using the reaction of cyclohexanecarboxyaldehyde (**1b**). The secondary benzylic carboxylic acid-derived redox active esters possessing methyl (**3bc**), ethyl (**3be**), and allyl (**3bf**) groups were suitable substrates. Tertiary benzylic groups containing cyclic (**3bg**) and acyclic (**3bd** and **3bh**) scaffolds could be coupled with the acyl group efficiently. Unactivated tertiary alkyl group was engaged in this decarboxylative alkylation (**3bb**). Amide (**3bi**) and benzyl ether (**3bj**) substituents did not inhibit the reaction. Overall, the reactivity seemed to be correlated with the stability of the generated alkyl radical (**3bc** vs **3bd** and **3bg** vs **3bb**, **3bi**). α-Amino- and α-alkoxy-substituted ketones, which are known as synthetically useful intermediates, were easily prepared by this reaction (**3bk**−**3bn**). The relatively low yield of **3bm** and **3bn** might be due to the decomposition of the protecting groups such as acetyl or silyl substituents by basic reaction conditions. It is noteworthy that pharmaceutical drugs such as Loxoprofen and Gemfibrozil were acylated, respectively (**3bo** and **3bp**).

A broad range of primary and secondary aliphatic aldehydes were efficiently coupled with the redox active ester **2d** to produce the dialkyl ketones (Table 2, bottom). Citronellal was directly alkylated (**3cd**). Unprotected alcohol and thioether groups were compatible (**3dd** and **3ed**). Acyclic and cyclic secondary alkyl aldehydes were also good substrates (**3fd**−**3hd**). The alkene moiety that sometimes poisons transition-metal catalysis did not inhibit the reaction (**3fd**). The cyclopropyl ketone could be synthesized from cyclopropanecarboxaldehyde via this organocatalytic reaction (**3gf**). Heterocyclic ketone containing a piperidine scaffold was prepared (**3hd**). Several combinations of aliphatic aldehydes and tertiary redox active esters were also shown (**3ab**, **3gk**, and **3hj**). The aldehydes derived from natural products such as lithocolic acid and cholic acid could participate in this decarboxylative alkylation reaction (**3ii** and **3jd**). Unfortunately, the reaction with the tertiary aliphatic aldehyde resulted in the recovery of substrates (data not shown). It would be due

Table 2. Substrate Scope[a]



[a]Reaction was performed with **1** (0.3 mmol), **2** (0.2 mmol), **N10** (0.02 mmol), and Cs_2CO_3 (0.04 mmol) in DMSO (0.4 mL) at 60 °C for 4 h. [b]Diastereomeric ratio is 55:45 determined by ^{1}H NMR analysis.

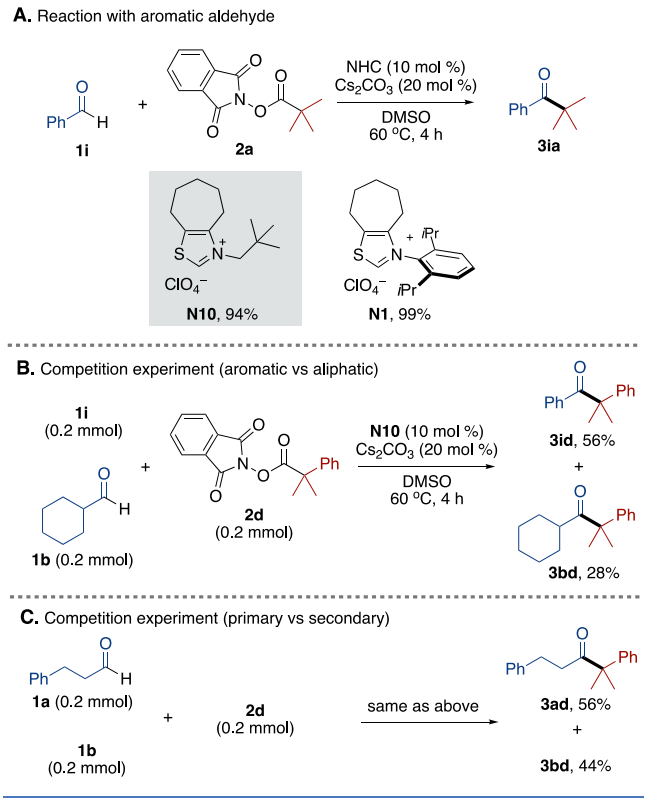
to the slow formation of Breslow intermediate caused by the steric bulkiness.

To gain the more information on catalytic activity of **N10**, several reactions were conducted. First, **N10** was subjected to the decarboxylative coupling with benzaldehyde **1i** to exhibit the comparable reactivity as the previous optimal catalyst **N1** (Scheme 2A).[6a] Thus, the newly designed **N10** was identified as a versatile NHC catalyst for the decarboxylative radical coupling of both aliphatic and aromatic aldehydes.

To understand the reaction mechanism, competition experiments were conducted (Schemes 2B and 2C). When the reaction of the redox ester **2d** with the same amounts of **1i**

https://dx.doi.org/10.1021/acscatal.0c02849
ACS Catal. 2020, 10, 8524−8529

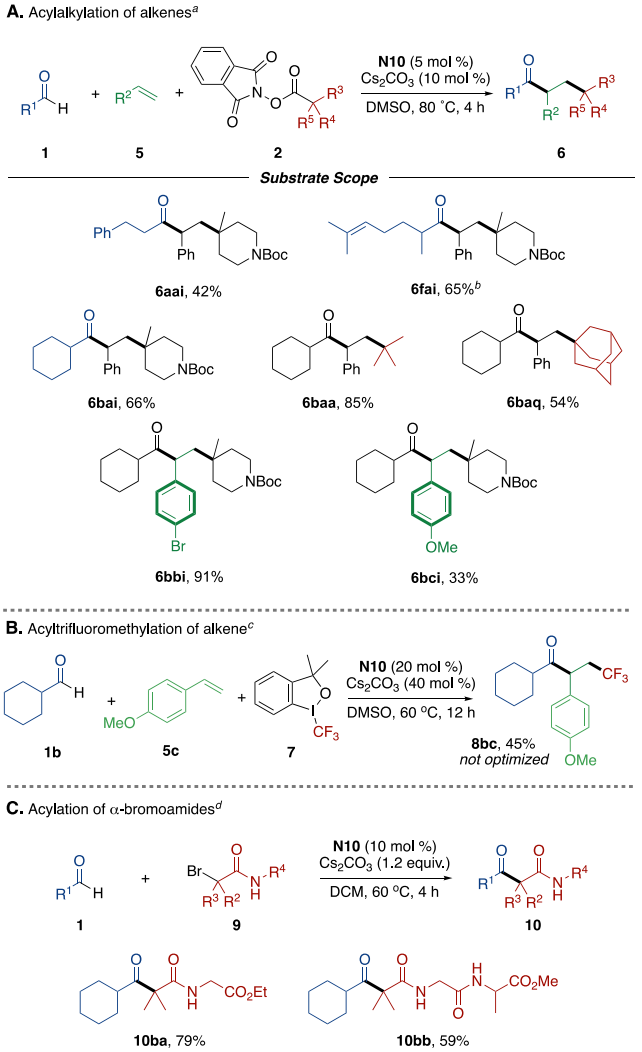
Scheme 2. Mechanistic Studies



and secondary aliphatic aldehydes **1b** was performed, alkyl aryl ketone **3id** was formed prior to dialkyl ketone **3bd** (Scheme 2B). Compared secondary aliphatic aldehyde **1b** with primary aliphatic aldehyde **1a**, the primary aliphatic aldehyde-derived product was preferentially obtained (Scheme 2C). These results indicated that the order of reactivity of aldehydes is as follows: aromatic > primary aliphatic > secondary aliphatic. We supposed that the deprotonation of the original formyl C−H producing enol or the enolate form of Breslow intermediates would be the rate-determining step in the present NHC catalysis. This is consistent with conventional ionic NHC organocatalysis.[15,16]

To explore the versatility of the newly designed NHC catalyst, we tested other NHC-catalyzed radical reactions that have been limited to aromatic aldehydes. For example, the **N10** catalyst allowed the use of aliphatic aldehyde as an acyl source for the vicinal alkylacylation of vinyl arenes **5**, using tertiary alkyl carboxylic acid-derived redox-active ester **2** through a radical relay mechanism (see Table 3A).[6b] Primary and secondary aliphatic aldehydes were suitable substrates (**6aai**, **6fai**, and **6bai**). Tertiary butyl and adamantly groups were successfully introduced to β-position of ketone products (**6baa** and **6baq**). Bromo and methoxy substituents in the vinyl arenes were tolerated (**6bbi** and **6bci**). When Togni reagent I was used instead of redox active esters, the acyltrifluoromethylation of alkene occurred to afford β-trifluoromethyl-substituted dialkylketone **8bc** (see Table 3B).[7b,c,e] The acyl and CF_3 fragments could be introduced to alkene moiety with complete regioselectivity. We also tested the unprecedented cross-coupling of aliphatic aldehyde and α-bromoamide (see Table 3C). α-Bromoamides derived from amino acid or dipeptide coupled efficiently with cyclohexanecarbaldehyde (**10ba** and **10bb**).

Table 3. Application to Other NHC-Catalyzed Radical Reaction



[a]Reaction was performed with aldehyde **1** (0.2 mmol), **5** (0.4 mmol), **2** (0.3 mmol), **N10** (0.01 mmol), and Cs_2CO_3 (0.02 mmol) in DMSO (0.4 mL) at 80 °C for 4 h. [b]The diastereomeric ratio is 1:1, as determined by ^{1}H NMR analysis. [c]Reaction was performed with **1b** (0.12 mmol), **5c** (0.1 mmol), **7** (0.2 mmol), **N10** (0.02 mmol), and Cs_2CO_3 (0.04 mmol) in DMSO (0.4 mL) at 60 °C for 12 h. [d]Reaction was performed with **1** (0.3 mmol), **9** (0.2 mmol), **N10** (0.02 mmol), and Cs_2CO_3 (0.24 mmol) in DCM (0.4 mL) at 60 °C for 4 h.

In summary, a newly designed thiazolium-type NHC having an *N*-neopentyl group and seven-membered backbone structure achieved the use of aliphatic aldehydes as acyl donors in the decarboxylative radical coupling with aliphatic carboxylic acid-derived redox-active esters. The NHC catalyst also enabled the vicinal alkylacylation of vinyl arenes using aliphatic aldehydes and redox-active esters through a radical relay mechanism. These reactions provided the new synthetic route to sterically hindered dialkyl ketones. Thus, the catalyst evolution expanded the scope of the NHC-catalyzed radical reactions, making versatile dialkyl ketone synthesis possible. At present, theoretical calculations to understand the NHC catalyst effect and the application of this radical NHC catalysis to the functionalization of biomolecules are currently ongoing in our laboratory.

https://dx.doi.org/10.1021/acscatal.0c02849
ACS Catal. 2020, 10, 8524−8529

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c02849.

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

■ AUTHOR INFORMATION

Corresponding Authors

Kazunori Nagao − *Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kanazawa 920-1192, Japan;* orcid.org/0000-0003-3141-5279; Email: nkazunori@p.kanazawa-u.ac.jp

Hirohisa Ohmiya − *Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kanazawa 920-1192, Japan; JST, PRESTO, Saitama 332-0012, Japan;* orcid.org/0000-0002-1374-1137; Email: ohmiya@p.kanazawa-u.ac.jp

Authors

Yuki Kakeno − *Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kanazawa 920-1192, Japan*

Mayu Kusakabe − *Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kanazawa 920-1192, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c02849

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant No. JP18H01971 to Scientific Research (B), JSPS KAKENHI Grant No. JP17H06449 (Hybrid Catalysis), and JST, PRESTO Grant No. JPMJPR19T2 (to H.O.).

■ REFERENCES

(1) For selected reviews on NHC organocatalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) Bugaut, X.; Glorius, F. Organocatalytic Umpolung: *N*-Heterocyclic Carbenes and Beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511−3522. (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387.

(2) For our recent reports on direct synthesis of dialkyl ketone from aliphatic aldehydes through NHC/Pd cooperative catalysis, see: (a) Yasuda, S.; Ishii, T.; Takemoto, S.; Haruki, H.; Ohmiya, H. Synergistic N-Heterocyclic Carbene/Palladium-Catalyzed Reactions of Aldehyde Acyl Anions with either Diarylmethyl or Allylic Carbonates. *Angew. Chem., Int. Ed.* **2018**, *57*, 2938−2942. (b) Haruki, H.; Yasuda, S.; Nagao, K.; Ohmiya, H. Dehydrative Allylation between Aldehydes and Allylic Alcohols through Synergistic N-Heterocyclic Carbene/Palladium Catalysis. *Chem. - Eur. J.* **2019**, *25*, 724−727. (c) Takemoto, S.; Ishii, T.; Yasuda, S.; Ohmiya, H. Synergistic *N*-Heterocyclic Carbene/Palladium-Catalyzed Allylation of Aldehydes with Allylic Carbonates. *Bull. Chem. Soc. Jpn.* **2019**, *92*, 937−940. (d) Ohnishi, N.; Yasuda, S.; Nagao, K.; Ohmiya, H. Synergistic N-Heterocyclic Carbene/Palladium-Catalyzed Aldehyde Acylation of Allylic Amines. *Asian J. Org. Chem.* **2019**, *8*, 1133−1135. Also see the following review: (e) Ohmiya, H. N-Heterocyclic Carbene-Based Catalysis Enabling Cross-Coupling Reactions. *ACS Catal.* **2020**, *10*, 6862−6869.

(3) For selected reviews on transition-metal-catalyzed hydroacylation of alkenes with aliphatic aldehydes, see: (a) Willis, M. C. Transition Metal Catalyzed Alkene and Alkyne Hydroacylation. *Chem. Rev.* **2010**, *110*, 725−748. (b) Murphy, S. K.; Dong, V. M. Enantioselective Hydroacylation of Olefins with Rhodium Catalysts. *Chem. Commun.* **2014**, *50*, 13645−13649. (c) Ghosh, A.; Johnson, K. F.; Vickerman, K. L.; Walker, J. A.; Stanley, L. M. Recent Advances in Transition Metal-Catalysed Hydroacylation of Alkenes and Alkynes. *Org. Chem. Front.* **2016**, *3*, 639−644.

(4) For selected reviews on HAT-catalyzed hydroacylation of alkenes with aliphatic aldehydes, see: (a) Deńes, F.; Pichowicz, M.; Povie, G.; Renaud, P. Thiyl Radicals in Organic Synthesis. *Chem. Rev.* **2014**, *114*, 2587−2693. (b) Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I. Site-Selective C−H Functionalization by Decatungstate Anion Photocatalysis: Synergistic Control by Polar and Steric Effects Expands the Reaction Scope. *ACS Catal.* **2018**, *8*, 701−713.

(5) Zhang, X.; MacMillan, D. W. C. Direct Aldehyde C−H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 11353−11356.

(6) (a) Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. *N*-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 3854−3858. (b) Ishii, T.; Ota, K.; Nagao, K.; Ohmiya, H. *N*-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 14073−14077. (c) Ota, K.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Synthesis of *δ*-Ketocarbonyls. *Org. Lett.* **2020**, *22*, 3922−3925.

(7) (a) Ishii, T.; Nagao, K.; Ohmiya, H. Recent Advances in Radical N-Heterocyclic Carbene Catalysis. *Chem. Sci.* **2020**, *11*, 5630−5636. (b) Li, J.-L.; Liu, Y.-Q.; Zou, W.-L.; Zeng, R.; Zhang, X.; Liu, Y.; Han, B.; He, Y.; Leng, H.-J.; Li, Q.-Z. Radical Acylfluoroalkylation of Olefins through *N*-Heterocyclic Carbene Organocatalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 1863−1870. (c) Zhang, B.; Peng, Q.; Guo, D.; Wang, J. NHC-Catalyzed Radical Trifluoromethylation Enabled by Togni Reagent. *Org. Lett.* **2020**, *22*, 443−447. (d) Kim, I.; Im, H.; Lee, H.; Hong, S. N-Heterocyclic Carbene-Catalyzed Deaminative Cross-Coupling of Aldehydes with Katritzky Pyridinium Salts. *Chem. Sci.* **2020**, *11*, 3192−3197. (e) Yang, H.-B.; Wang, Z.-H.; Li, J.-M.; Wu, C. Modular Synthesis of *α*-Aryl *β*-Perfluoroalkyl Ketones *via* N-Heterocyclic Carbene Catalysis. *Chem. Commun.* **2020**, *56*, 3801−3804. For examples of cooperative catalysis with photoredox catalyst, see: (f) Dai, L.; Xia, Z.-H.; Gao, Y.-Y.; Gao, Z.-H.; Ye, S. Visible-Light-Driven N-Heterocyclic Carbene Catalyzed *γ*- and *ε*-Alkylation with Alkyl Radicals. *Angew. Chem., Int. Ed.* **2019**, *58*, 18124−18130. (g) Davies, A. V.; Fitzpatrick, K. P.; Betori, R. C.; Scheidt, K. A. Combined Photoredox and Carbene Catalysis for the Synthesis of Ketones from Carboxylic Acids. *Angew. Chem., Int. Ed.* **2020**, *59*, 9143−9148. (h) Song, R.; Chi, Y. R. N-Heterocyclic Carbene Catalyzed Radical Coupling of Aldehydes with Redox-Active Esters. *Angew. Chem., Int. Ed.* **2019**, *58*, 8628−8630.

(8) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. A Family of Thiazolium Salt Derived N-Heterocyclic Carbenes (NHCs) for Organocatalysis: Synthesis, Investigation and Application in Cross-Benzoin Condensation. *Eur. J. Org. Chem.* **2011**, *2011*, 5475−5484.

(9) Nakanishi, I.; Itoh, S.; Fukuzumi, S. Electron-Transfer Properties of Active Aldehydes of Thiamin Coenzyme Models, and Mechanism of Formation of the Reactive Intermediates. *Chem. - Eur. J.* **1999**, *5*, 2810−2818.

(10) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. Direct Nucleophilic Acylation of Nitroalkenes Promoted by a Fluoride Anion/Thiourea Combination. *J. Am. Chem. Soc.* **2006**, *128*, 4932−4933.

(11) The reaction between a silylated thiazolium benzyl alcohol and **2a**, using stoichiometric amounts of TBAF and Cs_2CO_3 in DMSO at

60 °C, produced the corresponding ketone product, 2,2-dimethylpropiophenone in 33% yield. See ref 6a.
(12) To explore the effect of counteranion of the NHC precursor, a catalytic amount (10 mol %) of KI or KBr was added into the optimal conditions with N10, respectively. A slight decrease in product yields was observed (KI, 43% and KBr, 46%). Thus, the effect was not essential.
(13) When the product yield was low in Table 1C, significant amounts of the self-aldol product and the carboxylic acid that stem from the redox ester were observed.
(14) Leifert, D.; Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 74−108.
(15) (a) Moore, J. L.; Silvestri, A. P.; de Alaniz, J. R.; DiRocco, D. A.; Rovis, T. Mechanistic Investigation of the Enantioselective Intramolecular Stetter Reaction: Proton Transfer Is the First Irreversible Step. *Org. Lett.* **2011**, *13*, 1742−1745. (b) Domingo, L. R.; Zaragozá, R. J.; Saéz, J. A.; Arnó, M. Understanding the Mechanism of the Intramolecular Stetter Reaction. A DFT Study. *Molecules* **2012**, *17*, 1335−1353. (c) Collett, C. J.; Massey, R. S.; Maguire, O. R.; Batsanov, A. S.; O'Donoghue, A. C.; Smith, A. D. Mechanistic Insights into the Triazolylidene-Catalysed Stetter and Benzoin Reactions: Role of the *N*-Aryl Substituent. *Chem. Sci.* **2013**, *4*, 1514−1522.
(16) The triazolium type NHCs, which could facilitate the deprotonation step, did not work in this radical catalysis. This might be due to the lower reducing property of the corresponding Breslow intermediate than that of the thiazolium-derived Breslow intermediate.

https://dx.doi.org/10.1021/acscatal.0c02849
ACS Catal. 2020, 10, 8524−8529