JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Cite This: J. Am. Chem. Soc. 2019, 141, 3854−3858
Communication
pubs.acs.org/JACS

N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes

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Supporting Information

ABSTRACT: We found that *N*-heterocyclic carbene catalysis promoted the unprecedented decarboxylative coupling of aryl aldehydes and tertiary or secondary alkyl carboxylic acid-derived redox-active esters to produce aryl alkyl ketones. The mild and transition-metal-free reaction conditions are attractive features of this method. The power of this protocol was demonstrated by the functionalization of pharmaceutical drugs and natural product. A reaction pathway involving single electron transfer from an enolate form of Breslow intermediate to a redox ester followed by recombination of the resultant radical pair to form a carbon−carbon bond is proposed.

As a powerful tool for challenging synthetic reactions, *N*-heterocyclic carbene (NHC) catalysis, which exhibits a characteristic ability to access umpolung reactivity, has emerged.[1] NHC catalysis involving a two-electron reaction pathway has been extensively studied. NHC-mediated radical reactions are also known. For example, there are a number of enzymes utilizing thiamine diphosphate (ThDP) as a coenzyme to catalyze the decarboxylation of pyruvate in nature (Scheme 1A).[2] The resultant enamine, a so-called "Breslow intermediate," is known to perform single electron transfer to various electron acceptors such as lipoamides, flavin adenine dinucleotide and Fe_4S_4.[3] Inspired by this process, Studer and co-workers reported the pioneering example of NHC-based radical catalysis that enabled the oxidation of aldehydes to esters (Scheme 1B).[4] This process involves two continuous single electron oxidations of the Breslow intermediate by TEMPO to form the corresponding azolium ketone. Since this report, several groups have developed NHC-catalyzed radical functionalizations of α,β-unsaturated aldehydes.[5] However, these coupling partners have been limited to oxygen-centered radicals or highly specific carbon radicals.

Fukuzumi and co-workers studied the redox and electron transfer properties of enolate form of Breslow intermediates that are derived from aryl aldehydes and thiamine coenzyme analogues in the presence of a strong base (Scheme 1C).[6] Interestingly, the enolate form of Breslow intermediate has a strong reducing ability (E^0_{ox} = −0.95 ∼ −0.97 V) and fast electron transfer property. The resultant radical obtained by single electron oxidation was a persistent one. Based on this knowledge, we envisioned that the enolate form of Breslow intermediate could couple with redox active esters that can accept one electron and then liberate an alkyl radical. Herein, we report a new NHC-based redox catalysis, which allows for the decarboxylative coupling of aryl aldehydes and tertiary or secondary alkyl carboxylic acid-derived redox-active esters to produce aryl alkyl ketones (Scheme 1D).[7]

The ketone is an important functional group in organic chemistry. Various synthetic methods for accessing ketones have been developed. Recently, some groups have introduced new approaches that enable the direct conversion of aldehydes to ketones in a single step.[8] For example, MacMillan and co-workers developed the secondary and primary alkylation of aldehydes via the combination of nickel, hydrogen atom transfer, and photoredox catalysis.[8f] However, this methodology has not yet been expanded to the tertiary alkylation of aldehydes to construct quaternary carbon center.

The mechanistic details of our working hypothesis for the catalytic decarboxylative alkylation between aldehyde **1** and redox ester **2** are illustrated in Scheme 1E. Initially, the reaction between **1** and NHC produces a neutral Breslow intermediate (**A**). Deprotonation of the enol OH in **A** by a base (MX) generates the high reducing enolate form of the Breslow intermediate (**B**) (E^0_{ox} = −0.95 ∼ −0.97 V vs SCE in MeCN).[6] Next, the single electron transfer event between the enolate **B** and **2** provides a ketyl radical (**C**) and an alkyl radical (**D**), respectively.[9] Although **B** might not attain sufficient reduction potential for *N*-(acyloxy)phthalimide (**2**) (E^0_{red} < −1.28 V vs SCE in MeCN),[10] the electron transfer would still occur with the assistance of Lewis acidic activation of the phthalimide moiety with the counterion (M^+).[11] Finally, the radical−radical coupling between **C** and **D** followed by the elimination of NHC would afford the desired ketone product (**3**) and regenerate the NHC catalyst.

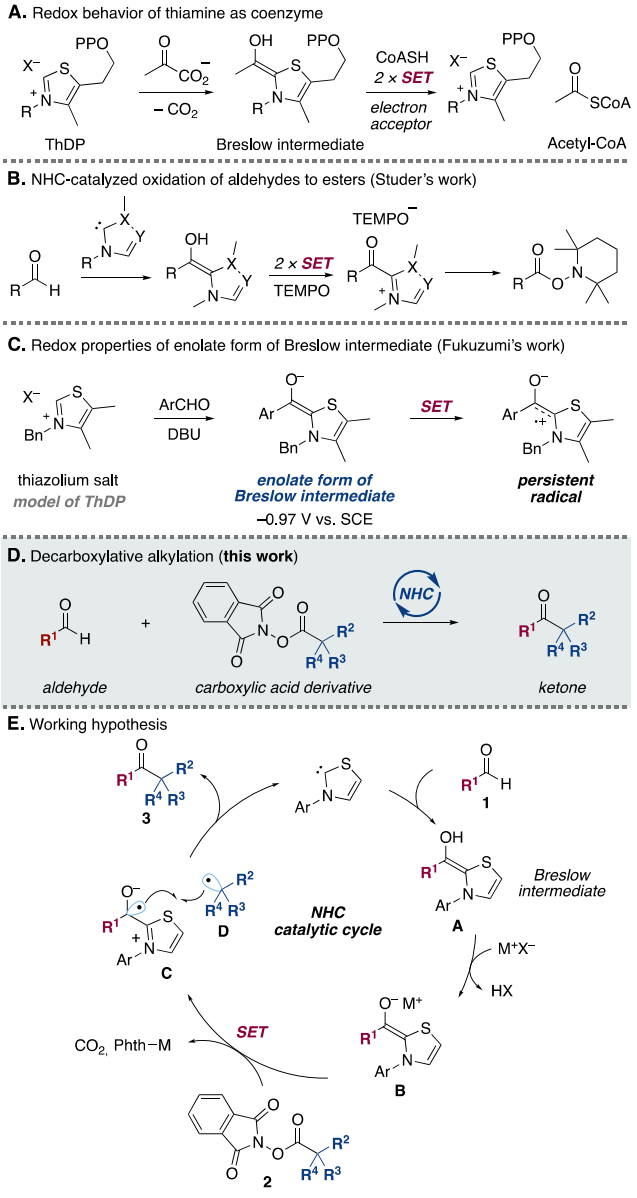
After judicious screening of the reaction conditions based on our working hypothesis, we found that the reaction between benzaldehyde (**1a**) (0.3 mmol) and *tert*-butyl *N*-(acyloxy)-phthalimide (**2a**) (0.2 mmol) occurred in the presence of catalytic amounts of the *N*-2,6-diisopropylphenyl-substituted seven-membered ring fused thiazolium salt **N1**[12] (10 mol %) as the NHC precursor and Cs_2CO_3 (20 mol %) in DMSO at 60 °C to afford *tert*-butylphenylketone (**3aa**) in 99% yield without any benzoin condensation product **4a** (Table 1, entry 1).[13]

The steric and electronic natures of the NHC catalyst were of great significance (Table 1, entries 2−7). A cyclohexane or dimethyl backbone instead of the cycloheptane backbone in

Received: January 24, 2019
Published: February 20, 2019

DOI: 10.1021/jacs.9b00880
J. Am. Chem. Soc. 2019, 141, 3854−3858

Scheme 1. Redox Chemistry of Breslow Intermediate and Application to Decarboxylative Coupling

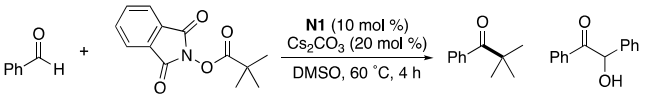


N1 decreased the product yield (entries 2 and 3). Introducing a smaller *N*-substituent such as a mesityl group caused a significant decrease in product yield (entry 4).[14] Other NHCs having triazolium, imidazolium or oxazolium structures were ineffective (entries 5–7).

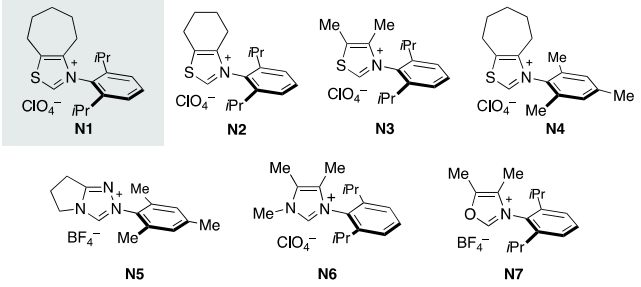
The choice of base was also critical for this reaction (Table 1, entries 8–13). As shown above, Cs_2CO_3 was found to be the best base.[11b] Other alkali metal carbonates decreased the product yields (entries 8–10). The use of strong organic bases such as DBU and TMG showed low reaction efficiencies. The weaker organic base, $^{i}Pr_2NEt$, significantly diminished the product yield.

With the optimized conditions in hand, we next turned our attention to investigate the scope of the aryl aldehydes and redox-active esters in the NHC-catalyzed decarboxylative alkylation (Table 2). Various aryl aldehydes were examined (Table 2, top). Neither electron-rich nor electron-deficient functional groups affected the product yield (**3ba**–**fa**). Notably, this transition-metal-free protocol was compatible

Table 1. Screening of Catalysts and Bases for Reaction between 1a and 2a[a]



entry	Change from standard conditions	Yield of **3aa** (%)[b]	Yield of **4a** (%)[b]
1	none	99	0
2	**N2** instead of **N1**	31	0
3	**N3** instead of **N1**	50	0
4	**N4** instead of **N1**	11	4
5	**N5** instead of **N1**	6	20
6	**N6** instead of **N1**	0	0
7	**N7** instead of **N1**	0	0
8	Li_2CO_3 instead of Cs_2CO_3	7	3
9	Na_2CO_3 instead of Cs_2CO_3	40	0
10	K_2CO_3 instead of Cs_2CO_3	74	0
11	DBU instead of Cs_2CO_3	12	0
12	TMG instead of Cs_2CO_3	26	8
13	$^{i}Pr_2NEt$ instead of Cs_2CO_3	4	8



[a]Reaction was carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), NHC (0.02 mmol), and Cs_2CO_3 (0.04 mmol) in DMSO (0.4 mL) at 60 °C for 4 h. [b]^{1}H NMR yield based on **2a**. DMSO = dimethyl sulfoxide. DBU = 1,8-diazabicyclo[5.4.0]-7-undecene. TMG = 1,1,3,3-tetramethylguanidine.

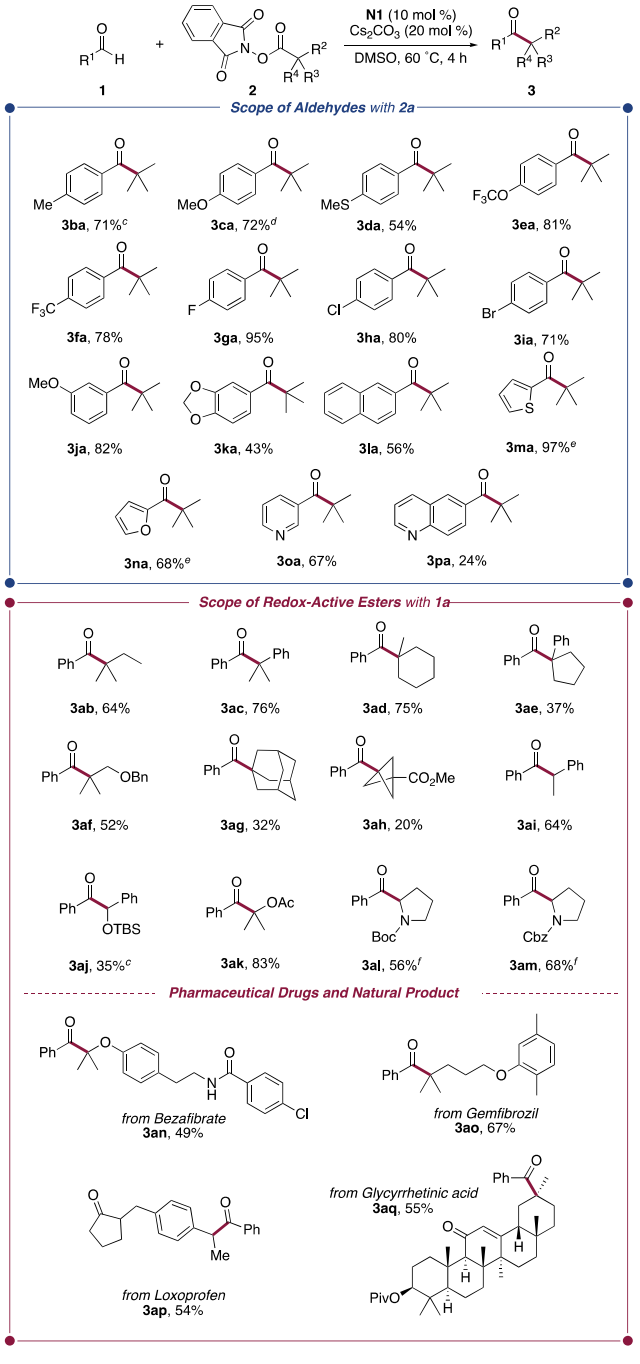
with halogen substituents (**3ga**–**ia**), which can be utilized for further modifications. Ether and acetal functional groups were tolerated (**3ja** and **3ka**). 2-Naphthaldehyde served as a substrate (**3la**). Heteroaromatic rings such as thiophene, furan, pyridine or quinoline were tolerated (**3ma**–**pa**). The reaction with aliphatic aldehydes was unsuccessful, possibly due to instability (short lifetime) of radical **C** in Scheme 1E.

Various tertiary or secondary alkyl carboxylic acid derived redox esters were evaluated (Table 2, middle). 2,2-Dimethylbutyric acid and 2-methyl-2-phenylpropanoic acid efficiently coupled with **1a** (**3ab** and **3ac**). Tertiary cyclohexyl or cyclopentyl groups could be introduced to the acyl moiety (**3ad** and **3ae**). Benzyl ether was compatible with this reaction (**3af**). This protocol could introduce the acyl group to sterically hindered complex polycyclic molecules such as adamantane and propellane, although the yields were low (**3ag** and **3ah**). Secondary alkyl carboxylic acid derivative could participate in the reaction (**3ai**). Reactions with primary carboxylic acid derivatives resulted in low product yield (data not shown).

α-Heteroatom-substituted alkyl carboxylic acid derived redox-active esters were successfully converted to the

DOI: 10.1021/jacs.9b00880
J. Am. Chem. Soc. 2019, 141, 3854–3858

Table 2. Substrate Scope[a,b]



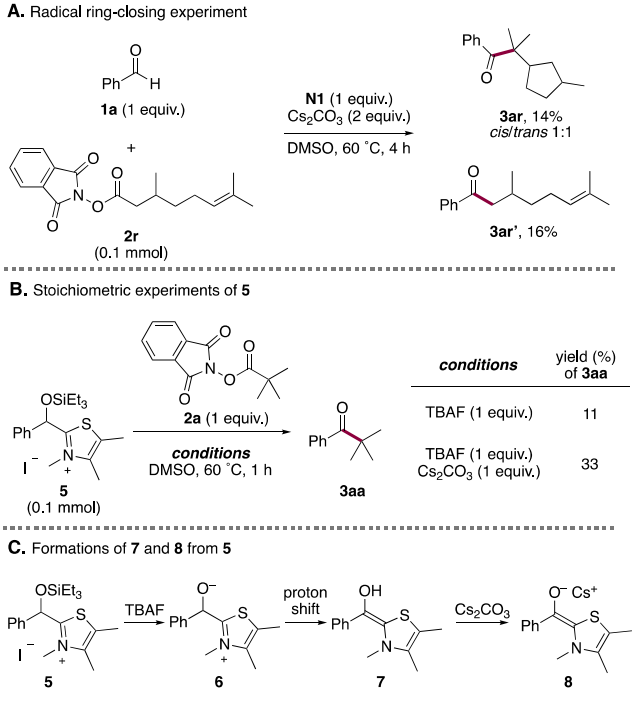
[a]Reaction was carried out with **1** (0.3 mmol), **2** (0.2 mmol), **N1** (0.02 mmol), and Cs_2CO_3 (0.04 mmol) in DMSO (0.4 mL) at 60 °C for 4 h. [b]Isolated yield. [c]**N1** (0.04 mmol) and Cs_2CO_3 (0.08 mmol). [d]24 h. [e]80 °C. [f]**N1** (0.03 mmol) and DBU (0.06 mmol) was used instead of Cs_2CO_3.

corresponding ketones. For example, the reaction of α-hydroxy-substituted alkyl carboxylic acids occurred to produce α-hydroxy ketones (**3aj** and **3ak**).[15] L-Proline derivatives protected by Boc or Cbz groups were also used as coupling partners, and racemic ketones were obtained (**3al** and **3am**).

The NHC-catalyzed decarboxylative alkylation protocol could be applied to the acylation of pharmaceutical drugs and natural product (Table 2, bottom). These acylated products are difficult to obtain by other methods. For example, redox esters derived from pharmaceutical drugs such as Bezafibrate, Gemfibrozil and Loxoprofen resulted in the formation of the corresponding ketones with these functional groups remaining untouched (**3an**, **3ao** and **3ap**). Glycyrrhetinic acid having a steroidal structure reacted with **1a** to give the acylated product as a single diastereomer (**3aq**).

The proposed catalytic cycle illustrated in Scheme 1E was supported by several experiments (Scheme 2). The reaction of

Scheme 2. Mechanistic Studies



1a with citronellic acid-derived redox ester **2r** in the presence of stoichiometric amounts of **N1** and Cs_2CO_3 afforded cyclic product **3ar** in 14% yield along with the direct coupling product **3ar′** in 16% yield (Scheme 2A). This result indicated the intermediacy of a carbon-centered radical in the reaction.[16]

To obtain information on the nature of the Breslow intermediate, we conducted stoichiometric experiments using silylated thiazolium benzyl alcohol **5** (Scheme 2B). Earlier, Scheidt and co-workers demonstrated that silyl ether **5** acts as Breslow intermediate equivalent **7** through desilylation with a fluoride base followed by a proton shift in the obtained **6** (Scheme 2C).[17] The reaction between **5** and **2a** in the presence of TBAF produced the corresponding ketone **3aa** in 11% yield. The formation of **3aa** would be due to the generation of a small amount of **8** through intermolecular deprotonation of **7** by **6**. The use of Cs_2CO_3 as an additional base increased the product yield (33%). Thus, the enolate form **8**, which is derived from **7**, promoted the SET process.

In summary, we have developed the NHC-catalyzed decarboxylative coupling reaction between aryl aldehydes and tertiary or secondary alkyl carboxylic acid-derived redox-active esters to deliver aryl alkyl ketones. The protocol allowed the simple and efficient preparation of functionalized ketones from two readily available carbonyl compounds. The mild and transition-metal-free reaction conditions are attractive features of this method. The power of this protocol was demonstrated by the functionalization of pharmaceutical drugs and natural product. A reaction pathway involving the single electron

DOI: 10.1021/jacs.9b00880
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transfer from an enolate form of Breslow intermediate to the redox ester followed by the recombination of the resultant radical pair is proposed. Mechanistic studies by intermediate analysis and theoretical calculations as well as studies on expanding this coupling to asymmetric variants are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b00880.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Number JP18H01971 to Scientific Research (B), JSPS KAKENHI Grant Number JP17H06449 (Hybrid Catalysis), Kanazawa University SAKIGAKE project 2018.

■ REFERENCES

(1) For selected reviews on NHC catalysis, see: (a) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307. (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485. (c) Zhang, C.; Hooper, J. F.; Lupton, D. W. *N*-Heterocyclic Carbene Catalysis via the α,β-Unsaturated Acyl Azolium. *ACS Catal.* **2017**, *7*, 2583.

(2) (a) Ragsdale, S. W. Pyruvate Ferredoxin Oxidoreductase and Its Radical Intermediate. *Chem. Rev.* **2003**, *103*, 2333. (b) Kluger, R.; Tittmann, K. Thiamin Diphosphate Catalysis: Enzymic and Non-enzymic Covalent Intermediates. *Chem. Rev.* **2008**, *108*, 1797. (c) Chabriere, E.; VernHde, X.; Guigliarelli, B.; Charon, M. H.; Hatchikian, E. C.; Fontecilla-Camps, J. C. *Science* **2001**, *294*, 2559. (d) Mansoorabadi, S. O.; Seravalli, J.; Furdui, C.; Krymov, V.; Gerfen, G. J.; Begley, T. P.; Melnick, J.; Ragsdale, S. W.; Reed, G. H. EPR Spectroscopic and Computational Characterization of the Hydroxyethylidene-Thiamine Pyrophosphate Radical Intermediate of Pyruvate: Ferredoxin Oxidoreductase. *Biochemistry* **2006**, *45*, 7122.

(3) (a) Chiu, C. C.; Pan, K.; Jordan, F. Modeling an Elementary Step of the Enzyme Pyruvate Oxidase: Oxidation of a Thiamin Diphosphate-Bound Enamine Intermediate by a Flavin Analog. *J. Am. Chem. Soc.* **1995**, *117*, 7027. (b) Bugg *Introduction to Enzyme and Coenzyme Chemistry*; Blackwell: Oxford, 2004.

(4) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. Biomimetic carbene-catalyzed oxidations of aldehydes using TEMPO. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727.

(5) For selected papers on NHC-catalyzed radical functionalization, see: (a) Du, Y.; Wang, Y. H.; Li, X.; Shao, Y. L.; Li, G. H.; Webster, R. D.; Chi, Y. R. *N*-Heterocyclic Carbene Organocatalytic Reductive β,β-Coupling Reactions of Nitroalkenes via Radical Intermediates. *Org. Lett.* **2014**, *16*, 5678. Zhang, Y.; Du, Y.; Huang, Z.; Xu, J.; Wu, X.; Wang, Y.; Wang, M.; Yang, S.; Webster, R. D.; Chi, Y. R. N-Heterocyclic Carbene-Catalyzed Radical Reactions for Highly Enantioselective β-Hydroxylation of Enals. *J. Am. Chem. Soc.* **2015**, *137*, 2416. (c) Li, B.-S.; Wang, Y.; Proctor, R. S. J.; Zhang, Y.; Webster, R. D.; Yang, S.; Song, B.; Chi, Y. R. Carbene-catalysed reductive coupling of nitrobenzyl bromides and activated ketones or imines via single-electron-transfer process. *Nat. Commun.* **2016**, *7*, 12933. (d) Wang, Y.; Du, Y.; Huang, X.; Wu, X.; Zhang, Y.; Yang, S.; Chi, Y. R. Carbene-Catalyzed Reductive Coupling of Nitrobenzyl Bromide and Nitroalkene via the Single-Electron-Transfer (SET) Process and Formal 1,4-Addition. *Org. Lett.* **2017**, *19*, 632. (e) Wu, X.; Zhang, Y.; Wang, Y.; Ke, J.; Jeret, M.; Reddi, R. N.; Yang, S.; Song, B.-A.; Chi, Y. R. Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis by Radical Processes. *Angew. Chem., Int. Ed.* **2017**, *56*, 2942. (f) White, N. A.; Rovis, T. Enantioselective N-Heterocyclic Carbene-Catalyzed β-Hydroxylation of Enals Using Nitroarenes: An Atom Transfer Reaction That Proceeds via Single Electron Transfer. *J. Am. Chem. Soc.* **2014**, *136*, 14674. (g) White, N. A.; Rovis, T. Oxidatively Initiated NHC-Catalyzed Enantioselective Synthesis of 3,4-Disubstituted Cyclopentanones from Enals. *J. Am. Chem. Soc.* **2015**, *137*, 10112. (h) Rehbein, J.; Ruser, S. M.; Phan, J. NHC-catalysed benzoin condensation − is it all down to the Breslow intermediate? *Chem. Sci.* **2015**, *6*, 6013. (i) Yang, W.; Hu, W.; Dong, X.; Li, X.; Sun, J. N-Heterocyclic Carbene Catalyzed γ-Dihalomethylenation of Enals by Single-Electron Transfer. *Angew. Chem., Int. Ed.* **2016**, *55*, 15783. (j) Chen, X.−Y.; Chen, K.−Q.; Sun, D.−Q.; Ye, S. N-Heterocyclic carbene-catalyzed oxidative [3 + 2] annulation of dioxindoles and enals: cross coupling of homoenolate and enolate. *Chem. Sci.* **2017**, *8*, 1936. (k) Zhao, K.; Enders, D. Merging N-Heterocyclic Carbene Catalysis and Single Electron Transfer: A New Strategy for Asymmetric Transformations. *Angew. Chem., Int. Ed.* **2017**, *56*, 3754.

(6) Nakanishi, I.; Itoh, S.; Suenobu, T.; Inoue, H.; Fukuzumi, S. Redox Behavior of Active Aldehydes Derived from Thiamin Coenzyme Analogs. *Chem. Lett.* **1997**, *26*, 707. (b) Nakanishi, I.; Itoh, S. Electron transfer properties of active aldehydes derived from thiamin coenzyme analogues. *Chem. Commun.* **1997**, 1927. (c) 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. (d) Nakanishi, I.; Itoh, S.; Suenobu, T.; Fukuzumi, S. Direct Observation of Radical Intermediates While Investiganting the Redox Behavior of Thiamin Coenzyme Models. *Angew. Chem., Int. Ed.* **1998**, *37*, 992.

(7) For our synergistic NHC-based 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. (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. (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**, *48*, DOI: 10.1246/bcsj.20190012.

(8) For selected papers on synthesis of ketones via formyl C−H activation of aldehydes, see: (a) Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. Nickel-Catalyzed Coupling of Aryl Iodides with Aromatic Aldehydes: Chemoselective Synthesis of Ketones. *J. Org. Chem.* **2002**, *67*, 1682. (b) Pucheault, M.; Darses, S.; Genet, J.-P. Direct Access to Ketones from Aldehydes via Rhodium-Catalyzed Cross-Coupling Reaction with Potassium Trifluoro(organo)borates. *J. Am. Chem. Soc.* **2004**, *126*, 15356. (c) Ko, S.; Kang, B.; Chang, S. Cooperative catalysis by Ru and Pd for the direct coupling of a chelating aldehyde with iodoarenes or organostannanes. *Angew. Chem., Int. Ed.* **2005**, *44*, 455. (d) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 10510. (e) Suchand, B.; Satyanarayana, G. Palladium-Catalyzed Environmentally Benign Acylation. *J. Org. Chem.* **2016**, *81*, 6409. (f) Zhang, X.; MacMillan, D.

DOI: 10.1021/jacs.9b00880
J. Am. Chem. Soc. 2019, 141, 3854−3858

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. (g) Mukherjee, S.; Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Glorius, F. Alkynylation of Csp^2 (O)-H Bonds Enabled by Photoredox-Mediated Hydrogen-Atom Transfer. *Angew. Chem., Int. Ed.* **2017**, *56*, 14723.

(9) Regnier, V.; Romero, E. A.; Molton, F.; Jazzar, R.; Bertrand, G.; Martin, D. What Are the Radical Intermediates in Oxidative N-Heterocyclic Carbene Organocatalysis? *J. Am. Chem. Soc.* **2019**, *141*, 1109.

(10) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. Photosensitized Decarboxylative Michael Addition through *N*-(Acy1oxy) Phthalimidesvia an Electron-Transfer Mechanism. *J. Am. Chem. Soc.* **1991**, *113*, 9401.

(11) (a) Tlahuext-Aca, A.; Garza-Sanchez, R. A.; Glorius, F. Multicomponent Oxyalkylation of Styrenes Enabled by Hydrogen-Bond-Assisted Photoinduced Electron Transfer. *Angew. Chem., Int. Ed.* **2017**, *56*, 3708. (b) Candish, L.; Teders, M.; Glorius, F. Transition-metal-free, visible-light-enabled decarboxylative borylation of aryl *N*-hydroxyphthalimide esters. *J. Am. Chem. Soc.* **2017**, *139*, 7440.

(12) (a) Pesch, J.; Harms, K.; Bach, T. Preparation of Axially Chiral *N,N′*-Diarylimidazolium and *N*-Arylthiazolium Salts and Evaluation of Their Catalytic Potential in the Benzoin and in the Intramolecular Stetter Reactions. *Eur. J. Org. Chem.* **2004**, *2004*, 2025. (b) 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.

(13) Solvent screening identified DMSO to be the best. The highly polar DMSO might stabilize the zwitterionic form of the ketyl radical (**C**). See Supporting Information for the details of solvent screening.

(14) The bulkiness of the *N*-substituent of **N1** might suppress the decomposition of the ketyl radical (**C**). See Supporting Information for the theoretical analysis of **C**.

(15) Merritt, E. A.; Olofsson, B. *α*-Functionalization of Carbonyl Compounds Using Hypervalent Iodine Reagents. *Synthesis* **2011**, *2011*, 517.

(16) (a) Yu, L.; Tang, M.-L.; Si, C.-M.; Meng, Z.; Liang, Y.; Han, J.; Sun, X. Zinc-Mediated Decarboxylative Alkylation of *Gem*-difluoroalkenes. *Org. Lett.* **2018**, *20*, 4579. (b) Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. Reduction of Organic Halides with Lanthanum Metal: A Novel Generation Method of Alkyl Radicals. *J. Org. Chem.* **2002**, *67*, 966.

(17) 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.

DOI: 10.1021/jacs.9b00880
J. Am. Chem. Soc. 2019, 141, 3854−3858