OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Chiral Nitroarenes as Enantioselective Single-Electron-Transfer Oxidants for Carbene-Catalyzed Radical Reactions

Hongling Wang,[†,‡,§] Yuhuang Wang,[¶,§] Xingkuan Chen,[‡,§] Chengli Mou,[#] Shuyan Yu,[‡] Huifang Chai,[*,#] Zhichao Jin,[†] and Yonggui Robin Chi[*,†,‡]

[†]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China

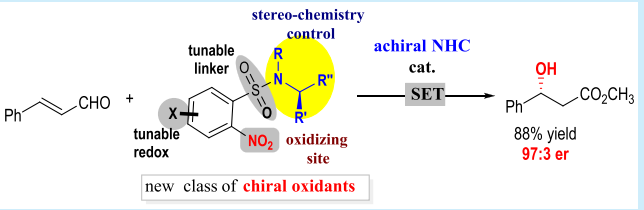
[#]Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China

[‡]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

[¶]BGI-Shenzhen, Beishan Industrial Zone, Yantian, Shenzhen, 518083, China

Supporting Information

ABSTRACT: A new class of chiral oxidants is developed. These readily accessible oxidants contain a nitro group for oxidation and a chiral sulfonamide moiety for stereoselectivity control. The chiral information from the oxidants can effectively transfer to the substrates in carbene-catalyzed β-hydroxylation of enals via single-electron-transfer radical processes. We expect these oxidants to find unique applications in other asymmetric oxidations and oxygen-atom-transferring reactions.



Asymmetric oxidation can be realized via the use of chiral catalysts with achiral oxidants.[1] Alternatively, the chiral induction can also be achieved by using chiral oxidants.[2] The latter approach may provide better solutions in certain cases, for example, when the chiral catalysts are less available or chiral inductions from catalysts are unsatisfactory. Several major classes of chiral oxidants have been proven to be powerful and efficient in asymmetric reactions, including chiral oxaziridines,[3] chiral hypervalent iodines,[4] chiral hydroperoxides,[5] and chiral dioxiranes.[6] In *N*-heterocyclic carbene (abbreviated as NHC or carbene) organic catalysis,[7] oxidation has become a key step in a large number of transformations. A main type of oxidant is quinone, first introduced by Studer[8] (Figure 1b). Other oxidants include O_2,[9] activated MnO_2,[10] TEMPO,[11] phenazine,[12] riboflavin,[13] aromatic nitro, and nitroso derivatives.[14] We have found nitroalkenes[15] and polyhalides[16] could behave as effective oxidants for the oxidation of aldehydes under NHC catalysis. Recently, Rovis[17a] and our laboratory[17b] independently reported the use of nitroarene molecules as oxidants for β-hydroxylation of enals via NHC-catalyzed radical reactions.[18] In all these oxidative reactions mediated by NHCs, the oxidants are achiral molecules. Here we report a new class of chiral oxidants containing a nitro group for oxidation and a chiral sulfonamide for stereoselectivity control (Figure 1c). These oxidants are easily prepared in large quantities with diverse structures by coupling commercially available nitrobenzenesulfonyl chloride with chiral amines. With these chiral oxidants, highly enantioselective β-hydroxylation of enals are realized by using a simple achiral NHC as the catalyst (Figure 1d). Analysis on the fate of the oxidants and relative control experiments explained the main side reaction of the enals, providing mechanistic insights to these radical reactions. Chiral oxidants that enable SET radical reactions with excellent chiral inductions have been studied minimally. In addition to NHC catalysis, we expect this class of chiral oxidants to find unique applications in other asymmetric oxidative transformations.

We first chose the β-hydroxylation of cinnamaldehyde (**1a**) under the catalysis of achiral triazolium NHC precatalyst **C1**[19a] at room temperature as a model reaction to search for suitable oxidants with good chiral inductions (Figure 2). To our delight, nearly all nitrobenzenesulfonamides prepared from chiral amines provided product **3a** with obvious enantiomeric excess. Results from a selected set of chiral oxidants are presented in Table 1. We started with benzenesulfonamides with NO_2 as an *ortho*-substituent to study the effect of the chiral amine moieties of the oxidants. The use of oxidant bearing (*R*)-1-phenylethylamine (**2a**) gave the enal β-hydroxylation product **3a** with a low while encouraging er value (56:44 er). Replacing the phenyl unit of the amine in **2a** with an isopropyl substituent (oxidant **2b**) led to **3a** with significantly improved er (27:73 er). A limited survey indicated that further changing the steric bulkiness of primary amines could lead to better chiral inductions (e.g., oxidant **2c**). Simple amino acid-derived oxidants (e.g., **2d**) could also induce moderate to good enantioselectivities. Pyrrolidine-based chiral

Received: August 5, 2019

DOI: 10.1021/acs.orglett.9b02736
Org. Lett. XXXX, XXX, XXX–XXX

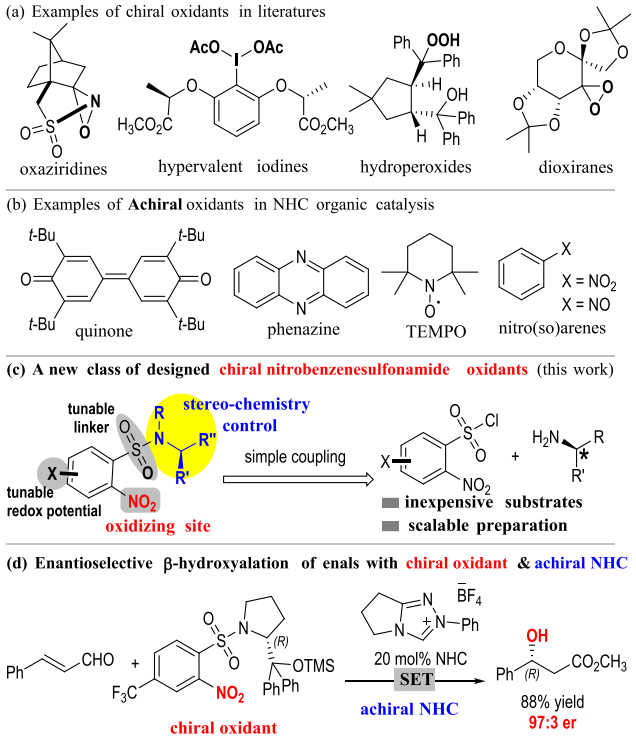


Figure 1. Designed chiral oxidants for asymmetric radical reactions.

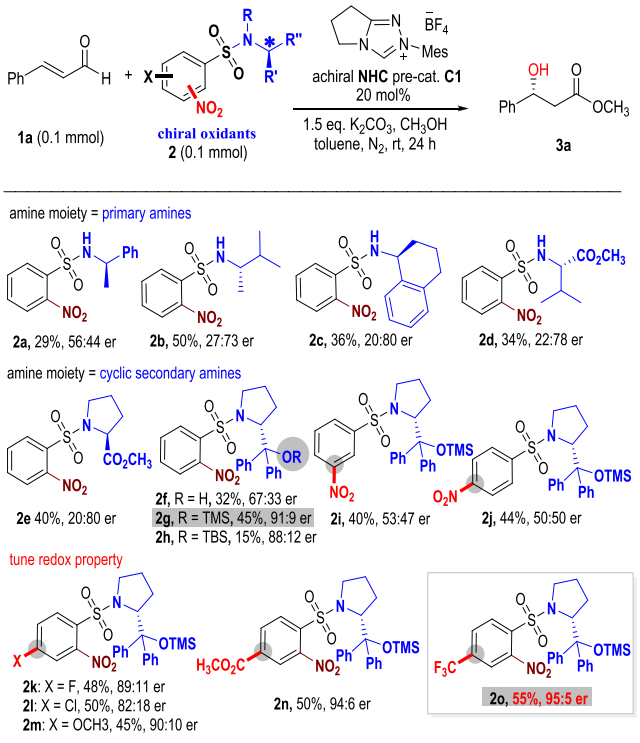
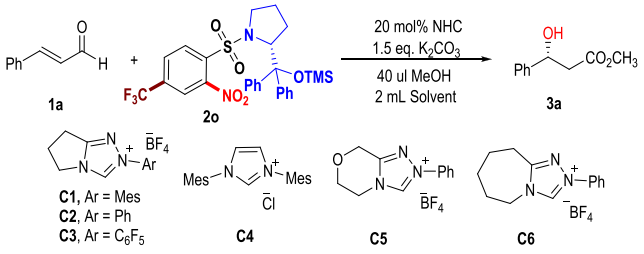


Figure 2. Search for chiral oxidants. All reactions were carried out in a glovebox under N_2 (see SI). Reactions were carried out at room temperature using **1a** (0.1 mmol), **2** (0.1 mmol), **C1** (20 mol %), K_2CO_3 (150 mol %), 40 μl of MeOH, and 2 mL of toluene, for 24 h. Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Enantiomeric ratios were determined via HPLC analysis on a chiral stationary phase; the absolute configuration was determined by comparing the optical rotation of **3a** with literature values.

Table 1. Condition Optimization on Achiral NHC Catalysts[a]



entry	NHC	solvent	yield (%)[b]	er[c]
1	--	Toluene	n.r.	--
2	**C1**	Toluene	55	95:5
3	**C2**	Toluene	63	94:6
4	**C3**	Toluene	30	92:8
5	**C4**	Toluene	48	81:19
6	**C5**	Toluene	60	94:6
7	**C6**	Toluene	43	81:19
8	**C2**	CH_2Cl_2	38	69:31
9	**C2**	THF	52	90:10
10	**C2**	Et_2O	70	95:5
11[d]	**C2**	Et_2O	67	97:3
12[e]	**C2**	Et_2O	91 (88)	97:3
13[f]	**C2**	Et_2O	77	96:4

[a]All reactions were carried out in a glovebox under N_2 (see SI). Reactions were carried out at room temperature using **1a** (0.1 mmol), **2o** (0.1 mmol), **NHC** (20 mol %), K_2CO_3 (150 mol %), 40 μl of MeOH, and 2 mL of solvent, for 24 h. [b]Estimated via ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses based on **2o**. [c]Enantiomeric ratio determined via HPLC analysis on a chiral stationary phase. [d]At −10 °C for 36 h. [e]0.15 mmol **1a** was used, at −10 °C for 36 h. [f]The reaction was carried out at 2.0 mmol scale based on **2o**.

secondary amines (proline derivatives) as part of the oxidants were then examined (**2e**−**2h**). Notably, oxidant bearing a diphenylprolinol trimethylsilyl ether unit (**2g**) gave **3a** with 45% yield and 91:9 er. The relative regio-position of NO_2 and the chiral sulfonamide moiety in the oxidants is critical for chiral induction. Placing NO_2 at the meta- or para-position led to nearly complete loss of reaction enantioselectivities (**2i** and **2j**). Lastly, we introduced a third substituent to the benzene core of the oxidant to tune the redox property of the NO_2 and to modulate the steric effects for better yields and enantioselectivities (**2k**−**2o**). The installation of an electron-withdrawing CF_3 unit at the para-position (relative to the amide) of the benzene core led to **3a** with 55% yield and 95:5 er (oxidant **2o**).

We then chose oxidant **2o** for further reaction optimizations to identify suitable achiral NHC catalysts and conditions (Table 1). Using toluene as solvent, K_2CO_3 as base, we examined achiral NHC precatalysts **C1**−**C6** for reactions at room temperature. *N*-Phenyl substituted achiral triazolium NHC precatalyst **C2**[19b] is more efficient than N-mesyl substituted catalyst **C1** and N−C_6F_5 substituted catalyst

DOI: 10.1021/acs.orglett.9b02736
Org. Lett. XXXX, XXX, XXX−XXX

C3.[19c] With C2 as catalyst, 3a was formed in 63% yield and 94:6 er (entry 3). Imidazolium salt C4 could also promote this oxidation reaction, albeit with a slightly lower yield and er (entry 4). A few other N-Ph substituted achiral triazolium NHC precatalysts (e.g., C5 and C6) were also examined, but did not give better results than C2 (entries 5 and 6). We then chose C2 as the NHC precatalyst to study the effects of solvents (entries 8−10) and found that Et_2O performed better than toluene, leading to 3a with an improved 70% yield and similar er (entry 10). Decreasing the reaction temperature from rt to −10 °C led to a small increase on er value (entry 11). We finally found that changing the loading of 1a and 2o from 1:1 (molar ratio) to 1.5:1 could lead to 3a in 88% isolated yield and 97:3 er at −10 °C (entry 12).

With an optimized condition in hand (Table 1, entry 12), we next examined the generality of this oxidative process for the β-hydroxylation of different enals (Figure 3). Placing

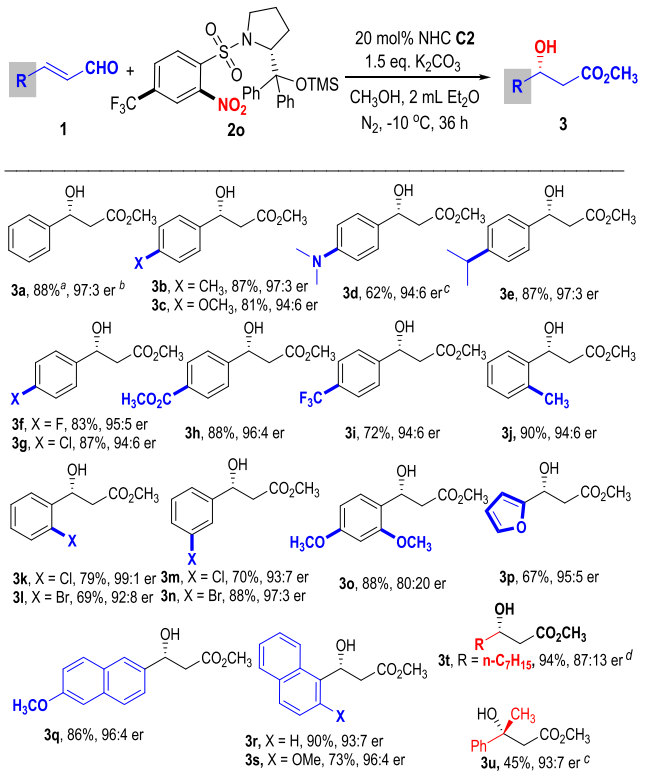
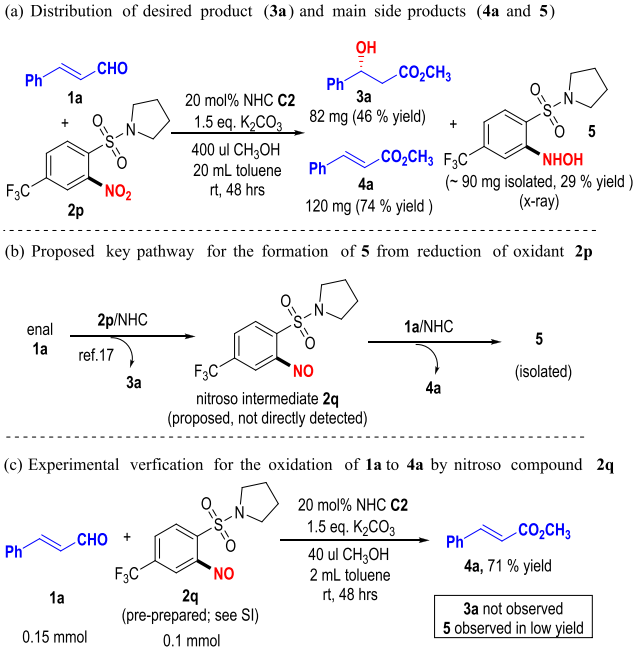


Figure 3. Substrates scope of enals. [a]Isolated yield based on 2o. [b]Enantiomeric ratio determined via HPLC analysis on a chiral stationary phase. [c]0.15 mmol 1 was used, at room temperature for 36 h. [d]Determined via HPLC analysis on chiral stationary phase after derivatization (see SI).

substituents with different stereo electronic properties to para-carbon of the β-phenyl enals was well tolerated, leading to the corresponding hydroxylation products with good yields and around 95:5 er values (3a−3i). Substituents at ortho- (3j−3l) or meta-position (3m, 3n) of the enal β-phenyl units led to slight increases on enantioselectivities. Furan- and naphthalene-substituted enals reacted effectively as well to give the corresponding β-hydroxylation products with excellent yields and er values (3p−3s). Enals with β-alkyl substituents reacted nicely as well to give products 3t with excellent yields and 87:13 er. An enal with two substituents at the β-carbon was also tolerated, giving the desired product in moderate yield and 92:8 er (3u).

We next performed several experiments to understand the fate of the oxidants by using a simplified achiral oxidant 2p as a model (Scheme 1). In addition to the desired enal β-

Scheme 1. Mechanistic Investigations



hydroxylation product 3a (obtained in 82 mg, 46% isolated yield based on 2p), two major side products were isolated with structures confirmed (Scheme 1a). One side product was α,β-unsaturated ester 4a derived from enal 1a. This ester was isolated in about 120 mg (74% yield relative to oxidant 2p). Another major byproduct was a hydroxyl amine (5) that was obtained in about 90 mg (29% yield relative to 2p) with structure confirmed by single crystal X-ray analysis. This observation, together with previous studies from Rovis and our own laboratory,[17] suggests a reaction pathway proposed in Scheme 1b. Under the catalysis of NHC, SET oxidation[18] of enal by oxidant 2p generate product 3a. During this step, the nitroarene oxidant was reduced to a nitroso intermediate (2q).[17] The nitroso intermediate (2q) then behaved as an oxidant[17a] to convert enal 1a to the corresponding α,β-unsaturated ester (4a) with the formation of hydroxylamine 5. To support the postulated pathway (oxidation of 1a to 4a by 2q), we synthesized the nitroso compound 2q and subjected it to the reaction of enal under NHC catalysis (Scheme 1c). Our experiments showed that with nitroso 2q as the oxidant, enal 1a was converted to the unsaturated ester with 71% yield. The β-hydroxylation product (3a) was not observed. Our experimental observation is different from Rovis's earlier proposal (see SI of Rovis's article),[17a] in which they proposed that nitroso compound could oxidize enal to the β-hydroxylation product. In our redox process, nitroso 2q was converted to hydroxyl amine 5 and multiple unidentified complexes. These unidentified complexes likely initiate from reactions involving hydroxyl amine 5 and the nitroso compound 2q.[20] As a technical note, similar reactions using chiral oxidant such as 2o gave complicated mixtures that were

DOI: 10.1021/acs.orglett.9b02736
Org. Lett. XXXX, XXX, XXX−XXX

challenging to analyze in part due to the instability of the TMS ether in the oxidant.

In summary, we have developed a new class of nitroarenes-based chiral oxidants for achiral NHC-catalyzed enantioselective transferring of oxygen atoms to enals via SET radical processes. These oxidants can be readily prepared with diverse structures in large quantities by coupling commercially available and inexpensive nitrobenzenesulfonyl chloride and chiral amines. Further exploration in using these new chiral oxidants for other asymmetric oxidation reactions beyond NHC catalysis is in progress in our laboratory. We are also developing effective methods for regenerating the oxidants in situ (by terminal oxidants such as oxygen), and thus, the oxidants can be used in catalytic amounts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02736.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1901109 and 1946060 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: robinchi@ntu.edu.sg.
*E-mail: hfchai@126.com.

ORCID

Hongling Wang: 0000-0002-5092-0476
Zhichao Jin: 0000-0003-3003-6437
Yonggui Robin Chi: 0000-0003-0573-257X

Author Contributions

§H.W., Y.W., and X.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Yongxin Li (NTU) for assistance with X-ray structure analysis. We acknowledge financial support from the National Natural Science Foundation of China (No. 21772029, 21801051), National Key Technologies R&D Program (No. 2014BAD23B01), The 10 Talent Plan (Shicengci) of Guizhou Province [2016]5649, Guizhou Province Returned Oversea Student Science and Technology Activity Program (2014)-2, Science and Technology Department of Guizhou Province [2018]2802, [2019]1020, Guizhou University, the Guizhou Province First-Class Disciplines Project (Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008, Open Fund of Guizhou Key Laboratory of Miao Medicine QMYY [2017]101, Guizhou University of Traditional Chinese Medicine (China). Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; RG108/16), A*STAR Individual Research Grant (A1783c0008), Nanyang Research Award Grant, and Nanyang Technological University.

■ REFERENCES

(1) For selected reviews, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) De Faveri, G.; Ilyashenko, G.; Watkinson, M. Recent Advances in Catalytic Asymmetric Epoxidation using the Environmentally Benign Oxidant Hydrogen Peroxide and its Derivatives. *Chem. Soc. Rev.* **2011**, *40*, 1722−1760. (c) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. Organocatalytic Asymmetric Epoxidation and Aziridination of Olefins and their Synthetic Applications. *Chem. Rev.* **2014**, *114*, 8199−8256.

(2) Parra, A.; Reboredo, S. Chiral Hypervalent Iodine Reagents: Synthesis and Reactivity. *Chem. - Eur. J.* **2013**, *19*, 17244−17260.

(3) (a) Williamson, K. S.; Michaelis, D. J.; Yoon, T. P. Advances in the Chemistry of Oxaziridines. *Chem. Rev.* **2014**, *114*, 8016−8036. (b) Davis, F. A. Recent Applications of N-sulfonyloxaziridines (Davis Oxaziridines) in Organic Synthesis. *Tetrahedron* **2018**, *74*, 3198−3214. (c) Tanaka, N.; Tsutsumi, R.; Uraguchi, D.; Ooi, T. N-Sulfonyl α-Imino Ester-derived Chiral Oxaziridines: Catalytic Asymmetric Synthesis and Application as a Modular Chiral Organic Oxidant. *Chem. Commun.* **2017**, *53*, 6999−7002.

(4) (a) Richardson, R. D.; Wirth, T. Hypervalent Iodine Goes Catalytic. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402−4404. (b) Ochiai, M. Stoichiometric and Catalytic Oxidations with Hypervalent Organo-λ^3-iodanes. *Chem. Rec.* **2007**, *7*, 12−23. (c) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. A Chiral Hypervalent Iodine (III) Reagent for Enantioselective Dearomatization of Phenols. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787−3790.

(5) (a) Adam, W.; Rao, P. B.; Degen, H.-G.; Saha-Möller, C. R. Metal-Template Effect in the Asymmetric Weitz−Scheffer Epoxidation of α, β-Enones By an Optically Active Hydroperoxide. *J. Am. Chem. Soc.* **2000**, *122*, 5654−5655. (b) Aoki, M.; Seebach, D. Preparation of TADOOH, a Hydroperoxide from TADDOL, and Use in Highly Enantioface- and Enantiomer-Differentiating Oxidations. *Helv. Chim. Acta* **2001**, *84*, 187−207.

(6) Shi, Y. Organocatalytic Asymmetric Epoxidation of Olefins by Chiral Ketones. *Acc. Chem. Res.* **2004**, *37*, 488−496.

(7) For selected reviews on NHC catalysis, see: (a) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. Catalysis with *N*-Heterocyclic Carbenes under Oxidative Conditions. *Chem. - Eur. J.* **2013**, *19*, 4664−4678. (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of *N*-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485−496. (c) Mahatthananchai, J.; Bode, J. W. On the Mechanism of *N*-Heterocyclic Carbene-Catalyzed Reactions Involving Acyl Azoliums. *Acc. Chem. Res.* **2014**, *47*, 696−707. (d) Menon, R. S.; Biju, A. T.; Nair, V. Recent Advances in Employing Homoenolates Generated by *N*-Heterocyclic Carbene (NHC) Catalysis in Carbon−Carbon Bond-Forming Reactions. *Chem. Soc. Rev.* **2015**, *44*, 5040−5052. (e) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by *N*-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387. (f) Wang, M. H.; Scheidt, K. A. Cooperative Catalysis and Activation with *N*-Heterocyclic Carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912−14922. (g) Zhang, C.; Hooper, J. F.; Lupton, D. W. *N*-Heterocyclic Carbene Catalysis via the α, β-Unsaturated Acyl Azolium. *ACS Catal.* **2017**, *7*, 2583−2596. (h) Chen, X.; Liu, Q.; Chauhan, P.; Enders, D. *N*-Heterocyclic Carbene Catalysis via Azolium Dienolates: An Efficient Strategy for Remote Enantioselective Functionalizations. *Angew. Chem., Int. Ed.* **2018**, *57*, 3862−3873. (i) Wang, Z.; Pan, D.; Li, T.; Jin, Z. *N*-heterocyclic Carbene (NHC)-Organocatalyzed Kinetic Resolutions, Dynamic Kinetic Resolutions, and Desymmetrizations. *Chem. - Asian J.* **2018**, *13*, 2149−2163.

DOI: 10.1021/acs.orglett.9b02736
Org. Lett. XXXX, XXX, XXX−XXX

(8) De Sarkar, S. D.; Studer, A. NHC-Catalyzed Michael Addition to α, β-Unsaturated Aldehydes by Redox Activation. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266−9269.
(9) (a) Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. Unexpected Ring-Opening Reactions of Aziridines with Aldehydes Catalyzed by Nucleophilic Carbenes under Aerobic Conditions. *Org. Lett.* **2006**, *8*, 1521−1524. (b) Maji, B.; Vedachalan, S.; Ge, X.; Cai, S.; Liu, X.-W. *N*-Heterocyclic Carbene-Mediated Oxidative Esterification of Aldehydes: Ester Formation and Mechanistic Studies. *J. Org. Chem.* **2011**, *76*, 3016−3023.
(10) (a) Corey, E. J.; Gilman, N. W.; Ganem, B. E. New Methods for the Oxidation of Aldehydes to Carboxylic Acids and Esters. *J. Am. Chem. Soc.* **1968**, *90*, 5616−5617. (b) Maki, B. E.; Scheidt, K. A. *N*-Heterocyclic Carbene-Catalyzed Oxidation of Unactivated Aldehydes to Esters. *Org. Lett.* **2008**, *10*, 4331−4334.
(11) Guin, J.; De Sarkar, S. D.; Grimme, S.; Studer, A. Biomimetic Carbene-Catalyzed Oxidations of Aldehydes Using TEMPO. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727−8730.
(12) (a) Rose, C. A.; Zeitler, K. Efficient Catalytic, Oxidative Lactonization for the Synthesis of Benzodioxepinones Using Thiazolium-Derived Carbene Catalysts. *Org. Lett.* **2010**, *12*, 4552−4555. (b) Uno, T.; Inokuma, T.; Takemoto, Y. NHC-Catalyzed Thioesterification of Aldehydes by External Redox Activation. *Chem. Commun.* **2012**, *48*, 1901−1903.
(13) (a) Zhao, X.; Ruhl, K. E.; Rovis, T. *N*-Heterocyclic-Carbene-Catalyzed Asymmetric Oxidative Hetero-Diels−Alder Reactions with Simple Aliphatic Aldehydes. *Angew. Chem., Int. Ed.* **2012**, *51*, 12330−12333. (b) Iwahana, S.; Iida, H.; Yashima, E. Oxidative Esterification, Thioesterification, and Amidation of Aldehydes by a Two-Component Organocatalyst System Using a Chiral *N*-Heterocyclic Carbene and Redox-Active Riboflavin. *Chem.—Eur. J.* **2011**, *17*, 8009−8013.
(14) (a) Yoshida, M.; Katagiri, Y.; Zhu, W.-B.; Shishido, K. Oxidative Carboxylation of Arylaldehydes with Water by a Sulfoxylalkyl-Substituted *N*-Heterocyclic Carbene Catalyst. *Org. Biomol. Chem.* **2009**, *7*, 4062−4066. (b) Wong, F. T.; Patra, P. K.; Seayad, J.; Zhang, Y.; Ying, J. Y. *N*-Heterocyclic Carbene (NHC)-Catalyzed Direct Amidation of Aldehydes with Nitroso Compounds. *Org. Lett.* **2008**, *10*, 2333−2336. (c) White, N. A.; Rovis, T. Oxidatively Initiated NHC-Catalyzed Enantioselective Synthesis of 3,4-Disubstituted Cyclopentanones from Enals. *J. Am. Chem. Soc.* **2015**, *137*, 10112−10115. (d) 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*, 12933−12940.
(15) (a) Du, Y.; Wang, Y.; Li, X.; Shao, Y.; Li, G.; Webster, R. D.; Chi, Y. R. *N*-Heterocyclic Carbene Organocatalytic Reductive β,β-Coupling Reactions of Nitroalkenes via Radical Intermediates. *Org. Lett.* **2014**, *16*, 5678−5681. (b) 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 Singel-Electron-Transfer (SET) Process and Formal 1,4-Addition. *Org. Lett.* **2017**, *19*, 632−635.
(16) Wu, X.; Zhang, Y.; Wang, Y.; Ke, J.; Jeret, M.; Reddi, R. N.; Yang, S.; Song, B.; Chi, Y. R. Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis via Radical Processes. *Angew. Chem., Int. Ed.* **2017**, *56*, 2942−2946.
(17) (a) 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*, 14674−14677. (b) 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*, 2416−2419.
(18) (a) Rehbein, J.; Ruser, S.-M.; Phan, J. NHC-catalysed benzoin condensation − is it all down to the Breslow intermediate. *Chem. Sci.* **2015**, *6*, 6013−6018. (b) 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*, 15783−15786. (c) Chen, X.−Y.; Chen, K.−Q.; Sun, D.−Q.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed Oxidative [3 + 2] Annulation of Dioxindoles and Enals: Aross Coupling of Homoenolate and Enolate. *Chem. Sci.* **2017**, *8*, 1936−1941. (d) Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. *N*-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 3854−3858. (e) 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*, 1109−1117.
(19) (a) Thomson, J. E.; Rix, K.; Smith, A. D. Efficient *N*-Heterocyclic Carbene-Catalyzed O- to C-Acyl Transfer. *Org. Lett.* **2006**, *8*, 3785−3788. (b) Sohn, S.; Bode, J. W. Catalytic Generation of Activated Carboxylates from Enals: A Product-Determining Role for the Base. *Org. Lett.* **2005**, *7*, 3873−3876. (c) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. An Efficient Synthesis of Achiral and Chiral 1,2,4-Triazolium Salts: Bench Stable Precursors for *N*-Heterocyclic Carbenes. *J. Org. Chem.* **2005**, *70*, 5725−5728.
(20) Chen, Y.-F.; Chen, J.; Lin, L.-J.; Chuang, G. J. Synthesis of Azoxybenzenes by Reductive Dimerization of Nitrosobenzene. *J. Org. Chem.* **2017**, *82*, 11626−11630.

DOI: 10.1021/acs.orglett.9b02736
Org. Lett. XXXX, XXX, XXX−XXX