OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

Organocatalyzed Aerobic Oxidation of Aldehydes to Acids

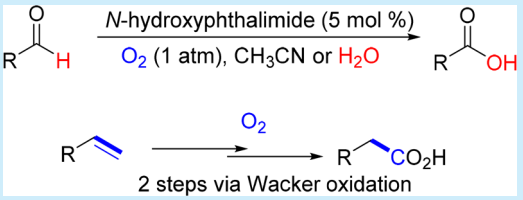
Peng-Fei Dai,[†] Jian-Ping Qu,*[,‡] and Yan-Biao Kang*[,†]

[†]Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

[‡]Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing 211816, China

Supporting Information

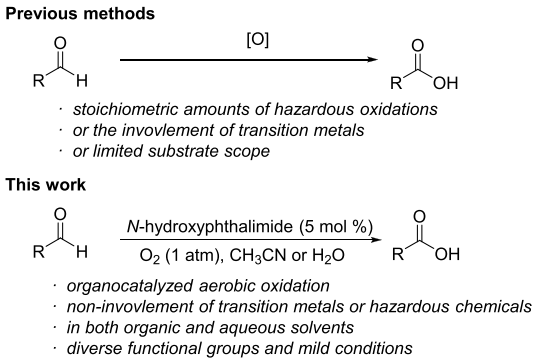
ABSTRACT: The first example organocatalyzed aerobic oxidation of aldehydes to carboxylic acids in both organic solvent and water under mild conditions is developed. As low as 5 mol % *N*-hydroxyphthalimide was used as the organocatalyst, and molecular O_2 was used as the sole oxidant. No transition metals or hazardous oxidants or cocatalysts were involved. A wide range of carboxylic acids bearing diverse functional groups were obtained from aldehydes, even from alcohols, in high yields.



Org. Lett.

Oxidation is one of the most fundamental reactions with great potential for both academic research and industry. It has long been known that aldehydes are very prone to oxidation, but transformations of aldehydes to carboxylic acids under mild and green conditions are still scarce.[1,2] They usually utilize stoichiometric amount of oxidants, such as $KMnO_4$,[3] H_5IO_6,[4] CrO_3,[5] $KHSO_5$,[6] $NaClO_2$,[7−9] silver nitrate,[10] copper(II) salt,[11] etc., which are normally expensive and/or hazardous to the environment (Scheme 1). Therefore, an efficient and environmentally benign transformation of aldehydes into carboxylic acids is highly desired.

Scheme 1. Oxidation of Aldehydes to Acids



Molecular oxygen is a clean and sustainable oxidant for oxidation reactions, and it possesses a unique advantage over the other oxidants in that it produces water as the only byproduct with a high atom economy. Unlike the catalytic aerobic oxidation of alcohols to carboxylic acids which has been well developed by using both homogeneous[12−18] and heterogeneous[19,20] catalysts, development of a catalytic process from aldehydes to carboxylic acids with molecular oxygen as a terminal remains limited,[21] despite the fact that the catalytic aerobic oxidation of aldehydes to carboxylic acids seems to be easily achieved. However, large quantities of nitrogen oxides are resources for air pollution, contributing to the formation of smog and acid rain as well as affecting tropospheric ozone. Therefore, the development of an efficient, practical, and inexpensive catalyst system for catalytic oxidation of aldehydes using molecular oxygen as a terminal oxidant without the involvement of transition metals or hazardous cocatalysts is highly desired.

We have reported that an *N*-hydroxyphthalimide (NHPI)[22−25] could generate benzyl radicals, and it provides an efficient approach to mono-/diselectivity control in aromatic nitrile[26] or ketone[27] synthesis. Recently, we found that *N*-hydroxyphthalimide was an efficient organocatalyst for the aerobic oxidation of aldehydes to carboxylic acids. Utilizing a catalytic amount of *N*-hydroxyphthalimide (5 mol %) in the presence of 1 atm of molecular O_2 without any other oxidant or cocatalyst leads to a wide range of carboxylic acids bearing diverse functional groups in high yields under mild conditions (30 °C) in both organic and aqueous conditions (Scheme 1). The noninvolvement of transition metals and hazardous reagent-free atmosphere make this method environmentally benign and useful in pharmaceutical synthesis. Herein, we report our results in detail.

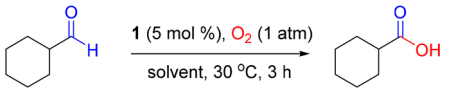
First, various solvents were investigated using *N*-hydroxyphthalimide (**1**) as catalysts in the oxidation of aldehyde **2a** (Table 1). Dioxane and toluene afford 53% yields with 16−30% recovered starting material **2** (entries 1 and 2), while alcohols, such as ″BuOH and MeOH, do not promote this oxidation reaction but only starting material **2** was recovered (entries 3 and 4). CH_3CN gives the best yield (entry 5). The reaction in water also proceeds smoothly and gives 92% yields (entry 6). The reaction condition in entry 5 was chosen for the standard reaction conditions where 5 mol % of *N*-hydroxyphthalimide was used as catalyst.

With the standard reaction conditions in hand, the scope of this method was investigated. Various alkyl aldehydes were

Received: January 9, 2019

DOI: 10.1021/acs.orglett.9b00101
Org. Lett. XXXX, XXX, XXX−XXX

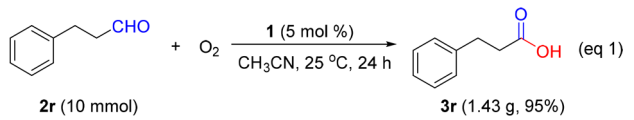
Table 1. Reaction Conditions[a]



entry	solvent	3a[b] (%)	2a[c] (%)
1	dioxane	53	16
2	PhMe	53	30
3	^{n}BuOH	ND	83
4	MeOH	ND	82
5	**CH_3CN**	**99**	0
6	**H_2O**	**92**	0

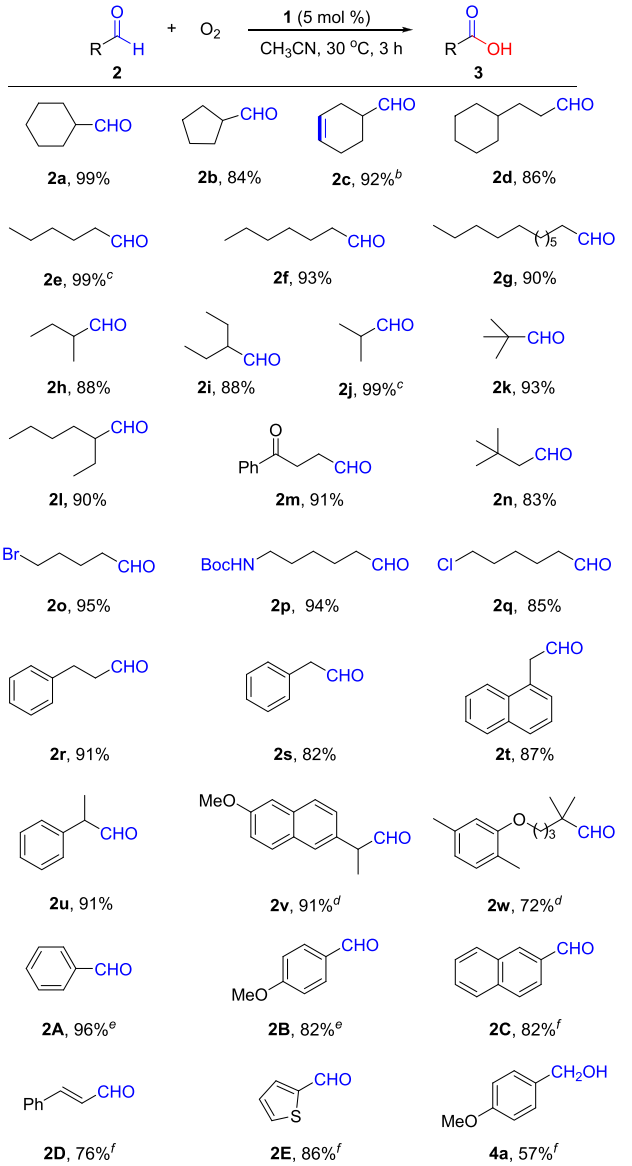
[a]Reaction conditions: **1** (5 mol %), **2a** (0.5 mmol), O_2 (1 atm), solvent (2 mL). [b]Yield of **3a** was determined by ^{1}H NMR (400 MHz) using CH_3NO_2 and MeO^{t}Bu as internal standards. ND = not determined. [c]Recovery yield of **2a** was determined by ^{1}H NMR.

subjected to the standard conditions, and the corresponding acids were obtained in 72% to quantitative yields (Scheme 2, **2a**–**w**). Substrate **2m** with a ketone functional groups affords the desired product in 91% yield, and halogen and carbamate can survive under such conditions as well (**2o**–**q**). The oxidation of α- and β-aryl-substituted aldehydes could be achieved with 82–91% yield (**2r**–**w**). The reactivity of branched alkyl aldehydes with this catalytic system was also investigated. The oxidation reaction proceeds reasonably well, and 83–99% yields could be obtained (**2h**–**l** and **2n**). Cyclohex-3-ene-1-carbaldehyde **2c**, which could interfere with the catalytic system due to its C=C bond, afforded 92% of the corresponding acid.[22] The oxidation conditions are operational for 2-(6-methoxynaphthalen-2-yl)propanal **2v**, a precursor of naproxen which is a nonsteroidal anti-inflammatory drug that relieves fever, pain, stiffness, and swelling. It afforded the desired product **3v** in 91% yield. Substrates containing an α-quaternary carbon center, for example, **2k** and **2w**, could also afford the desired carboxylic acids in good yields. Aryl acids can also be synthesized from aryl aldehydes under the oxidation conditions (**2A**–**E**). The corresponding aromatic acid products were obtained in 76–96% yields. The oxidation of aromatic aldehydes is much slower, and elevated temperatures are needed (**2A**,**B**). In some cases, ^{t}BuONO is added to accelerate the oxidation (**2C**–**E**). The reason is that the regeneration of PINO via the oxidation of NHPI needs the acylhydroperoxy intermediate, whereas such acylhydroperoxy intermediates derived from aromatic acids are not able to oxidize NHPI to PINO effeciently. The direct oxidation of alcohol **4a** to the corresponding acid afforded the product in 57% yield. The gram-scale (10 mmol) oxidation of **2r** produces 1.43 g of **3r** in 95% (eq 1).



The scope and functional-group compatibility in aqueous media was then tested with various functionalized aldehydes. Because of the lower solubility of substrates in water, the reaction normally takes a longer time than that in CH_3CN. Nevertheless, the reaction yields are comparable to the oxidations in CH_3CN. Various aldehydes were subjected to the aqueous conditions; the corresponding alkyl acid products

Scheme 2. Aerobic Oxidation of Aldehydes to Acids[a]



[a]Conditions: **2** (0.5 mmol), O_2 (1 atm), **1** (5 mol %), CH_3CN (2 mL), 3 h. [b]At 80 °C, 12 h. [c]Determined by ^{1}H NMR (400 MHz). [d]10 mol % NHPI, 80 °C, 10 h. [e]10 mol % NHPI, 90 °C, 1.5 d. [f]10 mol % NHPI, 2.0 equiv ^{t}BuONO, 2 mL of dry CH_3CN, 2 d.

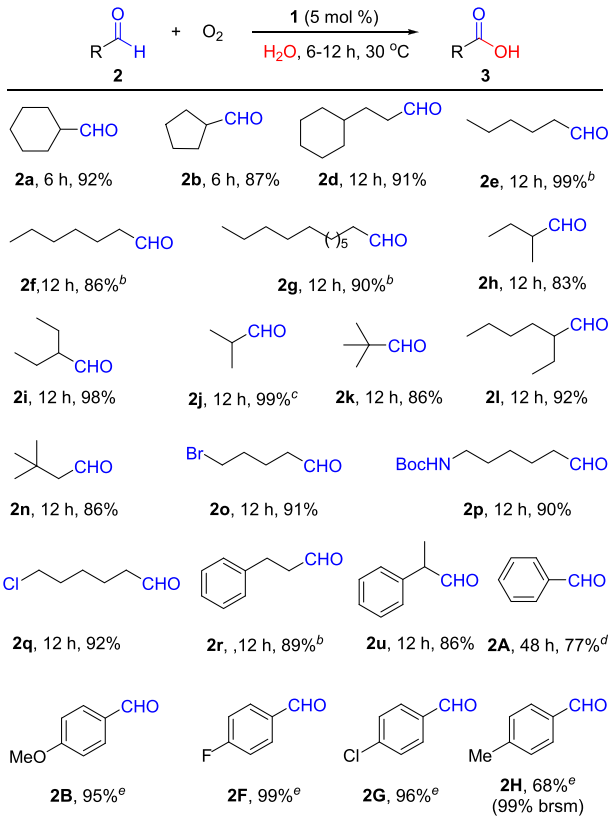
can be separated by a simple extraction with organic solvent in good to high yield (Scheme 3).

This method was then applied in a sequential aerobic oxidation sequence of alkenes, in which the alkenes were first oxidized to aldehyde via anti-Markovnikov Wacker oxidation[28] and finally to carboxylic acids using molecular oxygen as the sole oxidant for both steps (Scheme 4). The corresponding acid **6a**–**c** could be obtained in 60–87% yields.

To demonstrate the application potential of this method, it was used in the final stage oxidation for the synthesis of indomethacin (Scheme 5). For a compatible method, the Pinnick oxidation conditions, using 3–6 equiv of oxidant and additives, provided the desired indomethacin **9** in 78% yield. By this method, indomethacin **9** is achieved in 91% using 10 mol % of *N*-hydroxyphthalimide as catalyst using molecular oxygen.

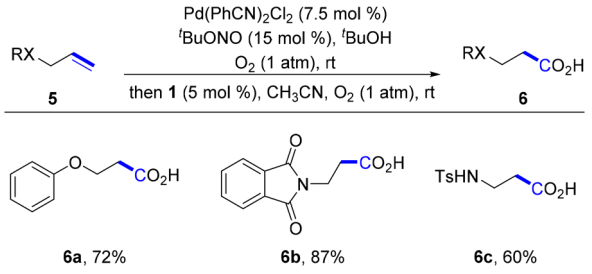
DOI: 10.1021/acs.orglett.9b00101
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Aerobic Oxidation of Aldehydes in Water[a]



[a]Conditions: **2** (0.5 mmol), O_2 (1 atm), **1** (5 mol %), H_2O (2 mL). [b]10 mol % NHPI, 80 °C. [c]Determined by ^1H NMR. [d]15 mol % NHPI, 80 °C, 2 d. [e]10 mol % NHPI and 30 mol % of ^{t}BuONO, 60 °C, 2 d.

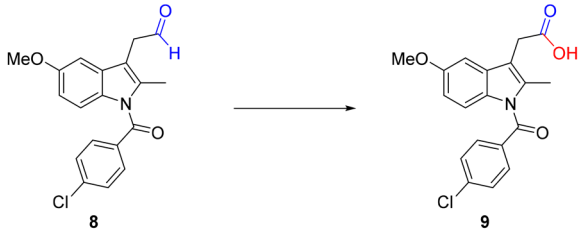
Scheme 4. Sequential Aerobic Oxidation of Alkenes to Carboxylic Acids



[a]Conditions: **5** (0.5 mmol), $Pd(PhCN)_2Cl_2$ (7.5 mol %), ^{t}BuONO (20 mol %), ^{t}BuOH, O_2 (1 atm); then **1** (5 mol %), O_2 (1 atm), CH_3CN (2 mL), 3 h.

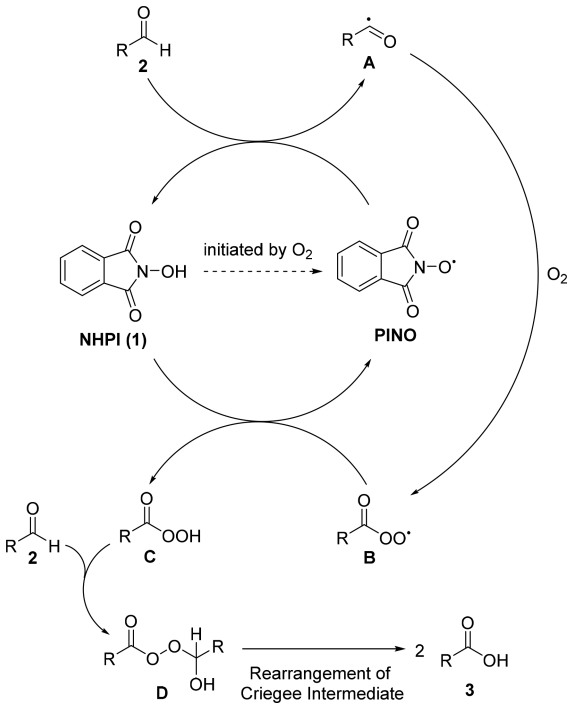
The reaction mechanism is proposed in Scheme 6. The abstraction of hydrogen by PINO affords acyl radical **A**, which abstracts oxygen to form **B**. Peroxide **C** forms with the regeneration of PINO via oxidation of NHPI by **B**. The oxidation of NHPI to PINO by **B** is supported by the fact that the oxidation of aromatic aldehydes is much slower than aliphatic aldehydes, where ^{t}BuONO is normally used as an additive to promote the regeneration of PINO.[23a] Peroxide **C** added to aldehyde **2** to form the Criegee intermediate **D** followed by a rearrangement to afford 2 mol of acid **3**. The initial PINO might be generated from the oxidation of NHPI by oxygen.[22b,23b]

Scheme 5. Comparison of Pinnick and Current Method in Synthesis of Pharmaceuticals via Later Stage Oxidation



Pinnick oxidation:
$NaClO_2$ (3 equiv), NaH_2PO_4 (3 equiv), $(CH_3)_2C{=}CHCH_3$, ^{t}BuOH (6 equiv), 78%
This method:
NHPI (10 mol %), O_2 (1 atm), 91%

Scheme 6. Proposed Mechanism



In conclusion, an efficient and practical organocatalyzed aerobic oxidation of aldehydes to carboxylic acids is presented utilizing a catalytic amount of *N*-hydroxyphthalimide in the presence of 1 atm of molecular O_2, which serves as the sole oxidant under mild conditions. A wide range of carboxylic acids bearing diverse functional groups were obtained from aldehydes (also alcohols) in high yields. Its operational simplicity and gram-scale oxidation and the ability to successively reuse the commercial available and inexpensive catalyst make this method environmentally benign and cost-effective. The generality of this methodology gives it the potential to be used on an industrial scale. This method might be a valuable alternative to traditional metal-mediated oxidations. In addition, a direct conversion of alkenes to their corresponding carboxylic acids is reported, and final-stage oxidation using this method was also accomplished to demonstrate the synthetic application.

DOI: 10.1021/acs.orglett.9b00101
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00101.

Experimental procedures and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ias_jpqu@njtech.edu.cn.
*E-mail: ybkang@ustc.edu.cn.

ORCID

Jian-Ping Qu: 0000-0002-5002-5594
Yan-Biao Kang: 0000-0002-7537-4627

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21672196, 21602001, 21831007) for financial support.

■ REFERENCES

(1) Collins, T. J. Designing ligands for oxidizing complexes. *Acc. Chem. Res.* **1994**, *27*, 279−285.
(2) *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Smith, M. B., March, J., Eds.; Wiley Interscience: New York, 2007.
(3) Mahmood, A.; Robinson, G. E.; Powell, L. An improved oxidation of an alcohol using aqueous permanganate and phase-transfer catalyst *Org. Org. Process Res. Dev.* **1999**, *3*, 363−364.
(4) Hunsen, M. Carboxylic acids from primary alcohols and aldehydes by a pyridinium chlorochromate catalyzed oxidation. *Synthesis* **2005**, *2005*, 2487−2490.
(5) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. 13. Researches on acetylenic compounds. Part I. The preparation of acetylenic ketones by oxidation of acetylenic carbinols and glycols. *J. Chem. Soc.* **1946**, 39−45.
(6) Travis, B. R.; Sivakumar, M. G.; Hollist, O.; Borhan, B. Facile oxidation of aldehydes to acids and esters with oxone. *Org. Lett.* **2003**, *5*, 1031−1034.
(7) Bal, B. S.; Childers, W. E.; Pinnick, H. W. Oxidation of α,β-unsaturated aldehydes. *Tetrahedron* **1981**, *37*, 2091−2906.
(8) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. Oxidation of primary alcohols to carboxylic acids with sodium chlorite catalyzed by TEMPO and bleach. *J. Org. Chem.* **1999**, *64*, 2564−2566.
(9) Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y. Oxoammonium salt/$NaClO_2$: an expedient, catalytic system for one-pot oxidation of primary alcohols to carboxylic acids with broad substrate applicability. *Chem. Commun.* **2009**, 1739−1741.
(10) Fehling, H. Die quantitative Bestimmung von Zucker und Stärkmehl mittelst Kupfervitriol. *Justus Liebigs Ann. Chem.* **1849**, *72*, 106−113.
(11) Tollens, B. Ueber ammon-alkalische Silberlösung als Reagens auf Aldehyd. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 1635−1639.
(12) Jiang, X.; Zhang, J.; Ma, S. Iron catalysis for room-temperature aerobic oxidation of alcohols to carboxylic acids. *J. Am. Chem. Soc.* **2016**, *138*, 8344−8347.
(13) Han, L.; Xing, P.; Jiang, B. Selective aerobic oxidation of alcohols to aldehydes, carboxylic acids, and imines catalyzed by a Ag-NHC complex. *Org. Lett.* **2014**, *16*, 3428−3431.
(14) Shimada, Y.; Hattori, K.; Tada, N.; Miura, T.; Itoh, A. Carboxylic acid synthesis by oxidation of alcohols. *Synthesis* **2013**, *45*, 2684−2688.
(15) Matsusaki, Y.; Yamaguchi, T.; Tada, N.; Miura, T.; Itoh, A. Aerobic photooxidative cleavage of vicinal diols to carboxylic acids using 2-chloroanthraquinone. *Synlett* **2012**, *23*, 2059−2062.
(16) Jiang, N.; Ragauskas, A. J. Selective aerobic oxidation of activated alcohols into acids or aldehydes in ionic liquids. *J. Org. Chem.* **2007**, *72*, 7030−7033.
(17) Heyns, K. Oxydative Umwandlungen an Kohlenhydraten. I. Bestimmung von l-Sorbose neben 2-Keto-1-gulonsäure. *Lieb. Ann. Chem.* **1947**, *558*, 177−187.
(18) ten Brink, G. J.; Arends, I. W.; Sheldon, R. A. Green, catalytic oxidation of alcohols in water. *Science* **2000**, *287*, 1636−1639.
(19) Mallat, T.; Baiker, A. Oxidation of alcohols with molecular oxygen on solid catalysts. *Chem. Rev.* **2004**, *104*, 3037−3058.
(20) Zhang, Y.; Cheng, Y.; Cai, H.; He, S.; Shan, Q.; Zhao, H.; Chen, Y.; Wang, Bo. Catalyst-free aerobic oxidation of aldehydes into acids in water under mild conditions. *Green Chem.* **2017**, *19*, 5708−5713.
(21) Liu, M.; Wang, H.; Zeng, H.; Li, C.-J. Silver(I) as a widely applicable, homogeneous catalyst for aerobic oxidation of aldehydes toward carboxylic acids in water-"silver mirror": From stoichiometric to catalytic. *Sci. Adv.* **2015**, *1*, e1500020.
(22) For review NHPI-catalyzed oxidations, see: (a) Recupero, F.; Punta, C. Free Radical Functionalization of Organic Compounds Catalyzed by N-Hydroxyphthalimide. *Chem. Rev.* **2007**, *107*, 3800−3842. (b) Melone, L.; Punta, C. Metal-free aerobic oxidations mediated by N-hydroxyphthalimide. A concise review. *Beilstein J. Org. Chem.* **2013**, *9*, 1296−1310.
(23) (a) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. A New Route to Lactam Precursors from Cycloalkanes: Direct Production of Nitrosocycloalkanes or Cycloalkanone Oximes by Using tert-Butyl Nitrite and N-Hydroxyphthalimide. *Angew. Chem., Int. Ed.* **2004**, *43*, 1120−1123. (b) Lin, R.; Chen, F.; Jiao, N. Metal-Free, NHPI Catalyzed Oxidative Cleavage of C−C Double Bond Using Molecular Oxygen as Oxidant. *Org. Lett.* **2012**, *14*, 4158−4161.
(24) Tiwari, B.; Khatana, A.; Singh, V.; Gupta, M. A Highly Efficient NHC-Catalyzed Aerobic Oxidation of Aldehydes to Carboxylic Acids. *Synthesis* **2018**, *50*, 4290−4294.
(25) (a) Mo, Y.; Jensen, K. F. Continuous N-Hydroxyphthalimide (NHPI)-Mediated Electrochemical Aerobic Oxidation of Benzylic C−H Bonds. *Chem. - Eur. J.* **2018**, *24*, 10260−10265. (b) Zelenka, J.; Svobodová, E.; Tarábek, J.; Hoskovcová, I.; Boguschová, V.; Bailly, S.; Sikorski, M.; Roithová, J.; Cibulka, R. Combining Flavin Photocatalysis and Organocatalysis: Metal-Free Aerobic Oxidation of Unactivated Benzylic Substrates. *Org. Lett.* **2019**, *21*, 114−119.
(26) Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. Pharmaceutical-oriented selective synthesis of mononitriles and dinitriles directly from methyl(hetero)arenes: access to chiral nitriles and citalopram. *J. Am. Chem. Soc.* **2016**, *138*, 3294−3297.
(27) Liu, J.; Hu, K.-F.; Qu, J.-P.; Kang, Y.-B. Organopromoted selectivity-switchable synthesis of polyketones. *Org. Lett.* **2017**, *19*, 5593−5596.
(28) Ning, X.-S.; Wang, M.-M.; Yao, C.-Z.; Chen, X.-M.; Kang, Y.-B. *tert*-Butyl Nitrite: Organic Redox Cocatalyst for Aerobic Aldehyde-Selective Wacker−Tsuji Oxidation. *Org. Lett.* **2016**, *18*, 2700−2703.

DOI: 10.1021/acs.orglett.9b00101
Org. Lett. XXXX, XXX, XXX−XXX