Organic LETTERS

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

Letter

pubs.acs.org/OrgLett

Cu-Catalyzed Redox-Neutral Ring Cleavage of Cycloketone *O*-Acyl Oximes: Chemodivergent Access to Distal Oxygenated Nitriles

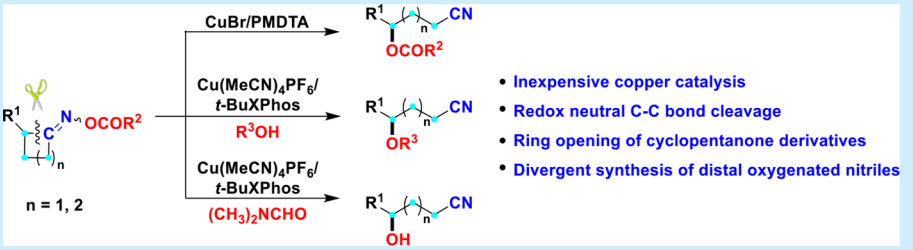
Wenying Ai,[†,‡] Yaqian Liu,[§] Qian Wang,[‡] Zhonglin Lu,*[,†] and Qiang Liu*[,‡]

[†]College of Chemistry, Beijing Normal University, Beijing 100875, China

[‡]Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing 100084, China

[§]Department of Chemistry, Renmin University of China, Beijing 100872, China

Supporting Information



ABSTRACT: A chemodivergent copper-catalyzed ring opening of cycloketone oximes via radical-mediated C−C bond cleavage under redox-neutral conditions is described. This method allows the divergent synthesis of γ- and δ-acyloxylated, alkoxylated, and hydroxylated nitriles while avoiding the use of toxic cyanide reagents. Moreover, these reactions proceed under very mild conditions with good functional group tolerance. Notably, ring-opening reactions of the less-strained substrate cyclopentanone oxime also proceeded well under the established conditions.

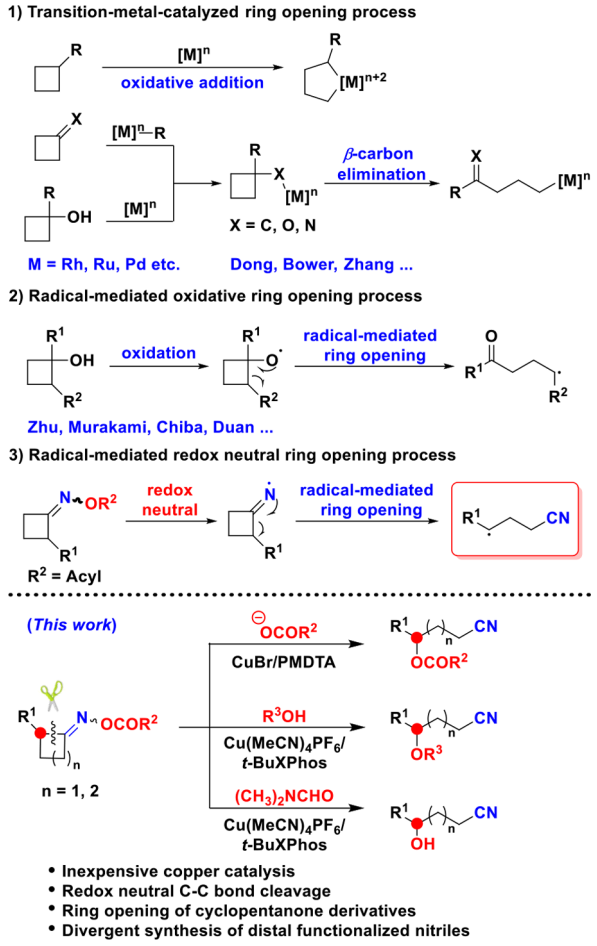
Cyclobutanes are important structural motifs for various unique transformations.[1] New C−C or C−X bonds can be constructed by cleavage of cyclobutane C−C bonds because of their high strain energy.[2] Most cyclobutane cleavage methodologies fall into two categories: (1) transition-metal-catalyzed C−C bond cleavage[2,3] and (2) radical-mediated oxidative ring opening.[4] The former strategy is usually triggered by oxidative addition or β-carbon elimination in the presence of transition metal catalysts such as Ru^0, Rh^I, and Pd^0 (Scheme 1, eq 1). The latter strategy usually utilizes different oxidants to induce a single electron transfer (SET) process. For example, Zhu and co-workers reported the Ag(I)- and Mn(III)-catalyzed oxidative ring opening of cyclobutanol substrates to access diverse remotely functionalized ketones, providing a straightforward approach to the synthesis of γ-substituted alkyl ketones (Scheme 1, eq 2).[4a−c,5] Precious transition metal catalysts and/or external oxidants are usually indispensable for realizing C−C cleavage in strained rings. Furthermore, other cleavage methodologies, such as thermal and photochemical electrocyclic ring openings[1c] and Grob fragmentation of 3-OTf-substituted benzocyclobutenone derivatives via an aryne species[6] are usually limited to cyclobutenes or benzocyclobutane substrates.[1c] Therefore, the development of new reactions to realize the ring opening of cyclobutane derivatives under redox-neutral conditions in the absence of precious metal catalysts is highly desirable[7] but remains challenging. Recently, iminium radicals have been generated from acyl oximes using a Cu-catalyzed SET process and further converted into a class of versatile N-heterocyclic scaffolds under redox-neutral conditions.[8] Therefore, we turned our attention to developing a new Cu-catalyzed C−C bond cleavage of cyclobutanone *O*-acyl oximes under redox-neutral conditions. As shown in Scheme 1 (eq 3), we envisioned that a cyclobutylideneiminyl radical could be generated by the one-electron reduction of cyclobutanone *O*-acyl oximes via copper catalysis, followed by a radical-mediated ring opening that might give a γ-cyanoalkyl radical species. We speculated that this new type of strained C−C bond cleavage method could avoid the use of precious metal catalysts and external oxidants.

During the preparation of this paper, this strategy was also successfully implemented by other research groups. Specifically, Zhao and Shi[9] reported a Cu-catalyzed Heck-like coupling of cyclobutanone oximes with olefins, and Zhou and co-workers developed a visible-light-promoted three-component cyanopropylation/etherification of cyclobutanone oximes with alkenes.[10] Meanwhile, Guo and co-workers reported a nickel-catalyzed cyanoalkylation of cyclobutanone oximes with heteroaromatic *N*-oxides and quinones.[11] Alongside these significant achievements, we herein disclose a highly selective and chemodivergent synthesis of γ- and δ-acyloxylated, -alkoxylated, and -hydroxylated alkyl nitriles via the Cu-catalyzed redox-neutral ring opening of cyclobutanone oximes. Notably, this transformation avoids using sacrificial oxidants and toxic cyanide reagents. This chemistry is

Received: November 29, 2017

DOI: 10.1021/acs.orglett.7b03707
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Cyclobutane Ring-Opening Reactions



significant for (1) employing an inexpensive copper catalyst, (2) achieving a challenging redox-neutral radical-mediated C−C bond cleavage, and (3) providing a novel strategy for the diverse synthesis of aliphatic nitriles, which are common structural motifs in natural products and versatile building blocks in organic synthesis.

We began by selecting oxime **1a** as a model substrate to examine the ring-opening cyanoacyloxylation reaction (Table S5). After thoroughly screening the reaction parameters (including Cu catalyst, solvent, and additive), we found that the combination of CuBr (10 mol %), pentamethyldiethylenetriamine (PMDTA, 10 mol %), and tetra-*n*-butylammonium bromide (TBAB, 20 mol %) gave the best result at room temperature. In particular, CuBr and PMDTA exhibited a better catalytic ability than other tested copper salts and ligands. Moreover, the presence of TBAB clearly facilitated the transformation.

With the optimized reaction conditions in hand, the scope of the Cu-catalyzed C-cyanoacyloxylation was explored (Figure 1). Substrates **1** bearing both electron-rich and electron-deficient substituents on the aromatic rings were successfully converted into carboxylated alkyl nitriles in good to excellent yields (**2a**−**h**). Furthermore, 2-phenylcyclobutan-1-one oximes with different acyl substituents led to the corresponding γ-acyloxylated alkyl nitriles regioselectively in moderate yields (**2i** and **2j**). The reaction of benzocyclobutenone oxime also proceeded smoothly in 75% yield, generating a single regioisomer (**2k**). Notably, the ring opening of the less-

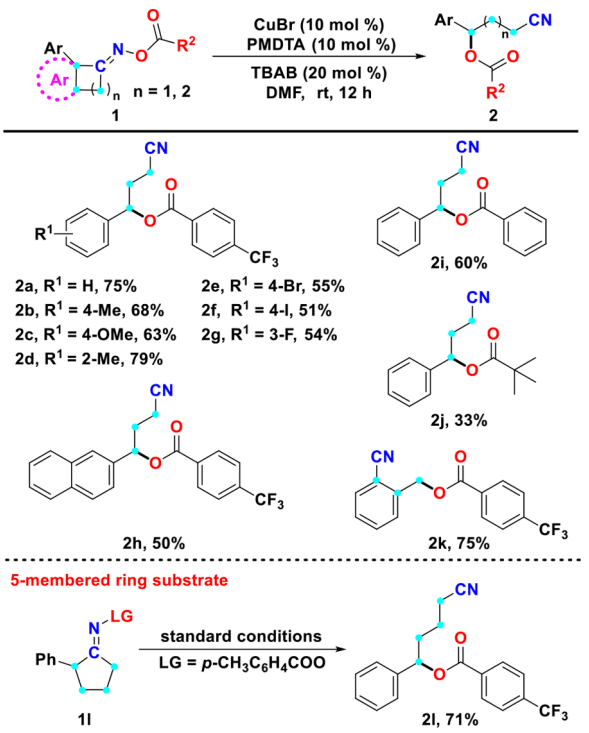


Figure 1. Synthesis of γ- and δ-carboxylated alkyl nitriles from cycloketone oximes.

strained substrate cyclopentanone oxime **1l** also proceeded efficiently under the optimized reaction conditions, affording the desired product **2l** in 71% yield. In contrast, no reactivity was observed for the five-membered-ring substrates used in recent related works on ring-opening reactions of cyclobutanone oximes.[9−11] We propose that the γ-cyanoalkyl cation intermediate is formed by oxidation of the alkyl radical by the Cu(II) species, which is further trapped by the carboxylate generated via reductive cleavage of the *O*-acyl oxime. Therefore, we hypothesized that induction of another nucleophile in excess amounts into this transformation would lead to the formation of other distally oxygenated alkyl nitriles.

Accordingly, we then examined the external nucleophile MeOH to investigate the feasibility of the synthesis of γ-methoxy alkyl nitriles using this strategy. To our delight, a systematic survey of reaction parameters showed that combining $Cu(MeCN)_4PF_6$ (5 mol %) and the Buchwald ligand *t*-BuXphos (5 mol %) afforded the γ-methoxylation product in 92% yield when MeOH was used as the solvent (Table S6). The Buchwald ligand clearly facilitated the transformation (Table S6, entries 1−7). Using MeOH as the solvent drastically increased the yield (Table S6, entry 8), while the catalyst loading could be further reduced to 5 mol % without a decrease in yield (Table S6, entries 9 and 10). Using these optimized reaction conditions, a series of cycloketone oximes were investigated (Figure 2). In general, aryl cyclobutanone oximes with electron-donating or electron-withdrawing substituents exhibited high reactivity for the selective generation of γ-alkoxy alkyl nitriles under the present reaction conditions (**3a**−**h**). Notably, aryl cyclopentanone oxime and 2-benzylcyclobutan-1-one oxime were both suitable substrates for this transformation (**3l** and **3m**). However, γ-methoxylation of 2-benzylcyclobutan-1-one oxime (**1m**) led to the formation of two regioisomers **3m** and **3l**, with 10:1 regioselectivity (Scheme S10). We also examined the alkoxylation reaction of

DOI: 10.1021/acs.orglett.7b03707
Org. Lett. XXXX, XXX, XXX−XXX

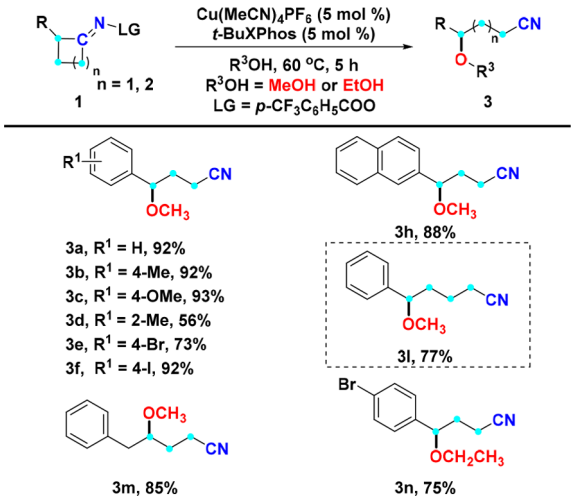


Figure 2. Synthesis of γ- and δ-alkoxy alkyl nitriles from cycloketone oximes.

1e by replacing MeOH with EtOH as the nucleophile. Pleasingly, the corresponding γ-ethoxylated alkyl nitrile **3n** was obtained in 75% yield under these conditions.

Interestingly, when the effect of the solvent on the γ-methoxylation reaction of aryl cyclobutanone oximes was studied, an unexpected γ-hydroxy alkyl nitrile was observed as the major product under treatment with DMF and MeOH as cosolvents (Table S6, entries 5−7). Motivated by this observation, we then considered how the hydroxyl group might be generated in this reaction system. Accordingly, we further developed a Cu-catalyzed C-cyanohydroxylation of cyclobutanone oximes.

Screening of the reaction conditions (including cosolvent, concentration, and ligand) showed that the catalytic system of $Cu(MeCN)_4PF_6$/*t*-BuXphos (20 mol %/40 mol %) gave a 66% isolated yield in DMF/MeOH (9:1, v/v) at 60 °C (Table S7, entry 6). Meanwhile, the catalyst $Ir(ppy)_3$ (2 mol %) gave a 72% isolated yield under similar conditions at room temperature (Table S7, entry 18), which was a more efficient result. Various cyclobutanone oximes were then assessed using these two synthetic methods (Figure 3). Both electron-rich and electron-deficient aryl cyclobutanone oximes reacted smoothly to afford the corresponding γ-hydroxy alkyl nitriles within a few hours. Although $Ir(ppy)_3$ exhibited better catalytic ability, the Cu-catalyzed reactions also gave good yields in most cases. Furthermore, an aryl cyclopentanone oxime was also successfully converted to the desired ring-opened product **4l** under these reaction conditions.

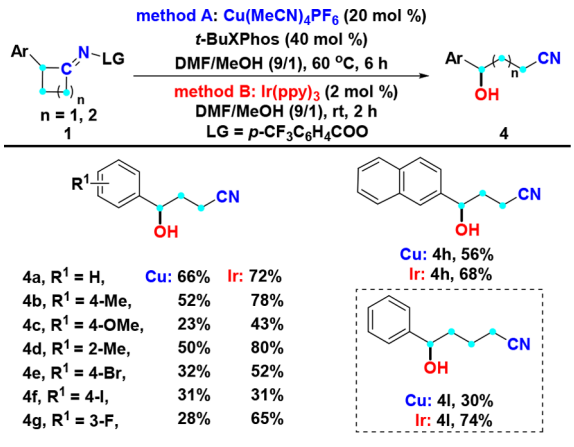
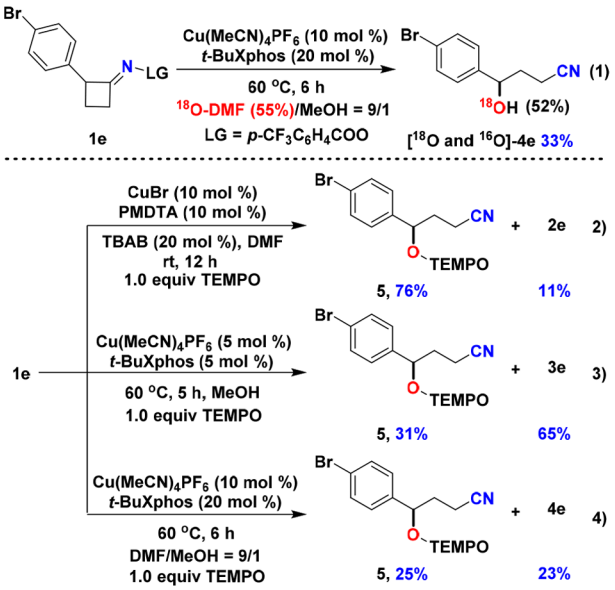


Figure 3. Synthesis of γ- and δ-hydroxy alkyl nitriles from cycloketone oximes.

Three reaction pathways were possible sources of the hydroxyl group, as follows (Scheme S6): (1) trace water in the solvent could provide hydroxide for nucleophilic substitution (pathway A); (2) trace molecular oxygen remaining in the reaction system could provide the hydroxyl group via a peroxide intermediate (pathway B); and (3) similar to Vilsmeier−Haack formylation,[12] the observed alcohols might be generated from DMF as the nucleophile (pathway C).

To elucidate the mechanism, control experiments were conducted. When the reaction was performed in the presence of water (2.0 equiv) or air, trace or no product was detected (Scheme S7). In contrast, when ^{18}O-DMF (55% enrichment) was used as the solvent, ^{18}O and ^{16}O products were detected in a 1.1:1 ratio (Scheme 2, eq 1). These observations

Scheme 2. Preliminary Mechanistic Studies

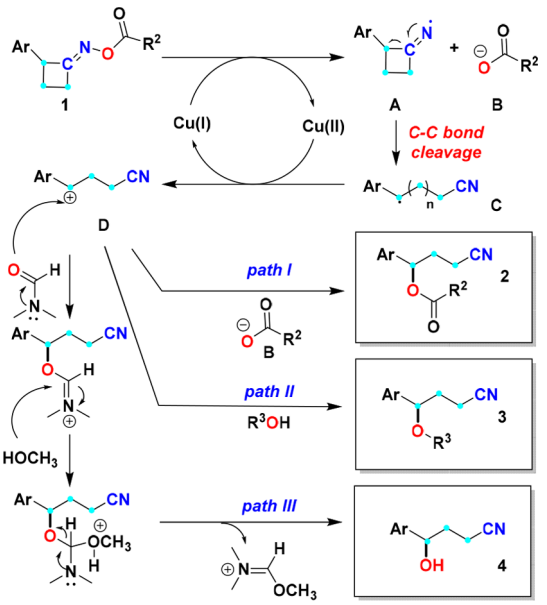


demonstrated that the source of the hydroxyl group was not water or molecular oxygen but rather DMF through reaction pathway C. Furthermore, a survey of solvent effects suggested that only DMF, DMA, and DMSO gave the desired product (Table S7, entries 11−15), which also supported hydroxyl group formation via pathway C. To further understand the ring-opening mechanisms, the reactions of **1e** with radical scavenger TEMPO under C-cyanoacyloxylation, -alkoxylation, and -hydroxylation conditions were examined. TEMPO-trapped product **5** was generated in 76%, 31%, and 25% yields under these three reaction conditions, respectively (Scheme 2, eqs 2−4). Moreover, the reactions of **1k** with the radical scavengers TEMPO and CBr_4 under C-cyanoacyloxylation conditions largely inhibited the reaction to form the product **2k**. The corresponding TEMPO- and Br-trapped products were isolated in these reactions (Scheme S9, eqs 1 and 2). These results demonstrated the involvement of the γ-cyanoalkyl radical as a key reaction intermediate.

On the basis of the above experimental observations, a mechanism was proposed (Scheme 3). Initially, cyclobutanone

DOI: 10.1021/acs.orglett.7b03707
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Plausible Mechanism



oxime **1** is reduced by the Cu(I) catalyst to form iminyl radical **A**, carboxylate ion **B**, and a Cu(II) species. Next, strained iminyl radical **A** is converted to cyanoalkyl radical **C** via homolytic C−C bond cleavage. γ-Cyanoalkyl radical **C** can then be further oxidized by the Cu(II) species to produce carbocation species **D** along with regeneration of the Cu(I) catalyst. Subsequently, carbocation **D** can be trapped by carboxylate ion **B**, alcohol, or DMF to generate products **2**, **3**, and **4**, respectively.

In summary, we have developed a chemodivergent synthesis of γ-and δ-hydroxy, -alkoxy, and -acyloxy-substituted alkyl nitriles via Cu-catalyzed redox-neutral ring opening of cycloketone derivatives. This transformation avoids the use of precious metal catalysts, sacrificial oxidants, and toxic cyanide reagents. Moreover, it exhibits high chemoselectivity and regioselectivity and good functional group tolerance. The reactions of less-strained five-membered-ring substrates proceeded smoothly under the optimized reaction conditions. Preliminary mechanistic studies suggested that a Vilsmeier−Haack-like formylation process might be involved in C-cyanohydroxylation and that a γ-cyanoalkyl radical is a key reaction intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03707.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*qiang_liu@mail.tsinghua.edu.cn
*luzl@bnu.edu.cn

ORCID

Zhonglin Lu: 0000-0001-5473-2889
Qiang Liu: 0000-0002-8402-029X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Program for Thousand Young Talents of China and the 111 Project. We also thank Prof. Zhi He of Beijing Normal University for his insightful suggestions for this project.

■ REFERENCES

(1) (a) Belluš, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (c) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

(2) (a) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404. (b) Shaw, M. H.; Bower, J. F. *Chem. Commun.* **2016**, *52*, 10817. (c) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410.

(3) (a) Deng, L.; Xu, T.; Li, H.; Dong, G. *J. Am. Chem. Soc.* **2016**, *138*, 369. (b) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567. (c) Chen, P. H.; Savage, N. A.; Dong, G. *Tetrahedron* **2014**, *70*, 4135. (d) Lu, G.; Fang, C.; Xu, T.; Dong, G.; Liu, P. *J. Am. Chem. Soc.* **2015**, *137*, 8274. (e) Lu, Q.; Wang, B.; Yu, H.; Fu, Y. *ACS Catal.* **2015**, *5*, 4881. (f) Guo, R.; Zhang, G. *J. Am. Chem. Soc.* **2017**, *139*, 12891. (g) Guo, R.; Zheng, X.; Zhang, D.; Zhang, G. *Chem. Sci.* **2017**, *8*, 3002. (h) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17502. (i) Crépin, D.; Dawick, J.; Aïssa, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 620. (j) Matsuda, T.; Matsumoto, T. *Org. Biomol. Chem.* **2016**, *14*, 5023. (k) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (l) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049. (m) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455. (n) Takano, H.; Kanyiva, K. S.; Shibata, T. *Org. Lett.* **2016**, *18*, 1860.

(4) (a) Ren, R.; Zhao, H.; Huan, L.; Zhu, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12692. (b) Zhao, H.; Fan, X.; Yu, J.; Zhu, C. *J. Am. Chem. Soc.* **2015**, *137*, 3490. (c) Huan, L.; Zhu, C. *Org. Chem. Front.* **2016**, *3*, 1467. (d) Huang, F.-Q.; Wang, Y.-W.; Sun, J.-G.; Xie, J.; Qi, L.-W.; Zhang, B. *RSC Adv.* **2016**, *6*, 52710. (e) Huang, F. Q.; Xie, J.; Sun, J. G.; Wang, Y. W.; Dong, X.; Qi, L. W.; Zhang, B. *Org. Lett.* **2016**, *18*, 684. (f) Sawano, S.; Ishida, N.; Murakami, M. *Chem. Lett.* **2015**, *44*, 1521. (g) Ishida, N.; Okumura, S.; Nakanishi, Y.; Murakami, M. *Chem. Lett.* **2015**, *44*, 821. (h) Wang, S.; Guo, L. N.; Wang, H.; Duan, X. H. *Org. Lett.* **2015**, *17*, 4798. (i) Casey, B. M.; Eakin, C. A.; Flowers, R. A. *Tetrahedron Lett.* **2009**, *50*, 1264. (j) Wang, Y. F.; Toh, K. K.; Ng, E. P.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411.

(5) Wang, D.; Ren, R.; Zhu, C. *J. Org. Chem.* **2016**, *81*, 8043.

(6) (a) Shi, J.; Xu, H.; Qiu, D.; He, J.; Li, Y. *J. Am. Chem. Soc.* **2017**, *139*, 623. (b) Uchida, K.; Yoshida, S.; Hosoya, T. *Org. Lett.* **2017**, *19*, 1184.

(7) Uemura and co-workers reported an iridium-catalyzed radical C−C bond cleavage of cyclobutanone oximes to produce saturated nitriles. See: Nishimura, T.; Yoshinaka, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *Org. Lett.* **2005**, *7*, 2425.

(8) (a) Jiang, H.; An, X.; Tong, K.; Zheng, T.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 4055. (b) An, X. D.; Yu, S. *Org. Lett.* **2015**, *17*, 2692. (c) Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 14017. (d) Faulkner, A.; Race, N. J.; Scott, J. S.; Bower, J. F. *Chem. Sci.* **2014**, *5*, 2416.

(9) Zhao, B.; Shi, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 12727.

(10) Li, L.; Chen, H.; Mei, M.; Zhou, L. *Chem. Commun.* **2017**, *53*, 11544.

(11) Gu, Y. R.; Duan, X. H.; Yang, L.; Guo, L. N. *Org. Lett.* **2017**, *19*, 5908.

(12) (a) Blaser, D.; Calmes, M.; Daunis, J.; Natt, F.; Tardy-Delassus, A.; Jacquier, R. *Org. Prep. Proced. Int.* **1993**, *25*, 338. (b) Jolly, P. I.; Fleary-Roberts, N.; O'Sullivan, S.; Doni, E.; Zhou, S.; Murphy, J. A. *Org. Biomol. Chem.* **2012**, *10*, 5807. (c) Kantlehner, W. *Eur. J. Org. Chem.* **2003**, *2003*, 2530.

DOI: 10.1021/acs.orglett.7b03707
Org. Lett. XXXX, XXX, XXX−XXX