Organic LETTERS

Letter

pubs.acs.org/OrgLett

Rh(III)- and Zn(II)-Catalyzed Synthesis of Quinazoline *N*-Oxides via C−H Amidation−Cyclization of Oximes

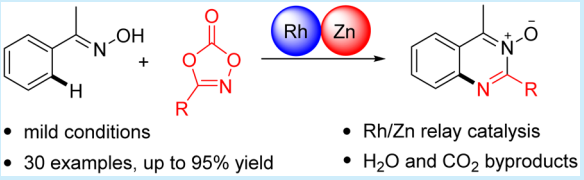
Qiang Wang,[†,‡] Fen Wang,[†] Xifa Yang,[†,‡] Xukai Zhou,[†,‡] and Xingwei Li*[,†]

[†]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

ABSTRACT: Quinazoline *N*-oxides have been prepared from simple ketoximes and 1,4,2-dioxazol-5-ones via Rh(III)-catalyzed C−H activation−amidation of the ketoximes and subsequent Zn(II)-catalyzed cyclization. The substrate scope and functional group compatibility were examined. The reaction features relay catalysis by Rh(III) and Zn(II).

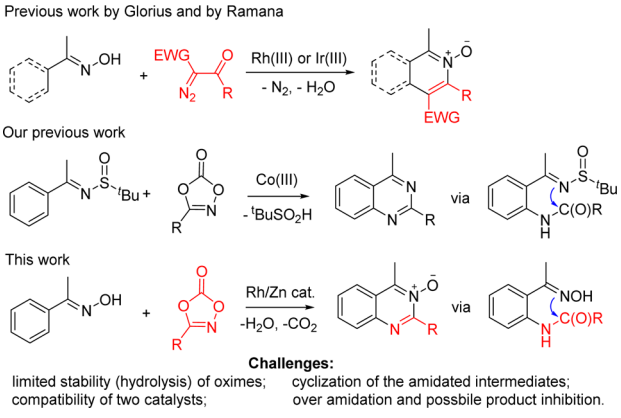


Construction of heterocycles represents one of the most important and fundamental processes in organic synthesis. In traditional synthetic approaches, prefunctionalized (bifunctional) starting materials are usually employed, where harsh reaction conditions are generally needed.[1] In the past decades, transition-metal-catalyzed annulation of arenes has been realized via C−H activation as an efficient and atom-economic strategy, which has been increasingly explored and has shown significant advantages in terms of step economy and availability of substrates.[2]

N-Oxides of azacycles are important structural motifs that are widely found in numerous pharmaceuticals, biologically active compounds,[3] and chiral ligands.[4] The presence of a N−O bond also serves as an important handle to activate the heterocycle, thus allowing diverse functionalization of heterocycles such as quinolines, isoquinolines, and quinazolines.[5] Although nitrogen-containing heterocycles have been conveniently prepared via C−H activation of arenes in the coupling with various unsaturated coupling partners,[6] reports on the synthesis of *N*-oxides of azacycles via direct C−H activation of arenes are rare. Recently, Glorius[7] and Ramana[8] reported on the synthesis of *N*-oxides of isoquinoline and pyridines via annulation of oximes with activated diazo compounds in the presence of Cp*Rh(III) and Cp*Ir(III) catalysts, respectively (Scheme 1). Despite the progress, synthesis of other *N*-oxides, including quinazoline *N*-oxides, remains underexplored. Quinazoline *N*-oxides have found significant applications in synthesis and can be converted into a plethora of valuable functionalities, which renders them key intermediates in organic synthesis and the pharmaceutical industry.[9] Although they are accessible via oxidation of quinazolines which in turn can be synthesized via a C−H activation process,[10] it is highly desirable to develop convenient and efficient single-step C−H activation approaches from simple starting materials.

We[10a] and others[10b−e] independently reported the synthesis of quinazolines via a C−H amidation−cyclization approach, in which the amidating reagent 1,4,2-dioxazol-5-one[11] exhibited high activity with operational simplicity. The cobalt-catalyzed

Scheme 1. C−H Annulation for Heterocycle Construction



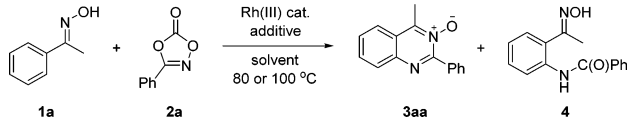
synthesis of quinazolines was made possible by the assistance of our bifunctional imine directing group.[10a,c] In particular, in the cyclization stage the amide carbonyl group was nucleophilically attacked by the imine nitrogen under uncatalyzed conditions.[10a] We reasoned that a related amidated intermediate can be employed for the synthesis of quinazoline *N*-oxides using a bimetallic relay catalysis so as to enhance the electrophilicity of the amide carbonyl. However, challenges remain because although amidation may readily occur, the cyclization relies heavily on the electrophilicity of amide carbonyl group and can be problematic (Scheme 1). Although introduction of a second (Lewis acidic) metal may promote the cyclization, the compatibility of two metals poses additional challenges. In addition, overamidation might occur to lead to decreased reaction selectivity.[10c] We now report the synthesis of quinazoline *N*-oxides via Rh(III)-catalyzed C−H activation of simple oximes under mild conditions.

Received: October 21, 2016
Published: November 14, 2016

DOI: 10.1021/acs.orglett.6b03155
Org. Lett. 2016, 18, 6144−6147

We embarked on our studies with the optimization of the reaction conditions of the coupling between oxime **1a** and dioxazolone **2a** catalyzed by $[Cp^*RhCl_2]_2$ in DCE (Table 1).

Table 1. Optimization Studies on Synthesis of a Quinazoline *N*-Oxide[a]



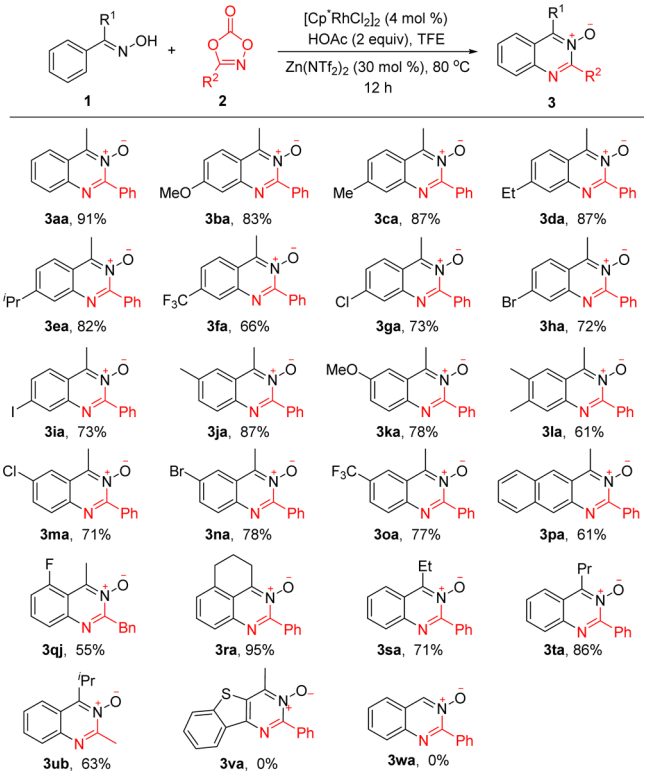
				yield (%)[b]	
entry	catalyst	additive (equiv)	solvent	**3aa**	**4**
1[c]	$[Cp^*RhCl_2]_2$	–	DCE	–	–
2[c]	$[Cp^*RhCl_2]_2$/$AgSbF_6$	–	DCE	<5	73
3[c]	$[Cp^*RhCl_2]_2$/$AgSbF_6$	CsOAc (0.3)	DCE	–	30
4[c]	$[Cp^*RhCl_2]_2$/$AgSbF_6$	$Zn(OTf)_2$ (0.3)	DCE	22	50
5[c]	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (0.3)	$PhCF_3$	17	35
6[c]	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (0.3)	acetone	30	22
7[c]	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (0.3)	MeOH	51	15
8[c]	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (0.3)	TFE	63	<5
9[d]	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (0.3)	TFE	78	<5
10[d]	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (0.3) HOAc (2.0)	TFE	83	<5
11[d]	$[Cp^*RhCl_2]_2$	$Zn(NTf_2)_2$ (0.3) HOAc (2.0)	TFE	89	<5
12[d]	–	$Zn(NTf_2)_2$ (0.3) HOAc (2.0)	TFE	–	–
13[d]	$[Cp^*RhCl_2]_2$	$AgNTf_2$ (0.3) HOAc (2.0)	TFE	13	65
14[d]	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$ (0.3) HOAc (2.0)	TFE	7	63

[a]Reaction conditions: oxime **1a** (0.1 mmol), **2a** (0.12 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %, if any), and additive(s) in a solvent (2 mL) under N_2 for 12 h. [b]Isolated yield. [c]100 °C. [d]80 °C.

No product was detected until $AgSbF_6$ was applied as a halogen scavenger, but only the simple amidation product **4** was obtained in good yield (entry 2). To our delight, the desired *N*-oxide **3aa** started to be obtained when $Zn(OTf)_2$[12] was applied as an additive (entries 3, 4). Changing the solvent to $PhCF_3$ afforded a similar yield of **3aa** even without any Ag(I) additive (entry 5), indicating that a chlorine scavenger can be inessential. After extensive screening of the solvent, TFE was identified as the optimal one. Interestingly, lowering the temperature from 100 to 80 °C improved the reaction efficiency (entry 9). Moreover, introduction of HOAc further increased the isolated yield of **3aa** to 83% (entry 10), and switching $Zn(OTf)_2$ to $Zn(NTf_2)_2$ then improved the yield to 89% (entry 11). Our control experiments confirmed that no desired reaction occurred in the absence of the rhodium catalyst (entry 12). However, when $Zn(NTf_2)_2$ was replaced with either $AgNTf_2$ or $Zn(OAc)_2$, poor yields of **3aa** were obtained (entries 13, 14).

We next examined the generality and limitations of this Rh(III)-catalyzed C−H activation−cyclization system. The scope with respect to the oxime was explored first in the coupling with **2a**. As given in Scheme 2, oximes bearing electron-donating and -withdrawing groups at the para position all reacted smoothly to provide the corresponding *N*-oxides in moderate to excellent yields. The reactions showed excellent regioselectivity for oximes bearing a *meta* substituent, and the coupling occurred at the sterically less hindered ortho position in good to high yields (**3ja**−**3pa**). The reaction proved sensitive to steric perturbation at the *ortho* position. Nevertheless, an *ortho*-F substituted oxime still coupled to afford the desired product **3qj** in 55% yield. It was found that oximes derived from 1-tetralone, propiophenone, and butyrophenone also reacted smoothly to yield the corresponding quinazoline *N*-oxides (**3ra**−**3ta**). Unfortunately, ketoxime with a heterocyclic backbone such as that of benzothiophene failed to undergo any desired reaction (**3va**), and the reaction of the corresponding aldoximes was unsuccessful (**3wa**).

Scheme 2. Scope of Oximes in Quinazoline *N*-Oxide Synthesis[a,b]



[a]All reactions were carried out using oxime **1** (0.2 mmol), dioxazolone **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $Zn(OTf)_2$ (30 mol %), HOAc (2 equiv), and TFE (5 mL) at 80 °C for 12 h under a N_2 atmosphere. [b]Isolated yield.

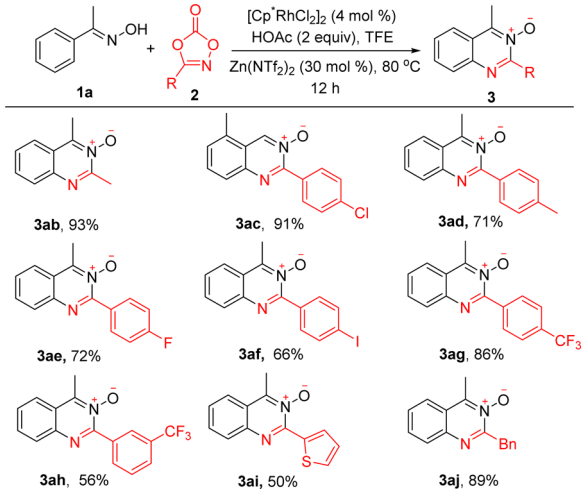
We further investigated the scope of the dioxazolone in the synthesis of quinazoline *N*-oxides (Scheme 3). Thus, aryl-substituted dioxazolones bearing both electron-donating and -withdrawing groups are all viable in this system (**3ac**−**3ah**). Furthermore, heterocycles such as thiophene-functionalized dioxazolones also reacted smoothly to afford product **3ai** in moderate yield. Moreover, benzyl- or methyl-substituted dioxazolones also showed great reactivity (**3ab**, **3aj**).

Synthetic application of an *N*-oxide product has been briefly demonstrated. Deoxygenation of **3aa** by Zn in the presence of water and NH_4Cl gave the corresponding quinazoline (**5**) in 71% yield (eq 1). Additionally, acetoxylation of the C4-methyl of **3ba** was achieved by refluxing with acetic anhydride to give ester **6** in 82% yield (eq 2).

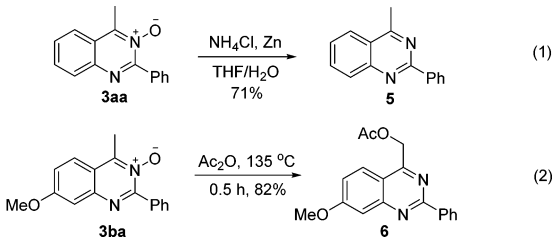
We next conducted preliminary mechanistic studies to gain insight into the mechanism of this annulation reaction (Scheme 4). To probe the cyclization process, *N*-(2-(1-(hydroxyimino)-ethyl)phenyl)benzamide (**4**) was prepared and was subjected to

DOI: 10.1021/acs.orglett.6b03155
Org. Lett. 2016, 18, 6144−6147

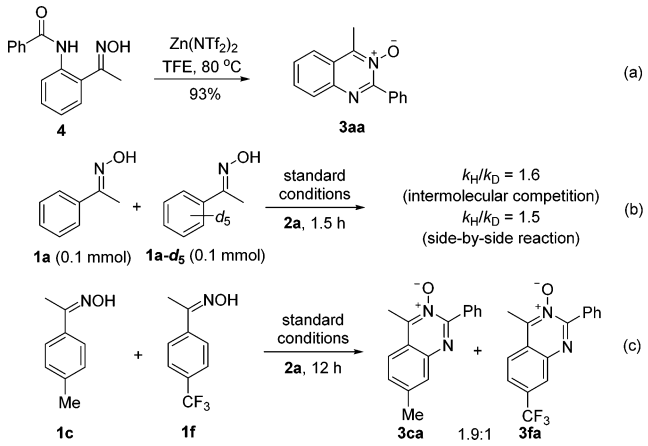
Scheme 3. Scope of Dioxazolones in the Synthesis of Quinazoline *N*-Oxides[a,b]



[a]All reactions were carried out using oxime **1a** (0.2 mmol), dioxazolone **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $Zn(OTf)_2$ (30 mol %), and HOAc (2 equiv) in TFE (5 mL) at 80 °C for 12 h under a N_2 atmosphere. [b]Isolated yield.



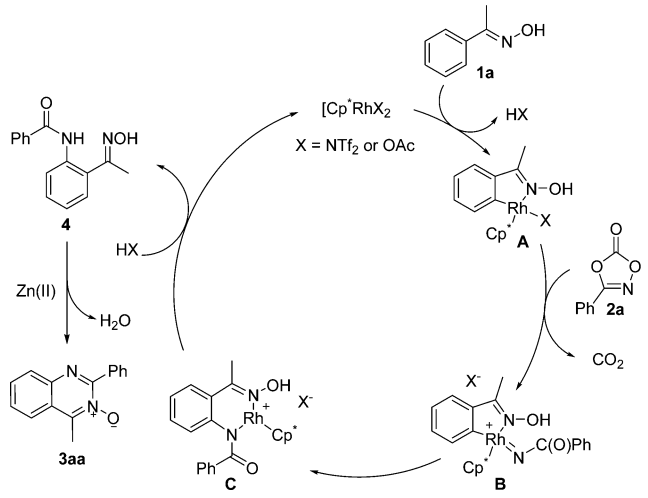
Scheme 4. Mechanistic Studies



catalysis only by $Zn(NTf_2)_2$ in TFE (80 °C, 12 h), from which the cyclized product **3aa** was isolated in 93% yield. Our control experiment also confirmed that HOAc alone does not promote this cyclization. These results indicated that **4** is an intermediate in the catalytic cycle, and it is the Zn(II) catalyst that effects the subsequent cyclization, thus providing a system of relay catalysis.[13] To probe the C−H activation process, kinetic isotope effect (KIE) experiments have been measured. Both parallel reactions (k_H/k_D = 1.5) and intermolecular competition (k_H/k_D = 1.6) using **1a** and **1a**-d_5 consistently gave a relatively small value, which indicates that cleavage of the C−H bond is likely not involved in the turnover-limiting step. Moreover, a competition experiment was performed to probe the electronic preference of the oxime substrate. Oximes **1c** and **1f** were allowed to compete in the coupling with **2a**, and the ratio of the products **3ca** and **3fa** was determined to be 1.9:1 on the basis of ^1H NMR spectroscopy. This result revealed that an electron-rich substrate showed slightly higher reactivity.

On the basis of these results and related reports,[10,11] a proposed catalytic cycle is given in Scheme 5. An active

Scheme 5. A Proposed Catalytic Cycle



rhodium catalyst $RhCp^*X_2$ (X = NTf_2 or OAc) was generated from the anion exchange between $[RhCp^*Cl_2]_2$ and $ZnNTf_2$ or HOAc. Next, cyclometalation of **1a** affords a rhodacyclic intermediate **A** together with an acid via a concerted metalation−deprotonation (CMD) mechanism. Coordination of dioxazolone **2a** is followed by elimination of CO_2 to give a nitrenoid species **B**, and subsequent migratory insertion of the Rh-aryl bond produces an amidate species **C**. Protonolysis of **C** releases the amidated intermediate **4**. Eventually, Zn(II)-catalyzed cyclization−condensation of **4** furnishes the final quinazoline *N*-oxide **3aa**.

In conclusion, we have realized an efficient synthesis of quinazoline *N*-oxides via rhodium(III)-catalyzed C−H amidation of readily available oximes. The amidation is orchestrated with a subsequent Zn(II)-catalyzed cyclization−condensation tandem. This annulation system proceeded in high efficiency under mild conditions with H_2O and CO_2 as the coproducts, obviating any need for oxidants. Further C−H functionalization−annulation systems and other novel transformations of oximes are 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/acs.orglett.6b03155.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xwli@dicp.ac.cn.

DOI: 10.1021/acs.orglett.6b03155
Org. Lett. 2016, 18, 6144−6147

ORCID

Xingwei Li: 0000-0002-1153-1558

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NSFC (Nos. 21525208 and 21472186) is gratefully acknowledged. We also acknowledge support by the new technology of methanol conversion from Dalian Institute of Chemical Physics (CAS) and by the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB17020300).

■ REFERENCES

(1) (a) Ashton, W. T.; Hynes, J. B. *J. Med. Chem.* **1973**, *16*, 1233. (b) D'yakonov, A. L.; Telezhenetskaya, M. V. *Chem. Nat. Compd.* **1997**, *33*, 221. (c) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329. (d) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (e) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (f) Li, J. W. H.; Vederas, J. C. *Science* **2009**, *325*, 161. (g) Zhang, J. T.; Yu, C. M.; Wang, S. J.; Wan, C. F.; Wang, Z. Y. *Chem. Commun.* **2010**, *46*, 5244. (h) Ohta, Y.; Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2010**, *12*, 3963. (i) Yan, Y. Z.; Zhang, Y. H.; Feng, C. T.; Zha, Z. G.; Wang, Z. Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 8077. (j) Han, B.; Yang, X. L.; Wang, C.; Bai, Y. W.; Pan, T. C.; Chen, X.; Yu, W. *J. Org. Chem.* **2012**, *77*, 1136. (k) Yuan, H.; Yoo, W. J.; Miyamura, H.; Kobayashi, S. *Adv. Synth. Catal.* **2012**, *354*, 2899. (l) Rizzo, S.; Waldmann, H. *Chem. Rev.* **2014**, *114*, 4621. (m) Rodrigues, T.; Reker, D.; Schneider, P.; Schneider, G. *Nat. Chem.* **2016**, *8*, 531. (n) Garcia-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 7586.

(2) For selected recent reviews on C−H activation, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (d) Hashiguchi, B. G.; Bischof, S. M.; Konnick, M. M.; Periana, R. A. *Acc. Chem. Res.* **2012**, *45*, 885. (e) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (f) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (g) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (h) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864. (i) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (j) Kuhl, N.; Schroder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (k) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (l) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (m) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (n) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308.

(3) (a) O'Donnell, G.; Poeschl, R.; Zimhony, O.; Gunaratnam, M.; Moreira, J. B. C.; Neidle, S.; Evangelopoulos, D.; Bhakta, S.; Malkinson, J. P.; Boshoff, H. I.; Lenaerts, A.; Gibbons, S. J. *J. Nat. Prod.* **2009**, *72*, 360. (b) Nicholas, G. M.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2001**, *64*, 341.

(4) (a) Malkov, A. V.; Kocovsky, P. *Eur. J. Org. Chem.* **2007**, *2007*, 29. (b) Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9708.

(5) (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (b) Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991. For a leading report, see: (c) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(6) Selected reviews: (a) Yang, Y.; Li, K.; Cheng, Y.; Wan, D.; Li, M.; You, J. *Chem. Commun.* **2016**, *52*, 2872. (b) Gulias, M.; Mascarenas, J. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 11000. Selected examples: (c) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (d) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (e) Zhao, D.; Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12426. (f) Yan, H.; Wang, H.; Li, X.; Xin, X.; Wang, C.; Wan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 10613. (g) Wang, Q.; Li, Y.; Qi, Z.; Xie, F.; Lan, Y.; Li, X. *ACS Catal.* **2016**, *6*, 1971.

(7) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204.

(8) Phatake, R. S.; Patel, P.; Ramana, C. V. *Org. Lett.* **2016**, *18*, 292.

(9) (a) Walser, A.; Flynn, T.; Mason, C.; Ian Fryer, R. *J. Heterocycl. Chem.* **1983**, *20*, 791. (b) Alzogaray, R. A.; Fontán, A.; Camps, F.; Masuh, H.; Orihuela, P. S.; Fernández, D.; Cork, A.; Zerba, E. *Molecules* **2005**, *10*, 1190.

(10) (a) Wang, F.; Wang, H.; Wang, Q.; Yu, S.; Li, X. *Org. Lett.* **2016**, *18*, 1306. (b) Wang, X.; Jiao, N. *Org. Lett.* **2016**, *18*, 2150. (c) Wang, X.; Lerchen, A.; Glorius, F. *Org. Lett.* **2016**, *18*, 2090. (d) Wang, J.; Zha, S.; Chen, K.; Zhang, F.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 2062. (e) Wang, H.; Lorion, M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 10386.

(11) (a) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534. (b) Sauer, J.; Mayer, K. K. *Tetrahedron Lett.* **1968**, *9*, 319. (c) Dube, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622. (d) Zhong, C. L.; Tang, B. Y.; Yin, P.; Chen, Y.; He, L. *J. Org. Chem.* **2012**, *77*, 4271. (e) Bizet, V.; Buglioni, L.; Bolm, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5639. (f) Wang, H.; Tang, G.; Li, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 13049. (g) Liang, Y.; Liang, Y.-F.; Tang, C.; Yuan, Y.; Jiao, N. *Chem. - Eur. J.* **2015**, *21*, 16395. (h) Park, J.; Chang, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14103. (i) Mei, R.; Loup, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 793.

(12) (a) Zhang, X.; Wang, F.; Qi, Z.; Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1586. (b) Yang, X.; Hu, X.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 1481.

(13) (a) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802. (b) Qiu, L.; Huang, D.; Xu, G.; Dai, Z.; Sun, J. *Org. Lett.* **2015**, *17*, 1810. (c) Li, L.; Wang, H.; Yu, S.; Yang, X.; Li, X. *Org. Lett.* **2016**, *18*, 3662.

DOI: 10.1021/acs.orglett.6b03155
Org. Lett. 2016, 18, 6144−6147