Organic LETTERS

Letter

pubs.acs.org/OrgLett

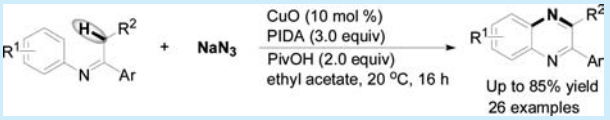
Copper-Catalyzed Cascade Cycloamination of α-Csp^3–H Bond of N-Aryl Ketimines with Azides: Access to Quinoxalines

Tengfei Chen, Xun Chen, Jun Wei, Dongen Lin,* Ying Xie, and Wei Zeng*

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510641, China

Supporting Information

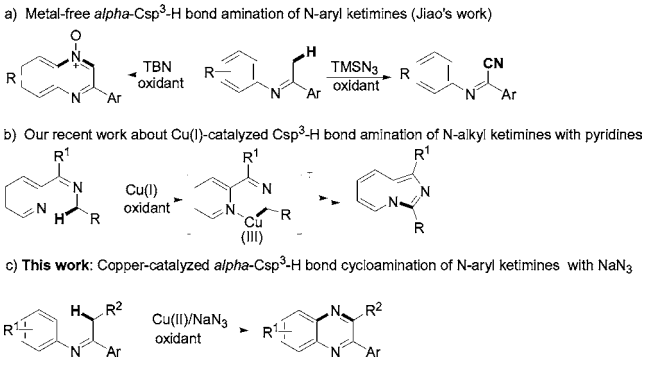
ABSTRACT: A copper-catalyzed cycloamination of α-Csp^3–H bond of N-aryl ketimines with sodium azide has been developed. This methodology provides an efficient access to quinoxalines and features mild reaction conditions and readily available ketimines with diverse functional group tolerance.



Transition-metal-catalyzed C–N bond-forming reactions are widely used in organic synthesis.[1] Among the various methodologies, direct C–H amination represents one of the most efficient transformations for atom-economical construction of C–N bonds without the need for a prefunctionalized site. In this regard, nitrene insertion into the C–H bond[2] and chelation-assisted C–H bond aminations have been well-established for assembling nitrogen-containing compounds.[3] Neverthless, in view of the fact that *N*-heterocycles are commonly encountered in many natural products, pharmaceuticals, and others, the exploration of versatile C–H amination approaches for constructing particular complex molecules still remains challenging and important.[4]

On the other hand, as versatile synthetic units, imines and their corresponding C=N bond addition reactions with organometallic reagents, Mannich donors, etc. provide a powerful method for preparing various nitrogen-containing compounds.[5] In comparison, α-Csp^3–H bond functionalization of ketimines,[6] especially for the α-Csp^3–H bond amination, has rarely been reported. To date, Jiao described that metal-free α-Csp^3–H bond aminations of N-aryl ketimines could efficiently convert ketoimines to α-iminonitriles[7] and quinoxaline N-oxides[8] through multiple single-electron transfer (SET) processes using $TMSN_3$ and *tert*-butyl nitrite (TBN) as the nitrogen source, respectively (Scheme 1a). Moreover, our group also developed a copper-catalyzed α-Csp^3–H bond amination of *N*-alkyl ketimines involving free radical intermediates to construct multifunctional imidazo[1,5-*a*]-pyridines using *N*-heteroarenes as amine sources (Scheme 1b).[9] These results imply that the α-Csp^3–H bond of ketimines instead of the imino bond (C=N bond) easily suffers from a free radical attack to form methylene radical intermediates under oxidative conditions. Previously, our group focused on developing novel organic reactions starting from imines to construct different nitrogen-containing compounds.[6c−e,9,10] Inspired by the above-mentioned works and due to the versatile biological activities of quinoxalines (Figure 1),[11] we expected that quinoxalines could be furnished from ketoimines and azides when transition-metal salts are employed as catalysts. Herein we describe a copper-catalyzed α-Csp^3–H bond cycloamination of N-aryl ketimines for the synthesis of a quinoxaline skeleton using sodium azide as the nitrogen source (Scheme 1c).

Scheme 1. α-Csp^3–H Bond Functionalizations of Ketimines



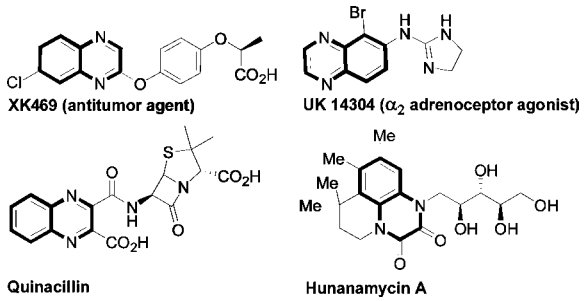


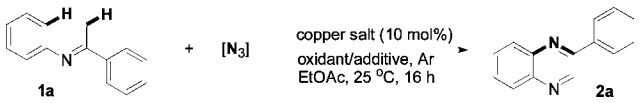
Figure 1. Selected examples of bioactive quinoxalines.

The α-Csp^3–H bond cycloamination cascade of *N*-phenylketoimine (**1a**) with tosyl azide (TsN_3) was initially chosen as a model reaction to screen various copper catalysts in the presence of $PhI(OAc)_2$ and AcOH in ethyl acetate at 25 °C under an Ar atmosphere for 16 h (Table 1, entries 1–7). As

Received: March 11, 2016
Published: April 25, 2016

DOI: 10.1021/acs.orglett.6b00709
Org. Lett. 2016, 18, 2078–2081

Table 1. Optimization of the Reaction Parameters[a]



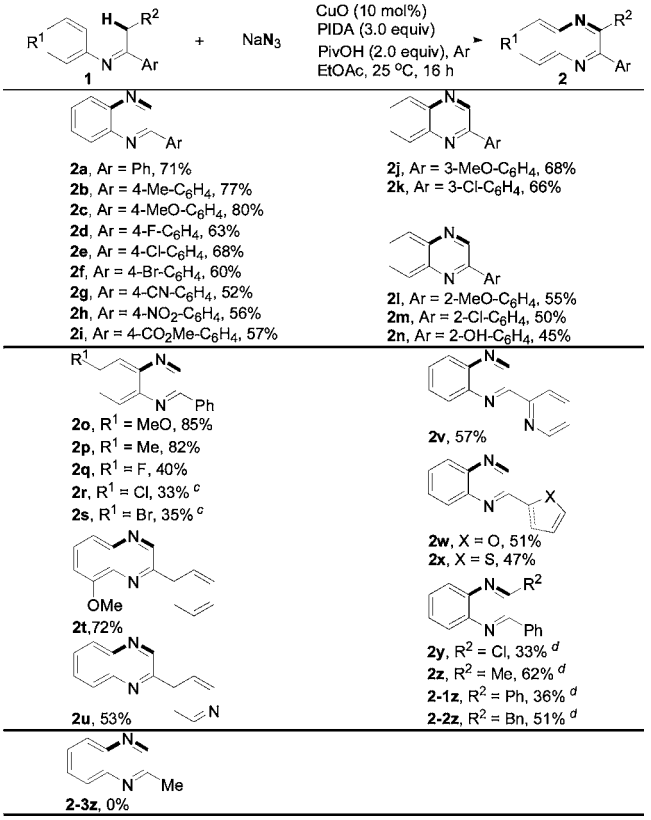
entry	catalyst	azide	oxidant	additive	yield (%)[b]
1	$Cu(OAc)_2$	TsN_3	$PhI(OAc)_2$	AcOH	9
2	$CuCl_2$	TsN_3	$PhI(OAc)_2$	AcOH	5
3	$CuBr_2$	TsN_3	$PhI(OAc)_2$	AcOH	trace
4	$CuSO_4$	TsN_3	$PhI(OAc)_2$	AcOH	14
5	CuI	TsN_3	$PhI(OAc)_2$	AcOH	5
6	CuBr	TsN_3	$PhI(OAc)_2$	AcOH	trace
7	CuO	TsN_3	$PhI(OAc)_2$	AcOH	19
8	CuO	$TMSN_3$	$PhI(OAc)_2$	AcOH	39
9	CuO	$PhCON_3$	$PhI(OAc)_2$	AcOH	0
10	CuO	NaN_3	$PhI(OAc)_2$	AcOH	49
11	CuO	NaN_3	BQ[c]	AcOH	0
12	CuO	NaN_3	Ag_2CO_3	AcOH	0
13	CuO	NaN_3	PhIO	AcOH	0
14	CuO	NaN_3	AgOAc	AcOH	19
15	CuO	NaN_3	$PhI(OAc)_2$	$PhCO_2H$	29
16	CuO	NaN_3	$PhI(OAc)_2$	TsOH	0
17	CuO	NaN_3	$PhI(OAc)_2$	iPrOH	0
18	CuO	NaN_3	$PhI(OAc)_2$	PivOH	71
19	CuO	NaN_3	$PhI(OAc)_2$	PivOH	63[d]
20	CuO	NaN_3	$PhI(OAc)_2$	PivOH	49[e]
21	CuO	NaN_3	$PhI(OAc)_2$	PivOH	57[f]

[a]Unless otherwise noted, all the reactions were carried out using ketoimine (**1a**) (0.10 mmol) and azide (0.30 mmol) with a copper catalyst (10 mol %) in the presence of an oxidant (3.0 equiv) and additive (2.0 equiv) in ethyl acetate (2.0 mL) at 25 °C for 16 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield. [c]BQ refers to 1,4-benzoquinone. [d]The reaction temperature is 10 °C. [e]The reaction temperature is 45 °C. [f]2.0 mmol of **1a** and 6.0 mmol of sodium azide were used.

expected, we quickly found that copper salts, such as $Cu(OAc)_2$, $CuCl_2$, $CuSO_4$, CuI, and CuO, could furnish the desired 2-phenylquinoxaline **2a** in 5−19% isolated yields. CuO was slightly superior to others and proved to be the best copper catalyst (entry 7). Subsequently, we continued to evaluate various azides including $PhCON_3$, $TMSN_3$, and NaN_3 for further improvement of the cycloamination conversion using CuO as the catalyst. After the extensive screening, NaN_3 was found to be a good candidate which could moderately increase the yield of **2a** from 19% to 49% (compare entries 7−9 with 10), whereas $PhCON_3$ was ineffective (entry 9). Moreover, to render the reaction catalytic in CuO, we then tested a variety of oxidants in the NaN_3/CuO/AcOH system and found the oxidant also played a crucial role in this transformation (entries 10−14). Among them, $PhI(OAc)_2$ could effectively enhance the α-imino Csp^3−H bond cycloamination and afford a 49% yield of **2a** (entry 10). Finally, several proton-donor additives including pivalic acid (PivOH), acetic acid, isopropyl alcohol, and benzoic acid were further investigated in the NaN_3/CuO/$PhI(OAc)_2$ system (entries 14−18), and PivOH was found to be the most efficient in the formation of product **2a** (entries 18, 71% yield) possibly due to the fact that PivOH could improve the solubility of CuO in the reaction system. Additionally notable is that lowering or increasing the reaction temperature could not further improve the reaction yields (compare entries 19 and 20 with 18) (see the Supporting Information (SI) for the more details). Also, when a large-scale reaction was performed, we could still obtain a 57% yield of **2a** (entry 21).

With the optimized conditions in hand, we then turned our attention to explore the generality of the current procedure by testing various *N*-arylketoimines (**1**) employing sodium azide as the nitrogen source. As shown in Scheme 2, the cycloamination

Scheme 2. Substrate Scope[a,b]

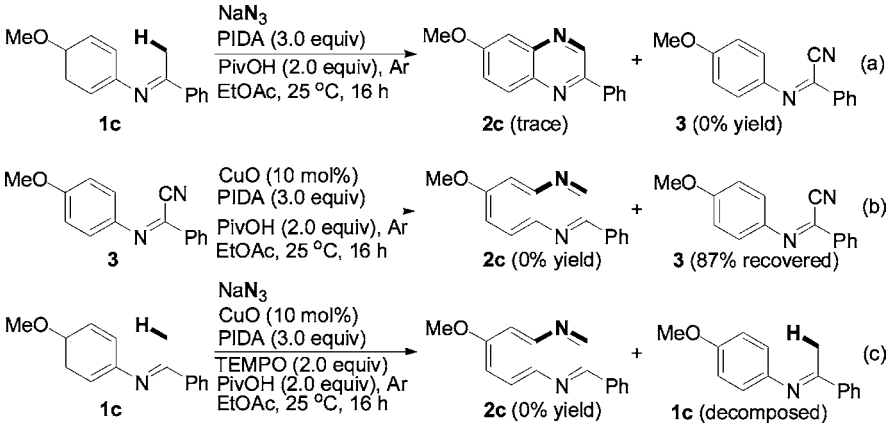


[a]Unless otherwise noted, all the reactions were carried out using ketoimine (**1**) (0.10 mmol) and sodium azide (0.30 mmol) with CuO (10 mol %) in the presence of PIDA (3.0 equiv) and PivOH (2.0 equiv) in ethyl acetate (2.0 mL) at 25 °C for 16 h under Ar in a sealed reaction tube, and then followed by flash chromatography on SiO_2. [b]Isolated yield. [c]The reaction time is 24 h. [d]The reaction temperature is 50 °C.

reactivity of *N*-arylketoimines (**1**) was obviously dependent on the electronic and steric properties of the substituents. We first evaluated substitution effects on the *C*-ketoimino phenyl rings (Ar). The α-imino Csp^3−H bond cycloamination cascade was compatible with electronically diverse functional groups at the 4′-position of Ar, and 4-substitution on the phenyl rings with electron-donating group (Me, MeO) afforded excellent yields of **2b** (77% yield) and **2c** (80% yield), respectively. In contrast, electron-withdrawing halide, nitro, nitrile, and ethoxylcarbonyl groups moderately decreased the reaction conversion and produced 52−68% yields of **2d**−**2i**. Notably, a similar substitution effect was also observed in the *N*-ketoimino phenyl rings (**2o**−**2s**, 35−85% yields). Subsequently, we prepared the *C*-(2- or 3- substituted phenyl)ketoimines and found their corresponding cycloamination efficiency was maintained irrespective of the type of substituent and the substituted position in *C*-imino phenyl rings (**2j**−**2n**). For examples, *C*-(2-methoxyl)phenyl, *C*-(3-methoxylphenyl, *C*-(2-

DOI: 10.1021/acs.orglett.6b00709
Org. Lett. 2016, 18, 2078−2081

Scheme 3. Preliminary Mechanistic Studies

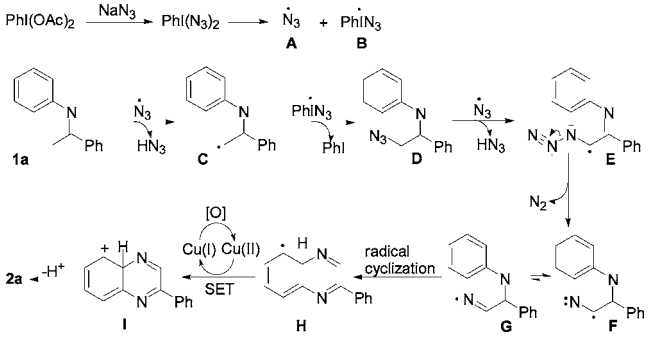


chloro)phenyl, and *C*-(3-chloro)phenyl-substituted ketoimines all allowed for this transformation and afforded the desired quinoxalines with 50−68% yields (**2j**−**2m**). More importantly, *C*-heteroaryl ketoimines were also tolerated under our reaction conditions to assemble 2-(4-pyridyl)quinoxaline (**2u**, 53% yield), 2-(3-pyridyl)quinoxaline (**2v**, 57% yield), 2-(2-furyl)-quinoxaline (**2w**, 51% yield), and 2-(2-thienyl)quinoxaline (**2x**, 47% yield). Finally, when we introduced the chloro, methyl, phenyl, and benzyl group to the α-imino Csp^3 position, the cycloamination reaction still worked and produced the corresponding 2,3-substituted quinoxalines (**2y**−**2**−**2z**) in acceptable yields (33−62%). Unfortunately, when bisalkyl-substituted ketoimines were subjected to the standard reaction conditions, no desired quinoxaline **2**−**3z** was observed.

Several control experiments were performed to investigate the possible mechanism of this Csp^3−H bond cycloamination. First, the α-Csp^3−H bond cycloamination of ketimine (**1c**) with sodium azide was conducted in the absence of CuO under the PIDA/PivOH/EtOAc/Ar reaction conditions at 25 °C for 16 h; no desired quinoxaline (**2c**) was observed, and most of the starting material **1c** was decomposed under our reaction system. This result suggested that the CuO catalysts played a key role in the formation of quinoxalines; Moreover, PIDA also could not furnish a nitrile intermediate[6] (**3**) under metal-free conditions (Scheme 3a). Next, further subjection of α-iminonitrile intermediate **3** to the CuO/PIDA/PivOH system under Ar could still not result in the formation of the desired product **2c**, and the substrate **3** was recovered in 87% isolated yield (Scheme 3b). This fact ruled out the possibility that α-iminonitrile intermediates were involved in this cycloamination process. Finally, addition of 2.0 equiv of TEMPO to the CuO/PIDA/PivOH/Ar reaction system of **1c** remarkably inhibited the α-Csp^3−H bond cycloamination of ketimines (Scheme 3c), which revealed that a SET process and radical intermediates were possibly involved in this reaction.

Based on the above-mentioned control experiments, a plausible mechanism is proposed in Scheme 4. The initial reaction of $PhI(OAc)_2$ with sodium azide (NaN_3) afforded $PhI(N_3)_2$,[12] and then $PhI(N_3)_2$ decomposed to produce azide radical **A** and iodine radical **B** via the N−I(III) bond homolysis.[13] Next, the regioselective hydrogen abstraction of the α-Csp^3−H bond from **1a** by azide radical **A** afforded the methylene radical **C**, which could be cross-coupled with radical intermediate **B** to give α-imino azide **D**. Once again, azide radical **A** would abstract the α-Csp^3−H bond of azide **D** to furnish the α-imino methylene radical **E**.[13a] Subsequently,

Scheme 4. Proposed Mechanism



denitrogenation and isomerization of **E** was followed by radical cyclization to generate the intermediate **H**. Finallly, **H** could be converted into the target quinoxaline **2a** via a single-electron transfer[14] and aromatization process.

In conclusion, we have developed a novel and simple efficient copper-catalyzed cycloamination cascade of the α-Csp^3−H bond of N-aryl ketimines, in conjunction with sodium azide as the nitrogen source, for the rapid assembly of quinoxalines under mild reaction conditions. This method tolerates a wide range of readily available ketoimines with diverse functional groups. Further investigations to elucidate the reaction mechanism and extend the synthetic applications of this transformation 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.6b00709.

Detailed experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra for all isolated compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: denlin@scut.edu.cn.
*E-mail: zengwei@scut.edu.cn.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.6b00709
Org. Lett. 2016, 18, 2078−2081

■ ACKNOWLEDGMENTS

The authors thank the NSFC (No. 21372085) and Science and Technology Program of Guangzhou (No. 156300075) for financial support.

■ REFERENCES

(1) For selected reviews, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Yang, Q.; Wang, Q.; Yu, Z. *Chem. Soc. Rev.* **2015**, *44*, 2305. (c) Louillat, M. − L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (d) Majek, M.; von Wangelin, A. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 5919. (e) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

(2) For selected reviews, see: (a) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (d) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384. (f) Zhang, Q.; Wu, C.; Zhou, L.; Li, J. *Organometallics* **2013**, *32*, 415. (g) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (h) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (i) Scamp, R. J.; Rigoli, J. W.; Schomaker, J. M. *Pure Appl. Chem.* **2014**, *86*, 381. (j) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899.

(3) For selected examples and reviews, see: (a) He, G.; Zhang, S. − Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124. (b) He, G.; Zhao, Y.; Zhang, S. − Y.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (c) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F. − J.; Shi, B. − F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (d) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496. (e) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706. (f) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (g) Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. *Nat. Commun.* **2015**, *6*, 6462. (h) Gou, Q.; Liu, G.; Liu, Z. − N.; Qin, J. *Chem. - Eur. J.* **2015**, *21*, 15491. (i) Louillat, M. − L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (j) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040.

(4) For selected examples, see: (a) Zheng, Q.-Z.; Feng, P.; Liang, Y. − F.; Jiao, N. *Org. Lett.* **2013**, *15*, 4262. (b) Ma, H.; Li, D.; Yu, W. *Org. Lett.* **2016**, *18*, 868.

(5) For selected examples and reviews, see: (a) Lian, Y.; Hummel, J. K.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 12548. (b) Chen, T. Y.; Tsutsumi, R.; Montgomery, P.; Volchkov, I.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 1798. (c) Li, Y.; Li, B. − J.; Wang, W. − H.; Huang, W. − P.; Zhang, X. − S.; Chen, K.; Shi, Z. − J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. (d) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (e) Williams, F. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 4459. (f) Zhu, S.; Lu, X.; Luo, Y.; Zhang, W.; Jiang, H.; Yan, M.; Zeng, W. *Org. Lett.* **2013**, *15*, 1440. (g) Yamada, K.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874.

(6) (a) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098. (b) Zhang, Y.; Chen, Z.; Wu, W.; Zhang, Y.; Su, W. *J. Org. Chem.* **2013**, *78*, 12494. (c) Xie, Y.; Chen, T.; Fu, S.; Li, X. − S.; Deng, Y.; Jiang, H.; Zeng, W. *Chem. Commun.* **2014**, *50*, 10699. (d) Chen, X.; Xie, Y.; Xiao, X.; Li, G.; Deng, Y.; Jiang, H.; Zeng, W. *Chem. Commun.* **2015**, *51*, 15328. (e) Xie, Y.; Chen, T.; Fu, S.; Jiang, H.; Zeng, W. *Chem. Commun.* **2015**, *51*, 9377.

(7) Chen, F.; Huang, X.; Cui, Y.; Jiao, N. *Chem. - Eur. J.* **2013**, *19*, 11199.

(8) Chen, F.; Huang, X.; Li, X.; Shen, T.; Zou, M.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 10495.

(9) Li, M.; Xie, Y.; Ye, Y.; Zou, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2014**, *16*, 6232.

(10) (a) Luo, Y.; Lu, X.; Ye, Y.; Guo, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2012**, *14*, 5640. (b) Dang, L.; Liang, L.; Qian, C.; Fu, M.; Ma, T.; Xu, D.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2014**, *79*, 769. (c) Fu, S.; Jiang, H.; Deng, Y.; Zeng, W. *Adv. Synth. Catal.* **2011**, *353*, 2795. (d) Zhu, S.; Lu, X.; Luo, Y.; Zhang, W.; Jiang, H.; Yan, M.; Zeng, W. *Org. Lett.* **2013**, *15*, 1440. (e) Zhu, S.; Dong, J.; Fu, S.; Jiang, H.; Zeng, W. *Org. Lett.* **2011**, *13*, 4914. (f) Chen, J.; Lu, X.; Lou, W.; Ye, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2012**, *77*, 8541.

(11) For selected examples, see: (a) Hazeldine, S. T.; Polin, L.; Kushner, J.; White, K.; Bouregeois, N. M.; Crantz, B.; Palomino, E.; Corbett, T. H.; Horwitz, J. P. *J. Med. Chem.* **2002**, *45*, 3130. (b) Munk, S. A.; Harcourt, D.; Arasasingham, P.; Gluchowski, C.; Wong, H.; Burke, J.; Kharlamb, A.; Manlapaz, C.; Padillo, E.; Williams, L.; Wheeler, L.; Garst, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1745. (c) Hugo, W. B.; Stretton, R. G. *Nature* **1964**, *202*, 1217. (d) Hu, Y.; Wang, K.; MacMillan, J. B. *Org. Lett.* **2013**, *15*, 390. (d1) Kim, Y. B.; Kim, Y. H.; Park, J. Y.; Kim, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 541. (e) Sato, K.; Shiratori, O.; Katagiri, K. *J. Antibiot.* **1967**, *20*, 270. (f) Sessler, J. L.; Maeda, H.; Mizuno, F.; Lynch, V. M.; Furuta, H. *J. Am. Chem. Soc.* **2002**, *124*, 13474. (g) Crossley, M. J.; Johnston, L. A. *Chem. Commun.* **2002**, 1122.

(12) (a) Arimoto, M.; Yamaguchi, H.; Fujita, E.; Ochiai, M.; Nagao, Y. *Tetrahedron Lett.* **1987**, *28*, 6289. (b) Arimoto, M.; Yamaguchi, H.; Fujita, E.; Nagao, Y.; Ochiai, M. *Chem. Pharm. Bull.* **1989**, *37*, 3221.

(13) (a) Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7094. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (d) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406.

(14) Zhang, P.; Sun, W.; Li, G.; Hong, L.; Wang, R. *Chem. Commun.* **2015**, *51*, 12293.

DOI: 10.1021/acs.orglett.6b00709
Org. Lett. 2016, 18, 2078−2081