Organic LETTERS

Letter

pubs.acs.org/OrgLett

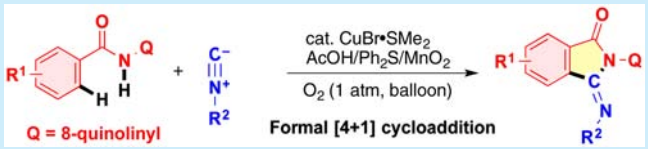
Copper-Catalyzed Formal [4 + 1] Cycloaddition of Benzamides and Isonitriles via Directed C−H Cleavage

Kazutaka Takamatsu, Koji Hirano,* and Masahiro Miura*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

Supporting Information

ABSTRACT: A copper-catalyzed formal [4 + 1] cycloaddition of benzamides and isonitriles via 8-aminoquinoline-directed C−H cleavage has been developed. The reaction proceeds well even in the presence of a base metal catalyst, $CuBr{\cdot}SMe_2$, alone to deliver the corresponding 3-iminoisoindolinones in good yields. Moreover, the unique acceleration effects of diphenyl sulfide are also disclosed.



Isonitriles constitute an important class of compounds in organic synthesis because they are unique, versatile, and useful C1 sources as well as good equivalents to toxic carbon monoxide. Particularly, there are many successful reports of cycloaddition reactions with isonitriles for the synthesis of a variety of N-heterocycles.[1] Additionally, they are frequently employed as a C1 coupling partner in the metal-catalyzed C−H functionalization.[2] However, to date, only noble palladium[3] and rhodium[4] complexes, in conjunction with stoichiometric Cu or Ag oxidants, are known to catalyze this type of transformation.[5] Thus, further development of direct cycloaddition with isonitriles in base metal catalysis is very appealing. Herein, we report a copper-catalyzed formal cycloaddition of benzamides and isonitriles via an 8-aminoquinoline-directed C−H cleavage. The reaction proceeds smoothly even in the presence of a copper catalyst alone to deliver the cycloadducts, 3-iminoisoindolinones,[6] in good yields. This is the first successful example of the copper-catalyzed C−H functionalization with isonitriles, to the best of our knowledge.

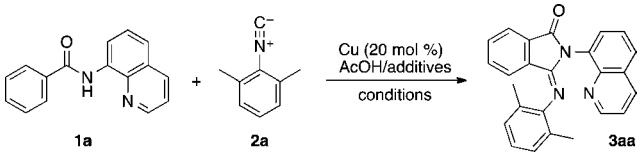
Recently, our group[7] and others[8] have focused on inexpensive, less toxic, and abundant copper salts and developed a number of copper-mediated C−H functionalization reactions. In particular, nitrogen-based directing groups allow such common metal species to serve as good alternatives to precious transition elements (e.g., Pd and Rh) and sometimes unique activators for otherwise challenging C−H transformations. During our continuous studies on this chemistry, we attempted a copper-catalyzed direct cycloaddition of benzamide **1a** (0.25 mmol) that bears the 8-aminoquinoline-based bidentate coordination group[9] and xylyl-substituted isonitrile **2a** (0.38 mmol) (Table 1). In an early experiment, the desired 3-iminoisoindolinone **3aa** was formed in 56% GC yield upon treatment of **1a** with **2a** in the presence of a $Cu(OAc)_2$ catalyst, AcOH, and activated MnO_2 under O_2 (1 atm, balloon) in DMF at 150 °C (entry 1). Some other copper salts also promoted the reaction (entries 2−5), with $Cu(OAc)_2$ and $CuBr{\cdot}SMe_2$ proving to be optimal (entries 1 and 3). Utilizing $CuBr{\cdot}SMe_2$ with better reproducibility, we next investigated the solvent effects (entries 6−8): aprotic polar DMSO and diglyme also worked well, while less polar *o*-xylene was detrimental. Particularly, diglyme gave a much cleaner result, and the GC yield reached 77% after 24 h (entry 7). Subsequent evaluations of additives identified unique acceleration effects of Ph_2S: the addition of Ph_2S allowed the reaction to complete within 7 h at 170 °C, and **3aa** was obtained in 88% GC yield (74% isolated yield) with recovery of Ph_2S (>94%, by GC analysis) (entry 9). Without any sulfides, no full conversion occurred even at 170 °C (entry 10).[10] The structure of **3aa**, including (*E*)-geometry of the imine moiety, was unambiguously confirmed by X-ray analysis.[11] Some additional observations are to be noted: both MnO_2 and O_2 were necessary for a satisfactory yield (entries 11 and 12); even with excess $CuBr{\cdot}SMe_2$ or $Cu(OAc)_2$, the yield of **3aa** was low to moderate in the absence of the above-mentioned two oxidants (entries 13 and 14); the copper salt was essential for the cycloaddition (entry 15); the 8-aminoquinoline moiety in **1a** was critical, and other monodentate and bidentate functional groups did not work at all under the conditions in entry 9 (**A**−**C**, Table 1); as a general trend, excess **2a** (>0.75 mmol) significantly dropped the rate (data not shown).

With the optimized conditions in hand (Table 1, entry 9), we then performed the copper-catalyzed formal [4 + 1] cycloaddition of various benzamides **1** with isonitrile **2a** (Scheme 1). In addition to the simple **1a**, electron-donating *tert*-butyl and methoxy groups at the para position were tolerated, and the corresponding iminoisoindolinones **3ba** and **3ca** were obtained in 73% and 63% yields, respectively. The copper catalysis also accommodated electron-withdrawing trifluoromethyl (**3da**), chloro (**3ea**), and bromo (**3fa**) substituents, but they showed somewhat lower efficiency and generally required a longer reaction period to full conversion. A similar trend was observed in the case of the methyl substituent at the congested ortho position (**3ga**). The reaction of meta-substituted substrates occurred preferably at the more sterically accessible C−H (**3ha**/**3ha′** and **3ia**/**3ia′**),[12] except for the *meta*-chlorobenzamide (**3ja**/**3ja′**). Also note that the regioisomers could be readily separated

Received: July 10, 2015
Published: August 3, 2015

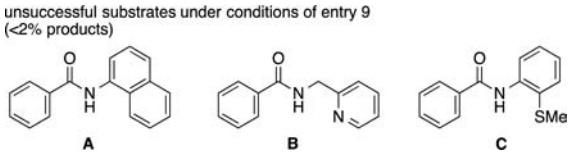
DOI: 10.1021/acs.orglett.5b01986
Org. Lett. 2015, 17, 4066−4069

Table 1. Optimization Studies for Copper-Catalyzed Formal [4 + 1] Cycloaddition of Benzamide 1a and Isonitrile 2a[a]



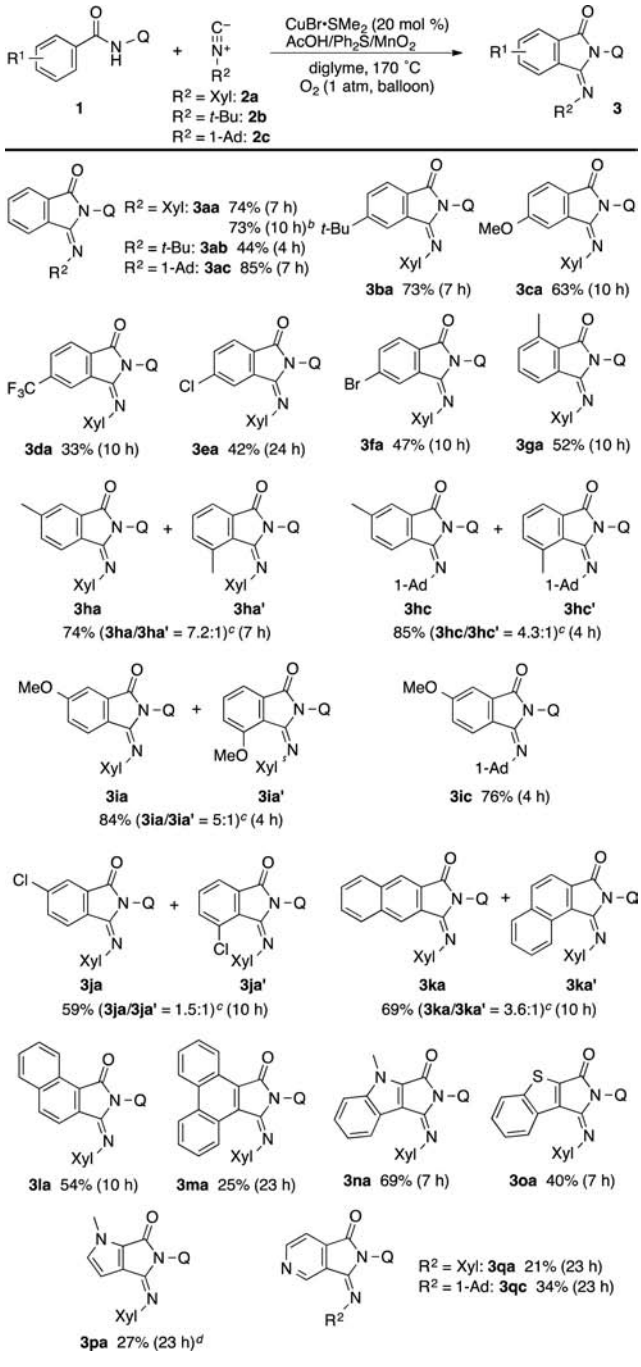
entry	Cu	additives (equiv)	conditions	3aa, % yield[b]
1	$Cu(OAc)_2$	MnO_2 (2.0)	DMF, 150 °C, 7 h, O_2	56
2	CuI	MnO_2 (2.0)	DMF, 150 °C, 4 h, O_2	27
3	$CuBr{\cdot}SMe_2$	MnO_2 (2.0)	DMF, 150 °C, 7 h, O_2	57
4	CuCl	MnO_2 (2.0)	DMF, 150 °C, 4 h, O_2	37
5	$Cu(OTf)_2$	MnO_2 (2.0)	DMF, 150 °C, 4 h, O_2	trace
6	$CuBr{\cdot}SMe_2$	MnO_2 (2.0)	DMSO, 150 °C, 7 h, O_2	61
7	$CuBr{\cdot}SMe_2$	MnO_2 (2.0)	diglyme, 150 °C, 24 h, O_2	77
8	$CuBr{\cdot}SMe_2$	MnO_2 (2.0)	*o*-xylene, 150 °C, 4 h, O_2	2
9	$CuBr{\cdot}SMe_2$	MnO_2 (2.0), Ph_2S (1.0)	diglyme, 170 °C, 7 h, O_2	88 (74)
10	CuBr	MnO_2 (2.0)	diglyme, 170 °C, 7 h, O_2	53
11	$CuBr{\cdot}SMe_2$	Ph_2S (1.0)	diglyme, 170 °C, 4 h, O_2	0
12	$CuBr{\cdot}SMe_2$	MnO_2 (2.0), Ph_2S (1.0)	diglyme, 170 °C, 7 h, N_2	29
13[c]	$CuBr{\cdot}SMe_2$	Ph_2S (1.0)	diglyme, 170 °C, 7 h, N_2	2
14[c]	$Cu(OAc)_2$	Ph_2S (1.0)	diglyme, 170 °C, 7 h, N_2	32
15	none	MnO_2 (2.0), Ph_2S (1.0)	diglyme, 170 °C, 7 h, O_2	0

[a]Reaction conditions: Cu (0.050 mmol), AcOH (0.25 mmol), additives, **1a** (0.25 mmol), **2a** (0.38 mmol), solvent (1.5 mL), O_2 (1 atm, balloon) or N_2. [b]Yield estimated by GC method. Yield of isolated product given in parentheses. [c]With 0.50 mmol of Cu.



from each other by silica gel column chromatography. Higher condensed naphthalene (**3ka**/**3ka**′ and **3la**) and phenanthrene (**3ma**) compounds were also applicable substrates. Moreover, some heteroarenes participated in the direct cycloaddition: indole- (**3na**), benzothiophene- (**3oa**), pyrrole- (**3pa**), and pyridine- (**3qa**) fused iminoisoindolinone analogues were formed in synthetically acceptable yields. In the cases of the pyrrole and pyridine (**3pa** and **3qa**), the starting amides were recovered in ca. 10% (by GC and GCMS analysis), but the rest could not be identified. On the other hand, the isonitrile was relatively limited in scope,[13] but bulky *tert*-butyl- and 1-adamantyl-substituted isonitriles could be employed (**3ab**,[11] **3ac**, **3hc**/**3hc**′, **3ic**, and **3qc**). Particularly, the coupling of **1i** with

Scheme 1. Products in Copper-Catalyzed Formal [4 + 1] Cycloaddition of Various Benzamides 1 and Isonitriles 2[a]



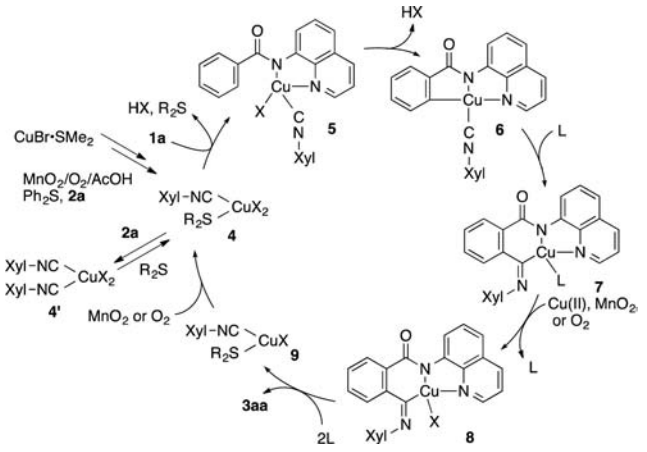
[a]Conditions: $CuBr{\cdot}SMe_2$ (0.050 mmol), AcOH (0.25 mmol), Ph_2S (0.25 mmol), activated MnO_2 (0.50 mmol), **1** (0.25 mmol), **2** (0.38 mmol), diglyme (1.5 mL), O_2 (1 atm, balloon). Yields of isolated products are given. The reaction time is shown in parentheses. [b]On a 2.5 mmol scale. [c]Regioisomeric ratios. Both isomers could be isolated by column chromatography. [d]Without Ph_2S. Q = 8-quinolinyl, Xyl = 2,6-dimethylphenyl.

1-adamantylisonitrile (**2c**) formed the single regioisomer **3ic** in 76% yield.[14] It is also noteworthy that the catalytic reaction could be conducted on a 2.5 mmol scale without any difficulties (**3aa**), thus indicating the good reliability and practicality of the present process.

DOI: 10.1021/acs.orglett.5b01986
Org. Lett. 2015, 17, 4066−4069

A proposed mechanism for the reaction of **1a** with **2a** is shown in Scheme 2. The initial off-cycle oxidation of CuBr·SMe_2 (I) and

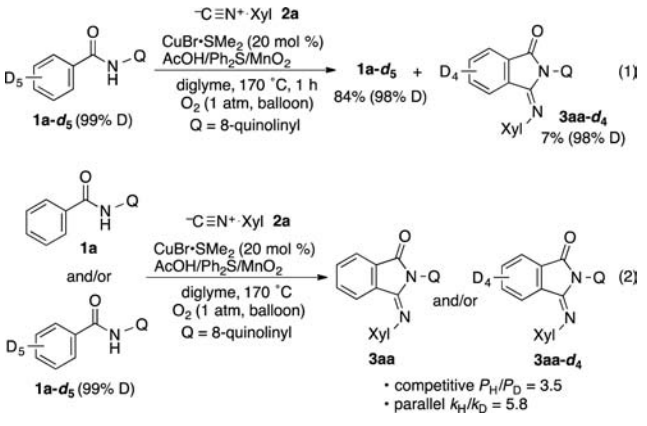
Scheme 2. Plausible Mechanism (X = Br or OAc, L = Xyl-NC (2a) or R_2S)



coordination of the isonitrile **2a** and sulfides form the active copper complex **4**. Subsequent deprotonation of relatively acidic NH in **1a**[15] generates the key N,N-bidentately chelated metalacycle **5**, which is apparently supported by control experiments with other benzamides **A**–**C** (Table 1). The ortho C–H cleavage (**5** → **6**) is followed by the insertion of the isonitrile to the C–Cu moiety[16] to afford the intermediate **7**. Productive reductive elimination is then induced by the oxidation into Cu(III) species,[17] en route to the cycloadduct **3aa** (**7** → **8** → **9**). Reoxidation of the liberated Cu(I) **9** by MnO_2 and/or O_2 regenerates the starting **4** to complete the catalytic cycle. The (*E*)-geometry of the imine moiety in **3aa** can be thermodynamically controlled by the steric repulsion between the Xyl group and quinoline ring. Given the critical effects of MnO_2 and O_2 even under stoichiometric conditions (entries 13 and 14 in Table 1), they can work in both oxidation steps (**7** → **8** and **9** → **4**). Although the exact role of the external Ph_2S still remains unclear, it can suppress the formation of inactive, isonitrile-overcoordinated copper **4′**, which is consistent with some phenomena observed in the optimization studies: the reduced reaction rate in the presence of excess isonitriles and nearly quantitative recovery of Ph_2S.[18]

To shed some light onto the C–H cleavage step, we performed deuterium-labeling experiments (Scheme 3). At an

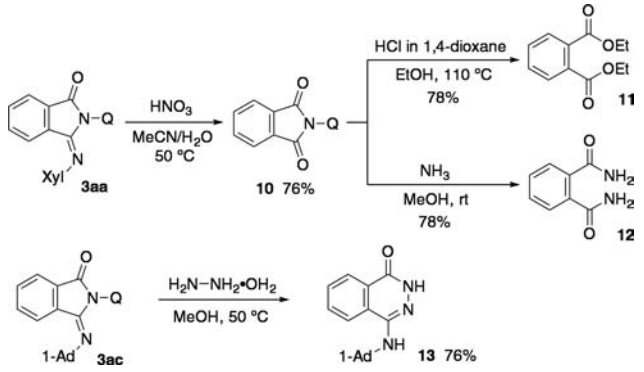
Scheme 3. Deuterium-Labeling Experiments



early stage of the reaction with **1a**-d_5 (1 h), both the product and recovered starting material did not lose any deuteriums (eq 1), thus suggesting the irreversible C–H cleavage under catalytic conditions. Additionally, the competitive and parallel reactions gave large KIE values of 3.5 and 5.8, respectively (eq 2). Thus, the C–H cleavage would be involved in the rate-determining step. However, further efforts are essential for clarification of the mechanism.[19]

The iminoisoindolinone products **3** could be easily transformed into various 1,2-dicarboxylic acid derivatives (Scheme 4).

Scheme 4. Transformation of Products



The xylyl-substituted **3aa** was hydrolyzed upon treatment with HNO_3 aq. affording the *N*-quinolinylphthalimide **10**. Subsequent ethanolysis and aminolysis furnished diethyl phthalate (**11**) and phthalamide (**12**), respectively, in good overall yields. Furthermore, the reaction of **3ac** with hydrazine provided the corresponding 4-aminophthalazinone skeleton **13**, which frequently occurs in bioactive molecules.[20]

In conclusion, we have developed a copper-catalyzed formal [4 + 1] cycloaddition of benzamides and isonitriles via directed C–H cleavage. Suitable oxidants (i.e., activated MnO_2 and O_2) and a Ph_2S additive enable the first Cu catalysis in the aromatic C–H coupling with isonitriles.[21] The products can also be readily converted to useful acyclic and cyclic compounds. Our ongoing work seeks to uncover the detailed mechanism and develop relevant Cu-based C–H activation catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01986.

Detailed experimental procedures, characterization data of compounds (PDF)
CIF file of **3ab** (CIF)
CIF file of **3aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: k_hirano@chem.eng.osaka-u.ac.jp.
*E-mail: miura@chem.eng.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Nos. 15K13696 (Grant-in-Aid for Exploratory Research) and

DOI: 10.1021/acs.orglett.5b01986
Org. Lett. 2015, 17, 4066–4069

15H05485 (Grant-in-Aid for Young Scientists (A)) to K.H. and 24225002 (Grant-in-Aid for Scientific Research (S)) to M.M.

REFERENCES

(1) Recent reviews: (a) Chakrabarty, S.; Choudhary, S.; Doshi, A.; Liu, F.-Q.; Mohan, R.; Ravindra, M. P.; Shah, D.; Yang, X.; Fleming, F. F. *Adv. Synth. Catal.* **2014**, *356*, 2135. (b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698. (c) Kruithof, A.; Ruijter, E.; Orru, R. V. A. *Chem. - Asian J.* **2015**, *10*, 508.

(2) Selected reviews and accounts: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (f) Lewis, L. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (g) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, *2008*, 3013. (h) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (i) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (l) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (m) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (n) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. (o) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (p) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (q) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (r) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (s) Hirano, K.; Miura, M. *Chem. Lett.* **2015**, *44*, 868.

(3) (a) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604. (b) Wang, Y.; Zhu, Q. *Adv. Synth. Catal.* **2012**, *354*, 1902. (c) Nanjo, T.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2012**, *14*, 4270. (d) Jiang, H.; Gao, H.; Liu, B.; Wu, W. *RSC Adv.* **2014**, *4*, 17222. (e) Wang, D.; Cai, S.; Ben, R.; Zhou, Y.; Li, X.; Zhao, J.; Wei, W.; Qian, Y. *Synthesis* **2014**, *46*, 2045. (f) Liu, Y.-J.; Xu, H.; Kong, W.-J.; Dai, H.-X.; Yu, J.-Q. *Nature* **2014**, *515*, 389. (g) Zheng, Q.; Luo, P.; Lin, Y.; Chen, W.; Liu, X.; Zhang, Y.; Ding, Q. *Org. Biomol. Chem.* **2015**, *13*, 4657.

(4) Zhu, C.; Xie, W.; Falck, J. R. *Chem. - Eur. J.* **2011**, *17*, 12591.

(5) For related transformation with carbon monoxide under palladium, ruthenium, and cobalt catalysis, see: (a) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898. (b) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (c) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (d) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4688. (e) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.* **2015**, *6*, 4610.

(6) For biological activity of 3-iminoisoindolinones, see: Murthy, A. R. K.; Wong, O. T.; Reynolds, D. J.; Hall, I. H. *Pharm. Res.* **1987**, *4*, 21.

(7) (a) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (b) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993. (c) Hirano, K.; Miura, M. *Chem. Commun.* **2012**, *48*, 10704. (d) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457. (e) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 11045. (f) Miura, M.; Nishino, M.; Hirano, K.; Satoh, T.; Odani, R. *Heterocycles* **2014**, *88*, 595. (g) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 2892. (h) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10784. (i) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2015**, *80*, 2384. (j) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2015**, *80*, 3242.

(8) Selected examples: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (c) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (d) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (e) Mizuhara, T.; Inuki, S.; Oishi, S.; Fujii, M.; Ohno, H. *Chem. Commun.* **2009**, 3413. (f) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632. (g) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 1644. (h) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415. (i) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (j) Tang, C.; Jiao, N. *J. Am. Chem. Soc.* **2012**, *134*, 18924. (k) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043. (l) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342. (m) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842. (n) Urones, B.; Martínez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 11044. (o) Martínez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 2801. (p) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (q) Li, Q.; Zhang, S.-Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, *16*, 1764. (r) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496. (s) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706.

(9) For pioneering work by Daugulis, see: (a) Zaitsev, V. Z.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. Recent reviews: (b) Corbet, M.; De Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (d) Castro, L. C. M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410.

(10) The addition of *i*-Pr_2S and Me_2S gave **3aa** in 75% and 70% GC yields, respectively, under otherwise identical conditions of entry 9 in Table 1. The Me_2S-free CuBr also worked well in the presence of Ph_2S (86% GC yield of **3aa** under otherwise identical conditions of entry 9). However, it is relatively unstable under atmosphere and somewhat difficult to handle. Thus, we identified the more user-friendly CuBr·SMe_2 to be optimal.

(11) Crystallographic data for the structures of **3aa** and **3ab** have been deposited with the Cambridge Crystallographic Data Center. See the Supporting Information for details. The (*E*)-configuration of products other than **3aa** and **3ab** was assigned by analogy.

(12) The minor regioisomer **3ia′** undergoes the rapid *E*/*Z* interconversion of the imine moiety at room temperature, which was detected by ^{1}H NMR in a $CDCl_3$ solution. See the Supporting Information for details.

(13) We tested less hindered isonitriles, including 2-naphthyl and 4-methoxyphenyl ones. However, the products were formed in <30% yield. Although the exact reason is not clear, such isonitriles competitively decomposed under the standard conditions, which was judged by GC and GCMS analysis.

(14) We have no explanation at present.

(15) The ^{1}H NMR chemical shifts of NH in **1a**, **A**, **B**, and **C** are 10.76, 8.21, 7.61, and 9.26 ppm, respectively (in $CDCl_3$, 25 °C).

(16) We cannot exclude the possibility of the insertion into the N−Cu in **6**. See: (a) Toyofuku, M.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2008**, *130*, 10504. (b) Shiro, D.; Fujiwara, S.; Tsuda, S.; Iwasaki, T.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2015**, *44*, 465. However, simple N−H adducts across the isonitrile moiety were not observed under any Cu-promoted conditions as far as we tested.

(17) (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (b) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (c) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068. (d) Casitas, A.; Canta, M.; Solá, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.

(18) For positive effects of sulfides in Pd- and Cu-promoted C−H functionalization, see: (a) Ohmura, T.; Kijima, A.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 6070. (b) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2011**, *13*, 276. (c) Zhang, G.; Zhao, Y.; Ge, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 2559.

(19) We observed no negative effects upon treatment with radical inhibitors, including TEMPO and galvinoxyl.

(20) (a) Prime, M. E.; Courtney, S. M.; Brookfield, F. A.; Marston, R. W.; Walker, V.; Warne, J.; Boyd, A. E.; Kairies, N. A.; von der Saal, W.; Limberg, A.; Georges, G.; Engh, R. A.; Goller, B.; Rueger, P.; Rueth, M. J. *Med. Chem.* **2011**, *54*, 312. (b) Elagawany, M.; Ibrahim, M. A.; Ahmed, H. E. A.; El-Etrawy, A. S.; Ghiaty, A.; Abdel-Samii, Z. K.; El-Feky, S. A.; Bajorath, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2007.

(21) The present conditions did not promote the direct carbonyl insertion under CO pressure.

DOI: 10.1021/acs.orglett.5b01986
Org. Lett. 2015, 17, 4066−4069