

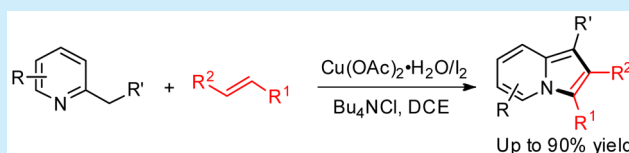
Indolizine Synthesis via Oxidative Cross-Coupling/Cyclization of Alkenes and 2-(Pyridin-2-yl)acetate Derivatives

Ren-Rong Liu, Jian-Jun Hong, Chuan-Jun Lu, Meng Xu, Jian-Rong Gao, and Yi-Xia Jia*

College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, China

S Supporting Information

ABSTRACT: A novel copper/ I_2 -mediated oxidative cross-coupling/cyclization of 2-(pyridin-2-yl)acetate derivatives and simple olefins is developed, which provides a straightforward and efficient access to structural diversely indolizines. A series of 1,3-di- and 1,2,3-trisubstituted indolizines are easily synthesized in modest to excellent yields.



Indolizine derivatives are one of the major classes of heterocycles. Functionalized indolizines have found wide applications in natural products and synthetic pharmaceuticals, which are associated with a broad spectrum of biological activities, such as antifungal, anticancer, and SGL T1 antagonists (Figure 1).¹ Other attractive bioactivities of

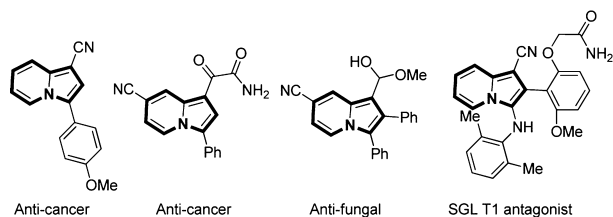


Figure 1. Selected structures bearing an indolizine core.

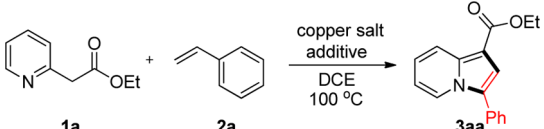
indolizines include antitubercular, phosphatase inhibitive, antioxidant, or anti-inflammatory.² Consequently, the development of efficient methods for rapid construction and functionalization of indolizines has gained much attention. Documented approaches to indolizines mainly include the following: Scholtz reaction,³ Tschischibabin reaction,⁴ dipolar cycloadditions of pyridinium and related heteroaromatic ylides with electron-deficient alkynes or alkenes,⁵ cyclization of pyridines with alkenyldiazoacetates,⁶ C–H functionalization reaction,⁷ transition-metal-catalyzed cycloisomerizations of alkynylpyridine derivatives,⁸ and transannulations of pyridotriazoles with alkynes.⁹ Despite primordial importance in synthetic chemistry, these methods often involve multistage synthesis and suffer from limited substrate availability in some cases. Therefore, a straightforward, convenient, and regioselective route to synthesize indolizines using basic chemical materials is highly attractive.

Alkenes have been recognized as important starting materials in synthetic chemistry because of their low cost and ready availability. Selective oxidative difunctionalization of alkenes is an extremely powerful chemical transformation as evidenced by the extensively developed transformations, such as diamination,

aminooxygenation, aminofluorination, and so on.¹⁰ Recently, difunctionalization of alkenes has been successfully applied as an important strategy for the synthesis of heterocycle compounds, such as furans, oxazoles, and quinolones.¹¹ However, to the best of our knowledge, the construction of indolizines from simple alkenes by oxidative difunctionalization has not been reported. As a part of our continuing interest in the synthesis of functionalized indolizine,¹² we report herein a copper/ I_2 -mediated oxidative cross-coupling/cyclization of alkenes and 2-(pyridin-2-yl)acetate derivatives that provides a straightforward and efficient access to structural diversely indolizines in modest to excellent yields.¹³

Our initial efforts were focused on the oxidative cross-coupling/cyclization reaction using ethyl 2-(pyridin-2-yl)acetate **1a** and styrene **2a** as the model substrates (Table 1). It was found that the reaction afforded the desired product **3aa** in 15% yield by employing $Cu(OAc)_2 \cdot H_2O$ as a mediator in DCE at 100 °C after 24 h (Table 1, entry 1). A series of additives were then introduced to the reaction system to improve the yield. The introduction of different ammonium compounds slightly improved the yields, and the desired product was isolated in 31% yield when 1.0 equiv of NBu_4Cl was added (Table 1, entries 2–5). To our delight, the addition of 1.0 equiv of molecular iodine remarkably enhanced the yield to 52% (Table 1, entry 7). Following this result, other iodine salts (NaI, KI, KIO_3) were tested; however, no further increase of the yields was observed (Table 1, entries 8–10). It was noted that no desired product was detected in the absence of $Cu(OAc)_2 \cdot H_2O$, even with TBHP as the oxidant (Table 1, entries 11 and 12). Reducing the amount of $Cu(OAc)_2 \cdot H_2O$ led to a decreased yield (Table 1, entry 13). A lower yield was also observed when the amount of molecular iodine was increased to 2.0 equiv (Table 1, entry 14). Subsequent optimization showed that the combination of NBu_4Cl and molecular iodine could further improve the product yield to 70% (Table 1, entry 15). Other copper salts were then

Received: May 7, 2015

Table 1. Optimization of the Reaction Conditions^a


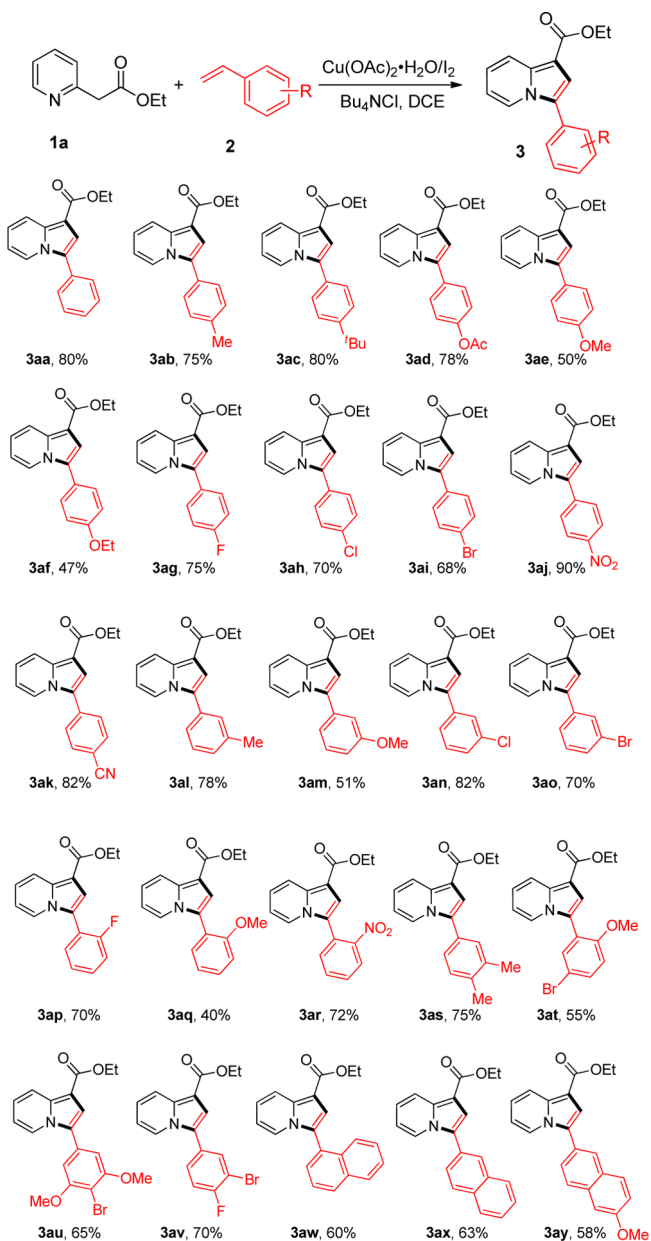
entry	copper salt	additive	yield ^b (%)
1	Cu(OAc) ₂ ·H ₂ O		15
2	Cu(OAc) ₂ ·H ₂ O	NBu ₄ F	25
3	Cu(OAc) ₂ ·H ₂ O	NBu ₄ Cl	31
4	Cu(OAc) ₂ ·H ₂ O	NBu ₄ I	20
5	Cu(OAc) ₂ ·H ₂ O	NBu ₄ Br	23
6	Cu(OAc) ₂ ·H ₂ O	Ag ₂ O	13
7	Cu(OAc) ₂ ·H ₂ O	I ₂	52
8	Cu(OAc) ₂ ·H ₂ O	NaI	22
9	Cu(OAc) ₂ ·H ₂ O	KI	30
10	Cu(OAc) ₂ ·H ₂ O	KIO ₃	32
11		I ₂	0
12		I ₂ /TBHP	trace
13 ^c	Cu(OAc) ₂ ·H ₂ O	I ₂	31
14 ^d	Cu(OAc) ₂ ·H ₂ O	I ₂	40
15	Cu(OAc) ₂ ·H ₂ O	I ₂ /NBu ₄ Cl	70
16	CuI	I ₂ /NBu ₄ Cl	trace
17	CuCl ₂	I ₂ /NBu ₄ Cl	trace
18 ^e	Cu(OAc) ₂ ·H ₂ O	I ₂ /NBu ₄ Cl	80

^aReaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), 3.0 equiv of copper salt, and 1.0 equiv of additive in DCE (1.0 mL) at 100 °C for 24 h. ^bIsolated yield. ^c1.0 equiv of Cu(OAc)₂·H₂O was used. ^d2.0 equiv of I₂ was used. ^e**2a** (0.2 mmol) and **1a** (0.4 mmol, 2.0 equiv) were used.

examined, while CuI and CuCl₂ showed almost no catalytic activity in this reaction (Table 1, entries 16 and 17). As 2-(pyridin-2-yl)acetate **1a** was partially decomposed under the above conditions, we thus modified the molar ratio of **1a**/**2a** from 1:2 to 2:1, which improved the product yield to 80% based on the amount of styrene (Table 1, entry 18).

With the optimal reaction conditions in hand (Table 1, entry 17), we then examined the scope of this reaction by varying the styrenes, and the results are summarized in Scheme 1. Generally, the reactions produced the corresponding indolizines in good yields. Styrenes bearing electron-withdrawing substituents on the benzene ring furnished the desired product in higher yields than those bearing electron-donating substituents (Scheme 1, **3aj–ak** vs **3ad–ae**). No obvious steric effect was observed for the substituted groups on the benzene ring of styrene in this reaction, and the expected indolizines were afforded in modest yields for the *ortho*-substituted styrenes (**3ap–ar,at,aw**). Several important functional groups such as –NO₂ (**3aj,ar**), –CN (**3ak**), and halogens –F, –Cl, –Br (**3ag–ai,an–ap,at–av**) were well tolerated, which allows further functionalization toward the synthesis of structural diversely indolizines. Additionally, terminal alkenes containing a naphthalene moiety were also employed to produce the indolizine products in modest yields (**3aw–ay**).

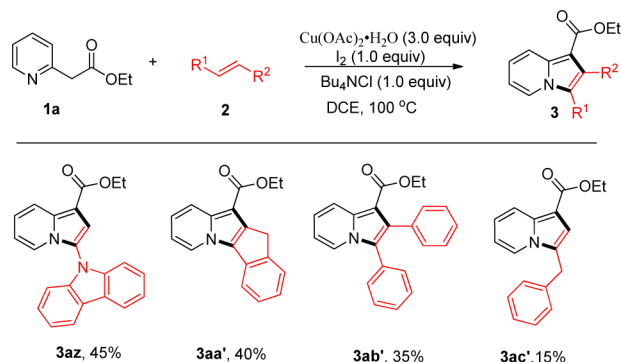
In addition to styrenes, other types of alkenes were also examined in the reaction (Scheme 2). When alkene **2z** was used, indolizine **3az** bearing a carbazole motif was isolated in 45% yield. Gratifyingly, 1,2-disubstituted alkenes were also suitable substrates for the reaction to generate the corresponding 1,2,3-trisubstituted indolizines. Thus, the reaction of 1H-indene **2a'** with **1a** produced a tetracyclic polysubstituted

Scheme 1. Scope of Styrene^a

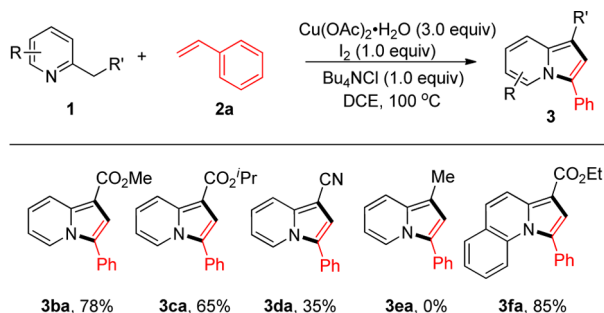
^aReaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), 3.0 equiv of Cu(OAc)₂·H₂O, 1.0 equiv of I₂, and 1.0 equiv of NBu₄Cl in DCE (1.0 mL) at 100 °C for 24 h.

indolizine **3aa'** in 40% yield. Moreover, the reaction of *trans*-1,2-diphenylethene **2b'** produced indolizine **3ab'** in 35% yield. Aliphatic alkene was also tested in the reaction, whereas the corresponding indolizine **3ac'** was obtained in a relatively lower yield.

Next, we investigated the scope of the pyridine derivatives under the optimized conditions, and the results are listed in Scheme 3. Different 2-(pyridin-2-yl)acetates **1** reacted well with styrene **2a** to deliver the corresponding indolizines in modest to good yields (78% for methyl ester **3ba** and 65% for isopropyl ester **3ca**). Notably, substrate **1** containing a CN group was found to be a suitable substrate, and its reaction with styrene **2a** afforded the product **3da** in 35% yield. Nevertheless, no reaction occurred for the substrate **1** without an additional electron-withdrawing group (for example, R' = Me, **3ea**),

Scheme 2. Scope of Substituted Olefin^a

^aReaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), 3.0 equiv Cu(OAc)₂·H₂O, 1.0 equiv I₂, and 1.0 equiv NBu₄Cl in DCE (1.0 mL) at 100 °C for 24 h.

Scheme 3. Scope of Pyridine Derivative^a

^aReaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), 3.0 equiv Cu(OAc)₂·H₂O, 1.0 equiv of I₂, and 1.0 equiv of NBu₄Cl in DCE (1.0 mL) at 100 °C for 24 h.

showing the limitation of the present reaction. Moreover, the reaction of 2-(quinolin-2-yl)acetate substrate with styrene **2a** proceeded well to furnish the corresponding product benz[e]-indolizines **3fa** in 85% yield.

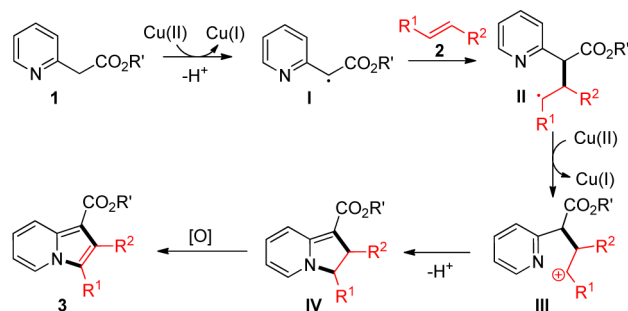
The control experiment showed that product **3aa** was not observed when a radical scavenger 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) was added to the reaction system (eq 1),



which indicated that the reaction might undergo a radical pathway. A plausible mechanism is depicted in Scheme 4. Single-electron oxidation of 2-(pyridin-2-yl)acetate **1** yields the radical intermediate **I**. Subsequent radical addition of **I** to alkene **2** generates a new radical intermediate **II** and forms the new C–C bond. The radical **II** was then oxidized by Cu(II) to carbocation intermediate **III**, followed by an intramolecular nucleophilic attack of nitrogen atom of pyridine to afford dihydroindolizine **IV**. Intermediate **IV** is then oxidized and aromatized to the final indolizine product **3** under the reaction conditions.

In conclusion, we have developed a straightforward and efficient copper/I₂-mediated oxidative cross-coupling/cyclization of 2-(pyridin-2-yl)acetate and simple olefins, delivering

Scheme 4. Plausible Mechanism



functionalized indolizines in modest to excellent yields. Due to easy availability of the starting materials and wide substrate scope, this protocol would be highly prospective in organic synthesis.

■ ASSOCIATED CONTENT

S Supporting Information

Complete experimental procedure and characterization data for the prepared compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01334.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yxjia@zjut.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of P.R. China (21372202 and 21402175), the New Century Excellent Talents in University (NCET-12-1086), and Zhejiang Natural Science Fund for Distinguished Young Scholars (R14B020005).

■ REFERENCES

- (1) (a) Micheal, J. P. *Alkaloids* **2001**, 55, 91. (b) Micheal, J. P. *Nat. Prod. Rep.* **2002**, 19, 742. (c) Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209. (d) Behnisch, A.; Behnisch, P.; Eggenweiler, M.; Wallenhorst, T. *Indolizine*. In *Houben-Weyl*; Thieme: Stuttgart, 1994; Vol. E6b/1, p 323. (e) Zhao, B.; Chen, K.; Hu, L. CN102977098, 2013. (f) Sharma, P.; Kumar, A.; Sharma, S.; Rane, N. *Bioorg. Med. Chem. Lett.* **2005**, 15, 937. (g) James, D. A.; Koya, K.; Li, H.; Liang, G. Q.; Xia, Z. Q.; Ying, W. W.; Wu, Y. M.; Sun, L. J. *Bioorg. Med. Chem. Lett.* **2008**, 18, 1784. (h) Li, H.; Xia, Z.; Chen, S.; Koya, K.; Ono, M.; Sun, L. *Org. Process Res. Dev.* **2007**, 11, 246.
- (2) (a) Muthusaravanan, S.; Perumal, S.; Yogeewari, P.; Sriram, D. *Tetrahedron Lett.* **2010**, 51, 6439. (b) Gundersen, L.-L.; Negussie, A. H.; Rise, F.; Østby, O. B. *Arch. Pharm.* **2003**, 336, 191. (c) Donnell, A. F.; Dollings, P. J.; Butera, J. A.; Dietrich, A. J.; Lipinski, K. K.; Ghavami, A.; Hirst, W. D. *Bioorg. Med. Chem. Lett.* **2010**, 20, 2163. (d) Weide, T.; Arve, L.; Prinz, H.; Waldmann, H.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2006**, 16, 59. (e) Østby, O. B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, 3763.
- (3) (a) Scholtz, M. *Ber. Dtsch. Chem. Ges.* **1912**, 45, 734. (b) Boekelheide, V.; Windgassen, R. J., Jr. *J. Am. Chem. Soc.* **1959**, 81, 1456.
- (4) (a) Tschitschibabin, A. E. *Ber. Dtsch. Chem. Ges.* **1927**, 60, 1607. (b) Hurst, J.; Melton, T.; Wibberley, D. G. *J. Chem. Soc.* **1965**, 2948. (c) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, 5, 43.

- (5) (a) Poissonnet, G.; Theret-Bettiol, M.-H.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2273. (b) Katritzky, A. R.; Qiu, G.; Yang, B.; He, H.-Y. *J. Org. Chem.* **1999**, *64*, 7618.
- (6) Barluenga, J.; Lonzi, G.; Riesgo, L.; Lopez, L. A.; Tomas, M. J. *Am. Chem. Soc.* **2010**, *132*, 13200.
- (7) (a) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. *Org. Lett.* **2012**, *14*, 957. (b) Wang, X.; Li, S.-Y.; Pan, Y.-M.; Wang, H.; Liang, H.; Chen, Z.; Qin, X. *Org. Lett.* **2014**, *16*, 580. (c) Yang, Y.; Cheng, K.; Zhang, Y. *Org. Lett.* **2009**, *11*, 5606. (d) Xia, J.-B.; You, S.-L. *Org. Lett.* **2009**, *11*, 1187. (e) Wu, Q.; Zhao, D.; Qin, X.; Lan, J.; You, J. *Chem. Commun.* **2011**, *47*, 9188. (f) Xia, J.-B.; Wang, X.-Q.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 456. (g) Amaral, M. F. Z. J.; Baumgartner, A. A.; Vessecchi, R.; Clososki, G. C. *Org. Lett.* **2015**, *17*, 238.
- (8) (a) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (b) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (c) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783. (d) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (e) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (f) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 43. (g) Kaloko, J.; Hayford, A. *Org. Lett.* **2005**, *7*, 4305. (h) Bai, Y.; Zeng, J.; Ma, J.; Gorityala, B. K.; Liu, X. W. *J. Comb. Chem.* **2010**, *12*, 696. (i) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863. (j) Meng, X.; Liao, P.; Liua, J.; Bi, X. *Chem. Commun.* **2014**, *50*, 11837.
- (9) (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) Helan, V.; Gulevich, A. V.; Gevorgyan, V. *Chem. Sci.* **2015**, *6*, 1928.
- (10) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (c) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (d) Francesca, C.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (e) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (f) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147. (g) Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020. (h) Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 10202. (i) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856. (j) Xie, Y.; Hu, J.; Xie, P.; Qian, B.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 18327. (k) Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 2529. (l) Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7156. (m) Su, Y.; Sun, X.; Wu, G.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 9808.
- (11) (a) Hilt, G.; Bolze, P.; Kieltsch, I. *Chem. Commun.* **2005**, 1996. (b) Zheng, M.; Huang, L.; Wu, W.; Jiang, H. *Org. Lett.* **2013**, *15*, 1838. (c) Huang, L.; Jiang, H.; Qi, C.; Liu, X. *J. Am. Chem. Soc.* **2010**, *132*, 17652. (d) Huang, Z.; Jin, L.; Feng, Y.; Peng, P.; Yi, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7151. (e) Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5661. (f) Gao, Q.; Liu, S.; Wu, X.; Wu, A. *Org. Lett.* **2014**, *16*, 4582.
- (12) (a) Liu, R.-R.; Cai, Z.-Y.; Lu, C.-J.; Ye, S.-C.; Xiang, B.; Gao, J.; Jia, Y.-X. *Org. Chem. Front* **2015**, *2*, 226. (b) Liu, R.-R.; Ye, S.-C.; Lu, C.-J.; Xiang, B.; Gao, J.; Jia, Y.-X. *Org. Biomol. Chem.* **2015**, *13*, 4855. (c) Liu, R.-R.; Lu, C.-J.; Zhang, M.-D.; Gao, J.-R.; Jia, Y.-X. *Chem.—Eur. J.* **2015**, *21*, 7057.
- (13) During submission of this manuscript, Lei and co-workers reported a similar work using I₂/TBHP as catalyst: Tang, S.; Liu, K.; Long, Y.; Gao, X.; Gao, M.; Lei, A. *Org. Lett.* **2015**, *17*, 2404.