Organic LETTERS

Letter

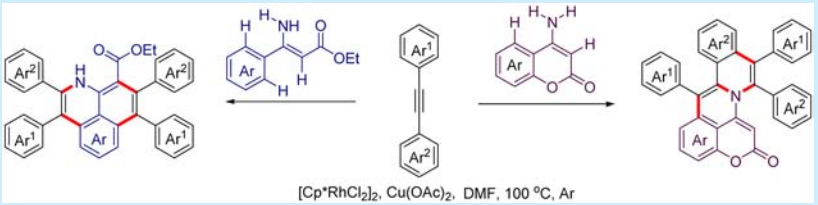
pubs.acs.org/OrgLett

# Synthesis of Polyheteroaromatic Compounds via Rhodium-Catalyzed Multiple C−H Bond Activation and Oxidative Annulation

Shiyong Peng, Suna Liu, Sai Zhang, Shengyu Cao, and Jiangtao Sun*

School of Pharmaceutical Engineering & Life Science, and Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology, Changzhou University, Changzhou 213164, P. R. China

Supporting Information

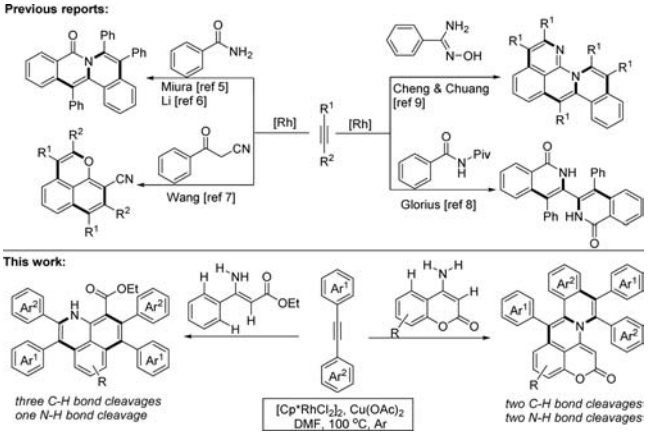



**ABSTRACT:** Polyheteroaromatic compounds are potential optoelectronic conjugated materials due to their electro- and photochemical properties. Transition-metal-catalyzed multiple C−H activation and sequential oxidative annulation allows rapidly assembling of those compounds from readily available starting materials. A rhodium-catalyzed cascade oxidative annulation of β-enamino esters or 4-aminocoumarins with internal alkynes is described to access those compounds, featuring multiple C−H/N−H bond cleavages and sequential C−C/C−N bond formations in one pot.

Polycyclic heteroaromatic compounds have received considerable attention due to their electrochemical and photochemical properties as well as their potential utility as organic electronics and luminescence materials.[1] The preparation of such conjugated π-systems generally proceeds via a transition-metal-catalyzed cross-coupling reaction, but multistep synthesis is often required.[2] Thus, it is of great importance to develop novel and efficient protocols to access those compounds from readily available starting materials through simple operations.

Transition-metal-catalyzed C−H bond activation affords a powerful way for the rapid construction of structurally diverse compounds from easily accessible starting materials.[3] Following this strategy, an array of complex polyheterocycles has been easily prepared through multiple sequential C−H/N−H bond activations and oxidative annulation from aromatic compounds and alkynes (Scheme 1).[4] For example, Miura and Satoh described the synthesis of polyarenes and polysubstituted isoquinolines.[5] Li reported polycyclic amides synthesis by Rh-catalyzed double C−H activation.[6] Wang developed a Rh-catalyzed cascade oxidative annulation of benzoylacetonitriles with alkynes to afford naphtho[1,8-*bc*]pyrans.[7] Recently, Glorious demonstrated the preparation of polysubstituted bisheterocycles from 1,3-diyne via a double Rh-catalyzed C−H activation.[8] Cheng and Chuang reported the synthesis of highly substituted naphthyridine-based polyheteroaromatic compounds through Rh-catalyzed procedures.[9] Despite these elegant approaches, the development of novel methodologies to access polyheteroaromatic compounds is still in high demand. Herein, we report our strategy on the rhodium-catalyzed multiple C−H and N−H bond cleavages and sequential oxidative annulation to prepare polycyclic heteroaromatic compounds from β-enamino esters and 4-aminocoumarins (which can be regarded as cyclic β-enamino esters). Furthermore, although enamides have been widely employed as valuable precursors in transition-metal-catalyzed C−H bond activation to produce pyrroles and pyridines,[10] to our knowledge, the use of β-enamino esters in multiple C−H bond activation has not been reported.[11]

**Scheme 1. Strategies toward Polyheteroaromatic Compounds via Rh-Catalyzed Multiple C−H Activation**




Initially, we used alkyne **1a** and unprotected β-enamino ester **2a** as model substrates to test the feasibility of the reaction. To our delight, the combination of $[Cp^*RhCl_2]_2$ (5 mol %) and

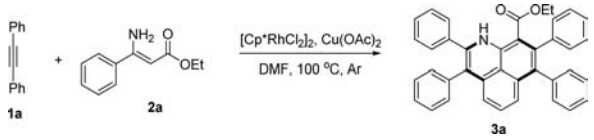
**Received:** September 1, 2015
**Published:** October 6, 2015




DOI: 10.1021/acs.orglett.5b02510
*Org. Lett.* 2015, 17, 5032−5035

$Cu(OAc)_2$ (2 equiv) in DMF at 100 °C for 24 h afforded **3a** in 73% yield (Table 1, entry 3). The structure of **3a** was

**Table 1. Optimization of the Reaction Conditions**[a]



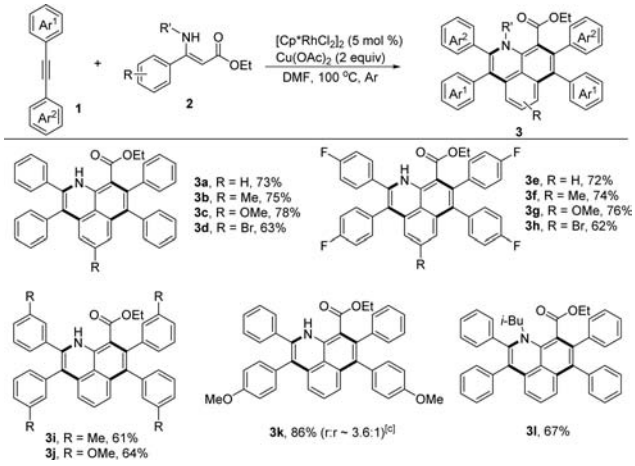

| entry | catalyst | oxidant | additive | solvent | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $[Cp^*RhCl_2]_2$ | | | DMF | |
| 2 | | $Cu(OAc)_2$ | | DMF | |
| **3** | **$[Cp^*RhCl_2]_2$** | **$Cu(OAc)_2$** | | **DMF** | **73** |
| 4 | $Pd(dppf)Cl_2$ | $Cu(OAc)_2$ | | DMF | |
| 5 | $[RhCl(COD)]_2$ | $Cu(OAc)_2$ | | DMF | |
| 6 | $[Cp^*RhCl_2]_2$ | AgOAc | | DMF | <10 |
| 7 | $[Cp^*RhCl_2]_2$ | $Ag_2CO_3$ | | DMF | <10 |
| 8[c] | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | CsOAc | DMF | |
| 9[d] | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | $AgSbF_6$ | DMF | 57 |
| 10 | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | DMSO | |
| 11 | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | MeCN | <10 |
| 12 | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | DCE | 61 |
| 13 | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | toluene | 46 |
| 14 | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | dioxane | 20 |
| 15[e] | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | DMF | 48 |
| 16[f] | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | DMF | 30 |
| 17[g] | $[Cp^*RhCl_2]_2$ | $Cu(OAc)_2$ | | DMF | 74 |

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.1 mmol), catalyst (5 mol %), oxidant (0.2 mmol), solvent (2.0 mL), 100 °C, 24 h under argon. [b]Isolated yield. [c]CsOAc (0.1 mmol). [d]$AgSbF_6$ (10 mol %). [e]1 mol % of $[Cp^*RhCl_2]_2$ was used, 48 h. [f]0.1 mmol of $Cu(OAc)_2$ was used, 48 h. [g]0.4 mmol of $Cu(OAc)_2$ was used.

confirmed by NMR spectroscopy and its high-resolution mass spectrum, which had been further proved by X-ray analysis.[12] In the absence of an oxidant or rhodium catalyst, the reaction did not occur (entries 1 and 2). In addition, the use of $Pd(dppf)Cl_2$ or $[RhCl(cod)]_2$ did not promote this transformation (entries 4 and 5). Other oxidants, such as AgOAc and $Ag_2CO_3$, resulted in low conversion (entries 6 and 7). The effect of additive was also investigated. The presence of a weak base such as CsOAc totally deterred the reaction (entry 8). The addition of $AgSbF_6$ was also detrimental and led to moderate yield (entry 9). Solvent screening disclosed that 1,2-dichloroethane (DCE) and toluene were also effective but gave **3a** in moderate yields (entries 12 and 13). In contrast, the use of dimethyl sulfoxide (DMSO), acetonitrile (MeCN), and dioxane gave low yields (entries 10, 11, and 14). Moreover, low catalyst loading also resulted in significantly lower yield of **3a** (entry 15). Furthermore, reducing the amount of $Cu(OAc)_2$ to 1 equiv also led to low yield of **3a** (entry 16). In contrast, 4 equiv of $Cu(OAc)_2$ gave a yield to that of entry 3 (entry 17).

Under the optimal reaction conditions (Table 1, entry 3), the substrate scope of internal alkynes and *β*-enamino esters has been further investigated (Scheme 2). The reaction of 1,2-diphenylethyne **1a** with *para*-substituted aryl *β*-enamino esters gave the corresponding products in acceptable yields (**3b**−**d**). The reaction of 1,2-bis(4-fluorophenyl)ethyne with **2a** or *para*-substituted aryl *β*-enamino esters also provided the desired products in moderate yields (**3e**−**h**). 1,2-Di-3-methyl- or 3-methoxyphenyethyne were also tolerated in this reaction and gave the corresponding products in moderate yields (**3i** and

**Scheme 2. Scope of Rh-Catalyzed Tandem Oxidative Annulation of *β*-Enamino Esters with Alkynes**[a,b]

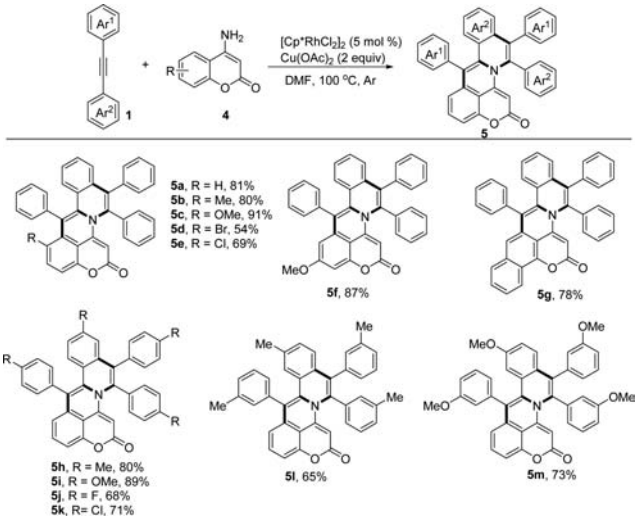



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.1 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2$ (0.2 mmol), DMF (2.0 mL), 100 °C, 24 h under argon. [b]Yields of isolated products. [c]A mixture of two regioisomers; r:r ~ 3.6:1 based on $^1H$ NMR analysis.

**3j**). Subsequently, the unsymmetrical alkyne was examined but afforded two isomers in a 3.6:1 ratio (**3k**). Notably, the *N*-isobutyl-substituted *β*-enamino ester also worked well and gave the desired polyheteroaromatic compound **3l** in 67% yield.

Next, to demonstrate the generality of this protocol, we turned to use 4-aminocoumarins as substrates, and the results are summarized in Scheme 3. Different from *β*-enamino esters,

**Scheme 3. Scope of Rh-Catalyzed Tandem Oxidative Annulation of 4-Aminocoumarins with Alkynes**[a,b]




[a]Reaction conditions: **1** (0.3 mmol), **4** (0.1 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2$ (0.2 mmol), DMF (2.0 mL), 100 °C, 24 h under argon. [b]Yield of isolated products.

the 4-aminocoumarins contain only one hydrogen atom at the *ortho* position of the phenyl moiety. Thus, the reaction pathway might be quite different. Indeed, under the same reaction conditions (Table 1, entry 3), the tandem multiple C−H activation and sequential annulation occurred smoothly to give the corresponding products in moderate to high yields. The structure of **5** was determined by NMR and HRMS analysis

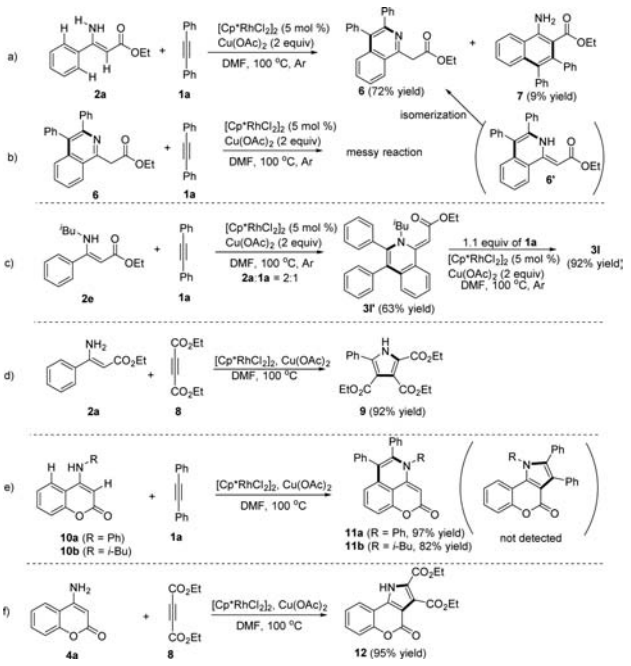


DOI: 10.1021/acs.orglett.5b02510
*Org. Lett.* 2015, 17, 5032−5035

and further confirmed by X-ray diffraction analysis of single crystals of **5a** and **5d**.[12] Next, the reaction of alkyne **1a** with various substituted 4-aminocoumarins was performed. The electron-rich 4-aminocoumarins gave the corresponding products in higher yield than the electron-deficient ones (**5b**, **5c**, **5f**, **5g** to **5d** and **5e**). Specially, compound **5c** was isolated in 91% yield. Next, the reactions between **4a** and various alkynes were carried out. As observed, the electron-rich alkynes gave the corresponding products in higher yields than the electron-deficient alkynes (**5h** and **5i** to **5j** and **5k**). The 3-methyl- or methoxy-substituted diphenylalkynes also proceeded well to give the desired products in moderate yields (**5l** and **5m**).

To better understand the reaction mechanism, control experiments were conducted (Scheme 4). Under standard

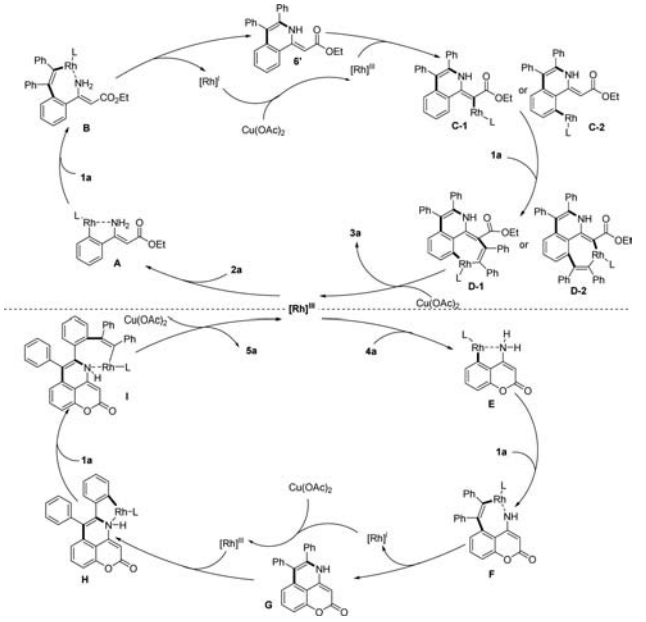
**Scheme 4. Control Experiments**




reaction conditions, the reaction of **2a** and **1a** in a 2:1 ratio led to the isolation of **6** (72% yield) and **7** (9% yield) in an 8:1 ratio (Scheme 4, a), which indicated that the oxidative cleavage of the C−H bond of the phenyl ring and N−H bond were preferred rather than the annulation of C($sp^2$)−H of the enamine moiety with the C−H bond of the phenyl ring. However, treatment of **6** with **1a** in the presence of $[Cp^*RhCl_2]_2$ (5 mol %) and $Cu(OAc)_2$ (2 equiv) led to a messy reaction (Scheme 4, b), which indicated the reaction probably involved the initial formation of **6′** followed by isomerization to more stable **6**. Furthermore, the reaction of 2 equiv of **2e** with 1 equiv of **1a** provided **3l′** as the major isomer, which can be further converted to **3l** under standard conditions. Next, when alkyne **8** was used, the pyrrole **9** was obtained in 92% yield (Scheme 4, d).[12] Next, the reaction of N-substituted 4-aminocoumarins **10a** and **10b** with **1a** were performed (Scheme 4, e). The oxidative annulation of N−H bond with C−H bond of phenyl ring occurred and gave the corresponding products **11a** and **11b** in 97% and 82% yield, respectively, whereas the fused pyrroles were not detected, which is quite different from the palladium-catalyzed procedure.[13] However, the reaction of **4a** with **8** led to the formation of fused pyrrole **12** in 95% yield (Scheme 4, f).

On the basis of the above results, plausible reaction mechanisms are proposed (Scheme 5). For the reaction of **1a**

**Scheme 5. Proposed Reaction Mechanisms**




with **2a**, coordination of the enamine N atom of **2a** to $Rh^{III}$ followed by *ortho* C−H activation generates rhodacycle **A**. Next, coordinative insertion of **1a** into the Rh−C bond leads to seven-membered rhodacycle **B**. Reductive elimination of **B** provides intermediate **6′** and the $Rh^{I}$ species, which has been reoxidized to the $Rh^{III}$ species. Further C−H activation of **6′** would likely give rise to Rh−C intermediate **C-1** or **C-2**.[7] Insertion of another molecule of **1a** into the Rh−C bond provides seven-membered rhodacycle **D-1** or **D-2**, which subsequently undergoes reductive elimination to afford **3a** as the final product and regenerate active $Rh^{III}$ species by $Cu(OAc)_2$.[7] Similarly, coordination of the aminocoumarin (**4a**) nitrogen atom to $Rh^{III}$ followed by C−H activation of the phenyl ring affords five-membered rhodacycle **E**, which undergoes alkyne insertion into the Rh−C bond to generate rhodacycle **F**. Reductive elimination of **F** then provides intermediate **G**. Next, this intermediate would undergo another C−H and N−H cleavage followed by alkyne insertion and reductive elimination to afford final product **5a**.

The solubility of larger polyheteroaromatic compounds is often problematic. However, compounds **3** and **5** have very good solubility in dichloromethane and chloroform at ambient temperature (>$10^{-3}$ M). To further understand the physical properties of these polyheteroaromatic compounds, we performed the measurement of absorption and emission spectra of **3a**, **3c**, **3d**, **3i**, **5a**, **5c**, **5k**, and **5i** in dichloromethane (Figure 1). The fluorescence spectra of **3a** and **3i** show emission maxima at 450−470 nm with broad bandwidths and weak intensities (see the Supporting Information).

In summary, we have demonstrated the rhodium-catalyzed multiple C−H bond activation of *β*-enamino esters and 4-aminocoumarins and tandem oxidative annulation with internal alkynes to afford polycyclic heteroaromatic compounds in moderate to high yields. Plausible reaction mechanisms for the oxidative tandem annulation have been proposed. We



DOI: 10.1021/acs.orglett.5b02510
*Org. Lett.* 2015, 17, 5032−5035

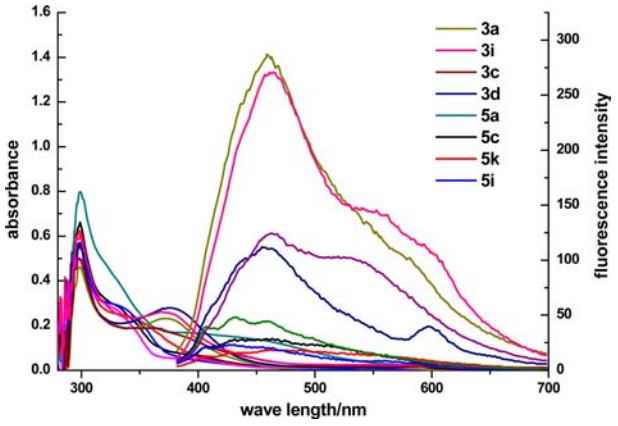



**Figure 1.** Absorption and Fluorescence.

anticipate that this protocol will facilitate the discovery of novel optoelectronic conjugated materials.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02510.

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

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: jtsun08@gmail.com, jtsun@cczu.edu.cn.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the NSF of China (No. 21172023), a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, and Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110) for their financial support.

## ■ REFERENCES

(1) For selected reviews, see: (a) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891. (b) Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028. (c) Anthony, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 452. (d) Allard, S.; Forster, M.; Souharce, B.; Thiem, H.; Scherf, U. *Angew. Chem., Int. Ed.* **2008**, *47*, 4070. (e) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208.

(2) For selected examples, see: (a) Tong, L.; Ho, D. M.; Vogelaar, N. J.; Schutt, C. E.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 7291. (b) Müller, M.; Kübel, C.; Müllenm, K. *Chem. - Eur. J.* **1998**, *4*, 2099. (c) Lu, J.; Zhang, J.; Shen, X.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 8035.

(3) For selected reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Wencel-Delord, J.; Drçge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Satoh, T.; Miua, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (d) Song, G. Y.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (e) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (f) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (g) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Tetrahedron Lett.* **2014**, *55*, 5705. (h) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155. (i) Mo, J.; Wang, L.; Liu, Y.; Cui, X. *Synthesis* **2015**, *47*, 439. (j) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107.

(4) For reviews, see: (a) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 66. For selected examples, see: (b) Huang, H.; Dong, L.; Han, B.; Peng, C.; Chen, Y. *Chem. - Eur. J.* **2012**, *18*, 8896. (c) Pham, M. V.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 3484. (d) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950. (e) Zhang, X.-S.; Zhang, Y.-F.; Li, Z.-W.; Luo, F.-X.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5478. (f) Wu, J.; Xu, W.; Yu, Z.-X.; Wang, J. *J. Am. Chem. Soc.* **2015**, *137*, 9489. (g) Davies, D. L.; Ellul, C. E.; Macgregor, S. A.; McMullin, C. L.; Singh, K. *J. Am. Chem. Soc.* **2015**, *137*, 9659.

(5) (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 2867. (c) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744.

(6) (a) Song, G.; Gong, X.; Li, X. *J. Org. Chem.* **2011**, *76*, 7583. (b) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487.

(7) Tan, X.; Liu, B.; Li, X.; Li, B.; Xu, S.; Song, H.; Wang, B. *J. Am. Chem. Soc.* **2012**, *134*, 16163.

(8) Yu, D.-G.; de Azambuja, F.; Gensch, T.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 9650.

(9) Jayakumar, J.; Parthasarathy, K.; Chen, Y.-H.; Lee, T.-H.; Chuang, S.-C.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9889.

(10) For selected examples, see: (a) Rakshit, S.; Patureau, F.-W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (b) Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7790. (c) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (d) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (e) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2012**, *48*, 8105. (f) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2013**, *15*, 136. (g) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176. (h) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 608. (i) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. - Eur. J.* **2014**, *20*, 1839. (j) Ge, Q.; Li, B.; Song, H.; Wang, B. *Org. Biomol. Chem.* **2015**, *13*, 7695.

(11) (a) Ke, J.; He, C.; Liu, H.; Li, M.; Lei, A. *Chem. Commun.* **2013**, *49*, 7549. (b) Gao, P.; Liu, J.; Wei, Y. *Org. Lett.* **2013**, *15*, 2872. (c) Senadi, G. C.; Hu, W.-P.; Garkhedkar, A. M.; Boominathan, S. S. K.; Wang, J.-J. *Chem. Commun.* **2015**, *51*, 13795.

(12) See the Supporting Information for the X-ray structure. CCDC 1418480 (**3a**), 1418481 (**5a**), 1418482 (**5d**), and 1418483 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) Peng, S.; Wang, L.; Huang, J.; Sun, S.; Guo, H.; Wang, J. *Adv. Synth. Catal.* **2013**, *355*, 2550.



DOI: 10.1021/acs.orglett.5b02510
*Org. Lett.* 2015, 17, 5032−5035