Organic LETTERS
Letter
pubs.acs.org/OrgLett

Controllable *O*-Nucleometalation Cyclization Strategy: Access to Divergent Ring-Functionalized Molecules

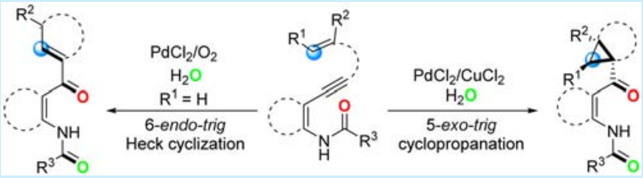
Jia Zheng,[†] Zun Li,[†] Wanqing Wu,*[,†] and Huanfeng Jiang*[,†,‡]

[†]Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

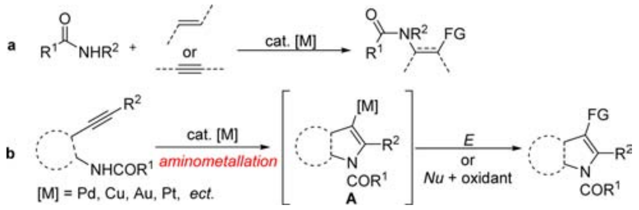
Supporting Information

ABSTRACT: The vinyl moiety-assisted selective *O*-nucleopalladation is reported, which offers rapid constructions of cycloolefins and cyclopropanes via oxidant-induced cyclization of enynes. O_2 resulted in the unexpected 6-*endo*-Heck cyclization, while $CuCl_2$ led to a 5-*exo-trig* pathway and synergetic S_N2-type C−C bond formation. Amide works as an *O*-transferred nucleophilic group to activate the alkyne moiety, which induced divergent annulation processes. Moreover, the regenerated amides could be used for further modifications.



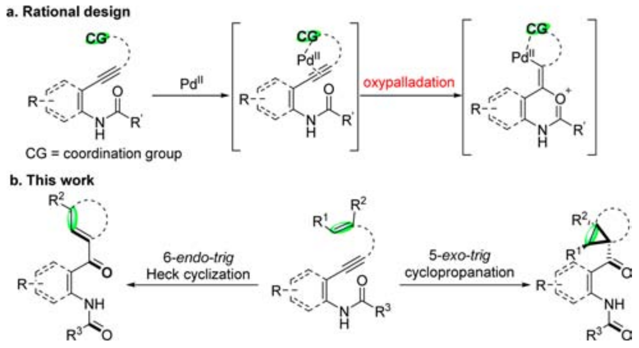
Transition-metal-catalyzed transformation has emerged as a powerful tool for versatile organic synthesis, which allows the assembly of multiple C−C and C−heteroatom bonds in a straightforward manner.[1,2] The nucleometalation of C−C multiple bonds occupies a significant place in these areas.[2] When two different nucleophiles coexist in one system, the stronger one or intramolecular one is usually predominant in such a process.[3] Obviously, it is challenging to enhance the selectivity of nucleometalation of the weaker one, which is also significant for developing novel routes. The amide moiety, containing two nucleophilic atoms, is used widely for nucleometalation.[2b,c] Typically, the amide skeleton always acts as an *N*-nucleophile to attack the transition-metal-activated C−C multiple bonds, which is the fundamental and initial step for transition-metal-catalyzed inter- or intramolecular hydroamidations and related cascade reactions (Scheme 1a).[4] For example, alkynamide, a useful building block, has been extensively used to construct *N*-containing heterocycles via intramolecular aminometalation to afford intermediate A, which is captured by electrophiles or oxidative coupling with nucleophiles (Scheme 1b).[5]

Scheme 1. Cyclizations via *N*-Nucleometalation of Amide



In comparison, the amide moiety acting as an *O*-nucleophile in organic transformations is relatively rare.[6] As demonstrated by our previous research, a weak coordination group in appropriately remote sites offers a relatively stable transition state due to the chelation.[7] We envisioned that such a coordination effect could induce the nucleometalation from the nearer nucleophile (Scheme 2a). Based on this strategy, we herein disclose an amide-assisted oxidant-controlled cascade reaction via ligand-induced *O*-nucleophilic cyclization. By utilizing the vinyl moiety, which was reported as a ligand with π-bond coordination,[7b,8] selective nucleopalladation was achieved. The conditions could be tuned to switch from a Heck 6-*endo-trig* annulation to a 5-*exo-trig* cyclopropanation (Scheme 2b).

Scheme 2. Cyclizations via Selective *O*-Nucleometalation

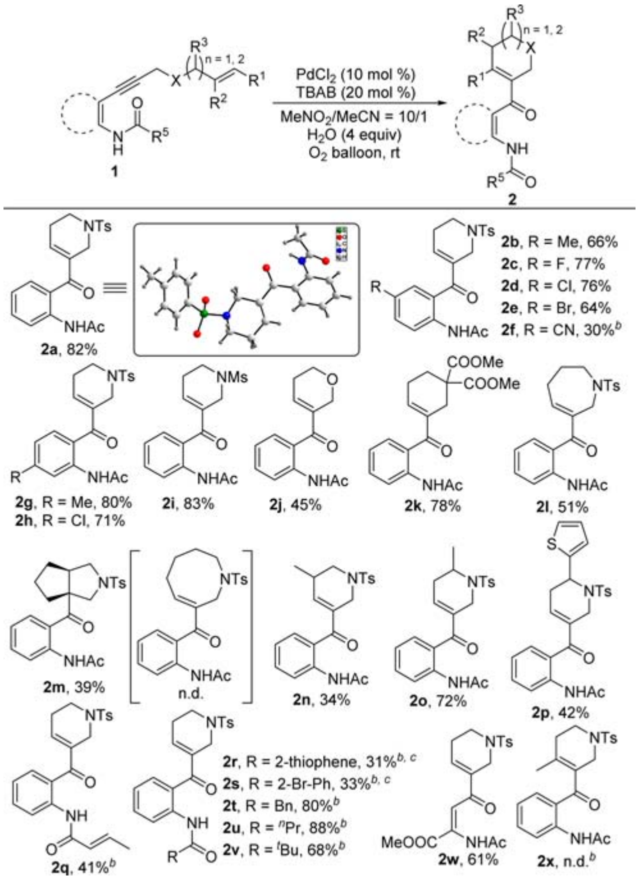


After extensive screening of different parameters, the optimal reaction conditions A and B were determined (see the Supporting Information for details). The structures of **2a** and **3h** were clearly confirmed by X-ray crystallography. The reaction scope for 6-*endo*-Heck coupling was first examined (Scheme 3). Substrates bearing both electron-donating and electron-withdrawing groups on the phenyl ring efficiently

Received: September 9, 2016
Published: November 30, 2016

DOI: 10.1021/acs.orglett.6b02710
Org. Lett. 2016, 18, 6232−6235

Scheme 3. Scope of 6-*endo*-Heck Cyclization[a]

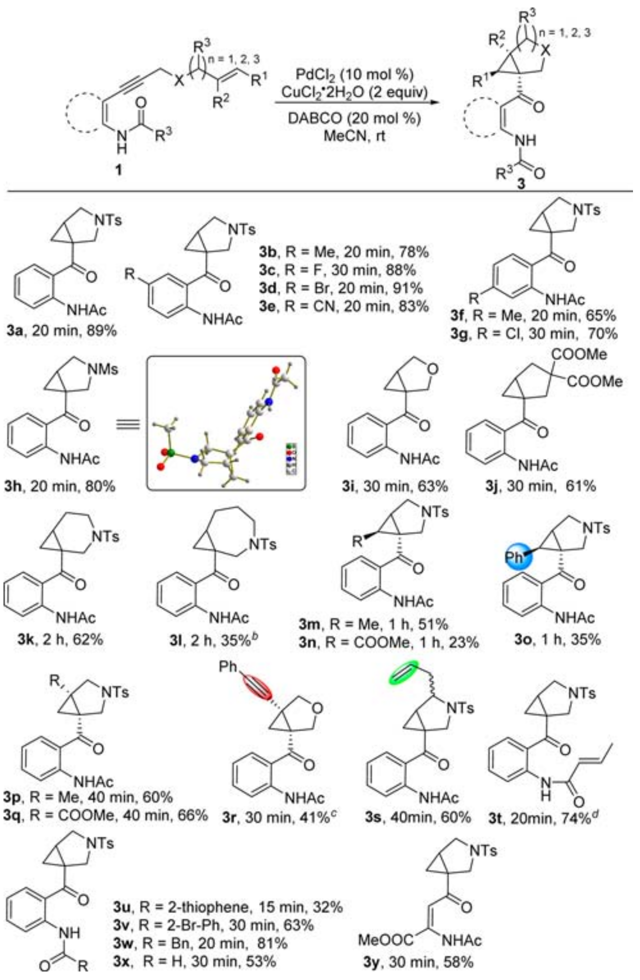


[a]Reaction conditions A: all reactions were performed with **1** (0.10 mmol), $PdCl_2$ (10 mol %), TBAB (20 mol %), and H_2O (4 equiv) in 1.0 mL of $MeNO_2/MeCN$ (10/1) at room temperature with an O_2 balloon for 12 h. Isolated yield. [b]For 15 h. [c]At 100 °C.

afforded the corresponding products **2b–h** in good to excellent yields. Both 4- and 5-substituted methyl and halogen groups on the phenyl ring did not significantly affect the reaction (**2b–e,g,h**), and the corresponding products could be obtained in 64–80% yields. However, the cyano group led to a marked drop of yield (**2f**). To construct more kinds of cycloolefins, 1,*n*-enynes with different atom bridges were tested (**2i–k**). When Ts-protected substrate was switched to the Ms-protected one, **2i** was obtained in 83% yield. The transformations of enynes with O and C bridges proceeded smoothly to give **2j** and **2k** in 45% and 78% yields, respectively. Seven-membered-ring product **2l** could also be obtained in moderate yields. Interestingly, continuing to extend the chain length of enynes offered octahydrocyclopenta[*c*]pyrrole **2m** (confirmed by X-ray crystallography) without the expected eight-membered-ring product. Substitution on the olefin unit exhibited a negative effect on this transformation, which only gave **2n** in 34% yield. As expected, the branched-substituted enynes underwent 6-*endo* annulation smoothly to afford **2o** and **2p** in considerable yields. Compared with acrylamide and aromatic amide (**2q–s**), the substrates with aliphatic amide groups resulted in much higher yields of the 6-*endo*-Heck products (**2t–v**). The reaction also proceeded smoothly with an enamide-containing enyne to give the corresponding cycloalkane **2w** in 61% yield. However, the substrate bearing methyl group on the terminal position of the alkene failed to afford the cyclization product **2x** even at higher temperature.

Then, the scope of Pd-catalyzed 5-*exo-trig* cyclopropanation was investigated with a variety of *N*-acetamide enynes **1** (Scheme 4). Typical functional groups including halogen, cyano, and methyl were all tolerated in this reaction. The transformations of 4-substituted substrates (**3b–e**) gave relatively higher yields than those of the 5-substituted ones (**3f,g**). *N*-Ms-containing substrate could be transferred to **3h** in 80% yield. Gratifyingly, the products with 3-oxabicyclo[3.1.0]-hexane and bicyclo[3.1.0]hexane cores could be obtained in good yields as well (**3i,j**). Similarly, extending the chain length of enynes appeared to lower the reactivity since the intramolecular coordination of alkene would decrease (**3k,l**). Substituents on the alkene terminal position have obvious effects on this transformation. A moderate yield of **3m** was obtained when R^1 was methyl. For the component with methyl acrylate, only a rather low yield of **3n** was observed. It is noteworthy that even **3o** was successfully obtained in 35% yield. According to previous reports, such a substrate could not be converted into bicyclic cyclopropane.[9] In addition, the reactions proceeded well when R^2 equaled methyl and ester

Scheme 4. Scope of 5-*exo-trig* Cyclopropanation[a]

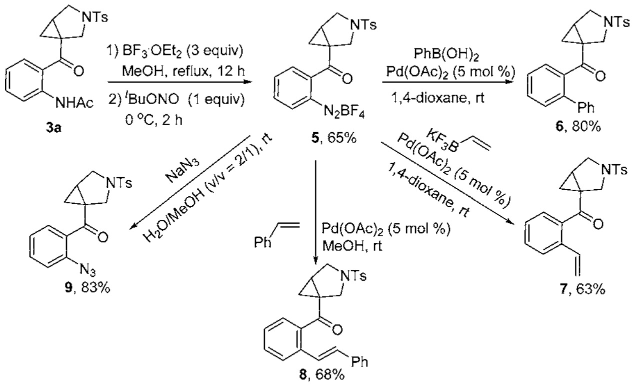


[a]Reaction conditions B: all reactions were performed with **1** (0.10 mmol), $PdCl_2$ (10 mol %), $CuCl_2{\cdot}2H_2O$ (2 equiv), and DABCO (20 mol %) in 1.0 mL MeCN at room temperature. Isolated yield. [b]At 60 °C. [c]50 mol % DABCO was used. [d]Without DABCO.

groups, furnishing the desired products in good yields (**3p,q**). Furthermore, the introduction and retention of alkynyl group is a challenge under the intermolecular nucleopalladation conditions. Pleasingly, another alkyne group was compatible in our system to obtain the alkynyl-substituted oxabicyclo[3.1.0]hexane **3r** in 41% yield. When the substrate bore both allyl and homoallyl groups, there was a selective insertion of allyl group with retention of the homoallyl group. No second insertion of alkene was observed,[10] and only cyclopropane **3s** was provided in 60% yield regioselectively, which indicates that the S_N2 type C−C formation proceeded much faster than the intramolecular insertion of alkene in this catalytic system. For different amide groups, acrylamide groups were also tolerated, which afforded the product **3t** in 74% yield. Substrates with a 2-thiophene group only gave the desired product **3u** in 32% yield due to its ability to coordinate to copper. In addition, all 2-bromobenzamide, phenylacetamide, and formamide groups worked well under the optimal conditions, leading to the formation of cyclopropanes in moderate to good yields (**3v−x**). To our delight, when the phenyl core was replaced with an alkenyl moiety, this protocol was also applicable to give product **3y** in 58% yield.

Subsequently, the newly formed product **3a** was employed for the derivatizations to further explore the synthetic versatility of this strategy (Scheme 5). The regenerated amide group was easily turned into diazonium salt via simple deacetylation−diazotation,[11] suggesting that the aromatic C-2 position could be directly functionalized. As shown in Scheme 5, arylation of **5** was achieved to give product **6** in 80% yield. The Suzuki coupling reaction between **5** and potassium vinyltrifluoroborate provided the desired alkene derivative **7** in good yield. The Heck-type reaction also proceeded smoothly to afford alkenylated compound **8** in 68% yield under mild conditions. Moreover, the azido moiety could be easily introduced to the aromatic ring, affording **9** in 83% yield.

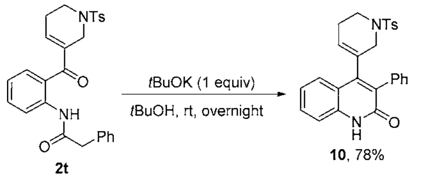
Scheme 5. Synthetic Utility of This Transformation



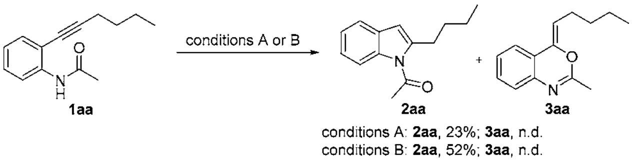
Furthermore, the amide skeleton could also convert into *N*-containing heterocycles effectively. The functionalized quinolinone **10** was obtained in 78% yield from **2t** under the treatment of 1 equiv of ^{t}BuOK in ^{t}BuOH (Scheme 6).

To demonstrate our assumption of ligand-assisted *oxy*-palladation, the substrate without alkene moiety (**1aa**) was employed. As shown in Scheme 7, either conditions A or B afforded the *N*-nucleophilic product **2aa** without the *O*-nucleophilic product **3aa**, which indicates the selective nucleopalladation process was induced by the intramolecular weak coordination.

Scheme 6. Synthesis of Quinolinone from Product 2t

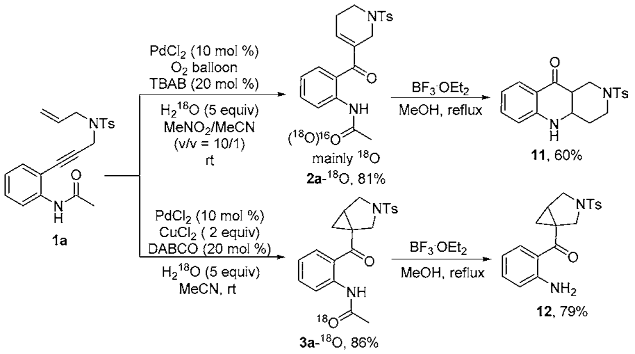


Scheme 7. Effect of the Intramolecular Alkene Moiety



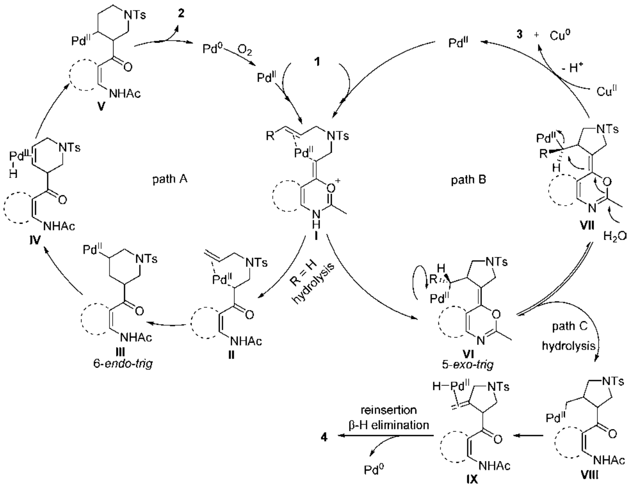
To gain more insight into the mechanism, the oxygen source was investigated by ^{18}O-labeled experiments to confirm that this transformation grabbed the oxygen atom from water. Subsequently, the deprotection reactions of both ^{18}O-labeled products **2a** and **3a** were performed, and the results suggested that the amide oxygen atom transferred to form ketone and the oxygen atom of regenerated amide came from water (Scheme 8). Moreover, Michael addition would occur after deacylation of **2a**, which provided compound **11** in 60% yield.

Scheme 8. Mechanistic Studies



On the basis of the above results and previous reports,[9,10a] plausible mechanisms for the reaction are proposed (Scheme 9). The catalytic cycle would start with the activation of the alkyne by amide to produce vinyl-Pd^{II} species **I**, which undergoes *trans*-oxypalladation rather than halopalladation. For path A, the transformation proceeds slower with the weak oxidant O_2, which makes the intermediate **I** inclined to be hydrated to afford the intermediate **II**. Subsequently, intermediate **II** converts to Pd^{II} species **III** and then to a Pd−alkene complex **IV** through a 6-*endo* Heck process. Sequential reinsertion/β-H elimination offers migration of the olefin in **V** via intermediate **VI**, which finally provides cyclene **2**. In contrast to path A, with $CuCl_2$, the fast subsequent intramolecular *cis*-insertion of alkene affords alkyl-Pd^{II} species **VI**, followed by *σ*′-bond rotation to give **VII**. As an excess of halide ions exists, there should be competition between C−C and C−halo bond formations.[10a] However, with the aid of water, S_N2-type attack at the Pd^{II}-bound carbon by the vinyl acetate proceeds more easily than halide ion. Mediated by Cu^{II}, the oxidative cleavage of C−Pd^{II} bond affords cyclopropane formation as well as regeneration of amide group to give the

Scheme 9. Proposed Mechanisms



product **3**. 5-*exo*-Heck product was observed as byproduct which should be formed via path C: hydrolysis of alkyl-Pd^{II} species **VI** generates intermediate **VIII**. Then β-hydride elimination and migration of the olefin in **IX** lead to the formation of **4**. Regeneration of amide in path B undergoes a synergetic S$_N$2-type process, which is different from hydrolysis in paths A and C.

In summary, divergent cyclizations of enynes via a ligand-assisted selective *O*-nucleopalladation strategy have been developed. This novel approach enabled rapid assembly of various highly functionalized cyclene and cyclopropane skeletons, and shows high regioselectivity, excellent functional group compatibility, and atom economy. To our knowledge, this is the first example of Pd-catalyzed controllable regioselective 6-*endo*-Heck annulation and 5-*exo-trig* cyclopropanation of 1,*n*-enynes as well as the first report of copper(II) as an oxidant for the carbon nucleophile attacked oxidant cleavage of the alkyl C−Pd bond. The amide moiety is supposed to work not only as an *O*-transferred nucleophilic group but also as the transformable group to achieve further modifications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02710.

Typical experimental procedure and characterization data for all products (PDF)
Crystallographic data for **2a** (CIF)
Crystallographic data for **2m** (CIF)
Crystallographic data for **3h** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cewuwq@scut.edu.cn.
*E-mail: jianghf@scut.edu.cn.

ORCID

Huanfeng Jiang: 0000-0002-4355-0294

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Key Research and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21472051, 21420102003, and 21490572), and Pearl River S&T Nova Program of Guangzhou (201610010160) for financial support.

■ REFERENCES

(1) (a) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (b) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (c) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783. (d) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

(2) (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (c) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657.

(3) (a) Beccalli, E. M.; Borsini, E.; Broggini, G.; Palmisano, G.; Sottocornola, S. *J. Org. Chem.* **2008**, *73*, 4746. (b) Wu, W.; Gao, Y.; Jiang, H.; Huang, Y. *J. Org. Chem.* **2013**, *78*, 4580. (c) van Esseveldt, B. C. J.; van Delft, F. L.; de Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* **2003**, *5*, 1717. (d) Huang, H.; He, G.; Zhu, G.; Zhu, X.; Qiu, S.; Zhu, H. *J. Org. Chem.* **2015**, *80*, 3480. (e) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5170.

(4) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596.

(5) (a) Tang, S.; Xie, Y.; Li, J.; Wang, N. *Synthesis* **2007**, *2007*, 1841. (b) Ling, F.; Li, Z.; Zheng, C.; Liu, X.; Ma, C. *J. Am. Chem. Soc.* **2014**, *136*, 10914. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Perboni, A.; Sferrazza, A.; Stabile, P. *Org. Lett.* **2010**, *12*, 3279. (d) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412. (e) Dai, W.; Guo, D.; Sun, L.; Huang, X. *Org. Lett.* **2003**, *5*, 2919. (f) Zhang, L.; Ye, D.; Zhou, Y.; Liu, G.; Feng, E.; Jiang, H.; Liu, H. *J. Org. Chem.* **2010**, *75*, 3671. (g) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7168. (h) Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2007**, *2007*, 1775. (i) Allegretti, P. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 17266.

(6) (a) Rao, W.; Yin, X.; Shi, B. *Org. Lett.* **2015**, *17*, 3758. (b) Momiyama, N.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 2230. (c) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12992. (d) Saito, T.; Ogawa, S.; Takei, N.; Kutsumura, N.; Otani, T. *Org. Lett.* **2011**, *13*, 1098.

(7) (a) Huang, L.; Wang, Q.; Wu, W.; Jiang, H. *ChemCatChem* **2014**, *6*, 561. (b) Huang, L.; Wang, Q.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2014**, *356*, 1949. (c) Huang, L.; Wang, Q.; Wu, W.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 7734.

(8) (a) Gandeepan, P.; Cheng, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 5738. (b) Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 2084. (c) Tobisu, M.; Hyodo, I.; Onoe, M.; Chatani, N. *Chem. Commun.* **2008**, *44*, 6013.

(9) (a) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906. (b) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (c) Liu, B.; Song, R.-J.; Ouyang, X.-H.; Li, Y.; Hu, M.; Li, J.-H. *Chem. Commun.* **2015**, *51*, 12819.

(10) (a) Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160. (b) Lu, X. *Top. Catal.* **2005**, *35*, 73. (c) Lu, X.; Wang, Z. *Polyhedron* **2000**, *19*, 577.

(11) Schmidt, B.; Berger, R. *Adv. Synth. Catal.* **2013**, *355*, 463.