Organic LETTERS

Letter

pubs.acs.org/OrgLett

Nickel-Catalyzed Addition-Type Alkenylation of Unactivated, Aliphatic C−H Bonds with Alkynes: A Concise Route to Polysubstituted γ-Butyrolactones

Mingliang Li, Yudong Yang, Danni Zhou, Danyang Wan, and Jingsong You*

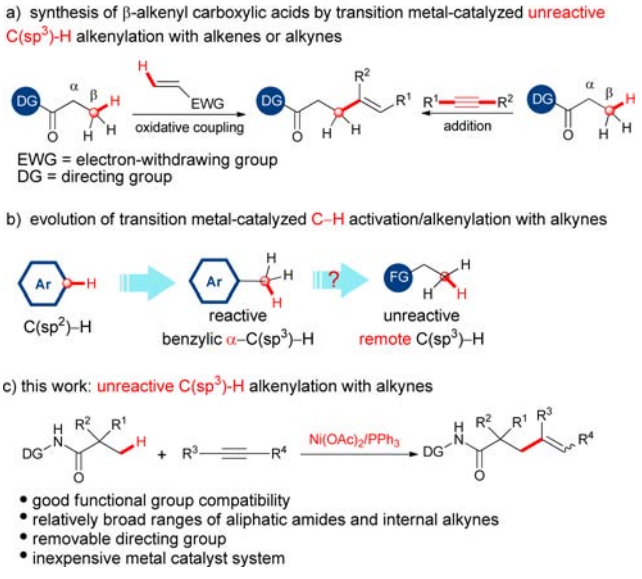
Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, China

Supporting Information

ABSTRACT: Through the nickel-catalyzed chelation-assisted C−H bond activation strategy, the addition-type alkenylation of unreactive β-C(sp^3)−H bonds of aliphatic amides with internal alkynes is developed for the first time to produce γ,δ-unsaturated carboxylic amide derivatives. The resulting alkenylated products can further be transformed into polysubstituted γ-butyrolactones with pyridinium chlorochromate (PCC).

Recently, transition-metal-catalyzed C−H bond activation has emerged as a highly effective strategy for the construction of synthetically enabling synthons and richly functionalized molecules.[1−3] The synthesis of γ,δ-unsaturated aliphatic carboxylic acids has been attracting much attention due to their versatility in organic transformations.[4] Both transition-metal-catalyzed β-C(sp^3)−H addition of aliphatic acid derivatives with alkynes and olefination with alkenes would be ideal methods to enrich the diversity of structurally limited β-alkenyl carboxylic acid derivatives (Scheme 1a). In addition to step economy and simplicity, the addition-type alkenylation is also a highly atom-economical process because every atom of two substrates remains in the targeted molecule. Over the past few years, it was determined that the unactivated C(sp^3)−H bonds of aliphatic amides can efficiently couple with electron-deficient alkenes through the palladium-catalyzed chelation-assisted C−H activation, albeit the resulting β- or γ-alkenyl carboxylic amides inevitably undergo tandem intramolecular hetero-Michael addition to result in lactams.[5] In contrast, the addition of C(sp^3)−H bonds of aliphatic acid derivatives with alkynes is still underrepresented. This is not surprising considering the following possible reasons. First, an alkyne can compete with a carboxylic acid derivative for access to the coordination sites at the metal center, which disturbs the cleavage of an unreactive C(sp^3)−H bond.[6] Second, the relatively strong π-coordination interaction of alkyne to the metal center may result in a higher barrier to migratory insertion of alkyne into cyclometalated species.[7] Although the addition of (hetero)aryl C(sp^2)−H bonds with alkynes has been well explored in recent years,[8] expansion this chemistry to C(sp^3)−H sites is doubtless a conceptual and practical challenging task. To the best of our knowledge, there is only one example describing the rhodium-catalyzed alkenylation of C(sp^3)−H bonds with internal alkynes, but the transformation is limited to the reactive benzylic α-C(sp^3)−H bond of 8-methylquinoline.[9] The alkenylation of unreactive remote C(sp^3)−H bonds with alkynes still remains unsolved (Scheme 1b).

Scheme 1. Transition-Metal-Catalyzed Chelation-Assisted C(sp^3)−H Alkenylation



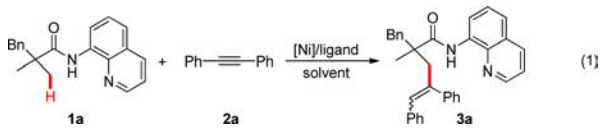
Nickel, an abundant and inexpensive transition metal, has shown potential in direct C−H bond functionalization.[10] Recent reports have demonstrated that nickel can efficiently catalyze the addition reactions of C(sp^2)−H bonds of electron-deficient heteroarenes and fluoroarenes with internal alkynes via a hydronickelation.[8c,11] In 2011, Chatani reported the Ni-catalyzed chelation-assisted oxidative cycloaddition of C(sp^2)−H bonds of aromatic amides with alkynes via the formation of a bicyclic nickelacyle intermediate.[12] Recently, the nickel-

Received: April 17, 2015
Published: April 30, 2015

DOI: 10.1021/acs.orglett.5b01128
Org. Lett. 2015, 17, 2546−2549

catalyzed direct functionalization of unactivated C(sp^3)−H bonds has also achieved initial progress, including the dehydrogenative [4 + 2] cyclization of formamides with alkynes, and the arylation, alkylation, and intramolecular amidation of aliphatic amides.[13] Inspired by the above works, we surmised that addition-type alkenylation of unactivated C(sp^3)−H bonds with internal alkynes could be feasible with the assistance of a suitable bidentate directing group to form a bicyclic nickelacyle species (Scheme 1c).

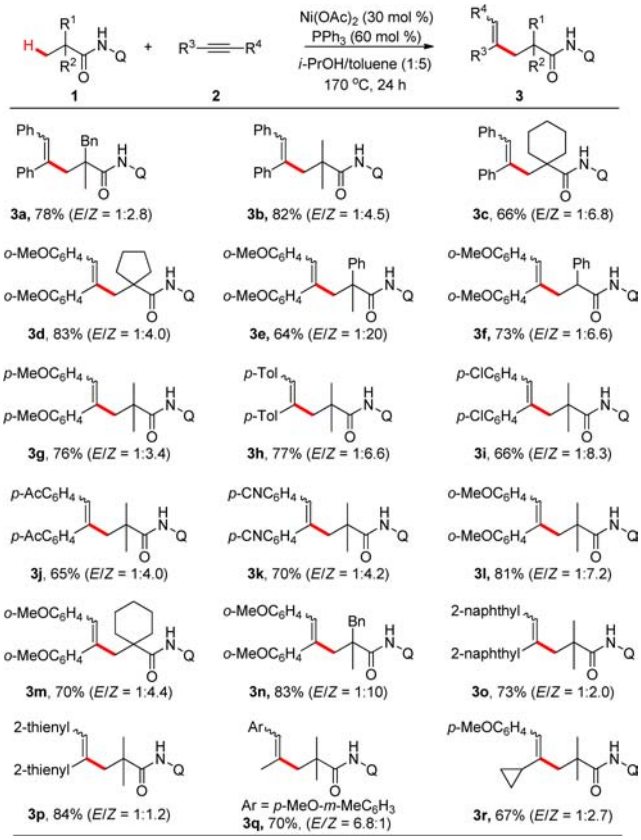
Considering that 8-aminoquinoline is a highly efficient bidentate directing group in transition-metal-catalyzed C−H bond activation,[10b,14] our study was initiated with the reaction of 2,2-dimethyl-3-phenyl-*N*-(quinolin-8-yl)propanamide **1a** and 1,2-diphenylethyne **2a** (eq 1). To our delight, the desired



product **3a** was obtained in 28% yield (E/Z = 1/2.8) in the presence of $Ni(cod)_2$ and PPh_3 in toluene (Table S1, entry 1). The yield was decreased to less than 10% in the absence of PPh_3 (Table S1, entry 6). Other phosphine ligands proved to be less efficient (Table S1, entries 10−13). The addition of *i*-PrOH as cosolvent could improve the yield to 54% when $Ni(OAc)_2$ was used instead of $Ni(cod)_2$ (Table S1, entry 21).[15] Other nickel(II) sources such as $Ni(acac)_2$ and $Ni(OTf)_2$ gave diminished yields, and no desired product was afforded when $NiCl_2$ and $Ni(dppe)Cl_2$ were used (Table S1, entries 16−19). Finally, the alkenylated product could be obtained in 78% yield in the presence of $Ni(OAc)_2$ (30 mol %) and PPh_3 (60 mol %) in a mixture of *i*-PrOH and toluene (1:5). Efforts to improve the yield proved fruitless by using other bidentate directing groups, such as pyridin-2-yl methanamine and 2-(methylthio)-aniline (Table S1, entries 25−26). With the optimized conditions in hand, we next screened the substrate scope (Scheme 2). A range of 2,2-disubstituted propanamides bearing linear or cyclic chains were transformed into the alkenylated products in moderate to high yields (**3a−d**). It is noteworthy that the alkenylation only occurred at the C(sp^3)−H bond and the C(sp^2)−H bond functionalization was not detected when 2-phenyl substituted amides were attempted (**3e** and **3f**). In addition to the methyl group adjacent to an α-quaternary carbon center, the methyl adjacent to an α-tertiary carbon center could also undergo the C(sp^3)−H bond alkenylation with an internal alkyne (**3f**). The reaction conditions exhibited good alkyne compatibility, and an E/Z value of up to 1:20 could be obtained (**3g−r**). The alkynes with both electron-donating and -withdrawing groups on the aromatic rings worked well, giving the corresponding products in moderate to high yields (**3g−n**). No obvious steric effect was found even with 1,2-di(naphthalen-2-yl)ethyne (**3o**). The internal alkyne with a heteroaromatic moiety could also furnish the corresponding product in a high yield (**3p**). The reactions with unsymmetrical alkynes delivered the desired products in good yields (**3q** and **3r**).

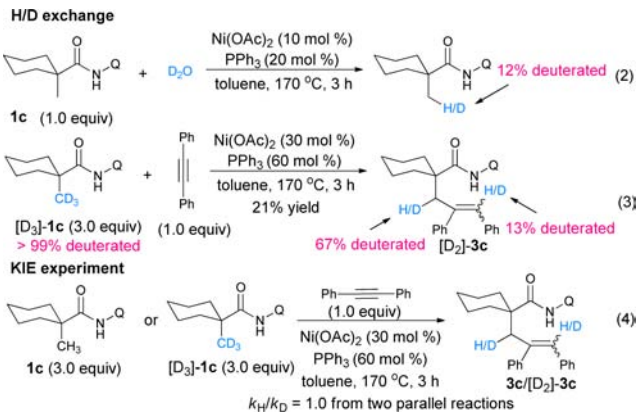
To gain insight into the reaction mechanism, H/D exchange reactions were carried out. When the reaction was performed with D_2O instead of an alkyne, 12% of the methyl hydrogen in **1c** was deuterated, thus indicating the C−H bond activation is reversible (Scheme 3, eq 2). When [D_3]-**1c** was subjected to the reaction conditions, 13% of the hydrogen on the resulting

Scheme 2. Nickel-Catalyzed C(sp^3)−H Alkenylation of Aliphatic Amides with Internal Alkynes[a,b,c]



[a]Reactions were carried out with $Ni(OAc)_2$ (30 mol %), PPh_3 (60 mol %), amide **1** (0.6 mmol), and internal alkyne **2** (0.2 mmol) in a mixture of *i*-PrOH (0.1 mL) and toluene (0.5 mL) at 170 °C for 24 h. [b]Isolated yields. [c]The ratio of E/Z was determined by ^1H NMR. Q = 8-quinolinyl.

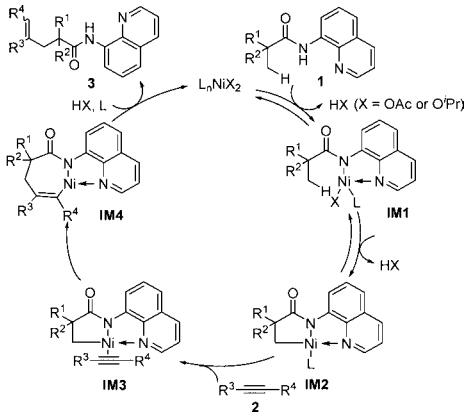
Scheme 3. Mechanistic Experiments



C═C bond was deuterated, which implied that the hydrogen source in protonolysis might come from the generated AcOH in the reaction system (eq 3). KIE (kinetic isotope effect) experiments were carried out with two independent reactions. The KIE value was found to be k_H/k_D = 1.0, indicating that the cleavage of the methyl C−H bond with a nickel species was not involved in the rate-determining step (eq 4). Based on the above results, a tentative mechanism of alkenylation was proposed in Scheme 4. Initially, a bidentate chelation process of

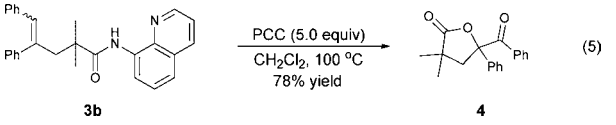
DOI: 10.1021/acs.orglett.5b01128
Org. Lett. 2015, 17, 2546−2549

Scheme 4. Plausible Mechanism of Alkenylation



amide **1** with a Ni(II) species forms complex **IM1**. The following C(sp^3)−H nickelation delivers the cyclometallic intermediate **IM2**, followed by a coordination of internal alkyne **2** to the nickel(II) center. The resulting intermediate **IM3** undergoes a migratory insertion of the alkyne to lead to a seven-member metallacycle **IM4**. The sterically congested structure of **IM3** is supposed to render the migratory insertion at higher temperature. After a protonation with AcOH (or *i*-PrOH if it exists), the product **3** is released, and the Ni(II) species is regenerated to accomplish a catalytic cycle.

The γ-butyrolactone framework is prevalent in naturally occurring products that often exhibit a diverse array of biological activities.[16] Despite significant progress made in the synthesis of such structures,[17] exploring an effective and concise synthetic alternative to construct polysubstituted γ-butyrolactones from the abundant, yet less functionalized molecules is still very attractive and desirable. Based on the alkenylation of the C(sp^3)−H bond of aliphatic amides, our effort was next devoted to the synthesis of polysubstituted γ-butyrolactones. A logical synthetic route to γ-butyrolactones should involve removal of the 8-aminoquinoline directing group/intramolecular annulation sequence. This tedious route prompted us to explore a more efficient and concise method. Inspired by PCC-promoted intramolecular alkoxyhydroxylation of alkenes to form cyclic ethers,[18] we deemed that a similar oxidative cyclization could occur with imidic acids, which are tautomerized from the corresponding amides, to furnish the lactone structure. Gratifyingly, when amide **3b** reacted with PCC in CH_2Cl_2 at 100 °C, γ-butyrolactone **4** was obtained in 78% yield in concomitance with the removal of the 8-aminoquinoline moiety (eq 5). No desired product was

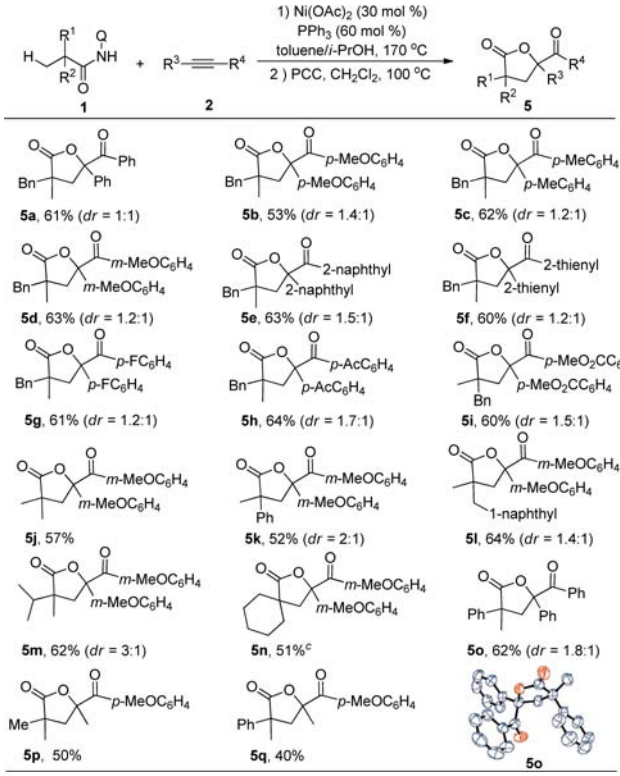


(5)

afforded when other oxidants, including ceric ammonium nitrate (CAN), 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ), phenyliodine diacetate (PIDA), and Dess-Martin periodinane, were employed (Table S2, entries 1−4).

After the feasibility of the synthetic approach to γ-butyrolactones was evaluated, we investigated the substrate scope in the sequential C(sp^3)−H alkenylation/lactonization reactions (Scheme 5). It was found that electron-rich, -neutral, and -poor symmetrical diarylacetylenes all proceeded well to

Scheme 5. Construction of γ-Butyrolactones[a,b]



[a]Reactions conditions: (1) $Ni(OAc)_2$ (30 mol %), PPh_3 (60 mol %), amide **1** (0.6 mmol, 1 M), internal alkyne **2** (0.2 mmol), *i*-PrOH/toluene (1:5), 170 °C, 24 h. (2) PCC (5.0 equiv), CH_2Cl_2, 100 °C, 48 h. [b]Two-step overall yields. The *dr* value was determined by ^{1}H NMR. [c]48 h were required in the alkenylation.

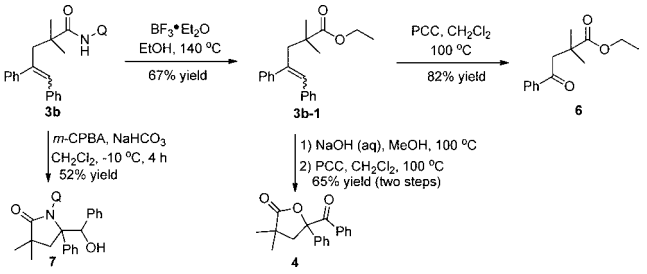
provide the desired products in satisfactory yields (**5a**−**o**). The structure of **5o** was confirmed by single crystal X-ray analysis. It is noteworthy that an array of functional groups including OCH_3, Ac, and CO_2Me were compatible with the reaction conditions, which could offer the opportunity for further transformations. The spiro γ-butyrolactone **5n**, a feature which often occurs in biologically active molecules, could also be formed in a moderate yield. Unsymmetrical alkynes were also investigated, and the corresponding products **5p** and **5q** were obtained in synthetically useful yields.[19]

Furthermore, γ,δ-unsaturated carboxylic amides have proven to be versatile synthons for organic transformations. Besides γ-butyrolactones, the alkenylated products **3b** could also be converted into γ-carbonyl ester **6** and γ-lactam **7**. Meanwhile, the γ-butyrolactones **4** could also be obtained via the hydrolysis and subsequent oxidation of γ,δ-unsaturated ester **3b-1** (Scheme 6).

In conclusion, we have developed for the first time the nickel-catalyzed addition of unactivated C(sp^3)−H bonds with both symmetrical and unsymmetrical alkynes. A broad set of aliphatic amides can be readily alkenylated in moderate to good yields. A sequential C(sp^3)−H alkenylation/lactonization procedure has been developed to afford a complementary method to construct polysubstituted γ-butyrolactones from the less functionalized aliphatic carboxylic acid derivatives. For the first time, PCC has proven to be an efficient reagent in the formation of γ-butyrolactones from β-alkenylated amides. Removal of the 8-aminoquinoline directing group is not indispensable for lactonization. In addition, the alkenylated

DOI: 10.1021/acs.orglett.5b01128
Org. Lett. 2015, 17, 2546−2549

Scheme 6. Transformations of Alkenylated Amide



products can also serve as versatile intermediates for further transformations. Further studies to extend the reaction scope are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, X-ray crystallographic data, copy of ^{1}H−^{1}H NOESY spectra of **3b**, and copies of ^{1}H, ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01128.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jsyou@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from 973 Program (2011CB808601) and the National NSF of China (Nos. 21432005, 21272160, and 21321061).

■ REFERENCES

(1) (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (f) Bariwal, J.; Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 9283. (g) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (h) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29.

(2) For selected reviews on the synthesis of natural products via C−H activation, see: (a) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (b) Chen, D. Y.-K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(3) For a review on the synthesis of functionalized molecules via C−H activation, see: Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 66.

(4) For selected application examples of γ,δ-unsaturated aliphatic carboxylic acids, see: (a) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811. (b) Ishikawa, H.; Elliott, G. L.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596. (c) Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504. (d) Faustino, H.; Alonso, I.; Mascareñas, J. L.; López, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6526. (e) Campbell, E. L.; Skepper, C. K.; Sankar, K.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2013**, *15*, 5306.

(5) (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (b) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216. (c) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 5267.

(6) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.

(7) *Hydrofunctionalization*; Ananikov, V. P., Tanaka, M., Eds.; Springer-Verlag: Berlin, 2013.

(8) For selected examples on transition-metal-catalyzed alkenylation of (hetero)aryl C−H bonds with alkynes, see: (a) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (b) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (d) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910. (e) Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264. (f) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424.

(9) Liu, B.; Zhou, T.; Li, B.; Xu, S.; Song, H.; Wang, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 4191.

(10) (a) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (b) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.

(11) (a) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (b) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (c) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6410. (d) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887.

(12) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952.

(13) (a) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264. (b) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (c) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (d) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944. (e) Wu, X.; Zhao, Y.; Ge, H. *Chem.—Eur. J.* **2014**, *20*, 9530.

(14) Corbet, M.; Campo, F. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896.

(15) For a selected example of using *i*-PrOH as a hydrogen source, see: Ohashi, M.; Taniguchi, T.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 14900.

(16) For biological properties, see: (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426. (b) Willey, J. M.; Gaskell, A. A. *Chem. Rev.* **2011**, *111*, 174.

(17) For selected examples on the synthesis of γ-butyrolactone by catalysis, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat. Chem.* **2011**, *3*, 216. (c) Huang, L.; Wang, Q.; Liu, X.; Jiang, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5696. (d) Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 16492. (e) McInturff, E. L.; Mowat, J.; Waldeck, A. R.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 17230.

(18) (a) Schlecht, M. F.; Kim, H.-J. *Tetrahedron Lett.* **1986**, *27*, 4889. (b) McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc.* **1994**, *116*, 7921. (c) Beihoffer, L. A.; Craven, R. A.; Knight, K. S.; Sisson, C. R.; Waddell, T. G. *Trans. Met. Chem.* **2005**, *30*, 582.

(19) For the plausible mechanism of the PCC-promoted lactonization, see the Supporting Information (SI), Part IV.

DOI: 10.1021/acs.orglett.5b01128
Org. Lett. 2015, 17, 2546−2549