

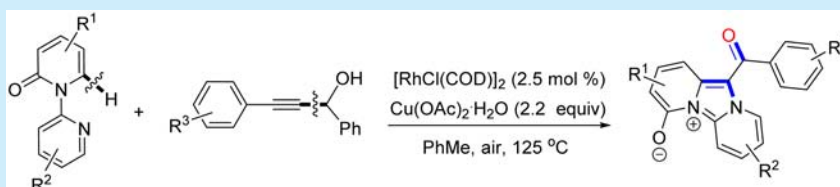
Rhodium-Catalyzed/Copper-Mediated Tandem C(sp²)-H Alkynylation and Annulation: Synthesis of 11-Acylated Imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium-4-olates from 2*H*-[1,2'-Bipyridin]-2-ones and Propargyl Alcohols

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S Supporting Information



ABSTRACT: A rhodium-catalyzed/copper-mediated tandem C(sp²)-H alkynylation and intramolecular annulation of 2*H*-[1,2'-bipyridin]-2-ones with propargyl alcohols for the synthesis of 11-acylated imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium-4-olates is described.

2-Pyridones represent an important class of nitrogen-containing heterocycles in biologically active compounds and versatile synthetic intermediates in organic synthesis.¹ As such, there is continuing interest in new synthetic methods that provide selective access to substituted 2-pyridone derivatives.² To date, a number of approaches that allow regioselective functionalization of 2-pyridones, including alkylation,³ arylation,⁴ and alkenylation,⁵ at the C-3, C-5, or C-6 positions of the 2-pyridone ring, have been successfully reported. However, despite certain advances, regioselective alkynylation of 2-pyridones still remains a challenge. The tedious procedure and harsh reaction conditions for prefunctionalization of 2-pyridones prevent the use of Sonogashira-type coupling reactions for introducing alkynyl functionality. On the other hand, alkynes, as easily accessible building blocks in organic synthesis, provide chemists with a fertile testing ground for the construction of complex organic molecules.⁶ In this regard, solutions for the alkynylation of 2-pyridones are highly desirable as they would enable access to an important range of natural and unnatural products containing a 2-pyridone moiety.

Recently, transition-metal-mediated C-H alkynylation for the introduction of alkynyl functionality⁷ has received much attention from the synthetic community. It is appealing to employ terminal alkynes as alkynylation reagents in C-H alkynylation. Due to the polymerization of terminal alkynes under high temperatures, only a narrow scope of electron-rich heteroarenes such as thiophenes or highly electron-poor arenes with reactive acidic C-H bonds has been successfully achieved.⁸ Instead, haloalkynes⁹ and terminal alkynes bearing a bulky silyl group¹⁰ have been used, while the substrate scope still remains

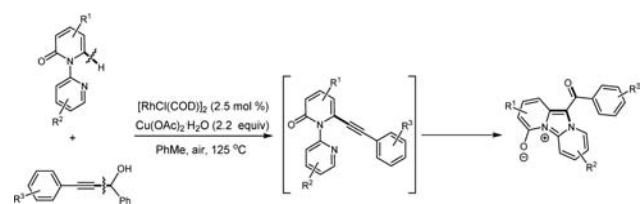
limited. The recently reported benziodoxolone-based hypervalent iodine reagent proved to be an efficient and general alkynylation reagent. However, it was only suitable for triisopropylsilyl-based alkynylodonium reagents, while aryl- or alkyl-substituted substrates could not afford the alkynylation products.¹¹ It is worth noting that *tert*-propargyl alcohols have been involved in Sonogashira-type reactions as masked terminal alkynes.¹² Moreover, Miura discovered that [Rh(OH)(COD)]₂ could catalyze regio- and stereoselective homocoupling of γ -substituted *tert*-propargyl alcohols via β -carbon elimination with the liberation of a ketone in which an alkynyl rhodium generated in situ was proposed as the key intermediate.¹³ Inspired by these results, we were thus prompted to design the rhodium-catalyzed direct C-H alkynylation of 2-pyridones utilizing propargyl alcohols as the alkynyl coupling partner.

In an attempt to obtain the direct C-6 selective C-H alkynylation product of 2*H*-[1,2'-bipyridin]-2-one, a red compound, 11-acylated imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium-4-olate, was isolated serendipitously (Scheme 1). Herein, we report a rhodium-catalyzed/copper-mediated tandem C(sp²)-H alkynylation and intramolecular annulation of 2*H*-[1,2'-bipyridin]-2-ones with propargyl alcohols, leading to the formation of 11-acylated imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium-4-olates in good to excellent yields.

Initial experiments were performed with 2*H*-[1,2'-bipyridin]-2-one **1a** and 2-methyl-4-phenyl-3-buten-2-ol **2a'** in the presence of 1.5 mol % of [RhCl(COD)]₂¹⁴ and 2.2 equiv of Cu(OAc)₂·H₂O

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Scheme 1. Rhodium-Catalyzed/Copper-Mediated Synthesis of 11-Acylated Imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium-4-olates

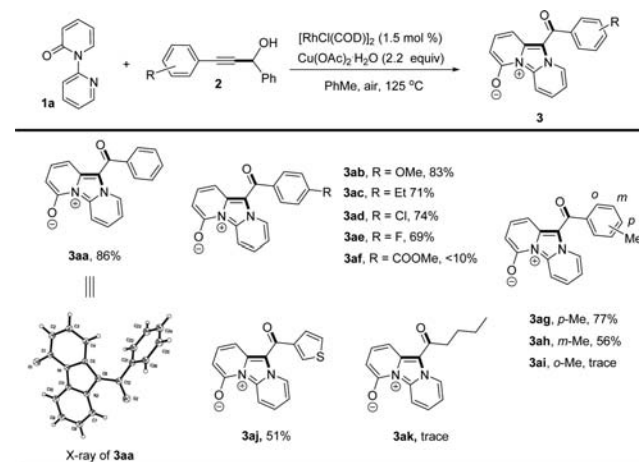
as oxidant. The unexpected red compound **3aa**, which contains the 11-acylated imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium skeleton, was generated in about 39% isolated yield instead of the desired alkynylation product (Table 1, entry 1). The definite structure of

Table 1. Optimization of the Reaction Conditions^a

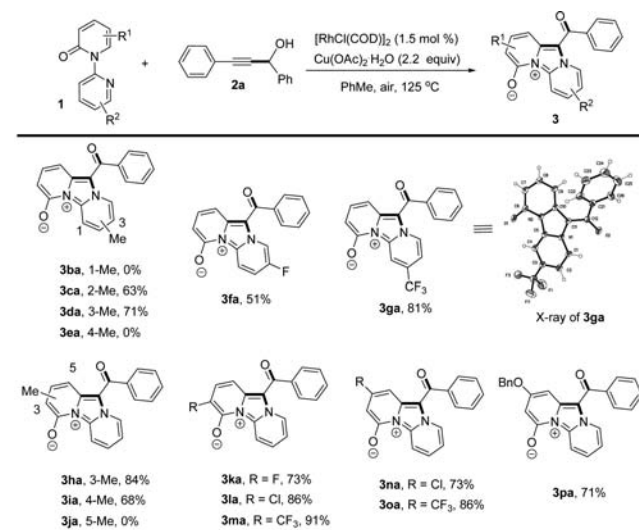
entry	substrate	conditions	yield (%)
1	2a'	[RhCl(COD)] ₂ , 125 °C, PhMe	39
2	2a	[RhCl(COD)] ₂ , 125 °C, PhMe	86
3	2b'	[RhCl(COD)] ₂ , 125 °C, PhMe	12
4	2c'	[RhCl(COD)] ₂ , 125 °C, PhMe	34
5	2d'	[RhCl(COD)] ₂ , 125 °C, PhMe	0
6	2e'	[RhCl(COD)] ₂ , 125 °C, PhMe	8
7	2a	[Rh(CO) ₂ Cl] ₂ , 125 °C, PhMe	42
8	2a	[Rh(OH)COD] ₂ , 125 °C, PhMe	76
9	2a	Rh ₂ (OAc) ₄ , 125 °C, PhMe	64
10	2a	[Cp*RhCl] ₂ , 125 °C, PhMe	39
11	2a	Cp*Rh(OAc) ₂ , 125 °C, PhMe	37
12 ^b	2a	[RhCl(COD)] ₂ , 125 °C, PhMe	0
13 ^c	2a	Cu(OAc) ₂ ·H ₂ O, 125 °C, PhMe	0
14	2a	[RhCl(COD)] ₂ , 125 °C, PhCl	62
15	2a	[RhCl(COD)] ₂ , 125 °C, DCE	55
16	2a	[RhCl(COD)] ₂ , 125 °C, DMF	trace

^aConditions: **1a** (0.20 mmol), **2** (0.40 mmol, 2 equiv), **[M]** (1.5 mol %), Cu(OAc)₂·H₂O (2.2 equiv), and solvent (2 mL) under air for 4 h. Yield of isolated products based on **1a**. ^bReaction performed in the absence of Cu(OAc)₂·H₂O. ^cReaction performed in the absence of [RhCl(COD)]₂.

3 was confirmed by X-ray crystallographic studies of **3aa** and **3ga**, as shown in Scheme 2 and Scheme 3 (vide infra). The formation of the 11-acylated imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium skeleton is interesting. To the best of our knowledge, efficient construction of imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium, a recurring structural motif found in many pharmaceuticals and functional materials, has rarely been reported.¹⁵ However, further studies to increase the yield of product **3aa** by using **2a'** as the alkynylation reagent failed. To our delight, when 1,3-diphenylprop-2-yn-1-ol **2a** was used as the alkynylation reagent instead, the reaction was accelerated and compound **3aa** could be isolated in 86% yield (entry 2). To the best of our knowledge, this

Scheme 2. Substrate Scope for Propargyl Alcohols^a

^aConditions: A mixture of derivative **1a** (0.20 mmol), propargyl alcohols **2** (0.40 mmol), [RhCl(COD)]₂ (1.5 mol %), Cu(OAc)₂·H₂O (0.44 mmol, 2.2 equiv), and toluene (2 mL) was added to a Schlenk tube under an air atmosphere. Then the mixture was stirred at 125 °C (bath temperature, preheated) under air for 4 h. Isolated products based on **1a**.

Scheme 3. Substrate Scope for 2*H*-[1,2'-Bipyridin]-2-ones^a

^aConditions: A mixture of derivative **1** (0.20 mmol), propargyl alcohols **2a** (0.40 mmol), [RhCl(COD)]₂ (1.5 mol %), Cu(OAc)₂·H₂O (0.44 mmol, 2.2 equiv), and toluene (2 mL) was added to a Schlenk tube under an air atmosphere. Then the mixture was stirred at 125 °C (bath temperature, preheated) under air for 4 h. Isolated products based on **1**.

represents the first report that 1,3-diphenylprop-2-yn-1-ol **2a** could be used as alkynylation reagents for the introduction of the alkynyl functionality via Csp³–Csp single bond cleavage.¹⁶ Ongoing studies to try other propargyl alcohols as alkynylation reagents instead of **2a** revealed that **2a** was the best C–H alkynylation reagent for 2*H*-[1,2'-bipyridin]-2-one (entries 3–5). We have also examined the possibility of employing a terminal alkyne instead of **2a** for this transformation, which gave **3aa** in only 8% yield (entry 6). Further investigation of the rhodium catalyst precursors demonstrated that [RhCl(COD)]₂ was the best choice for this transformation (entries 7–11). Control experiments revealed that no desired product **3aa** was

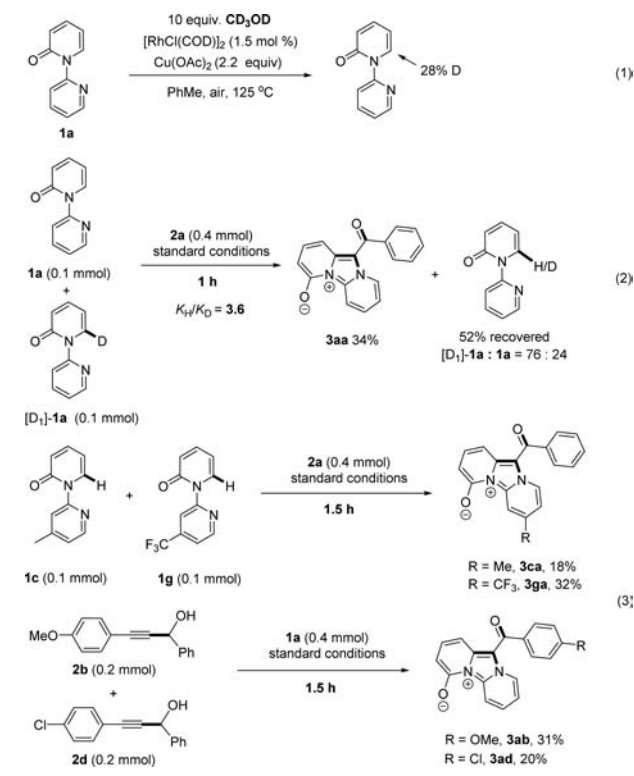
detected in the absence of either $[\text{RhCl}(\text{COD})]_2$ or $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (entries 12 and 13). Investigation on solvent effects indicated that toluene was the most suitable solvent (entries 14–16).

Under the optimized reaction conditions in Table 1, we sought to further explore the scope and limitation of this transformation. First, a series of propargyl alcohols were investigated (Scheme 2). To our satisfaction, propargyl alcohols containing electron-donating or electron-withdrawing substituents such as OMe, Et, Cl, and F at the *para* position on the phenyl ring were well-tolerated to provide the corresponding products in good yields (3ab–3ae), while substrate 2e showed poor conversion (<10%). Substrates bearing a Me group at the *meta* or *para* position on the phenyl ring proceeded smoothly (3ag, 3ah), while that with a Me group at the *ortho* position failed to yield the desired product 3ai, possibly due to the steric hindrance. It is noteworthy that the methodology could be further extended to thiophene-containing substrate 2j to afford the corresponding product 3aj, which was isolated in about 51% yield. Further studies revealed that aliphatic propargyl alcohol 2k was not compatible with this transformation, and only trace 3ak could be detected in the reaction mixture.

Consequently, the scope for the 2*H*-[1,2'-bipyridin]-2-ones was further investigated (Scheme 3). First, the influence of substituent on the pyridyl directing group was investigated. Gratifyingly, it was found that installation of a Me substituent on the pyridyl C-2 or C-3 position furnished product 3ca or 3da in 63 and 71% yield, respectively. In contrast, when the C-1 or C-4 position of the pyridyl directing group was blocked with a Me group, the reaction was completely suppressed, probably as a result of steric factors (3ba and 3ea). Besides, the reaction also accommodated CF_3 and F groups on the pyridyl directing group (3fa and 3ga in 51 and 81% yields). The generality of the 2-pyridone ring was next examined. Installation of a Me group at the C-3 or C-4 position on the 2-pyridone ring had a negative influence on the transformation (3ha and 3ia). In contrast, when the Me group was at the C-5 position, the reaction was completely suppressed (3ja). Moreover, reaction of other 2*H*-[1,2'-bipyridin]-2-ones was also investigated. 2*H*-[1,2'-Bipyridin]-2-ones with a substituent group including F, Cl, or CF_3 at C-3 position of the 2-pyridone ring were compatible with this transformation, thus affording products 3ka, 3la, and 3ma in good yields. Besides, when the C-4 position of the 2-pyridone ring was fixed with a substituent such as Cl, CF_3 , or OBn, the reaction also worked well to provide 3na, 3oa, and 3pa in 73, 86, and 71% yields, respectively.

It is reasonable to believe that the reaction first underwent C–H alkynylation of substrate 1a,¹⁷ followed by intramolecular annulation of the resulting alkyne to generate the target 3aa. To gain insight into the C–H cleavage step, substrate 1a was treated with excess CD_3OD (10 equiv) for 4 h under standard reaction conditions, and partial D exchange (28%) was detected at the C-6 position (Scheme 4(1)). This result clearly indicated that a reversible deprotonative C–H bond activation step might exist in the transformation. Besides, by employing deuterium-labeled compound $[\text{D}_1]$ -1a as the substrate, the kinetic isotope effect (KIE) of the transformation was tested. The KIE value was determined to be 3.6, indicating that the C–H bond cleavage was the rate-determining step in the transformation (Scheme 4(2)). Moreover, competition experiments with substrates bearing varied electronic properties were also investigated, and formation of products derived from electron-deficient 2*H*-[1,2'-bipyridin]-

Scheme 4. Mechanism Studies



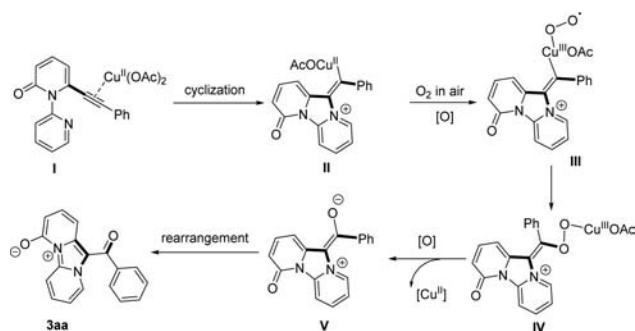
2-one 1g and electron-rich propargyl alcohol 2b was favored in this transformation (Scheme 4(3)).

Moreover, several controlled experiments were performed to gain insight into the annulation transformation (see Supporting Information (SI)). First, we carried out the reaction under N_2 atmosphere and found that the reaction turned messy with only trace 3aa isolated. In contrast, the reaction conducted using distilled PhMe under dry O_2 worked well to provide 3aa in 84% yield. Besides, the reaction in the presence H_2^{18}O under O_2 was also conducted, and the ^{18}O -atom-containing product $[\text{O}^{18}]\text{-3aa}$ was not detected at all. These results indicated that O_2 in air was vital to the transformation, and the source of oxygen atom in 3aa was from O_2 under air rather than from water. Besides, when a stoichiometric amount of radical inhibitor, TEMPO, was added to the reaction, only trace 3aa could be isolated, suggesting that the reaction proceeds through a radical process. Reaction of 1a with ethyl 2-diazoacetate as a carbene acceptor was also conducted to afford 3aa with the core containing 2-pyridone, thereby indicating that metal carbene intermediate was not involved in the transformation.

Given the above results and previous reports,¹⁸ a possible mechanism for the transformation of the alkynylation product to the final product 3aa was proposed (Scheme 5). First, complexation of $\text{Cu}(\text{OAc})_2$ with the alkynylation product yields intermediate I, which is followed by the intramolecular cyclization to deliver intermediate II. Oxidation of II with O_2 in air generates the peroxycopper III with the aid of the oxidative additive. Reductive elimination of intermediate III gives rise to the peroxycopper complex IV.¹⁸ Finally, the O–O bond cleavage of IV and consequent oxidation affords V, which undergoes rearrangement to afford product 3aa finally.

Finally, 5 mmol scale reactions were conducted using 1a and 1o as substrates, and the reaction proceeded smoothly to give products 3aa and 3oa in 81 and 84% yields, respectively (Scheme

Scheme 5. Proposed Mechanism



6). Moreover, we also characterized the UV–vis absorption of several representative products and found that the synthesized

Scheme 6. Gram-Scale Synthesis of Compounds 3aa and 3oa



polycyclic compounds showed strong UV–vis absorption in the range of 420–500 nm (see SI).

In summary, we have presented a convenient method for the synthesis of 11-acylated imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium-4-olate via rhodium-catalyzed/copper-mediated tandem C(sp²)–H alkynylation and intramolecular annulation of 2*H*-[1,2'-bipyridin]-2-ones with propargyl alcohols. The use of readily available substrates, a simple procedure, and mild reaction conditions (in particular, no requirement to exclude moisture or air) renders this method potentially useful for the synthesis of imidazo[1,2-*a*:3,4-*a'*]dipyridin-5-ium-4-olate skeletons in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00177.

Experimental details and spectral data for all products (PDF)

X-ray data for 3aa (CCDC 1445045) (CIF)

X-ray data 3ga (CCDC 1445046) (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757. (b) Lagoja, I. M. *Chem. Biodiversity* **2005**, *2*, 1. (c) Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168.

- (2) (a) Hill, M. D.; Movassaghi, M. *Chem. - Eur. J.* **2008**, *14*, 6836. (b) Bengtsson, C.; Almqvist, F. *J. Org. Chem.* **2010**, *75*, 972.
- (3) (a) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996. (b) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5679. (c) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *Chem. - Eur. J.* **2013**, *19*, 7691.
- (4) (a) Chen, Y.; Wang, F.; Jia, A.; Li, X. *Chem. Sci.* **2012**, *3*, 3231. (b) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 1377. (c) Anagnostaki, E. A.; Fotiadou, A. D.; Demertzidou, V.; Zografos, A. L. *Chem. Commun.* **2014**, *50*, 6879.
- (5) Itahara, T.; Ouseto, F. *Synthesis* **1984**, 1984, 488.
- (6) *Acetylene Chemistry: Chemistry, Biology, and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
- (7) (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Mangel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (b) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (e) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (f) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.
- (8) (a) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (b) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474. (c) Jie, X.; Shang, Y.; Hu, P.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3630. (d) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590. (e) Dong, J.; Wang, F.; You, J. *Org. Lett.* **2014**, *16*, 2884. (f) Liu, Y.-H.; Liu, Y.-J.; Yan, S.-Y.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 11650.
- (9) (a) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (b) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (c) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387.
- (10) (a) Kim, S. H.; Park, S. H.; Chang, S. *Tetrahedron* **2012**, *68*, 5162. (b) Liu, Y.-J.; Liu, Y.-H.; Yin, X.-S.; Gu, W.-J.; Shi, B.-F. *Chem. - Eur. J.* **2015**, *21*, 205.
- (11) (a) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112. (b) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (c) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722. (d) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780.
- (12) (a) Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* **2003**, *5*, 2997. (b) Li, T.; Wang, Z.; Zhang, M.; Zhang, H.-J.; Wen, T.-B. *Chem. Commun.* **2015**, *51*, 6777.
- (13) Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2005**, *127*, 15354.
- (14) Rhodium catalysis in C–H activation: (a) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.
- (15) Edward, J. T.; Sheffler, R. H. *J. Org. Chem.* **1985**, *50*, 4855.
- (16) (a) Qin, C.; Feng, P.; Ou, Y.; Shen, T.; Wang, T.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 7850. (b) Muller, C.; Iverson, C. N.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 9718.
- (17) For the mechanism of C–H alkynylation, see SI.
- (18) Cu^{II}/O₂ catalytic system examples: (a) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (b) Wang, Z.-Q.; Zhang, W.-W.; Gong, L.-B.; Tang, R.-Y.; Yang, X.-H.; Liu, Y.; Li, J.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8968. (c) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678.