

# Palladium-Catalyzed Condensation of *N*-Aryl Imines and Alkynylbenziodoxolones To Form Multisubstituted Furans

Beili Lu,<sup>†</sup> Junliang Wu,<sup>†</sup> and Naohiko Yoshikai\*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

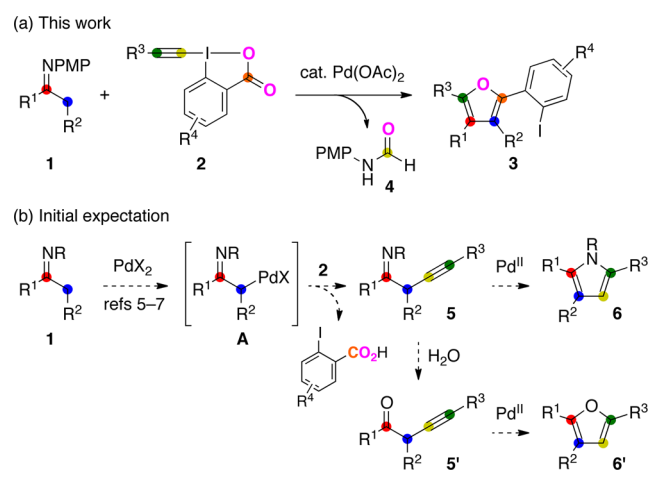
**S** Supporting Information

**ABSTRACT:** A palladium(II) catalyst promotes condensation of an *N*-aryl imine and an alkynylbenziodoxolone derivative to afford a multisubstituted furan, whose substituents are derived from the alkynyl moiety (2-position), the imine (3- and 4-positions), and the 2-iodobenzoate moiety (5-position), along with an *N*-arylformamide under mild conditions. The 2-iodophenyl group of the furan product serves as a versatile handle for further transformations. A series of isotope-labeling experiments shed light on the bond reorganization process in this unusual condensation reaction, which includes cleavage of the C–C triple bond and fragmentation of the carboxylate moiety.

Hypervalent iodine compounds have found increasing applications as oxidants and electrophilic reagents for organic synthesis.<sup>1</sup> Among them, those having a benziodoxolone skeleton have emerged as unique and effective reagents for the delivery of electrophiles such as trifluoromethyl and alkynyl groups to nucleophilic reaction partners.<sup>1c,d</sup> In these iodine(III) reagents, the 2-iodobenzoate moiety serves to modulate their stability and reactivity and upon transfer of the electrophile leaves as 2-iodobenzoic acid, which usually behaves as an innocent byproduct. Here we report on a coupling reaction of *N*-aryl imine **1** and ethynylbenziodoxolone (EBX) reagent **2**<sup>2,3</sup> under palladium(II) catalysis to afford multisubstituted furan **3** bearing substituents derived from the alkynyl moiety of **2** (2-position), **1** (3- and 4-positions), and the 2-iodobenzoate moiety of **2** (5-position), accompanied by the concomitant formation of *N*-arylformamide **4** (Scheme 1a). This reaction is unusual as a transformation of EBX in a few aspects such as cleavage of the C–C triple bond<sup>4</sup> and participation/fragmentation of the 2-iodobenzoate moiety.

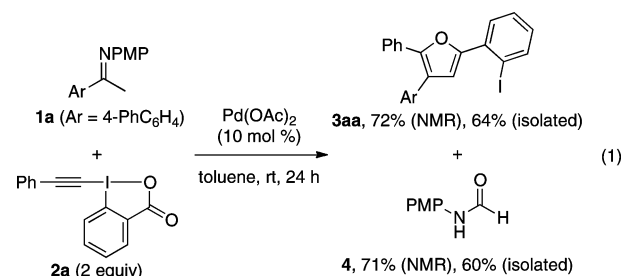
We recently reported on palladium(II)-catalyzed dehydrogenative synthesis of indoles,<sup>5</sup> pyrroles,<sup>6</sup> and aryl amines<sup>7</sup> through  $\alpha$ -palladation of an imine as a key elementary step (**1** to **A**; Scheme 1b). The present finding originated from our attempt to expand the synthetic versatility of  $\alpha$ -palladated imine **A**. Thus, we envisioned that interception of species **A** with EBX **2** would give a palladium(IV) intermediate,<sup>3b,e,f</sup> which would then undergo reductive elimination to afford  $\alpha$ -alkynylated imine **5** along with 2-iodobenzoic acid.<sup>3i,8</sup> With the aid of the Pd(II) catalyst, imine **5** might be cycloisomerized to pyrrole **6**.<sup>9,10</sup> Alternatively, hydrolysis of **5** would give  $\alpha$ -alkynyl ketone **5'**, which might

## Scheme 1. Pd(II)-Catalyzed Coupling of Imine and Alkynylbenziodoxolone (PMP = *p*-MeOC<sub>6</sub>H<sub>4</sub>)



also undergo Pd(II)-catalyzed cycloisomerization leading to furan **6'**.<sup>11</sup>

Contrary to the initial expectation, imine **1a** (0.2 mmol) derived from 4-acetylbiphenyl and *p*-anisidine reacted with phenyl-EBX **2a** (2 equiv) in the presence of Pd(OAc)<sub>2</sub> (10 mol %) in toluene under a nitrogen atmosphere at room temperature to afford 2,3,5-trisubstituted furan **3aa** in 72% yield (as determined by <sup>1</sup>H NMR; isolated in 64% yield) along with *N*-(4-methoxyphenyl)formamide (**4**) (71% NMR yield, 60% isolated yield) (eq 1). The structure of **3aa** was unambiguously



determined by X-ray crystallographic analysis [see the Supporting Information (SI)]. The phenyl, 4-phenylphenyl, and 2-iodophenyl groups of **3aa** appear to originate from the alkynyl moiety of **2a**, **1a**, and the 2-iodobenzoate moiety of **2a**,

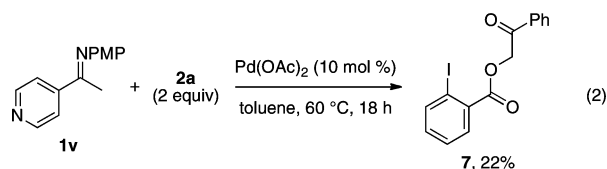
Received: June 14, 2014

Published: August 4, 2014

respectively. Also, the formyl group of **4** appears to come from **2a**. While the bond reorganization process in this reaction seems puzzling (vide infra), it is important to note that the combined molecular formula of **3aa** and **4** ( $C_{36}H_{28}INO_3$ ) is identical to that of **1a** and **2a**. Thus, despite the moderate yields due to formation of other intractable byproducts, the major products **3aa** and **4** appear to be formed through 1:1 coupling of **1a** and **2a**.

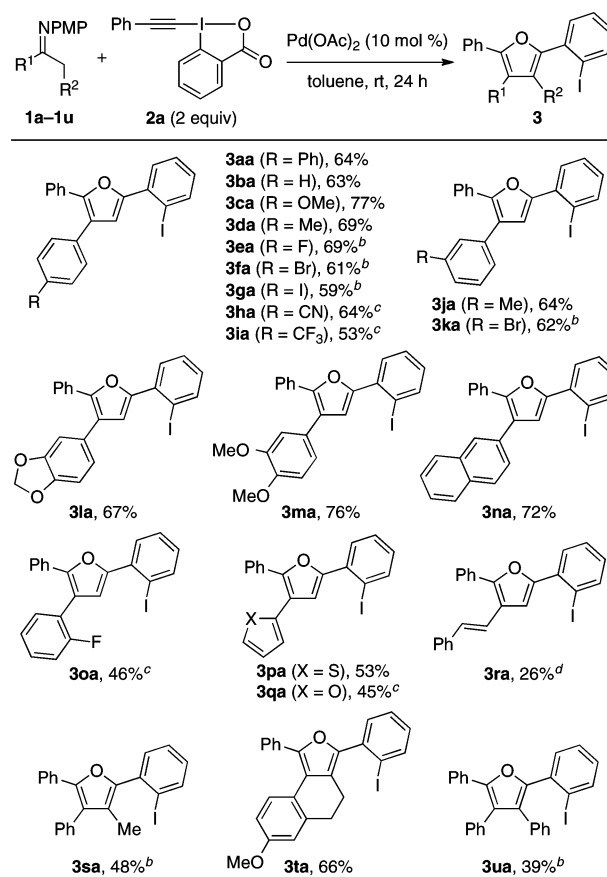
Screening of the reaction conditions was performed using 4'-methylacetophenone imine and **2a** (see Table S1 in the SI). Essential observations include the following: (1) Besides  $Pd(OAc)_2$ ,  $Pd_2(dba)_3$  and [1,2-bis(phenylsulfanyl)ethane]-palladium(II) acetate (White's catalyst) promoted the coupling reaction, albeit in lower yields, while  $PdCl_2$ ,  $PdCl_2(PPh_3)_2$ , and  $Pd(PPh_3)_4$  did not give the desired product at all. (2) The reaction did not take place with other metal catalysts such as AuCl and CuI or without a catalyst. (3) Additives such as AcOH and PivOH did not improve the product yield, while  $Bu_4NBr$ , LiCl, and  $K_2CO_3$  completely shut down the reaction. (4) The reaction took place in  $CH_2Cl_2$  as efficiently as in toluene, while coordinating solvents such as DMSO and DMF inhibited the reaction. It should also be noted that the use of 4'-methylacetophenone instead of the imine did not give the furan at all. The imines derived from parent aniline afforded the desired product in a comparable yield, while the reaction became sluggish with those derived from 4-dimethylaminoaniline and benzylamine (see Table S2).

Scheme 2 shows the scope of imines as explored by the coupling reaction with **2a**. A wide variety of imines derived from substituted acetophenones participated in the reaction to afford the corresponding furans **3aa**–**3oa** in moderate to good yields. The reaction tolerated both electron-donating and electron-withdrawing substituents on the imine, including bromine and iodine atoms as well as cyano and trifluoromethyl groups. Methyl imines bearing 2-thienyl, 2-furyl, and styryl groups also afforded the corresponding furan derivatives **3pa**, **3qa**, and **3ra**, albeit in modest yields. Unlike our indole/pyrrole synthesis,<sup>5,6</sup> imines bearing  $\beta$ -hydrogen atoms are tolerated. Thus, propiophenone- and 6-methoxy-1-tetralone-derived imines furnished the desired tetrasubstituted furans **3sa** and **3ta**, respectively. Likewise, tetraarylfuran **3ua** was obtained, albeit in a modest yield. The reaction of 4-pyridyl imine **1v** and **2a** did not afford the desired furan derivative, while 2-iodobenzoate ester **7** was obtained in 22% yield, presumably through ring-opening rearrangement and hydration of **2a** (eq 2).<sup>12</sup> Imines derived from aliphatic ketones such as pinacolone failed to participate in the present reaction.



Next, we explored the scope of EBXs (Scheme 3). Aryl-EBXs derived from a series of arylacetylenes participated in the coupling reaction with imine **1c** or **1d** to afford the corresponding furans **3cb**–**3cf**, **3dg**, and **3ch**–**3ck** in moderate to good yields with tolerance of substituents such as trifluoromethyl, cyano, nitro, bromo, and thienyl groups. By contrast, *n*-butyl-EBX reacted rather sluggishly, affording the desired furan **3dl** in only 8% isolated yield along with unidentified byproducts as well as unreacted imine (26%). No desired product could be obtained with trimethylsilyl-

## Scheme 2. Coupling of Various Imines with **2a**<sup>a</sup>

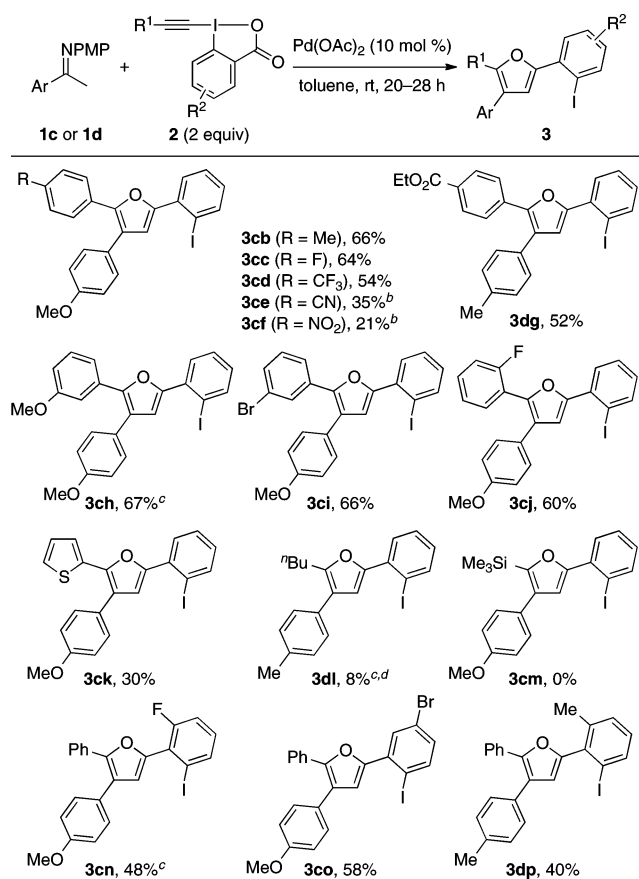


<sup>a</sup>The reaction was performed on a 0.2 mmol scale. <sup>b</sup>The reaction time was 48 h. <sup>c</sup>The reaction was performed at 40 °C for 20 h. <sup>d</sup>The reaction was performed at 70 °C for 24 h.

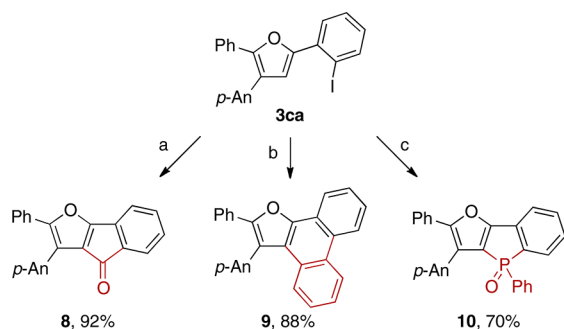
triisopropylsilyl-EBXs (see **3cm**). Phenyl-EBXs derived from substituted 2-iodobenzoic acids also reacted with **1c** or **1d** to afford the corresponding furan derivatives **3cn**, **3co**, and **3dp** in moderate yields.

The 2-iodophenyl moiety of the furan product serves as a versatile handle for further synthetic transformations (Scheme 4).  $Pd(0)$ -catalyzed cyclocarbonylation<sup>13</sup> of **3ca** proceeded smoothly to give indenone-embedded furan **8**. Domino Suzuki–Miyaura coupling/intramolecular direct arylation<sup>14</sup> using 2-bromophenylboronic acid afforded phenanthro[9,10-*b*]furan derivative **9**. A sequence of iodine–lithium exchange, electrophilic trapping with  $PhPCl_2$ , intramolecular phospho-Friedel–Crafts reaction,<sup>15</sup> and oxidation with  $H_2O_2$  furnished phosphole derivative **10** in good yield.

To gain insight into the bond reorganization process in the present reaction, we performed a series of experiments using <sup>13</sup>C- or <sup>18</sup>O-labeled imine **1c**\* and EBX **2a**\* (Scheme 5a; see the SI for the details of each experiment). As summarized in Scheme 5a, a one-to-one correspondence between the starting materials and the products was established for each of the color-coded carbon and oxygen atoms. Notably, the acetylenic carbon atoms of **2a**\* underwent bond cleavage, and the one originally bonded to the iodine atom ended up as the formyl carbon of **4**\*. The benzoate moiety of **2a**\* was also dissected to constitute the furan C5–O moiety of **3ca**\* and the formyl oxygen of **4**\*. We also performed a crossover experiment using imine **1d**, EBX **2a**, and 2-iodo-6-methylbenzoic acid under the standard conditions, which

Scheme 3. Coupling of 1c or 1d with Various EBXs<sup>a</sup>

<sup>a</sup>The reaction was performed on a 0.2 mmol scale. <sup>b</sup>The reaction was performed at 40 °C for 20 h. <sup>c</sup>The reaction time was 48 h. <sup>d</sup>CH<sub>2</sub>Cl<sub>2</sub> was used as the solvent instead of toluene.

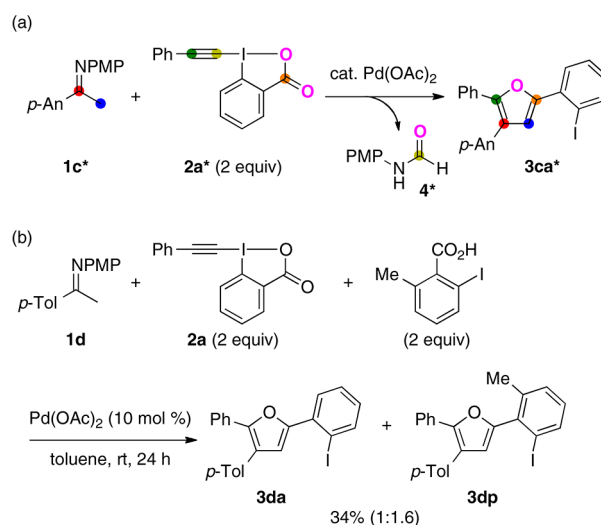
Scheme 4. Transformations of Furan **3ca** (*p*-An = 4-MeOC<sub>6</sub>H<sub>4</sub>)<sup>a</sup>

<sup>a</sup>Reaction conditions: (a) Pd<sub>2</sub>(dba)<sub>3</sub>, PCy<sub>3</sub>, CsOPiv, CO (1 atm), DMF, 110 °C, 12 h. (b) Pd<sub>2</sub>(dba)<sub>3</sub>, PCy<sub>3</sub>, 2-bromophenylboronic acid, DBU, DMF, 155 °C, 48 h. (c) (1) *n*BuLi, −78 °C, THF, 30 min; (2) PhPCl<sub>2</sub>, −78 to 60 °C, 4 h; (3) AlCl<sub>3</sub>, *i*Pr<sub>2</sub>NEt, −78 to 90 °C, 12 h; (4) H<sub>2</sub>O<sub>2</sub>, 30 min.

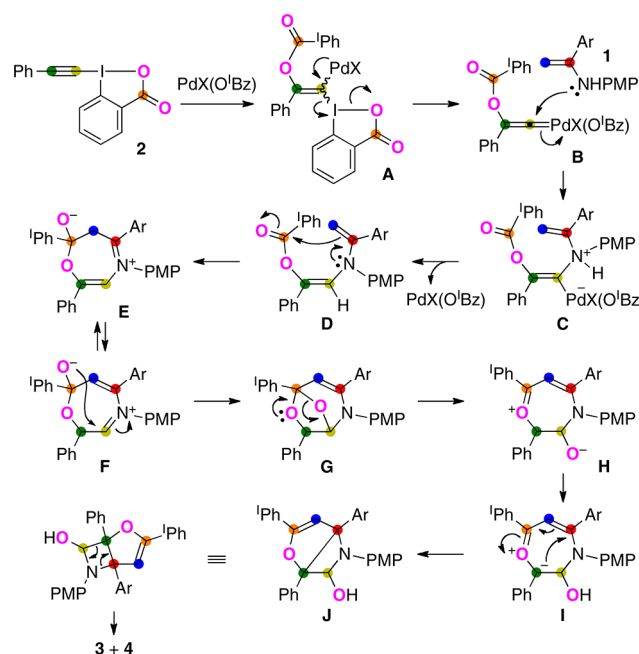
afforded a 1:1.6 mixture of the expected furan **3da** and another furan **3dp** bearing a 2-iodo-6-methylphenyl group at the 5-position (Scheme 5b). The formation of **3dp** indicates that the C2-aryl and C5-aryl moieties of the furan product do not necessarily come from the same EBX molecule.

Unfortunately, we have not been able to observe any intermediates that may shed further light on the reaction

Scheme 5. (a) Summary of Isotope Labeling Experiments and (b) Crossover Experiment



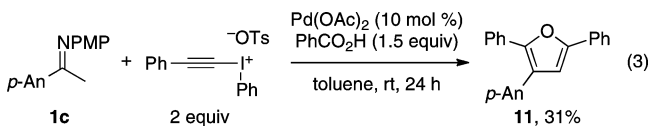
mechanism. Nevertheless, on the basis of the isotope-labeling and crossover experiments (Scheme 5) and the accepted wisdom in alkenyliodonium chemistry,<sup>2a</sup> we have attempted to draw a possible reaction pathway (Scheme 6).<sup>16</sup> The reaction may be

Scheme 6. Possible Reaction Pathway (<sup>1</sup>Bz = 2-Iodobenzoyl; <sup>1</sup>Ph = 2-Iodophenyl)

initiated by the addition of a palladium(II) 2-iodobenzoate species to the electrophilic C–C triple bond of EBX. Cleavage of the resulting vinyl–I(III) bond and reduction of I(III) to I(I) would then lead to palladium–vinylidene species **B**. Addition of an enamine form of the imine to **B** and subsequent protodepalladation would afford enamine intermediate **D** with elimination of the palladium(II) 2-iodobenzoate species. Although highly speculative, a sequence of skeletal rearrangements from **D** initiated by intramolecular attack of the enamine to the ester would eventually lead to oxazabicyclic intermediate **J**.

Ring opening of the azetidinium moiety of **J** would then afford furan **3** and formamide **4**.

Regardless of the mechanistic ambiguity, the result of the crossover experiment (Scheme 5b) implies the possibility of a three-component furan synthesis using imine, alkynyliodonium-(III) reagent, and carboxylic acid. Indeed, a preliminary experiment using imine **1c**, phenyl(2-phenylethynyl)iodonium tosylate, and benzoic acid afforded the desired trisubstituted furan **11** in 31% yield (eq 3).



In summary, we have found a palladium(II)-catalyzed coupling reaction of imines and EBXs to afford multisubstituted furans<sup>17</sup> that involves unique condensation and fragmentation processes. Our current studies are focused on the synthetic potential and mechanistic aspects of the three-component coupling of imine, alkynyliodonium reagent, and carboxylic acid.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures, compound characterization, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

nyoshikai@ntu.edu.sg

### Author Contributions

<sup>†</sup>B.L. and J.W. contributed equally.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation Singapore (NRF-RF-2009-05) and Nanyang Technological University. We thank Dr. Yongxin Li (Nanyang Technological University) for assistance with X-ray crystallographic analysis.

## ■ REFERENCES

- (1) For selected reviews, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, *2*, 121. (d) Brand, J. P.; Gonzalez, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, 47, 102.
- (2) (a) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927. (b) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.
- (3) For selected examples of transition metal-catalyzed reactions of EBXs, see: (a) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (b) Nicolai, S.; Erard, S.; Gonzalez, D. F.; Waser, J. *Org. Lett.* **2010**, *12*, 384. (c) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (d) Ohta, Y.; Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2010**, *12*, 3963. (e) Nicolai, S.; Piemontesi, C.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 4680. (f) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112. (g) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6743. (h) Liu, X.; Wang, Z.; Cheng, X.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 14330. (i) Wang, Z.; Li, X.; Huang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 14219. (j) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722.
- (4) For examples of transition-metal-catalyzed reactions involving C≡C bond cleavage except for alkyne metathesis, see: (a) Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 6677. (b) Liu, Q.;

Chen, P.; Liu, G. *ACS Catal.* **2013**, *3*, 178. (c) Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, *130*, 5030. (d) Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc.* **2006**, *128*, 11332. (e) Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9294. (f) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 6646.

(5) (a) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098. (b) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 9220. (c) Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* **2013**, *2*, 466.

(6) (a) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966. (b) Shi, Z.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 4892. (c) Meng, L.; Wu, K.; Liu, C.; Lei, A. *Chem. Commun.* **2013**, 49, 5853.

(7) (a) Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 5488. (b) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2012**, *14*, 5606.

(8) For transition-metal-free  $\alpha$ -alkynylation of carbonyl compounds with EBXs, see: (a) González, D. F.; Brand, J. P.; Waser, J. *Chem.—Eur. J.* **2010**, *16*, 9457. (b) González, D. F.; Brand, J. P.; Mondière, R.; Waser, J. *Adv. Synth. Catal.* **2013**, *355*, 1631.

(9) For a review of transition-metal-mediated synthesis of pyrroles and furans, see: Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084.

(10) While no example of cycloisomerization of propargyl imine to pyrrole has been reported, its isomers (e.g., alkynyl imine, allenyl imine) are known to participate in such a reaction.

(11) (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (c) Sheng, H.; Lin, S.; Huang, Y. *Synthesis* **1987**, 1022.

(12) The mechanism of the formation of **7** is not clear at this moment.

(13) Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.

(14) Wegner, H. A.; Scott, L. T.; de Meijere, A. *J. Org. Chem.* **2003**, *68*, 883.

(15) Hatakeyama, T.; Hashimoto, S.; Nakamura, M. *Org. Lett.* **2011**, *13*, 2130.

(16) The reaction of **1c** and **2a** in the presence of TEMPO (2 equiv) afforded **3ca** without a significant decrease in the yield (70%), suggesting that a free radical is not involved.

(17) For transition-metal-mediated furan synthesis through cross-coupling of two reactants, see ref 9 and the following recent examples: (a) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766. (b) Kramer, S.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 4681. (c) Huang, X.; Peng, B.; Luparia, M.; Gomes, L. F. R.; Veiros, L. F.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 8886. (d) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981. (e) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629. (f) Zheng, M.; Huang, L.; Wu, W.; Jiang, H. *Org. Lett.* **2013**, *15*, 1838. (g) Yang, Y.; Yao, J.; Zhang, Y. *Org. Lett.* **2013**, *15*, 3206.