Organic LETTERS

Letter

pubs.acs.org/OrgLett

Cu(I)-Catalyzed Tandem Reaction of Carbene Coupling and Horner–Wadsworth–Emmons Type Olefination: Access toward Enynes

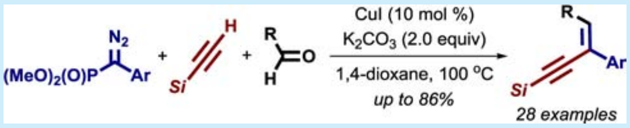
Yujing Zhou,[†] Fei Ye,[†] Qi Zhou,[†] Yan Zhang,[†] and Jianbo Wang*,[†,‡]

[†]Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

[‡]State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

S *Supporting Information*

ABSTRACT: A novel strategy to synthesize 1,3-enynes has been successfully developed based on Cu(I)-catalyzed cross-coupling of α-diazo phosphonates and alkynes with a subsequent Horner–Wadsworth–Emmons (HWE) type reaction. This method provides straightforward access to conjugated enynes with high efficiency, good stereoselectivity and excellent functional group compatibility. Copper(I) carbene migratory insertion plays a crucial role in this transformation.

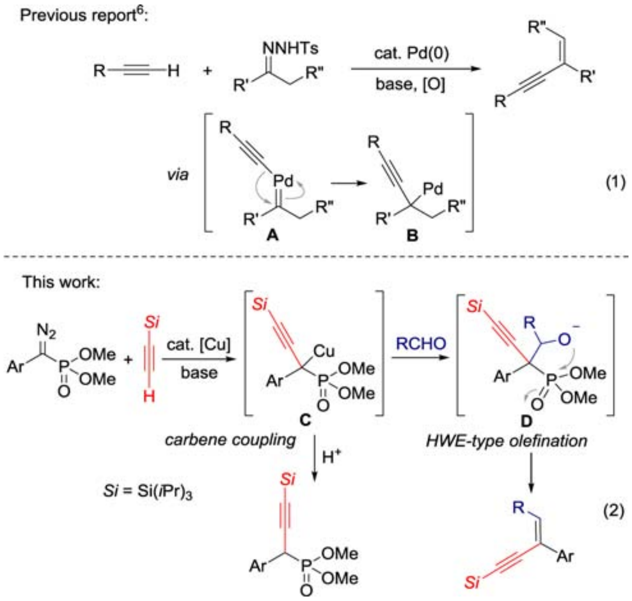


Conjugated enynes are of considerable interest in both synthetic chemistry and material sciences due to the wide existence of such structure units in various natural products and building blocks for organic conducting polymers.[1,2] Accordingly, significant efforts have been devoted to developing efficient strategies for the synthesis of enyne motifs. A basic strategy is the classic Wittig or Horner–Wadsworth–Emmons (HWE) reaction using organophosphorus derivatives bearing alkynyl groups as the substrates.[3] The transition-metal-catalyzed dimerization reaction of alkynes represents another interesting route, which produces the conjugated enynes in an atom-efficient manner.[4] Despite its attractiveness, the difficulty in controlling the regio- and stereoselectivity remains a huge barrier for the widespread application of this approach. Additionally, the transition-metal-catalyzed coupling reaction of alkynyl halides with stoichiometric organometallic alkenes,[5] as well as terminal or organometallic alkynes with vinyl halides,[6] can serve as complementary strategies to afford enynes in a stereoselective manner. While efficient, these methods generally suffer from drawbacks such as inconvenient handling of organometallic reagents and difficulty in accessing starting materials.

We have previously developed an enyne synthetic method based on the Pd-catalyzed reaction of terminal alkynes with *N*-tosylhydrazones.[7] The key step in this method is the formation of a Pd(II) carbene intermediate **A** and the subsequent migratory insertion (Scheme 1, eq 1). A similar strategy has also been extended to the Pd-catalyzed cross-coupling of terminal alkynes with ene-yne-ketones.[8]

On the other hand, the Cu(I)-catalyzed carbene cross-coupling reaction has emerged as a powerful method to form C–C bonds.[9] In this context, the commonly utilized carbene precursors, namely diazo compounds and *N*-tosylhydrazones, have been subjected to various coupling partners to generate alkyne[10] or allene scaffolds.[11] For example, the Cu(I) species **C** generated from carbene migratory insertion can be protonated to afford the alkyne product (Scheme 1, eq 2).[10a] Furthermore, successive formation of two C–C bonds has also been realized by employing an electrophile other than a proton as the trapping reagent.[12]

Scheme 1. Enyne Synthesis Based on Carbene Coupling



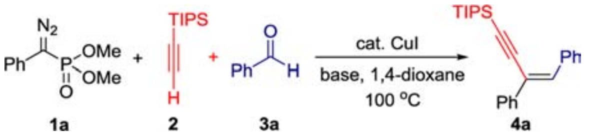
As a continuation of our interest in both carbene-involved cross-coupling reactions and the transformation of various functionalized diazo compounds, such as α-diazo phosphonates,[13] we envisioned that the copper intermediate **C** generated *in situ* could react with aldehyde and then undergo an HWE-type reaction through intermediate **D** to afford an

Received: March 5, 2016
Published: April 26, 2016

enyne product. Herein we report the development of a novel Cu(I)-catalyzed three-component cascade reaction that affords 1,3-enynes with good yields and high stereoselectivity.[14]

Our evaluation of the proposed transformation began with exposure of α-diazo phosphonate **1a** to terminal alkyne **2** and benzaldehyde **3a** as the coupling partners (Table 1). Employing CuI and mixed bases, the reactions were set up in different concentration first (Table 1, entries 1−2). The choice of base significantly influenced the conversion of the starting materials, and K_2CO_3 afforded the best result (Table 1, entries 2−4). Further increasing the concentration or the amount of base did not improve the efficiency (Table 1, entries 5−6). To our delight, reducing the catalyst loading to 10 mol % did not affect the outcome of the reaction (Table 1, entry 8). Interestingly, when we tried to enhance the yield by using the distilled benzaldehyde instead of the stocked one, a slightly diminished yield was observed (Table 1, entry 10), indicating an acidic additive may enhance the reactivity. Upon some experiments, we found that it was indeed the benzoic acid that promoted the reaction (Table 1, entry 11). Finally, different reaction temperatures were examined, and 100 °C proved to give the optimal results (Table 1, entries 12−13). Under the optimized reaction conditions, the product was obtained as a mixture of *Z* and *E* isomers with a ratio of 10:1.

Table 1. Optimization of the Reaction Conditions[a]

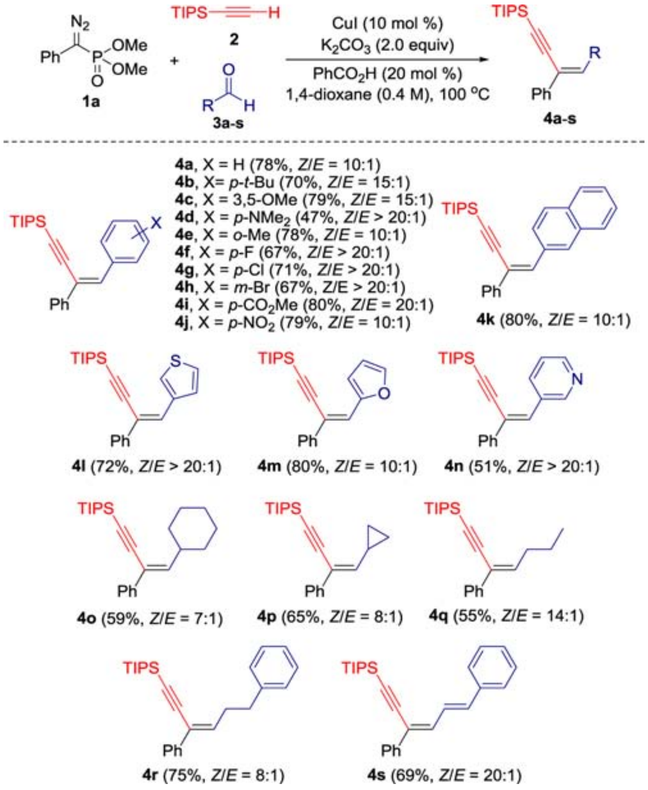


entry	CuI (mol %)	concn	base (equiv)	1a/2/3a	yield (%)[b]
1	20	0.2 M	Cs_2CO_3 (1) + NaH (1)	1:1:1.5	36
2	20	0.4 M	Cs_2CO_3 (1) + NaH (1)	1:1:1.5	50
3	20	0.4 M	Cs_2CO_3 (2)	1:1:1.5	58
4	20	0.4 M	K_2CO_3 (2)	1:1:1.5	74
5	20	0.5 M	K_2CO_3 (2)	1:1:1.5	76
6	20	0.4 M	K_2CO_3 (2.5)	1:1:1.5	75
7	20	0.4 M	K_2CO_3 (1.5)	1:1:1.5	60
8	10	0.4 M	K_2CO_3 (2)	1:1:1.5	75
9	10	0.4 M	K_2CO_3 (2)	1.2:1:1.5	57
10[c]	10	0.4 M	K_2CO_3 (2)	1:1:1.5	65
11[d]	**10**	**0.4 M**	**K_2CO_3 (2)**	**1:1:1.5**	**78**
12[d,e]	10	0.4 M	K_2CO_3 (2)	1:1:1.5	76
13[d,f]	10	0.4 M	K_2CO_3 (2)	1:1:1.5	61

[a] If not otherwise noted, all the reactions were carried out on a 0.20 mmol scale in 1,4-dioxane under a N_2 atmosphere at 100 °C for 12 h. [b] Isolated yields. [c] Freshly distilled benzaldehyde was used. [d] 20 mol % $PhCO_2H$ was added. [e] The reaction was carried out at 110 °C. [f] The reaction was carried out at 90 °C. TIPS: triisopropylsilyl.

Having identified the optimized reaction conditions, we examined the substrate scope with respect to aldehydes first. As revealed in Scheme 2, benzaldehydes bearing various functional groups proceeded smoothly to afford the desired products in good yields with a good *Z*/*E* ratio (over 10 to 1) (**4a**−**k**). The relatively bulky Me substituent at the *ortho* position did not hamper the reactivity (**4e**). Besides, the methodology allowed for employing the substrates bearing heterocyclic rings (**4l**−**n**) without deactivating the catalyst, generating the corresponding enyne products of versatile structures. This cascade protocol was also suitable for alkyl and alkenyl aldehydes, although a slight compromise of *Z*/*E* selectivity was observed (**4o**−**s**).

Scheme 2. Substrate Scope of Aldehyde[a]

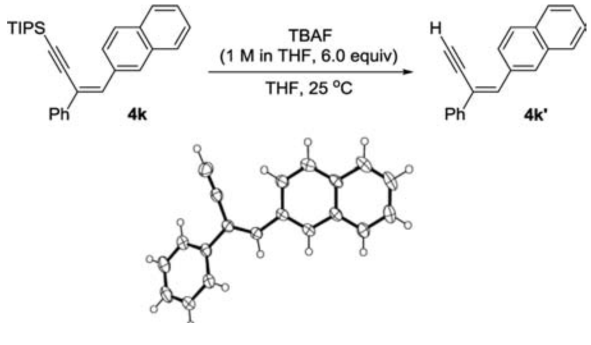


[a] Reaction conditions: α-diazo phenylmethylphosphonate **1a** (0.20 mmol), alkyne **2** (0.20 mmol), and aldehydes **3a**−**s** (0.30 mmol) in 1,4-dioxane (0.5 mL). All the yields refer to products isolated after column chromatography. *Z*/*E* ratio is determined by ^{1}H NMR of the crude products.

The *Z* configuration of the major products was established by ^{1}H NMR spectra data. It was further confirmed by the X-ray structure of desilylated compound **4k**′ (Scheme 3).[15]

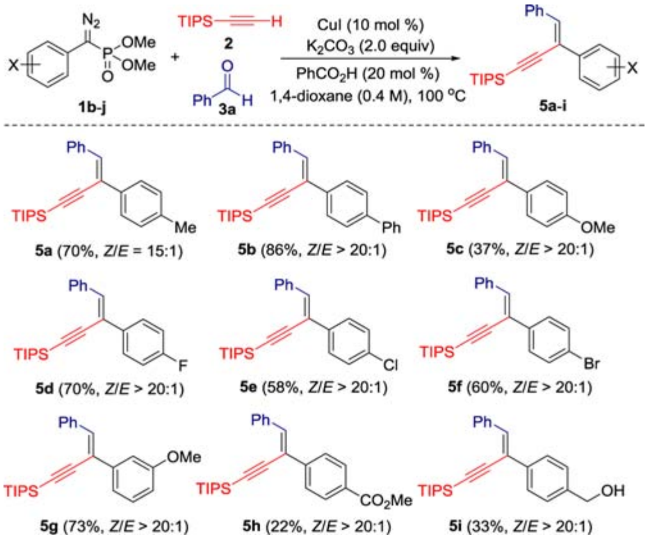
Subsequently, a series of aryl diazophosphonates were subjected to the standard conditions (Scheme 4). The substrates containing electron-donating groups were found to undergo the desired transformation to afford the corresponding conjugated enynes with improved stereoselectivity (**5a**−**c**). To

Scheme 3. Desilylation of Conjugated Enyne 4k and the Crystal Structure of the Product 4k′[a]



[a] TBAF: tetrabutylammonium fluoride.

Scheme 4. Substrate Scope of α-Diazo Phosphonates[a]

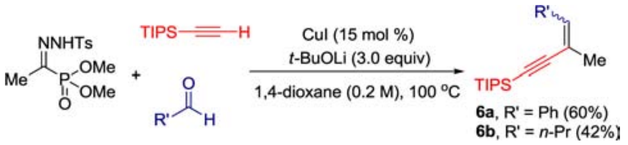


[a]Reaction conditions: α-diazo arylmethylphosphonates **1b–j** (0.20 mmol), alkyne **2** (0.20 mmol), and benzaldehyde **3a** (0.30 mmol) in 1,4-dioxane (0.5 mL). All the yields refer to the products isolated after column chromatography. *Z*/*E* ratio was determined by ^{1}H NMR spectra of the crude product.

our delight, this protocol is also compatible with halogen substituents, rendering the possibility for further transformation (**5d–f**). However, when we switched the substrates to the diazo compound bearing an ester group, the product was only obtained in modest yield (**5h**). This limitation may be attributed to the reluctance of this substrate to undergo a dediazonization step to generate a Cu(I) carbene intermediate. Gratifyingly, a diazo compound containing a free hydroxyl group was successfully converted into the corresponding product **5i**.

Finally, to further showcase the generality of this synthetic strategy, we also employed the *N*-tosylhydrazones in this cascade transformation, as the related alkyl diazophosphonates are not stable or have low boiling points for their preparation and purification. To our delight, we were able to obtain the desired enyne products by simply changing the base from K_2CO_3 to *t*-BuOLi (Scheme 5). However, the stereoselectivity of the double bonds became poor for these examples because of the decreased steric difference between the alkynyl and alkyl groups. In addition, the alkyl group is less electron-withdrawing than the aryl group, which may account for the slightly diminished yields.

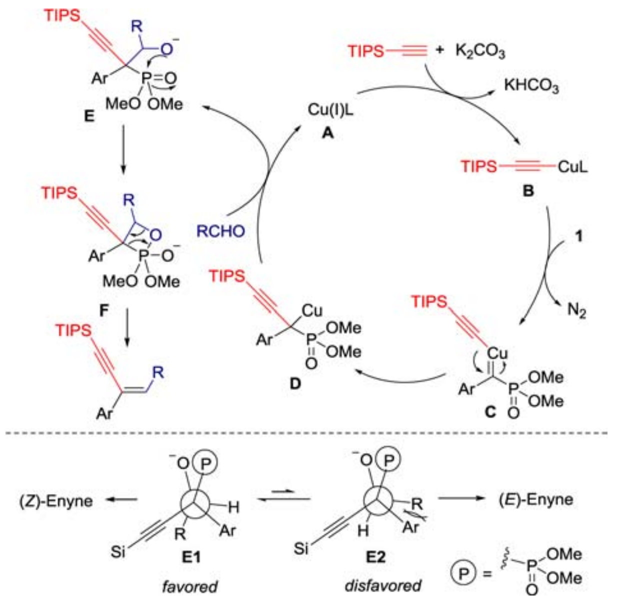
Scheme 5. Reaction with *N*-Tosylhydrazones[a]



[a]Reaction conditions: *N*-tosylhydrazone (0.30 mmol), alkyne **2** (0.20 mmol), and aldehyde (0.30 mmol) in 1,4-dioxane (1.0 mL). The yields refer to the products isolated after column chromatography.

The proposed reaction mechanism is shown in Scheme 6 based on the literature precedents for the related carbene coupling.[9,10a,16] First, alkynyl copper species **B** is formed with the assistance of a base. Then Cu(I) carbene intermediate **C** is generated from the diazo substrate, followed by the migratory insertion of the alkynyl group to afford the nucleophilic Cu(I) species **D**. Instead of undergoing a protonation step,[10a] this intermediate further reacts with aldehydes and affords the final product through an HWE-type reaction. The high *Z* stereoselectivity for the double bond formation should be attributed to the bulkiness disparity of the aryl ring and alkynyl group. For the intermediate **E** generated from the nucleophilic addition step, the conformer **E1** is more stable and thus the dominant species as compared to conformer **E2**, leading to the formation of (*Z*)-enyne as the major product.

Scheme 6. Proposed Reaction Mechanism and Rationale of the Stereoselectivity



In summary, we have developed a highly efficient three-component reaction for the synthesis of conjugated enynes, where one C–C bond and one C=C bond were formed successively in a one-pot manner. This method was applicable to a wide variety of easily accessible aldehydes and α-diazo phosphonates, affording the enyne products stereoselectively within a simple catalytic system. It is worth mentioning that α-diazo phosphonates are easily available and are relatively stable,[17] making this new enyne synthesis practically useful.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00631.

X-ray crystallographic data for **4′** (CIF)
Experiment details, spectra data and copies of ^{1}H and ^{13}C NMR spectra for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangjb@pku.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was supported by the 973 program (2015CB856600) and NSFC (Grants 21272010 and 21332002).

■ REFERENCES

(1) For reviews, see: (a) Nicolaou, K. C.; Dai, W.; Tsay, S.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172−1178. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (c) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (d) Henkelmann, J. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrman, W. A., Eds.; VCH: New York, 1996. (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901−2915. For examples, see: (f) Nussbaumer, P.; Leitner, I.; Mraz, K.; Stutz, A. *J. Med. Chem.* **1995**, *38*, 1831−1836. (g) Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006−10007. (h) Tsukamoto, S.; Takahashi, M.; Matsunaga, S.; Fusetani, N.; van Soest, R. W. M. *J. Nat. Prod.* **2000**, *63*, 682−684.

(2) For examples of enyne in material sciences, see: (a) Liu, Y.; Nishiura, M.; Wang, Y.; Hou, Z. *J. Am. Chem. Soc.* **2006**, *128*, 5592−5593. (b) Kaminker, R.; Popovitz-Biro, R.; van der Boom, M. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 3224−3226.

(3) For representative publications, see: (a) Wadsworth, W., Jr.; Emmons, W. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. (b) Wadsworth, D.; Schupp, O., III; Seus, E., Jr.; Ford, J. *J. Org. Chem.* **1965**, *30*, 680−685. (c) Maryanoff, B.; Reitz, A. *Chem. Rev.* **1989**, *89*, 863−927. (d) Shen, Y.; Qiu, W. *J. Chem. Soc., Chem. Commun.* **1987**, 703−704. (e) Karatholuvhu, M.; Fuchs, P. *J. Am. Chem. Soc.* **2004**, *126*, 14314−14315.

(4) For selected publications, see: (a) Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486−3487. (b) Ohshita, J.; Furumori, K.; Matsuguchi, A.; Ishikawa, M. *J. Org. Chem.* **1990**, *55*, 3277−3280. (c) Dash, A. K.; Eisen, M. S. *Org. Lett.* **2000**, *2*, 737−740. (d) Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 11107−11108. (e) Yang, C.; Nolan, S. P. *J. Org. Chem.* **2002**, *67*, 591−593. (f) Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* **2003**, *125*, 1184−1185. (g) Ogoshi, S.; Ueta, M.; Oka, M.; Kurosawa, H. *Chem. Commun.* **2004**, 2732−2733. (h) Komeyama, K.; Kawabata, T.; Takehira, K.; Takaki, K. *J. Org. Chem.* **2005**, *70*, 7260−7266. (i) Katayama, H.; Yari, H.; Tanaka, M.; Ozawa, F. *Chem. Commun.* **2005**, 4336−4338. (j) Ghosh, R.; Zhang, X.; Achord, P.; Emge, T. J.; Krogh-Jespersen, K.; Goldman, A. S. *J. Am. Chem. Soc.* **2007**, *129*, 853−866. (k) Tsukada, N.; Ninomiya, S.; Aoyama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919−2921. (l) Bassetti, M.; Pasquini, C.; Raneri, A.; Rosato, D. *J. Org. Chem.* **2007**, *72*, 4558−4561. (m) Matsuyama, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2008**, *350*, 2274−2278. (n) Wu, Y.; Lin, W.; Liu, C.; Wu, C. *Adv. Synth. Catal.* **2008**, *350*, 1841−1849. (o) Sakurada, T.; Sugiyama, Y.; Okamoto, S. *J. Org. Chem.* **2013**, *78*, 3583−3591. (p) Midya, G. C.; Parasar, B.; Dhara, K.; Dash, J. *Org. Biomol. Chem.* **2014**, *12*, 1812−1822.

(5) For selected publications, see: (a) Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, *1979*, 826−830. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972−980. (c) Stang, P. J.; Kitamura, T. *J. Am. Chem. Soc.* **1987**, *109*, 7561−7563. (d) Kang, S.; Kim, W.; Jiao, X. *Synthesis* **1998**, *1998*, 1252−1254. (e) Silveira, C. C.; Braga, A. L.; Vieira, A. S.; Zeni, G. *J. Org. Chem.* **2003**, *68*, 662−665. (f) Sorg, A.; Brückner, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4523−4526. (g) Hoshi, M.; Nakayabu, H.; Shirakawa, K. *Synthesis* **2005**, *2005*, 1991−2007. (h) Kakusawa, N.; Yamaguchi, K.; Kurita, J. *J. Organomet. Chem.* **2005**, *690*, 2956−2966. (i) Hoshi, M.; Kawamura, N.; Shirakawa, K. *Synthesis* **2006**, *2006*, 1961−1970. (j) Ahammed, S.; Kundu, D.; Ranu, B. C. *J. Org. Chem.* **2014**, *79*, 7391−7398. (k) Cornelissen, L.; Lefrancq, M.; Riant, O. *Org. Lett.* **2014**, *16*, 3024−3027. (l) Cheung, C.; Hu, X. *Chem. - Eur. J.* **2015**, *21*, 18439−18444.

(6) For selected publications, see: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470. (b) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716−4721. (c) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 4107−4110. (d) Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* **2001**, *42*, 8641−8644. (e) Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661−1664. (f) Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441−1444. (g) Feuerstein, M.; Chahen, L.; Doucet, H.; Santelli, M. *Tetrahedron* **2006**, *62*, 112−120. (h) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844−4850. (i) Xie, X.; Xu, X.; Li, H.; Xu, X.; Yang, J.; Li, Y. *Adv. Synth. Catal.* **2009**, *351*, 1263−1267. (j) Liu, Y.; Yang, J.; Bao, W. *Eur. J. Org. Chem.* **2009**, *2009*, 5317−5320. (k) Zhu, Y.; Li, T.; Qu, X.; Sun, P.; Yang, H.; Mao, J. *Org. Biomol. Chem.* **2011**, *9*, 7309−7312. (l) Saha, D.; Chatterjee, T.; Mukherjee, M.; Ranu, B. C. *J. Org. Chem.* **2012**, *77*, 9379−9383. (m) Huang, M.; Feng, Y.; Wu, Y. *Tetrahedron* **2012**, *68*, 376−381.

(7) Zhou, L.; Ye, F.; Ma, J.; Zhang, Y.; Wang, J. *Angew. Chem.* **2011**, *123*, 3572−3576.

(8) Xia, Y.; Liu, Z.; Ge, R.; Xiao, Q.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 11233−11235.

(9) For reviews, see: (a) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162−10173. (b) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236−247. (c) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586−2598. (d) Liu, Z.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 10024−10030.

(10) (a) Ye, F.; Ma, X.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2012**, *134*, 5742−5745. (b) Li, X.; Liu, X.; Chen, H.; Wu, W.; Qi, C.; Jiang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14485−14489.

(11) (a) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114−1117. (b) Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1236−1241. (c) Li, J.; Ding, D.; Liu, L.; Sun, J. *RSC Adv.* **2013**, *3*, 21260−21266. (d) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2014**, *16*, 4082−4085. (e) Ye, F.; Wang, C.; Ma, X.; Hossain, M. L.; Xia, Y.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 647−652. (f) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9512−9516.

(12) (a) Ye, F.; Hossain, M. L.; Xu, Y.; Ma, X.; Xiao, Q.; Zhang, Y.; Wang, J. *Chem. - Asian J.* **2013**, *8*, 1404−1407. (b) Wang, C.; Ye, F.; Wu, C.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 8748−8757.

(13) Zhou, Y.; Ye, F.; Wang, X.; Xu, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 6109−6118.

(14) For an enyne synthesis based on a Pd-catalyzed three-component coupling reaction, see: Sakai, N.; Komatsu, R.; Uchida, N.; Ikeda, R.; Konakahara, T. *Org. Lett.* **2010**, *12*, 1300−1303.

(15) CCDC 1440515 contains 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.

(16) For a computational study, see: (a) Wang, T.; Wang, M.; Fang, S.; Liu, J.-Y. *Organometallics* **2014**, *33*, 3941−3949. For an example of a related Pd-catalyzed reaction, see: (b) Wu, X.-X.; Shen, Y.; Chen, W.-L.; Chen, S.; Hao, X.-H.; Xia, Y.; Xu, P.-F.; Liang, Y.-M. *Chem. Commun.* **2015**, *51*, 8031−8033.

(17) For general reviews on diazo compounds, see: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (c) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577−6605. For a recent report on the preparation of α-diazo arylmethylphosphonates, see: (d) Ye, F.; Wang, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 11625−11628.