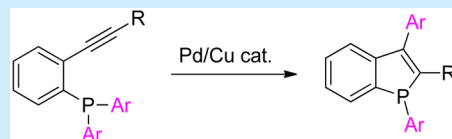


Intramolecular, Pd/Cu-Co-catalyzed P–C Bond Cleavage and Addition onto an Alkyne: A Route to Benzophospholes

Yang Zhou,[†] Zhenjie Gan,[†] Bo Su,[†] Jun Li,[†] Zheng Duan,^{*,†} and François Mathey^{*,†,‡}[†]College of Chemistry and Molecular Engineering, International Phosphorus Laboratory, International Joint Research Laboratory for Functional Organophosphorus Materials of Henan Province, Zhengzhou University, Zhengzhou 450001, P.R. China[‡]Nanyang Technological University, Division of Chemistry & Biological Chemistry, 21 Nanyang Link, Singapore 637371

S Supporting Information

ABSTRACT: Under Pd(II)/CuI cocatalysis, *o*-diarylphosphinophenylalkynes cyclize in boiling toluene via C–P bond cleavage and arylphosphination of the C≡C bond. This protocol provides an unprecedented atom- and step-efficient access to optoelectronically and biologically interesting benzophospholes.

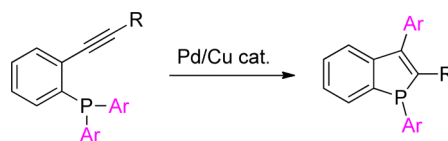


Tertiary phosphines have been broadly used as preferred ligands for transition-metal-centered catalysts due to their robust C–P bonds and the unique opportunity to modify the steric and electronic properties of the ligand. Meanwhile, the C–P bond activation of tertiary phosphines by transition metals is a fundamental reaction and an important research topic in both modern experimental and theoretical chemistry. Many years ago, it was discovered that transition metals can insert into the C–P bonds of tertiary phosphines.¹ Most of the examples concern the stoichiometric reactions between transition metals and phosphines to give stable phosphido complexes.^{1a–f} There are only limited examples of catalytic activation of C–P bonds of tertiary phosphines where the phosphine was used as a carbon source or a phosphorus source. For example, as a carbon source, several groups reported the application of triaryl phosphines as aryl donors in reactions with alkenes² or as coupling partners in palladium-catalyzed aryl–aryl couplings.³ Tetraphenylphosphonium salts were used as arylating reagents in Pd-catalyzed reactions with olefins, organoboron compounds, and terminal alkynes.⁴ However, only one of the substituents on phosphorus can be utilized in the aforementioned reactions. As a phosphorus source, a facile phosphination of substituted aryl bromides or aryl triflates with triaryl phosphines as phosphinating agents was developed by Chan's group.⁵ Tobisu and Chatani reported a direct synthesis of phospholes⁶ and dibenzo-fused six-membered phosphacycles⁷ through a Pd-catalyzed C–P bond cleavage of triaryl phosphines. That said, the cleaved aryl part was left as the byproduct. The only highly atom-efficient reaction was developed by Wu et al. through a Ni(0)-catalyzed arylphosphination of a highly strained three-membered ring system with triaryl phosphines via C–C and C–P bond cleavage.⁸

Very recently, we developed a simple method to synthesize benzophospholes from 2-(arylethynyl)phenyl phosphines via lithium-mediated selective P–C bond cleavage and cycloaddition, but an excess amount of lithium was used.⁹ Benzophospholes are frequently used in organic electronics,¹⁰ bioimaging probes,¹¹ and catalysts.¹² Several efficient methods have been developed for the preparation of these compounds.¹³

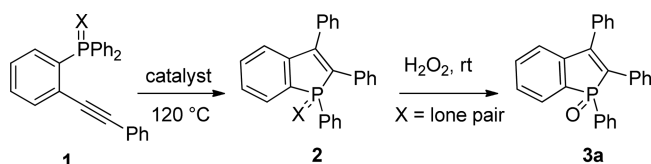
In connection with our efforts to develop new methods for selective activation of P–C bonds of triaryl phosphines, herein we report the first highly atom-efficient and step-economic Pd- and Cu-co-catalyzed arylphosphination of the C≡C triple bond to give 2,3-disubstituted benzophospholes from 2-(arylethynyl)-phenyl phosphines (Scheme 1) via activation of the stable P–Ar bond.

Scheme 1. Co-catalyzed Synthesis of Benzophospholes



We began our studies with **1a**, which was synthesized via the previously described simple protocol.⁹ We observed that when the reaction was carried at 120 °C in toluene with 10 mol % of Pd(OAc)₂ as a catalyst no reaction was observed (Table 1, entry 1). As we added 10 mol % of CuI as co-catalyst, surprisingly, the reaction proceeded smoothly to give **2a**. Subsequent in situ oxidation with H₂O₂ gave stable benzophosphole oxide **3a**, which was isolated in 41% yield (entry 2). The structure of **3a** was analyzed by ¹H, ¹³C, and ³¹P NMR and mass spectrometry and compared with the reported one.^{13a,c,e} No reaction was observed with CuI catalyst only (entry 3). Among the other palladium catalysts, Pd(PPh₃)₂Cl₂ was found to co-catalyze this reaction and gave the desired **3a** (entry 4). Pd(PPh₃)₄ and PdCl₂ did not catalyze this reaction (entries 5 and 6). CuBr showed a comparable activity to CuI, but the reaction time was longer (entry 7). The presence of the lone pair on phosphorus had a profound impact on the efficiency of the reaction, and both oxidation (entry 8) and coordination (entry 9) inhibited the formation of **2**.

Received: October 8, 2015

Table 1. Optimization of the Reaction Conditions^a

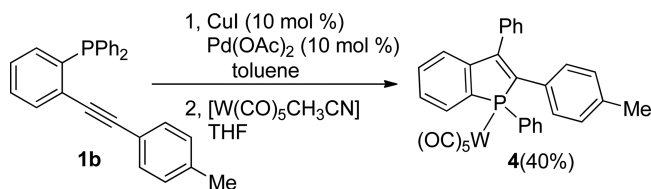
1a X = Lone pair
1aO X = O
1aB X = BH₃

entry	1	Pd (10 mol %)	Cu (10 mol %)	yield ^b (%)
1	1a	Pd(OAc) ₂		NR
2	1a	Pd(OAc) ₂	CuI	41
3	1a		CuI	NR
4	1a	Pd(PPh ₃) ₂ Cl ₂	CuI	40
5	1a	Pd(PPh ₃) ₄	CuI	trace
6	1a	PdCl ₂	CuI	trace
7	1a	Pd(OAc) ₂	CuBr	37 ^c
8	1aO	Pd(OAc) ₂	CuI	NR
9	1aB	Pd(OAc) ₂	CuI	NR

^aReaction conditions: **1** (1 mmol), 120 °C, toluene (5 mL), for 2 h.

^bIsolated yield of **3**. ^cFor 4 h.

To the best of our knowledge, this is the first catalytic addition of a P–Ph bond across a C≡C triple bond. In order to confirm this kind of reaction, we checked this catalytic system (using 10 mol % of Pd(OAc)₂ and 10 mol % of CuI as co-catalyst, at 120 °C, in toluene) with 2-(arylethynyl)phenylphosphine **1b**. The corresponding W(CO)₅ complex **4** was synthesized (Scheme 2),

Scheme 2. Synthesis of W(CO)₅ Complex **4**

and X-ray structural data of **4** were acquired (Figure 1), confirming the unexpected catalytic addition of P–C bond to a C≡C triple bond. It is clearly shown that there is one phenyl group at the 3-position of the final benzophosphole, which is definitely coming from the diphenylphosphino group. However, under same reaction conditions, no reaction between PPh₃ and diphenylacetylene was observed.

Next, we investigated the scope and limitations of this bimetallic catalyst system with various 2-(arylethynyl)-phenylphosphines (Table 2). From the results, we can see that the efficiency of the cyclization reaction is highly dependent on the electronic nature of the substrates. When **1a**, **1b**, and **1c** were used, the yields were moderate (entries 1–3, **3a** (41%), **3b** (52%), **3c** (43%)). Low yields were obtained with electron-donating methoxy-substituted **3e** (32%, entry 4), as only 7% of **3f** was achieved with amino substituted **1f**, and the yield of **3f** could be improved to 29% by replacing Pd(OAc)₂ with Pd(PPh₃)₂Cl₂ (entry 6). Compound **3f** can be used as a fluorescent probe for the environmental polarity in biological systems. It was previously synthesized by a stepwise formation of the phosphacycle and introduction of the phenyl group at 3-position, with workup stages after each transformation.¹¹ Good yields were obtained with electron-withdrawing F (72%, entry 7) and CF₃

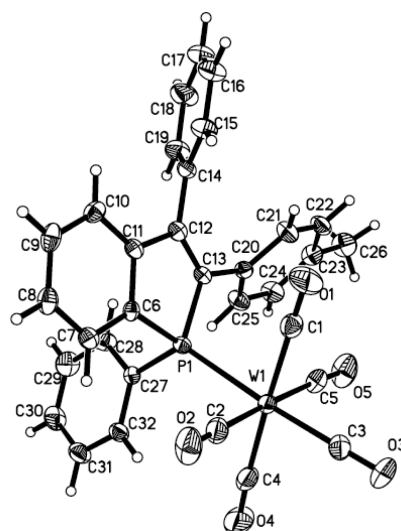


Figure 1. X-ray crystal structure of **4**. The level set for thermal ellipsoids of all atoms is 30%. Main bond lengths (Å) and angles (deg): P1–C6 1.808(4), C6–C11 1.403(5), C11–C12 1.490(5), C12–C13 1.347(5), C13–P1 1.825(4), P1–W1 2.5173(11); P1–C27 1.834(3), C6–P1–C13 90.96(18).

Table 2. Variation on the Substituents^a

entry	Ar	3 (yield /%) ^b	entry	Ar	3 (yield /%) ^b
1	Ph	1a 3a (41)	6 ^c		1f 3f (7)
2		1b 3b (52)			3f (29) ^d
3		1c 3c (43)	7		1g 3g (72)
4		1d 3d (45)	8		1h 3h (68)
5 ^c		1e 3e (32)	9		1i 3i (NR)

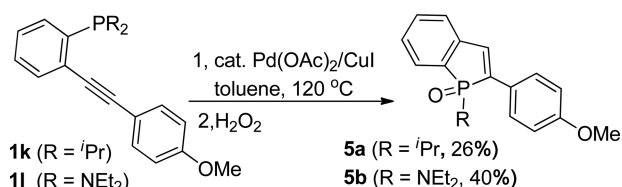
^aReaction conditions: **1** (1 mmol), Pd(OAc)₂ (0.1 mmol), CuI (0.1 mmol), toluene (5 mL), at 120 °C for 2 h. ^bIsolated yield. ^cFor 4 h.

^dPd(PPh₃)₂Cl₂ was used instead of Pd(OAc)₂

(68%, entry 8) substituents. No reaction was observed with 1-naphthyl-substituted **1i** (entry 9), which may be due to the steric hindrance of the naphthalene ring.

Furthermore, the cycloaddition with diisopropyl- (**1k**) or diethylamino-substituted phosphine (**1l**) took place smoothly to give benzophosphole oxide **5a** and **5b** after workup, respectively (Scheme 3). We propose that the proton on the 3-position in **5a**

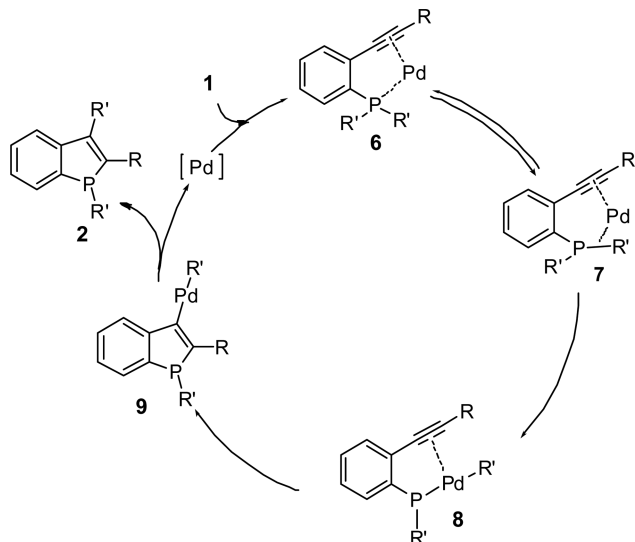
Scheme 3. Case of Alkyl and Amino Substituents



comes from the β -H elimination of an isopropyl-Pd intermediate. To the best of our knowledge, **1k** is the first example of Pd-catalyzed P–Csp³ bond cleavage.

We propose the following reaction mechanism² (Scheme 4): (1) both the lone pair on the phosphine and the alkynyl group are

Scheme 4. Proposed Mechanism



crucial for the success of this reaction, and coordination of Pd species with 2-(arylethynyl)phenylphosphine **1** gives a bidentate palladium complex **6**; (2) the presence of a vicinal alkynyl group facilitates the intramolecular activation of the P–R' bond by the Pd center via **7**; (3) insertion of Pd into the P–R' bond gives phosphido complex **8**; (4) phosphopalladation of vicinal alkyne gives a vinylic palladium intermediate **9**; (5) reductive elimination affords a benzophosphole **2** with regeneration of the Pd catalyst. The role of CuI is unclear at this moment; it might be crucial for the cycloaddition step since no cyclized compound was obtained without CuI.¹⁴ In the cases of **1k** (R' = ⁱPr) and **1l** (R' = NEt₂), **5** was formed from the β -H elimination of isopropyl–Pd intermediate **9**.

In conclusion, we have developed a new catalytic arylphosphination of the C $\equiv$ C bond with a Pd(OAc)₂/CuI bimetallic catalyst system via P–C bond activation of stable tertiary phosphines. This protocol provides an unprecedented atom- and step-efficient access to optoelectronically and biologically interesting 2,3-substituted benzophospholes by simultaneous cycloaddition and arylation. Extension of the scope and investigations on the mechanism of this reaction are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02926.

X-ray data for **4** (CIF)

Experimental section; NMR data for **2–5** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: duanzheng@zzu.edu.cn.

*E-mail: fmathey@ntu.edu.sg.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation (No. 21272218), Specialized Research Fund for the Doctoral Program of Higher Education (No. 20134101110004), Henan Science and Technology Department (No. 144300510011), Zhengzhou Science and Technology Department (No. 131PYSZ204) and Zhengzhou University of China.

■ REFERENCES

- (1) (a) Yeh, W.-Y.; Tsai, K.-Y. *Organometallics* **2010**, *29*, 604. (b) Kabir, S. E.; Ahmed, F.; Ghosh, S.; Hassan, M. R.; Islam, M. S.; Sharmin, A.; Tocher, D. A.; Haworth, D. T.; Lindeman, S. V.; Siddiquee, T. A.; Bennett, D. W.; Hardcastle, K. I. *J. Organomet. Chem.* **2008**, *693*, 2657. (c) Macgregor, S. A. *Chem. Soc. Rev.* **2007**, *36*, 67. (d) Parkins, A. W. *Coord. Chem. Rev.* **2006**, *250*, 449. (e) Bruce, M. I.; Humphrey, P. A.; Okucu, S.; Schmutzler, R.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta* **2004**, *357*, 1805. (f) Gracia, C.; Marco, G.; Navarro, R.; Romero, P.; Soler, T.; Urriolabeitia, E. P. *Organometallics* **2003**, *22*, 4910. (g) Keim, W.; Behr, A.; Gruber, B.; Hoffmann, B.; Kowaldt, F. H.; Kurschner, U.; Limbäcker, B.; Sisti, F. P. *Organometallics* **1986**, *5*, 2356. (h) Chakravarty, A. R.; Cotton, F. A. *Inorg. Chem.* **1985**, *24*, 3584. (i) Garrou, P. E. *Chem. Rev.* **1985**, *85*, 171.
- (2) (a) Zhou, H.; Li, J.-X.; Yang, H.-M.; Xia, C.-G.; Jiang, G.-X. *Org. Lett.* **2015**, *17*, 4628. (b) Lu, D.-P.; Xu, Y.; Liu, W.-J.; Guo, L.-J.; Sun, X.-X. *Helv. Chim. Acta* **2015**, *98*, 116. (c) Ma, M.-T.; Lu, J.-M. *Tetrahedron* **2013**, *69*, 2102.
- (3) Li, Z.-Y.; Zhou, H.-P.; Xu, J.-Y.; Wu, X.-M.; Yao, H.-Q. *Tetrahedron* **2013**, *69*, 3281.
- (4) (a) Hwang, L. K.; Na, Y.; Lee, J.; Do, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 6166. (b) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481.
- (5) (a) Kwong, F.-Y.; Lai, C.-W.; Yu, M.; Tian, Y.; Chan, K.-S. *Tetrahedron* **2003**, *59*, 10295. (b) Kwong, F.-Y.; Chan, K.-S. *Organometallics* **2001**, *20*, 2570. (c) Kwong, F.-Y.; Chan, K.-S. *Organometallics* **2000**, *19*, 2058. (d) Kwong, F.-Y.; Chan, K.-S. *Chem. Commun.* **2000**, 1069.
- (6) Baba, K.; Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11892.
- (7) Baba, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015**, *17*, 70.
- (8) Cao, J.; Huang, X.; Wu, L.-L. *Chem. Commun.* **2013**, *49*, 7747.
- (9) Xu, Y.-Z.; Wang, Z.-H.; Gan, Z.-J.; Xi, Q.-Z.; Duan, Z.; Mathey, F. *Org. Lett.* **2015**, *17*, 1732.
- (10) (a) Ren, Y.; Baumgartner, T. *Dalton Trans.* **2012**, *41*, 7792. (b) Tsuji, H.; Sato, K.; Sato, Y.; Nakamura, E. *Chem. - Asian J.* **2010**, *5*, 1294. (c) Tsuji, H.; Sato, K.; Sato, Y.; Nakamura, E. *J. Mater. Chem.* **2009**, *19*, 3364. (d) Matano, Y.; Imahori, H. *Org. Biomol. Chem.* **2009**, *7*, 1258. (e) Crassous, J.; Réau, R. *Dalton Trans.* **2008**, 6865.
- (11) Yamaguchi, E.; Wang, C.-G.; Fukazawa, A.; Taki, M.; Sato, Y.; Sasaki, T.; Ueda, M.; Sasaki, N.; Higashiyama, T.; Yamaguchi, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 4539.
- (12) Gicquel, M.; Zhang, Y.; Aillard, P.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 5470.
- (13) (a) Wu, B.; Santra, M.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7543. (b) Ma, S.; Ackermann, L. *Synthesis* **2014**, *46*, 2297. (c) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12975. (d) Matano, Y.; Hayashi, Y.; Suda, K.; Kimura, Y.; Imahori, H. *Org. Lett.* **2013**, *15*, 4458. (e) Chen, Y.-R.; Duan, W.-L. *J. Am. Chem. Soc.* **2013**, *135*, 16754. (f) Hayashi, Y.; Matano, Y.; Suda, K.; Kimura, Y.; Nakao, Y.; Imahori, H. *Chem. - Eur. J.* **2012**, *18*, 15972. (g) Fukazawa, A.; Ichihashi, Y.; Kosaka, Y.; Yamaguchi, S. *Chem. - Asian J.* **2009**, *4*, 1729. (h) Sanji, T.; Shiraishi, K.; Kashiwabara, T.; Tanaka, M. *Org. Lett.* **2008**, *10*, 2689. (i) Tsuji, H.; Sato, K.; Ilies, L.; Itoh, Y.; Sato, Y.; Nakamura, E. *Org. Lett.* **2008**, *10*, 2263.
- (14) Kamijo, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3230.