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

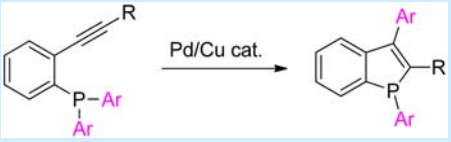
Yang Zhou,[†] Zhenjie Gan,[†] Bo Su,[†] Jun Li,[†] Zheng Duan,*[,†] and François Mathey*[,†,‡]

[†]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

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.

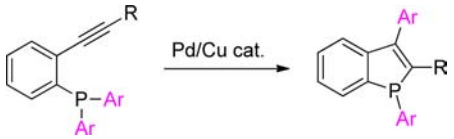


Tertiary phosphines have been broadly used as preferred ligands for transition-metal-centered catalysts due to their robust C−P bonds and the unique opportunity to modify the steric and electronic properties of the ligand. Meanwhile, the C−P bond activation of tertiary phosphines by transition metals 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 alkenes[2] 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 triarylphosphines as phosphinating agents was developed by Chan's group.[5] Tobisu and Chatani reported a direct synthesis of phospholes[6] and dibenzo-fused six-membered phosphacycles[7] through a Pd-catalyzed C−P bond cleavage of triarylphosphines. 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 triarylphosphines via C−C and C−P bond cleavage.[8]

Very recently, we developed a simple method to synthesize benzophospholes from 2-(arylethynyl)phenylphosphines 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 triarylphosphines, 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)-phenylphosphines (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 H_2O_2 gave stable benzophosphole oxide **3a**, which was isolated in 41% yield (entry 2). The structure of **3a** was analyzed by ^1H, ^{13}C, and ^{31}P 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, $Pd(PPh_3)_2Cl_2$ was found to co-catalyze this reaction and gave the desired **3a** (entry 4). $Pd(PPh_3)_4$ and $PdCl_2$ 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**.

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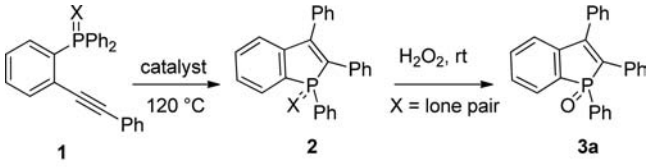
Table 1. Optimization of the Reaction Conditions[a]



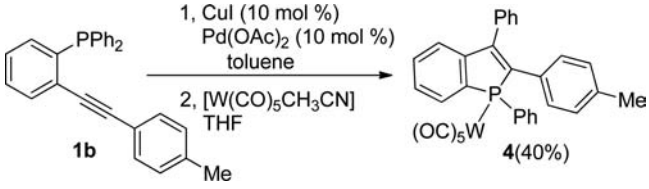
1a X = Lone pair
1aO X = O
1aB X = BH_3

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**	$Pd(PPh_3)_2Cl_2$	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

[a]Reaction conditions: **1** (1 mmol), 120 °C, toluene (5 mL), for 2 h. [b]Isolated yield of **3**. [c]For 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 PPh_3 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 $Pd(PPh_3)_2Cl_2$ (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 phospha-cycle 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 CF_3

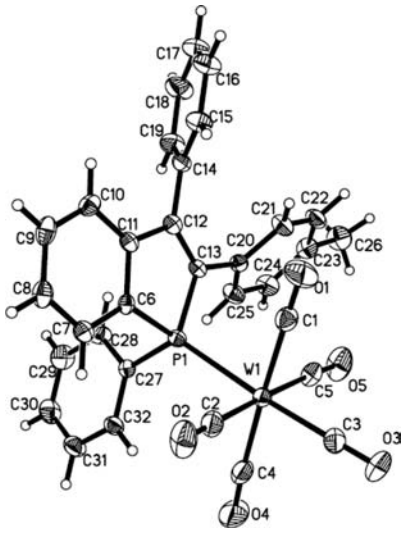
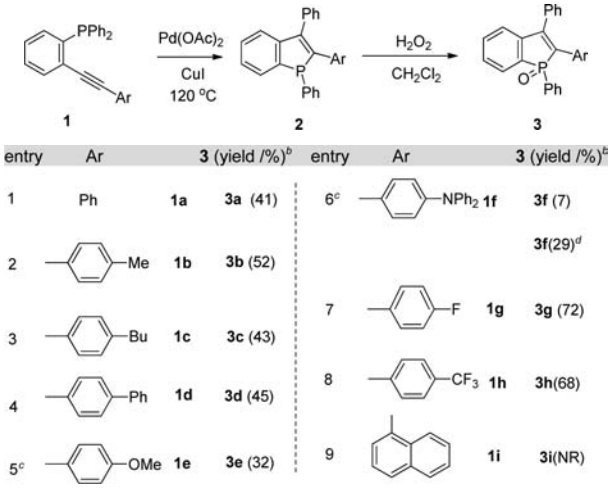


Figure 1. X-ray crystal structure of **4**. The level set for thermal ellipsoids of all atoms is 30%. Main bond lengths (Å) and angles (deg): P1−C6 1.808(4), C6−C11 1.403(5), C11−C12 1.490(5), C12−C13 1.347(5), C13−P1 1.825(4), P1−W1 2.5173(11); P1−C27 1.834(3), C6−P1−C13 90.96(18).

Table 2. Variation on the Substituents[a]



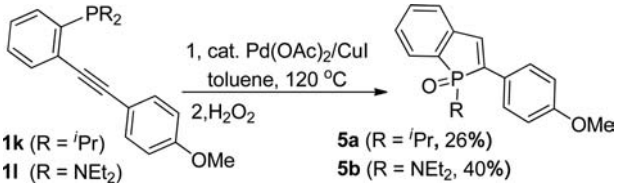
entry	Ar		3 (yield /%)[b]	entry	Ar		3 (yield /%)[b]
1	Ph	**1a**	**3a** (41)	6[c]	NPh_2	**1f**	**3f** (7)
2	Me	**1b**	**3b** (52)				**3f**(29)[d]
3	Bu	**1c**	**3c** (43)	7	F	**1g**	**3g** (72)
4	Ph	**1d**	**3d** (45)	8	CF_3	**1h**	**3h**(68)
5[c]	OMe	**1e**	**3e** (32)	9		**1i**	**3i**(NR)

[a]Reaction conditions: **1** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), CuI (0.1 mmol), toluene (5 mL), at 120 °C for 2 h. [b]Isolated yield. [c]For 4 h. [d]$Pd(PPh_3)_2Cl_2$ was used instead of $Pd(OAc)_2$

(68%, entry 8) substitutents. 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



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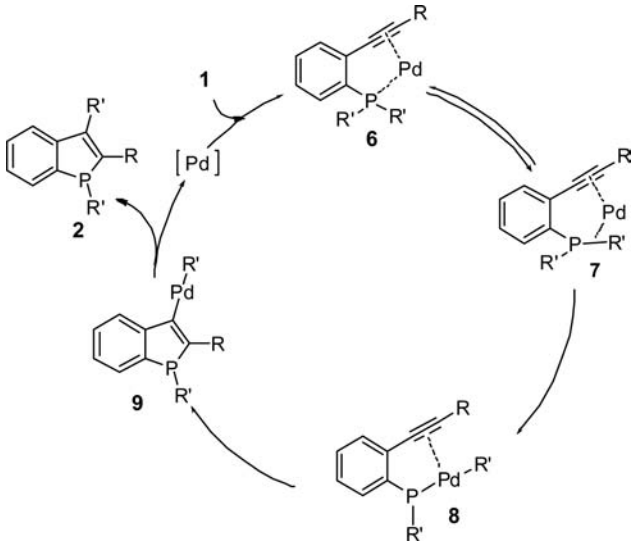
comes from the β-H elimination of an isopropyl-Pd intermediate. To the best of our knowledge, **1k** is the first example of Pd-catalyzed P−Csp^3 bond cleavage.

We propose the following reaction mechanism[2] (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′ = ^{i}Pr) and **1l** (R′ = NEt$_2$), **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≡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.

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