Pd-catalysed, Ag-assisted C2−H alkenylation of benzophospholes

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Pd-catalysed, Ag-assisted C2–H alkenylation of benzophospholes

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A palladium-catalysed, silver-assisted regioselective C2–H alkenylation of benzophospholes with terminal alkenes has been developed. The palladium catalysis accommodates styrenes and electron-deficient alkenes including ester, ketone, nitrile, and phosphonate. Thus, this protocol enables the rapid construction of various benzophosphole-vinylene conjugations from the two simple C–H starting substrates. Optical properties of newly synthesized C2-alkenylated benzophospholes are also investigated.

A benzophosphole is a pivotal heteroaromatic nucleus in the design of phosphorus-containing organic functional materials such as organic light-emitting diodes, solar cells, and imaging dyes, because of its unique photochemical, electrochemical, and physical properties.[1] Accordingly, many synthetic chemists have developed numerous ways to construct the phosphole rings, particularly, conjugated with other π systems. Among them, the C2-alkenylated benzophosphole is one of the intriguing heteroaryl-vinylene conjugation structures and receives attention in the field of phosphorus-containing material chemistry. Matano and Imahori reported the synthesis, characterization, and properties of several C2-alkenylated benzophospholes, in which the classical Mizoroki-Heck reaction or Kosugi-Migita-Stille cross-coupling reaction of the C2-bromobenzophosphole was employed for the key bond formation (Scheme 1a).[2] The starting brominated substrate was prepared from trimethylsilyl phenylacetylene via 3-step protocol, i.e., (1) DIBAL-H-mediated hydrobromination, (2) BuLi-mediated halogen-metal exchange/electrophilic trapping with $PhPCl_2$, and (3) desilylative bromination with NBS.[3] However, there still remains a large demand for the development of more concise and divergent strategy for the preparation of C2-alkenylated benzophospholes.

Meanwhile, recent advance in the metal-mediated C-H activation chemistry enables the rapid and diverse derivatization of simple (hetero)arenes because it can avoid preactivation, such as stoichiometric halogenation and metalation, of starting (hetero)arenes, which is inevitable in the classical metal-catalysed cross-coupling technology.[4] In particular, the metal-catalysed oxidative coupling between (hetero)arenes and alkenes, so-called the Fujiwara-Moritani reaction, is now a powerful synthetic tool for the construction of (hetero)arenes-vinylene π conjugation systems.[5] Although many *N*-, *S*-, and *O*-containing heteroarenes, such as indole, thiophene, and furane, are promising substrates in the Fujiwara-Moritani reaction, the successful reaction of a *P*-analogue, namely benzophosphole, has not been developed to date.[6] On the other hand, our research group recently reported the first successful example of palladium-catalysed C2-H arylation of benzophospholes with aryl halides.[7] In our continuing interest in this chemistry, we have now developed a palladium-catalysed, silver-assisted Fujiwara-Moritani-type reaction of benzophospholes with terminal alkenes (Scheme 1b). Given the availability of various C2-H benzophospholes from the corresponding 1,1-diarylethenes under our previous phosphorus dication-mediated conditions,[8] this protocol can provide a potentially divergent and straightforward approach to the benzophosphole-vinylene conjugation systems. Reaction optimization studies, substrate scope, preliminary mechanistic studies, and optical properties of newly synthesized C2-alkenylated benzophospholes are described herein.

Our optimization studies commenced with the C2-H benzophosphole **1a** and styrene (**2a**) to identify the suitable palladium catalyst and terminal oxidant (Table 1). In an early experiment, a toluene solution of **1a** (0.10 mmol) and **2a** (5.0 equiv) was heated in the presence $Pd(OAc)_2$ (10 mol %) and AgTFA (2.0 equiv) to afford the C2-alkenylated benzophosphole **3aa** (entry 1). The reaction was clean, and only the starting **1a** and targeted **3aa** were observed by ^{31}P NMR analysis of the crude mixture. The choice of the terminal oxidant was critical: AgTFA and AgOAc promoted the reaction while other Ag-based and Cu-based oxidants resulted in sluggish conversion (entries 2–6). The reaction also proceeded with a decreased amount of

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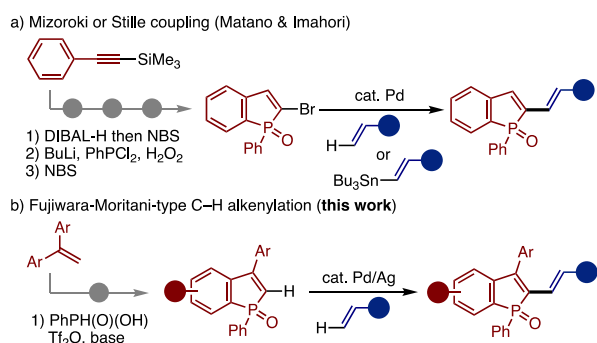
Scheme 1 Convergent approaches to C2-alkenylated benzophospholes.

Table 1 Optimization studies for Pd-catalysed C–H alkenylation of benzophosphole 1a with styrene (2a)[a]
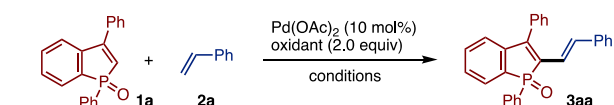
Entry	oxidant	conditions	ratio of 1a:3aa[b]
1	AgTFA	toluene, 110 ˚C, N$_2$	43:57
2	AgOAc	toluene, 110 ˚C, N$_2$	69:31
3	Ag$_2$CO$_3$	toluene, 110 ˚C, N$_2$	97:3
4	Ag$_2$O	toluene, 110 ˚C, N$_2$	95:5
5	Cu(TFA)$_2$	toluene, 110 ˚C, N$_2$	95:5
6	Cu(OAc)$_2$	toluene, 110 ˚C, N$_2$	92:8
7[c]	AgTFA	toluene, 110 ˚C, N$_2$	36:64
8[c]	AgTFA	toluene, 110 ˚C, air	37:63
9[c]	AgTFA	1,4-dioxane, 110 ˚C, air	22:78
10[c,d]	AgTFA	1,4-dioxane, 110 ˚C, air	10:90 (85)

[a] Conditions: 1a (0.10 mmol), 2a (0.50 mmol), Pd(OAc)$_2$ (0.010 mmol), oxidant (0.20 mmol), 20 h. [b] Estimated by ^{31}P NMR with P(O)(OEt)$_3$ as the internal standard. Isolated yield of 3aa is in parentheses. [c] With 2a (0.20 mmol). [d] With NaHCO$_3$ (0.20 mmol).

2a (2.0 equiv) even under atmospheric conditions (entries 7 and 8). Subsequent screening of solvent determined 1,4-dioxane to be better than toluene (entry 9). Additional investigation of additives revealed that NaHCO$_3$ further improved the reaction efficiency, and we finally isolated 3aa in 85% yield (entry 10). Some observations are to be noted: any regioisomers were not detected at all in site of the possibility of the phosphole P=O directed C–H activation on other aromatic rings.[9] Addition of P- and N-based supporting ligands showed negligible or negative effect on the reaction. No reaction occurred in the absence of any Pd salts (see the ESI for more details†).

With optimal conditions in hand, we investigated the scope of the reaction (Scheme 2). Several styrene derivatives that bear electron-donating and electron-withdrawing substituents at the para position were well tolerated (3ab–ae). The reaction with para-bromostyrene (2f) also provided the coupling

product 3af albeit in a moderate yield. In this case, the conversion of 1a was relatively low (ca. 55%), and the product with concomitant ptotodebromination, namely 3aa, was also formed in ca. 15% yield. Additionally, the π-conjugated biphenyl structure could be readily introduced (3ag). The sterically demanding ortho-methyl-substituted 2h was also amenable to the reaction whereas the more congested mesitylene-type substrate resulted in a lower conversion (3ai). On the other hand, the pentafluorophenylstyrene (2j) participated in the C-H alkenylation without any difficulty (3aj). Particularly notable is the successful coupling with the more π-extended naphthalene (3ak) and pyrene systems (3al). Furthermore, the double C–H alkenylation with 1,4-di(vinyl)benzene was also possible to form the corresponding phenylene-vinylene system 3am including two benzophosphole units in an acceptable yield. In addition to the styrene derivative, the palladium catalysis accommodated representative electron-deficient alkenes such as ketone, ester, nitrile, and phosphonate (3an–aq). The electron-deficient alkene generally showed lower reactivity than the styrene: this is probably because of the product inhibition. Actually, with 20 mol% of 3ao, the reaction of 1a with styrene (2a) under otherwise identical conditions dropped the yield of 3aa (69% yield vs 90% NMR yield under optimal conditions). The structures of 3al and 3aq were unambiguously confirmed by X-ray analysis (CCDC 2180994 and 2180995, respectively†). We note that the reaction could also be performed on a larger scale (1.0 mmol) albeit with somewhat lower efficiency (65%; 3aa). The feature of this strategy is that the functionalized benzophosphole nuclei are easily prepared from the corresponding 1,1-diarylethenes[7,8] and then readily undergo the C2–H alkenylation: electron-rich and -deficient benzophospholes 1b–f were coupled with styrene (1a) to deliver the targeted molecules 3ba–fa in moderate to good yields. Additionally, the methylene-bridged 1g and naphthophosphole 1h also participated in the reaction. In the case of 1h, the double C–H alkenylation with di(vinyl)benzene 2m was also possible to afford the corresponding largely π-conjugated system 3hm in a good yield.[10]

To get some insight into the reaction mechanism, we performed several control experiments. First, in place of the benzophosphole oxide 1a, the corresponding benzophosphole sulfide 1a-S and P(III) benzophosphole 1a-III were subjected to the standard conditions (Scheme 3a). However, the C2–H alkenylated benzophosphole sulfide 3aa-S and P(III) benzophosphole 3aa-III were not detected at all. In the case of 1a-S, the oxidized 1a was just recovered whereas a mixture of 1a and 3aa was observed from the reaction of 1a-III. These results suggest that neither 1a-S nor 1a-III themselves are reactive and stable under the standard reaction conditions. The H/D exchange reactions with acetic acid-d_4 were next conducted (Scheme 3b). Under the standard Pd/Ag conditions, 70% deuterium content was observed only at the C2 position, thus indicating that the C–H cleavage site-selectively occurs. Intriguingly, Pd(OAc)$_2$ alone did not catalyse any deuterium incorporation. On the other hand, several Ag salts promoted

the H/D exchange reaction, with AgTFA giving the 64% D value comparable to that under the standard conditions (see the ESI
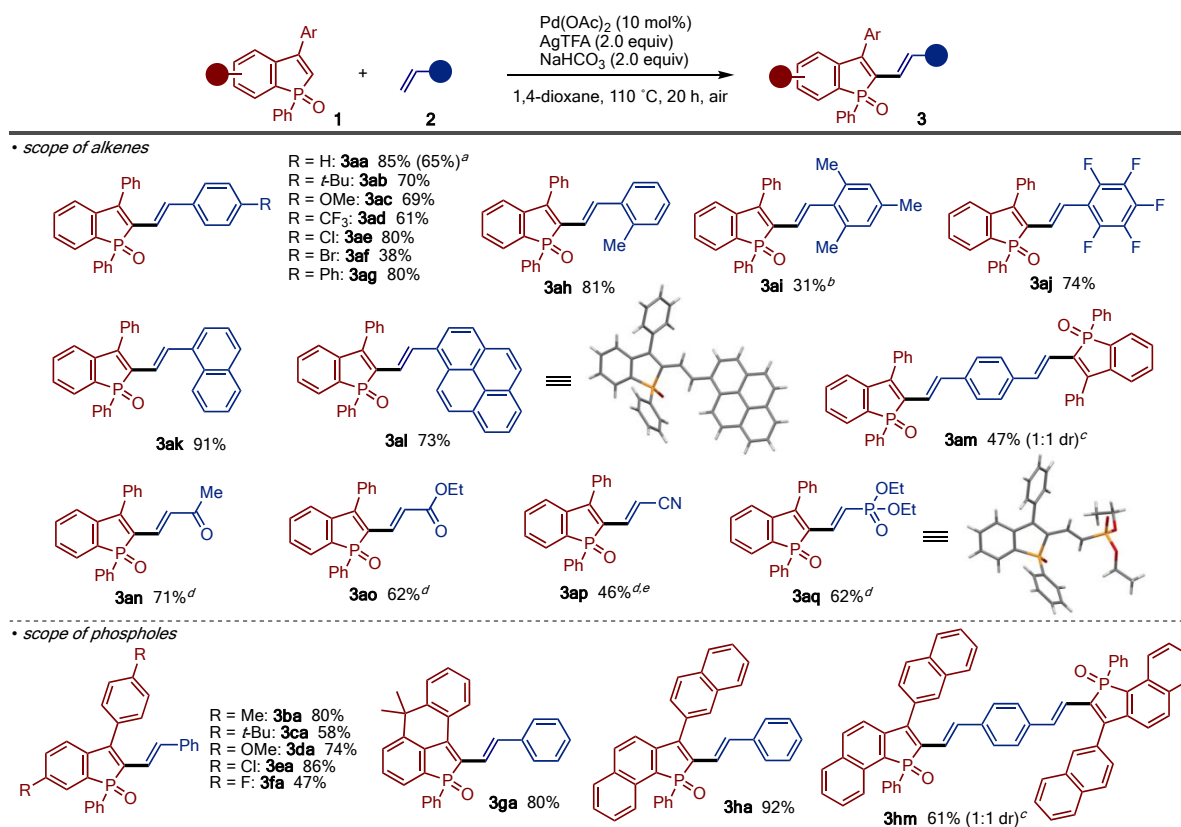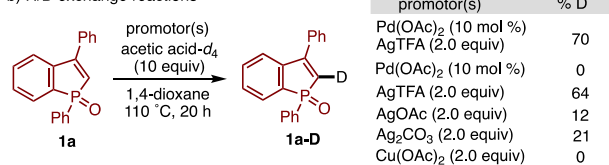

Scheme 2 Pd-catalysed C–H alkenylation of benzophospholes **1** with terminal alkenes **2**. Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), Pd(OAc)$_2$ (0.010 mmol), AgTFA (0.20 mmol), NaHCO$_3$ (0.20 mmol), 1,4-dioxane (1.0 mL), 110 ˚C, 20 h, air. Isolated yields are shown. [a] On a 1.0 mmol scale. [b] With Pd(OAc)$_2$ (0.020 mmol) at 150 ˚C. [c] With **1** (0.10 mmol) and **2** (0.050 mmol). [d] With Pd(OAc)$_2$ (0.020 mmol) and AgTFA (0.30 mmol). [e] E/Z = 92:8.
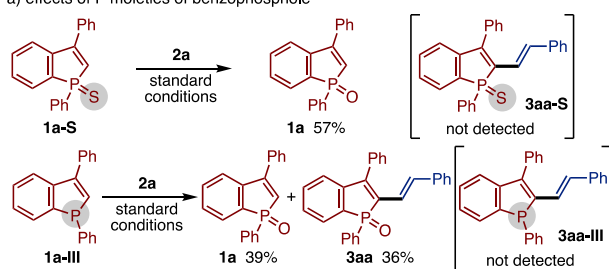

Scheme 3 Control experiments.

for additional data†). These phenomena indicate a pivotal role of Ag in the C–H cleavage step.

On the basis of the aforementioned control experiments and literature information,[5] we are tempted to propose that the mechanism of reaction of **1a** with **2a** is as follows (Scheme 4). The C2–H cleavage of **1a** mainly occurs by the action of AgTFA

to generate the corresponding Ag–benzophosphole intermediate **4**. Subsequent transmetalation with PdX$_2$ forms the Pd–benzophosphole species **5**. The C2–H alkenylated product **3aa** follows from insertion of styrene (**2a**) into the Pd–C bond of **5** and β-H elimination (**5** to **6** to **7** and **3aa**). The elimination of HX from HPdX **7** is followed by reoxidation with AgTFA to complete the catalytic cycle (**7** to **8** to PdX$_2$). Similar silver-assisted, palladium-catalysed C–H functionalisation reactions of thiophenes and (Cr-coordinated) fluoroarenes were reported, in which relatively acidic (hetero)aromatic C–Hs are cleaved with the silver carboxylate, carbonate, or oxide.[11] Such a reactivity trend is consistent with our observations in Scheme 3a, where the more electron-withdrawing P=O showed a better performance.[12] Although we cannot completely exclude the possibility of the unique directing effect of the P=O moiety, the relatively high acidity of C2–H in the benzophosphole oxide **1a** would play an important role in the C–H cleavage step.[13]

Finally, optical properties of some newly synthesized C2-alkenylated benzophospholes **3** were investigated (Figure S3 and Table S7 in the ESI†). To examine the effect of the Ph group at the C3 position, we initially measured UV-vis absorption and emission of **3aa**, **3ac**, **3ae**, and **3ak,** and compared the spectra with those of the corresponding C3-H derivatives, which were

synthesized and investigated by Matano and Imahori.[2] Whereas there was no significant difference in the H-, MeO-, and Cl-substituted benzophospholes (**3aa**, **3ac**, and **3ae**), the emission spectrum of the naphthalene-substituted **3ak** was
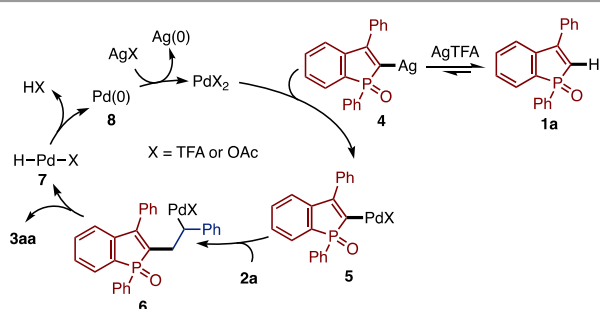
Scheme 4 Proposed reaction mechanism.

uniquely red-shifted by 40 nm. Our preliminary DFT calculations (Figures S4–S7 in the ESI†) suggest that the planarity of vinylene-naphthalene moiety of **3ak** specifically increases in the excited state, which is attributed to the observed red shift. Thus, the C3-substituent sometimes affects the π-conjugation of the C2-substituted benzophosphole. Actually, the orbital overlapping between the C2-vinylene moiety and C3-substituent was observed in the excited state. On the other hand, the peaks of absorption and emission of **3al** were shifted in the longer wavelength regions owing to the pyrene moiety. The quantum yields of the emissions of **3aa**, **3ac**, **3ae**, **3ak**, and **3al** were generally moderate to good. The structurally unprecedented methylene-bridged **3ga** also showed the red shifts in both absorption and emission spectra but with a moderate quantum yield, compared to the non-bridged **3aa**. The absorption spectrum of **3am** and **3hm** that contain two benzophosphole rings showed the remarkable bathochromic shift albeit with relatively low quantum yields of the emission.

In conclusion, we have developed a palladium-catalysed, silver-assisted Fujiwara-Moritani-type direct alkenylation of benzophospholes with terminal alkenes. To the best of our knowledge, this is the first successful example of the C–H alkenylation of benzophosphole nuclei.[14] The palladium catalysis can provide direct access to the benzophosphole-vinylene conjugation systems with versatile substitution patterns. Thus, the present strategy will find wide applications in the synthesis and design of phosphole-based new organic functional materials. Further development of C–H activation catalysts of the phosphole nuclei is ongoing in our laboratory and will be reported in due course.

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1　Reviews: (*a*) T. Baumgartner and R. Réau, *Chem. Rev.,* 2006, **106**, 4681; (*b*) Y. Matano and H. Imahori, *Org. Biomol. Chem.,* 2009, **7**, 1258; (*c*) M. P. Duffy, W. Delaunay, P.-A. Bouit and M. Hissler, *Chem. Soc. Rev.,* 2016, **45**, 5296. Selected examples: (*d*) H. Tsuji, K. Sato, L. Ilies, Y. Itoh, Y. Sato and E. Nakamura, *Org. Lett.,* 2008, **10**, 2263; (*e*) A. Fukazawa, H. Yamada and S. Yamaguchi, *Angew. Chem., Int. Ed.* 2008, **47**, 5582; (*f*) H. Tsuji, K. Sato, Y. Sato and E. Nakamura, *J. Mater. Chem.,* 2009, **19**, 3364; (*g*) H. Tsuji, K. Sato, Y. Sato and E. Nakamura, *Chem. Asian J.,* 2010, **5**, 1294; (*h*) C. Wang, M. Taki, Y. Sato, A. Fukazawa, T. Higashiyama and S. Yamaguchi, *J. Am. Chem. Soc.,* 2017, **139**, 10374.

2　Y. Matano, Y. Hayashi, YK. Suda, Y. Kimura and H. Imahori, *Org. Lett.* 2013, **15**, 4458.

3　(*a*) J. Kurita, M. Ishii, S. Yasuike and T. Tsuchiya, *Chem. Commun.,* 1993, 1309; (*b*) Y. Hayashi, Y. Matano, K. Suda, Y. Kimura, Y. Nakao and H. Imahori, *Chem. Eur. J.* 2012, **18**, 15972.

4　Selected recent reviews: (*a*) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.,* 2018, **47**, 6603; (*b*) P. Gandeepan, T. Muller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.,* 2019, **119**, 2192; (*c*) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.,* 2020, **120**, 1788.

5　Reviews: (*a*) L. Zhou and W. Lu, *Chem. Eur. J.,* 2014, **20**, 634; (*b*) J. Koubachi, N. E. Brahmi, G. Guillaumet and S. E. Kazzouli, *Eur. J. Org. Chem.,* 2019, 2568; (*c*) J. L. Bras and J. Muzart, *Catalysts* 2020, **10**, 571. Also see a related review on a cross-dehydrogenative coupling (CDC) reaction; (*d*) C.-Y. Huang, H. Kang, J. Li and C.-J. Li, *J. Org. Chem.*, 2019, **20**, 12705.

6　For examples of related phosphachromones and phosphacoumarins, see: (*a*) D. Kang, J. Cho and P. H. Lee, *Chem. Commun.,* 2013, **49**, 10501; (*b*) C.-E. Kim, J.-Y. Son, S. Shin, B. Seo and P. H. Lee, *Org. Lett.,* 2015, **17**, 908.

7　S. Xu, K. Nishimura, K. Saito, K. Hirano and M. Miura, *Chem. Sci.*, 2022, **13**, 10950.

8　K. Nishimura, K. Hirano and M. Miura, *Org. Lett.,* 2020, **22**, 3185.

9　(*a*) Y. Unoh, T. Satoh, K. Hirano and M. Miura, *ACS Catal.,* 2015, **5**, 6634; (*b*) A. Wakatsuki, M. Yukimoto, M. Minoura, K. Fujii, Y. Kimura and Y. Matano, *Dalton Trans.,* 2018, **47**, 7123; (*c*) C. Sire, H. Cattey, A. Tsivery, J.-C. Hierso and J. Roger, *Adv. Synth. Catal.*, 2022, **364**, 440.

10　We could not prepare C3-alkylated benzophospholes from the corresponding α-alkylstyrenes under the phosphenium dication protocol. The C2,C3-unsubstituted benzophosphole underwent full conversion, but a complicated mixture was observed probably because of its less stability.

11　(*a*) D. Whitaker, J. Burés and I. Larrosa, *J. Am. Chem. Soc.,* 2016, **138**, 8384; (*b*) S. Y. Lee and J. F. Hartwig, *J. Am. Chem. Soc.,* 2016, **13***8*, 15278; (*c*) M. D. Lotz, N. M. Camasso, A. J. Canty and M. S. Sanford, *Organometallis,* 2017, **36**, 165; (*d*) C. Colletto, A. Panigrahi, J. Fernámdez-Casado and I. Larrosa, *J. Am. Chem. Soc.,* 2018, **140**, 9638; (*e*) G. Athavan, T. F. N. Tanner, A. C. Whitwood, I. J. S. Fairlamb and R. N. Perutz, *Organometallis,* doi: 10.1021/acs.organomet.2c00063.

12　Ph$_2$P=O shows a larger Hammett substituent constant than Ph$_2$P=S and Ph$_2$P (σ_m = 0.38, 0.29, and 0.11, respectively), see: C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.,* 1991, **91**, 165.

13　For relatively low pK_a values of phosphole derivatives, see: (*a*) D. Delaere, N. Pham-Tran and M. T. Nguyen, *J. Phys. Chem. A,* 2003, **107**, 7514; (*b*) L. D. Quin, J. G. Bryson and C. G. Moreland, *J. Am. Chem. Soc.,* 1969, **91**, 3308. Also see: (*c*) K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron,* 2007, 63, 1568.

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14 Matano and Imahori reported the palladium-catalyzed annulation reaction of somewhat specialized indole- and benzothiophene-substituted benzophospholes with internal alkynes. See ref 3b.