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Multicomponent Coupling

A Highly Modular One-Pot Multicomponent Approach to Functionalized Benzo[*b*]phosphole Derivatives**

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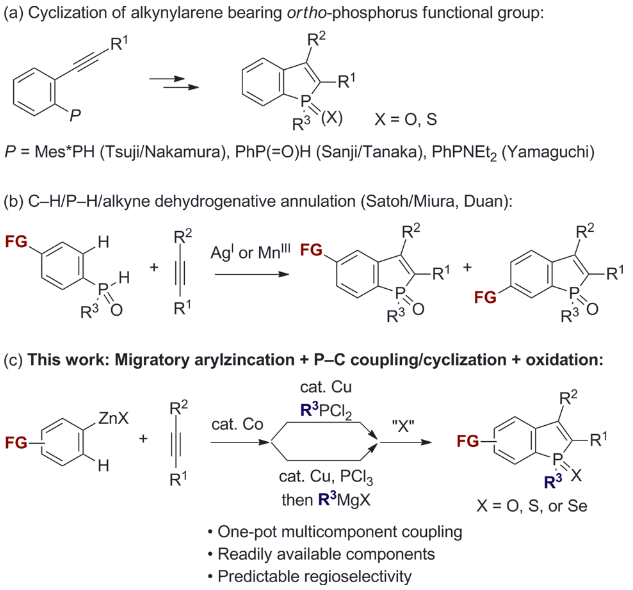
Abstract: *Benzo[b]phosphole derivatives have attracted significant attention for their unique optoelectronic properties with potential for application in materials science. Herein we report a modular approach to a benzo[b]phosphole derivative based on a one-pot sequential coupling of an arylzinc reagent, an alkyne, dichlorophenylphosphine (or phosphorus trichloride and a Grignard reagent), and an oxidant (for example H_2O_2, S, or Se). The approach allows for the construction of a library of previously inaccessible, structurally diverse benzo[b]phosphole derivatives with unprecedented ease.*

Benzo[*b*]phosphole is unique among the benzo[*b*]heterole series of heteroarenes because chemical modification of the phosphorus atom allows modulation of the electronic properties of the phosphorus-containing π system.[1] Until recently, there have been relatively few synthetic studies of this class of heteroarenes.[2,3] Between 2008 and 2009, the research groups of Tsuji and Nakamura et al., Sanji and Tanaka et al., and Yamaguchi and co-workers reported the practical synthesis of benzo[*b*]phosphole derivatives based on intramolecular cyclization of alkynylarenes bearing *ortho*-phosphorus functional groups (Scheme 1a).[4,5] These studies revealed intriguing optoelectronic properties for some of the benzo[*b*]phosphole derivatives[6] and their applicability to organic electronic devices.[7] In 2013, Satoh, Miura, and co-workers and Duan and Chen independently reported a novel and atom-economical approach to the preparation of benzo[*b*]phosphole oxides based on the dehydrogenative annulation of secondary arylphosphine oxides and internal alkynes mediated by silver or manganese salts (Scheme 1b).[8]



Scheme 1. Synthetic approaches to benzo[*b*]phosphole derivatives. FG = functional group.

Both approaches, however, present problems when considered for application in diversity-oriented synthesis. For this purpose, the intramolecular cyclization approach is not ideal as each cyclization precursor requires a multistep synthesis. A problem also arises with the oxidative annulation approach as a result of the regiochemistry of the "benzo" moiety. The reaction of a substituted arylphosphine oxide produces a regioisomeric mixture as a result of a radical mechanism involving the rearrangement of a spirocyclic intermediate.[8] Furthermore, regioselective annulation of an unsymmetrical diarylphosphine oxide is virtually impossible.[8b] Herein we report a highly modular approach to a functionalized benzo[*b*]phosphole derivative featuring the one-pot sequential coupling of an arylzinc reagent, an alkyne, dichlorophenylphosphine (or phosphorus trichloride and a Grignard reagent), and an oxidant (i.e., hydrogen peroxide, sulfur, or selenium) (Scheme 1c). As each reaction component is readily available, this approach allows for the facile regiocontrolled synthesis of benzo[*b*]phosphole derivatives with exceptional ease and structural diversity, particularly with respect to substituents on the benzo moiety and the phosphorus atom.

We recently developed a method for the synthesis of benzothiophene and benzoselenophene through cobalt-catalyzed migratory arylzincation of alkyne,[9] iodination of the resulting *ortho*-alkenylarylzinc species, and subsequent copper-catalyzed chalcogenative cyclization of *ortho*-alkenylaryl iodide.[10] In some limited cases, the zinc species could be directly trapped by elemental sulfur to afford the corresponding benzothiophene, presumably as a result of its modest electrophilicity. It was envisioned that the zinc species would react more readily with phosphorus electrophiles, such as $PhPCl_2$ and PCl_3. Once introduced, the electrophilic phosphorus group (i.e., PPhCl or PCl_2) would further react with

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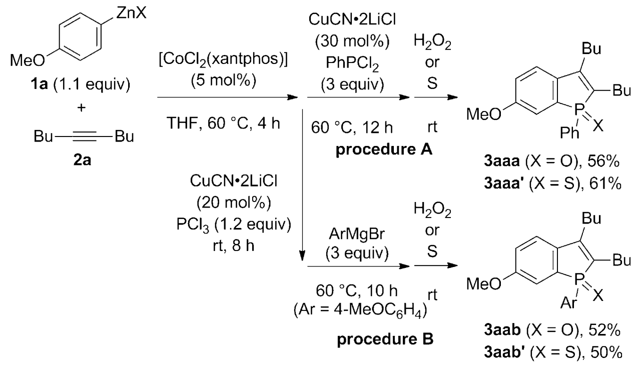
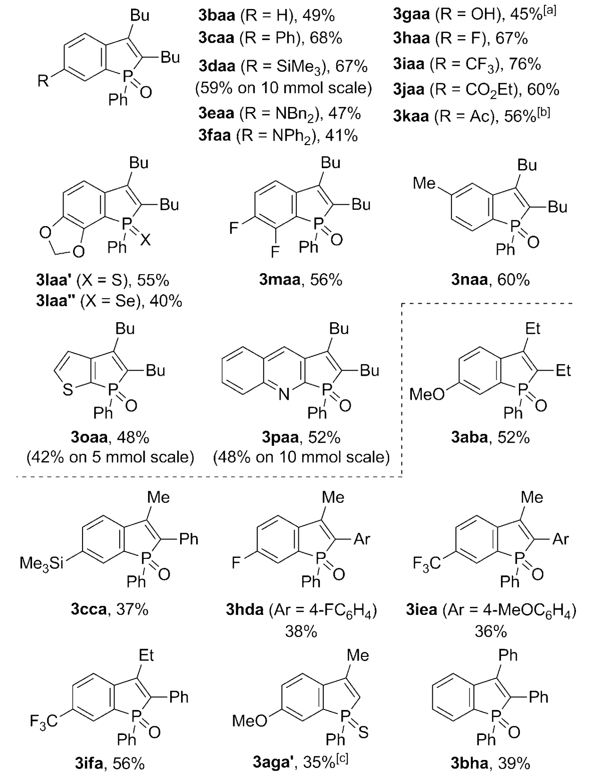
the *ortho*-alkenyl moiety to furnish a benzo[*b*]phosphole core structure.

Two one-pot procedures for the multicomponent synthesis of benzo[*b*]phosphole were devised (Scheme 2). In procedure A, the [$CoCl_2$(xantphos)]-catalyzed reaction (xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) of 4-methoxyphenylzinc reagent **1a** (1.1 equivalents) with 5-decyne (**2a**), followed by a copper-catalyzed reaction with $PhPCl_2$ (3 equivalents), and subsequent oxidation with hydrogen peroxide or sulfur powder, were performed sequentially in a single vessel. This procedure afforded benzo[*b*]phosphole oxide **3aaa** or benzo[*b*]phosphole sulfide **3aaa′** in approximately 60% yield. Procedure B allowed an even more modular synthesis of benzo[*b*]phosphole derivatives. By this method, the cobalt-catalyzed migratory arylzincation step was followed by copper-catalyzed reaction with PCl_3, addition of 4-methoxyphenylmagnesium bromide, and subsequent oxidation. This method afforded the desired benzophosphole derivatives **3aab** and **3aab′** in respectable yields of approximately 50%.



Scheme 2. Synthesis of benzo[*b*]phosphole oxides and sulfides through one-pot multicomponent coupling. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. The arylzinc reagent was prepared from *p*-methoxyphenylmagnesium bromide (1.1 equiv) and $ZnCl_2$·TMEDA (1.1 equiv).

The scope of the benzophosphole synthesis was firstly explored using procedure A (Scheme 3). A set of aryl- and heteroarylzinc reagents with different electron-donating abilities was coupled with 5-decyne and $PhPCl_2$ to furnish the corresponding benzo[*b*]phosphole oxides (or sulfide or selenide derivatives) **3baa**–**3paa** in moderate to good yields. The hydroxy- and acetyl-substituted derivatives **3gaa** and **3kaa** were synthesized in one-pot from arylzinc reagents bearing protected hydroxy (OBoc) and acetyl (C(=NAr)Me; Ar = 4-$MeOC_6H_4$) groups, respectively. The regiochemistry of the products bearing 6,7-methylenedioxy (**3laa′**, **3laa″**), 6,7-difluoro (**3maa**), and 5-methyl (**3naa**) groups reflect the regioselectivity of the migratory arylzincation step.[9a] This step is controlled by the directing effect of the oxygen or fluorine atom for compounds **3laa′**, **3laa″**, and **3maa**, and by the steric effect of the methyl group in compound **3naa**. The method was also employed for the multigram syntheses of compounds **3daa**, **3oaa**, and **3paa**.

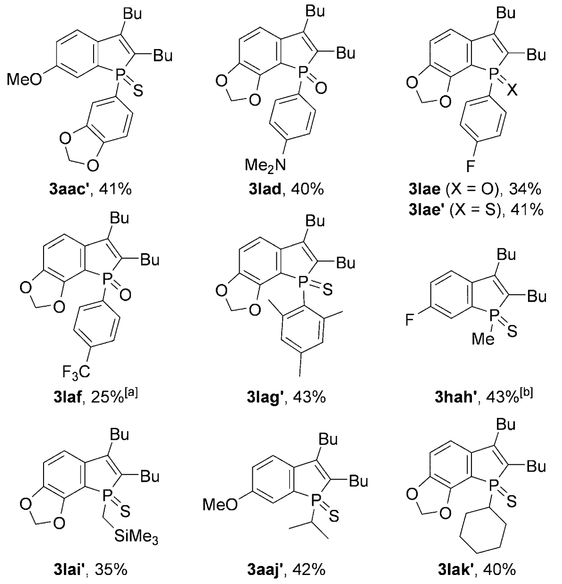


Scheme 3. Benzo[*b*]phosphole derivatives synthesized by procedure A. The reaction was performed on a 0.5 mmol scale. See the Supporting Information for detailed reaction conditions. [a] The hydroxy group of the arylzinc reagent was protected using a Boc group. [b] The acetyl moiety of the arylzinc reagent was protected in the form of *p*-anisidine imine. [c] 1-trimethylsilyl-1-propyne was used.

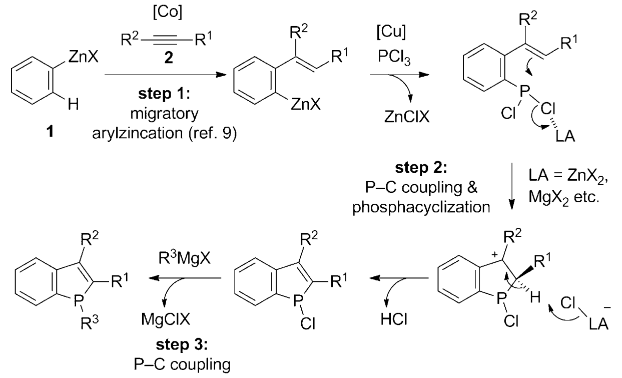
Substituents at the 2- and 3-positions of benzo[*b*]phosphole can be changed within the scope of the migratory arylzincation step.[9a] Thus, internal alkynes, such as dialkylalkyne,[11] alkylarylalkyne, and alkylsilylalkyne, were coupled with randomly chosen arylzinc reagents and $PhPCl_2$ to afford the corresponding benzophosphole derivatives in respectable yields. The regioselectivity for alkylarylalkyne is opposite to that observed in the dehydrogenative annulation (Scheme 1b).[8] The reaction of 1-trimethylsilyl-1-propyne was accompanied by spontaneous loss of the trimethylsilyl group (to form **3aga′**, Scheme 3). While migratory arylzincation of diarylalkyne has been reported to cause undesirable *E*/*Z* isomerization,[9a] we successfully synthesized the simple compound 2,3-diphenylbenzo[*b*]phosphole oxide (**3bha**) from the parent phenylzinc reagent and diphenylacetylene.

Procedure B allowed rapid construction of benzophosphole derivatives bearing a wide variety of substituents on the phosphorus atom (Scheme 4). This method involved the coupling of arylzinc reagent (**1a**, **1h** or **1l**), 5-decyne (**2a**), and PCl_3, followed by the addition of various Grignard reagents and then hydrogen peroxide or sulfur powder. This procedure furnished benzo[*b*]phosphole oxides or sulfides bearing a variety of aryl and alkyl groups on the phosphorus atom in decent yields ranging from 25% to 43%.

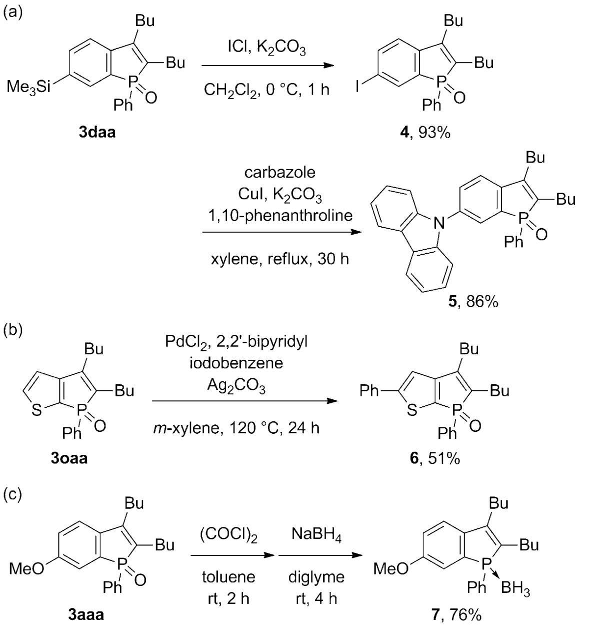
Scheme 5 shows a proposed pathway for sequential coupling procedure B, which involves a cobalt-catalyzed



Scheme 4. Benzo[*b*]phosphole derivatives synthesized by procedure B. The reaction was performed on a 0.5 mmol scale. See the Supporting Information for detailed reaction conditions. [a] 4-Trifluoromethylphenyllithium was used instead of the corresponding Grignard reagent. [b] The reaction with PCl_3 was performed at 60 °C.



Scheme 5. Proposed pathway for one-pot sequential coupling.



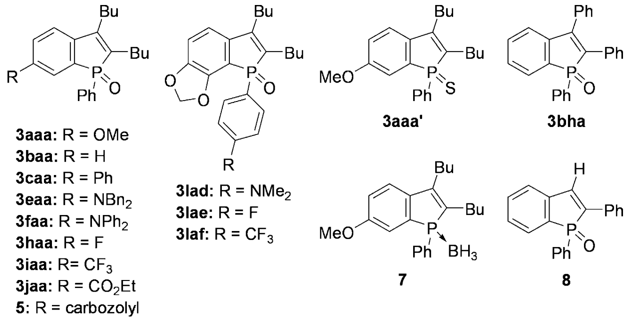
Scheme 6. Transformations of benzo[*b*]phosphole derivatives. See the Supporting Information for detailed reaction conditions.

migratory arylzincation (step 1),[9] trapping of the resulting *ortho*-alkenylarylzinc species with PCl_3 and the subsequent electrophilic phosphacyclization (step 2), and substitution of the P−Cl bond with the Grignard reagent (step 3). While intramolecular phospha-Friedel–Crafts cyclization reactions to form aryl−P bonds typically require a strong Lewis acid (for example $AlCl_3$) in a noncoordinating solvent to activate the P−Cl bond,[12,13] our phosphacyclization proceeds in THF under relatively mild conditions without such an external activator. This activity might be ascribed to the higher nucleophilicity of the alkenyl group than a typical aryl group in addition to the role of the arylzinc-derived metal salts (e.g., ZnX_2, MgX_2) in assisting the P−Cl bond cleavage.

The functional groups on the benzophosphole derivatives serve as potential sites for further synthetic transformations (Scheme 6). The trimethylsilyl-substituted derivative **3daa** was converted into a carbazole-conjugated benzo[*b*]phosphole oxide **5** through iododesilylation and copper-catalyzed C−N coupling (Scheme 6a). Direct phenylation by iodobenzene selectively at the C5-position of the phosphole-embedded thiophene **3oaa** was achieved using the $PdCl_2$/2,2′-bipyridyl catalytic system developed by Itami et al. (Scheme 6b).[14] The benzophosphole oxide **3aaa** could be directly converted into the corresponding benzophosphole-borane **7** in good yield by the method recently developed by Gilheany and Rajendran.[15]

As expected from earlier studies,[4,6,8] most of the benzophosphole derivatives (oxides in particular) were fluorescent in solution. As benzo[*b*]phosphole oxide can be regarded as a styrene derivative bridged by an electron-withdrawing phosphoryl group, the substituents at the 6-position and the phosphorus atom are expected to have a significant impact on the electronic properties. With this in mind, the UV/Vis absorption and emission spectra of selected benzophosphole derivatives were recorded (Table 1). The longest wavelength absorption maxima (λ_{abs}) and emission maxima (λ_{em}) fell within the ranges of $\lambda = 317$–394 nm and $\lambda = 385$–484 nm, respectively. The presence of electron-donating amino groups as substituents induced a significant red shift of both λ_{abs} and λ_{em} (entries 4 and 5), while no significant shift was observed with trifluoromethyl and ethoxycarbonyl groups (entries 7 and 8). High fluorescence quantum yields (0.57–0.94) were obtained with benzophosphole oxides bearing phenyl, amino, and carbazolyl substituents (entries 3–5 and 9). The substituent on the phosphorus atom also has a notable effect. While **3lad** bearing a 4-dimethylaminophenyl group was only weakly fluorescent (entry 10), **3lae** and **3laf**, with 4-fluorophenyl and 4-trifluoromethylphenyl groups, respectively, exhibited intense blue emission (entries 11 and 12). The benzophosphole sulfide **3aaa′** was virtually non-fluorescent (entry 13),[4c] while the borane complex **7** showed moderate

Table 1: Photophysical properties of selected benzo[*b*]phosphole derivatives.[a]



Entry	Cmpd	λ_{abs} [nm][b]	ε [cm^{-1} M^{-1}]	λ_{em} [nm][c]	Φ_F[d]
1	**3 aaa**	343	2270	434	0.39
2	**3 baa**	320	1870	387	0.11[e]
3	**3 caa**	336	5490	415	0.77
4	**3 eaa**	383	3180	479	0.57
5	**3 faa**	394	6400	484	0.63
6	**3 haa**	329	1170	412	0.15[e]
7	**3 iaa**	317	2460	385	0.12[e]
8	**3 jaa**	324	4700	388	0.21
9	**5**	340	9250	447	0.94
10	**3 lad**	347	5420	447	0.05
11	**3 lae**	350	4740	420	0.86
12	**3 laf**	350	3870	422	0.93
13	**3 aaa′**	344	1310	428	0.001
14	**7**	330	3540	420	0.25[e]
15	**3 bha**	344	7733	449 (451)[f]	0.66 (0.53)[f]
16[g]	**8**	347	8800	417	0.30
17[h]	**8**	348	9300	415	0.86

[a] In CH$_2$Cl$_2$. [b] Longest wavelength UV/Vis absorption maxima are shown. [c] Excited at $\lambda = 350$ nm. [d] Unless otherwise noted, fluorescence quantum yields were determined using quinine sulfate as a standard. [e] Anthracene was used as a standard. [f] In parentheses is shown solid-state fluorescence reported in Ref. [8a]. [g] Data taken from Ref. [4b] (in THF). [h] Data taken from Ref. [4c] (in THF).

fluorescence (entry 14). Not surprisingly, the present and literature data[4b,c,5a] for the 2,3-diphenyl and 2-phenyl analogues of **3baa** (**3bha** and **8**) shows elongation of λ_{abs} and λ_{em} by extended conjugation at the 2- and 3-positions (entries 2 and 15–17).

In summary, we have disclosed a new synthetic method for a functionalized benzo[*b*]phosphole derivative based on the sequential coupling of an arylzinc reagent, an alkyne, dichlorophenylphosphine (or phosphorus trichloride and a Grignard reagent), and an oxidant (H$_2$O$_2$, S, or Se). The one-pot procedure and the ready availability of each reaction component make the present method suitable for the rapid and diversity-oriented synthesis of benzo[*b*]phosphole derivatives and thus for the systematic modulation of the electronic properties of this unique π system. Further study will focus on the synthesis of novel benzophosphole-containing materials and the development of the modular synthesis of benzoheteroles containing various main-group elements.

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[1] a) M. Stolar, T. Baumgartner, *Chem. Asian J.* **2014**, *9*, 1212–1225; b) Y. Ren, T. Baumgartner, *Dalton Trans.* **2012**, *41*, 7792–7800; c) Y. Matano, H. Imahori, *Org. Biomol. Chem.* **2009**, *7*, 1258–1271; d) J. Crassous, R. Réau, *Dalton Trans.* **2008**, 6865–6876; e) T. Baumgartner, R. Réau, *Chem. Rev.* **2006**, *106*, 4681–4727.

[2] R. A. Aitken, *Science of Synthesis*, *Vol. 10* (Ed.: J. Thomas), Thieme, Stuttgart, **2000**, pp. 658–712.

[3] a) M. D. Rausch, L. P. Klemann, *J. Am. Chem. Soc.* **1967**, *89*, 5732–5733; b) W. Egan, R. Tang, G. Zon, K. Mislow, *J. Am. Chem. Soc.* **1971**, *93*, 6205–6216; c) W. Winter, *Tetrahedron Lett.* **1975**, *16*, 3913–3914; d) T. M. Balthazor, *J. Org. Chem.* **1980**, *45*, 2519–2522; e) T. Butters, W. Winter, *Chem. Ber.* **1984**, *117*, 990–1002; f) J. Kurita, M. Ishii, S. Yasuike, T. Tsuchiya, *J. Chem. Soc. Chem. Commun.* **1993**, 1309–1310; g) G. Märkl, G. Y. Jin, K. P. Berr, *Tetrahedron Lett.* **1993**, *34*, 3103–3106; h) J. G. Cordaro, D. Stein, H. Grützmacher, *J. Am. Chem. Soc.* **2006**, *128*, 14962–14971; i) M. Ogasawara, S. Arae, S. Watanabe, V. Subbarayan, H. Sato, T. Takahashi, *Organometallics* **2013**, *32*, 4997–5000.

[4] a) H. Tsuji, K. Sato, L. Ilies, Y. Itoh, Y. Sato, E. Nakamura, *Org. Lett.* **2008**, *10*, 2263–2265; b) T. Sanji, K. Shiraishi, T. Kashiwabara, M. Tanaka, *Org. Lett.* **2008**, *10*, 2689–2692; c) A. Fukazawa, Y. Ichihashi, Y. Kosaka, S. Yamaguchi, *Chem. Asian J.* **2009**, *4*, 1729–1740.

[5] See also: a) A. Fukazawa, M. Hara, T. Okamoto, E.-C. Son, C. Xu, K. Tamao, S. Yamaguchi, *Org. Lett.* **2008**, *10*, 913–916; b) A. Fukazawa, H. Yamada, S. Yamaguchi, *Angew. Chem.* **2008**, *120*, 5664–5667; *Angew. Chem. Int. Ed.* **2008**, *47*, 5582–5585.

[6] For the synthesis and properties of related benzo[*b*]phosphole π systems based on the method of Tsuchiya and co-workers (Ref. [3f]), see: Y. Hayashi, Y. Matano, K. Suda, Y. Kimura, Y. Nakao, H. Imahori, *Chem. Eur. J.* **2012**, *18*, 15972–15983.

[7] a) H. Tsuji, K. Sato, Y. Sato, E. Nakamura, *J. Mater. Chem.* **2009**, *19*, 3364–3366; b) H. Tsuji, K. Sato, Y. Sato, E. Nakamura, *Chem. Asian J.* **2010**, *5*, 1294–1297.

[8] a) Y. Unoh, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2013**, *125*, 13213–13217; *Angew. Chem. Int. Ed.* **2013**, *52*, 12975–12979; b) Y.-R. Chen, W.-L. Duan, *J. Am. Chem. Soc.* **2013**, *135*, 16754–16757.

[9] a) B.-H. Tan, J. Dong, N. Yoshikai, *Angew. Chem.* **2012**, *124*, 9748–9752; *Angew. Chem. Int. Ed.* **2012**, *51*, 9610–9614; b) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208–1219.

[10] B. Wu, N. Yoshikai, *Angew. Chem.* **2013**, *125*, 10690–10693; *Angew. Chem. Int. Ed.* **2013**, *52*, 10496–10499.

[11] As expected from Ref. [9a], the reaction of **1a**, an unsymmetrical dialkylalkyne (4-methylpent-2-yne), PhPCl$_2$, and sulfur gave a mixture of regioisomeric benzo[*b*]phosphole sulfides in a ratio of approximately 6:4 (determined by ^{1}H NMR spectroscopy using the fact that the major isomer has a methyl group at the 3-position).

[12] a) A. A. Diaz, J. D. Young, M. A. Khan, R. J. Wehmschulte, *Inorg. Chem.* **2006**, *45*, 5568–5575; b) T. Hatakeyama, S. Hashimoto, M. Nakamura, *Org. Lett.* **2011**, *13*, 2130–2133.

[13] For intermolecular phospha-Friedel–Crafts reaction, see: a) G. A. Olah, D. Hehemann, *J. Org. Chem.* **1977**, *42*, 2190–2190; b) Z.-W. Wang, L.-S. Wang, *Green Chem.* **2003**, *5*, 737–739.

[14] S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622–14623.

[15] K. V. Rajendran, D. G. Gilheany, *Chem. Commun.* **2012**, *48*, 817–819.