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One-Pot Benzo[*b*]phosphole Synthesis through Sequential Alkyne Arylmagnesiation, Electrophilic Trapping, and Intramolecular Phospha-Friedel–Crafts Cyclization

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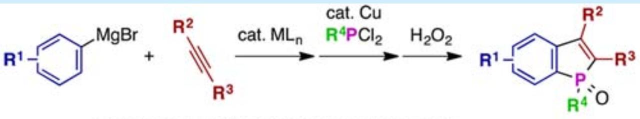
Supporting Information

ABSTRACT: A one-pot multicomponent synthesis of a benzo[*b*]phosphole derivative has been achieved by a sequence of transition-metal-catalyzed arylmagnesiation of an internal alkyne, electrophilic trapping of the resulting alkenylmagnesium species with a dichloroorganophosphine, and an intramolecular phospha-Friedel–Crafts reaction. With appropriate arylmagnesiation and P–C bond formation conditions, the present method allows for the modular and expedient preparation of benzophospholes bearing a variety of substituents on the phosphorus atom, the C2 and C3 atoms, and the "benzo" moiety.

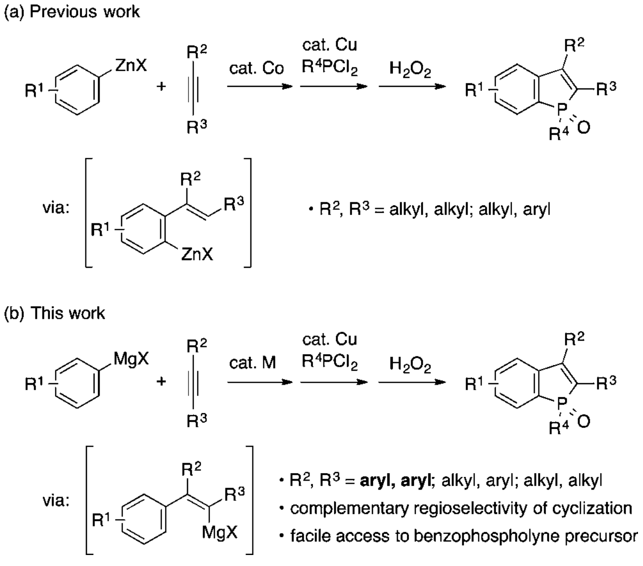


- Modular one-pot multicomponent assembly
- Ready availability of starting materials
- Enabling facile access to benzophospholyne precursor

Benzo[*b*]phosphole derivatives have garnered considerable interest for their semiconducting, fluorescent, and coordinating properties, which hold promise for application in various areas such as organic electronics, bioimaging, coordination chemistry, and catalysis.[1] While the synthesis of this class of compounds has been occasionally reported since the late 1960s,[2] recent years have witnessed the development of new efficient synthetic approaches. For example, approaches based on the intramolecular cyclization of alkynylarenes bearing *o*-phosphorus substituents have been developed,[3] and the thus-synthesized benzophosphole derivatives have been demonstrated to serve as n-type semiconducting materials for organic light-emitting devices[4] or environment-sensitive fluorescent bioimaging probes.[5] These and other studies illustrate the importance of the ability to flexibly modify peripheral substituents of the benzophosphole core and thus to tune its structural and electronic properties for desired applications.[6−8] Besides the intramolecular cyclization approaches, a highly atom-economical benzophosphole synthesis involving oxidative annulation of secondary phosphine oxides and internal alkynes has been developed.[9] More recently, our group has developed the one-pot construction of benzophospholes from arylzinc reagents, alkynes, and chlorophosphines,[10] capitalizing on cobalt-catalyzed migratory arylzincation as the key step (Scheme 1a).[11]

Each of the above-mentioned approaches, however, has a significant limitation. The intramolecular cyclization approaches require multistep preparation of the cyclization precursors and thus are not suitable for the rapid generation of various substituted benzophospholes.[3] The oxidative annulation suffers from randomization of the regiochemistry of the "benzo" moiety due to a mechanism involving a spirocyclic intermediate.[9] The problem becomes even worse when an unsymmetrical diarylphosphine oxide is used as the starting material. Our multicomponent approach is limited with respect to the scope of alkynes.[10] Because of the intrinsic limitation of the migratory arylzincation,[11] the method does not allow access to valuable 2,3-diarylbenzophosphole motifs.[4,5]

Scheme 1. Multicomponent Benzophosphole Synthesis Initiated by (Migratory) Arylmetalation of Alkyne



- R^2, R^3 = alkyl, alkyl; alkyl, aryl
- R^2, R^3 = **aryl, aryl**; alkyl, aryl; alkyl, alkyl
- complementary regioselectivity of cyclization
- facile access to benzophospholyne precursor

Herein we report that a transition-metal-catalyzed arylmagnesiation reaction of an alkyne[12,13] can be integrated into a

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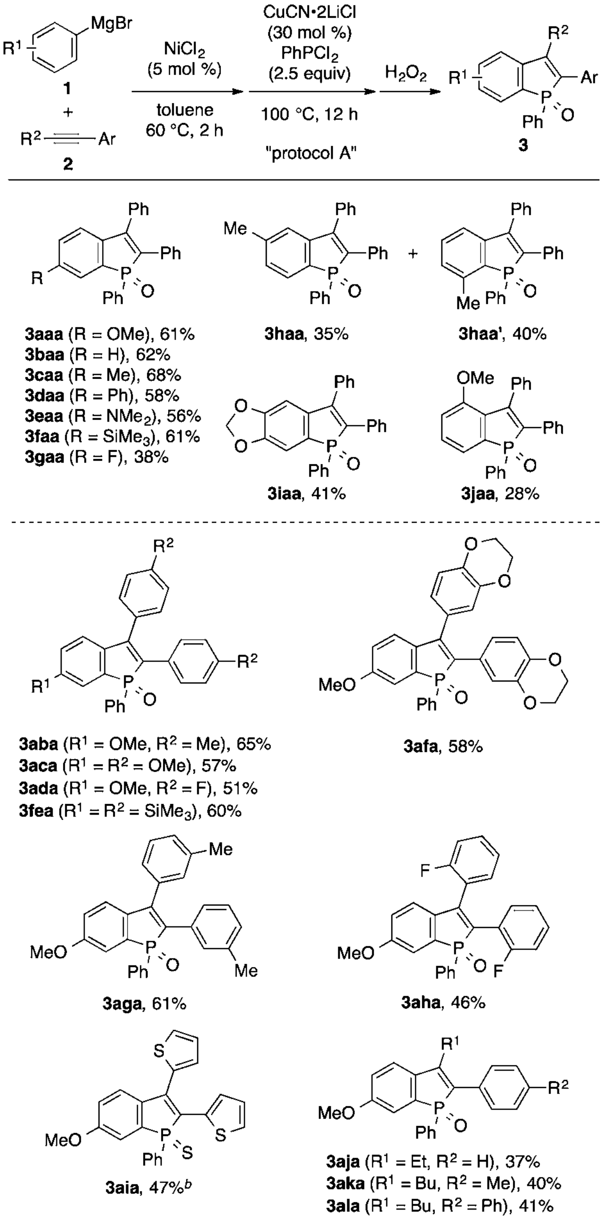
modular multicomponent protocol for benzophosphole synthesis. The arylmagnesiation is followed by electrophilic trapping of the resulting *cis-β*-styrylmagnesium species with a dichloroorganophosphine and a subsequent intramolecular phospha-Friedel–Crafts (PFC) reaction,[14] thereby affording a benzophosphole derivative in a one-pot operation (Scheme 1b). The new method has resolved some of the above limitations and significantly broadens the scope of accessible benzophospholes. The migratory arylzincation and the present arylmagnesiation approaches enable the preparation of alkoxy-substituted benzophospholes with complementary positional selectivities. The utility of the present benzophosphole synthesis is also demonstrated by the facile preparation of a precursor to 5,6-benzophospholyne and exploration of its reactivity.

To achieve the present benzophosphole synthesis, we employed the Ni-catalyzed alkyne arylmagnesiation reaction developed by Xue, Zhao, and Hor[13d] as the first step because it presents several advantages, including broad applicability to diarylalkynes, simplicity of the catalytic system, and near stoichiometric ratio of the arylmagnesium reagent and the alkyne. With careful optimization of the arylmagnesiation and C–P bond formation steps, we were able to establish a protocol for the desired multicomponent coupling (Scheme 2; see the Supporting Information for the optimization study). The addition of 4-methoxyphenylmagnesium bromide (**1a**) (1.2 equiv) to diphenylacetylene (**2a**) (1 equiv) in the presence of $NiCl_2$ (5 mol %) at 60 °C was followed by the reaction of the resulting alkenylmagnesium species with CuCN·2LiCl (30 mol %) and dichlorophenylphosphine (2.5 equiv) to afford, upon oxidation with H_2O_2, the desired benzophosphole oxide **3aaa** in a respectable isolated yield of 61% (protocol A). Unlike literature precedents on intramolecular PFC reactions,[14c−e] the addition of a Lewis acid such as $AlCl_3$ or $ZnCl_2$ was not necessary, presumably because the magnesium salt derived from the Grignard reagent itself served as a Lewis acid.

Scheme 2. Benzophosphole Synthesis Initiated by Ni-Catalyzed Alkyne Arylmagnesiation[a]



[a]The reactions were performed using 0.6 mmol of **1** and 0.5 mmol of **2**. [b]The benzophosphole product was oxidized using sulfur powder instead of H_2O_2.

A variety of *para*-substituted aryl Grignard reagents participated in the coupling reaction with diphenylacetylene and $PhPCl_2$ to afford the corresponding 6-substituted benzophosphole derivatives **3aaa**–**3gaa** in 38–68% yield. The reaction of *m*-tolylmagnesium bromide afforded a mixture of 5-methyl- and 7-methylbenzophosphole derivatives **3haa** and **3haa′** in a ca. 1:1 ratio as a result of non-regioselective PFC cyclization. By contrast, the PFC step in the reaction of 3,4-methylenedioxyphenylmagnesium bromide took place with exclusive regioselectivity, furnishing the 5,6-disubstituted product **3iaa** in 41% yield. *o*-Methoxyphenylmagnesium bromide was also amenable to the present method, affording the desired 4-methoxybenzophosphole **3jaa**, albeit in a modest yield. As expected from the scope of the Ni-catalyzed arylmagnesiation,[13d] a series of diarylalkynes participated in the coupling with 4-methoxyphenyl or 4-trimethylsilylphenyl Grignard reagent to afford the corresponding benzophosphole oxides **3aba**–**3aha** in ca. 50–60% yield. Besides the diarylalkynes, a bis(2-thienyl)alkyne could also be incorporated into a benzophosphole product (see **3aia**). The reaction of aryl(alkyl)alkynes regioselectively afforded 2-aryl-3-alkylbenzophosphole derivatives **3aja**–**3ala**, albeit in somewhat lower yields.

As expected from the regiochemistry of **3iaa**, the reaction of 3,4-methylenedioxyphenyl Grignard reagent **1i** and 1-phenyl-1-butyne (**2j**) with protocol A afforded the 5,6-methylenedioxybenzophosphole derivative **3ija** in a modest yield with exclusive regioselectivity (Scheme 3). This regioselectivity is particularly notable in comparison with the complementary regioselectivity achieved with our previous protocol based on the migratory arylzincation (Scheme 1a).[10] With that protocol, the reaction of the 3,4-methylenedioxyphenylzinc reagent and **2j** resulted in exclusive formation of 6,7-methylenedioxybenzophosphole **3ija′** as a result of regioselective 1,4-cobalt migration to the proximity of the ether moiety.

A modification of protocol A allows variation of the P substituent of the benzophosphole. Thus, using the dichlororganophosphine generated in situ from PCl_3 and an organozinc reagent instead of $PhPCl_2$ enabled the synthesis of benzophospholes bearing different *P*-aryl and -alkyl substituents in moderate yields (Table 1).

Scheme 3. Complementary Regioselectivities of Benzophosphole Syntheses from 3,4-Methylenedioxyphenylmetal Reagents

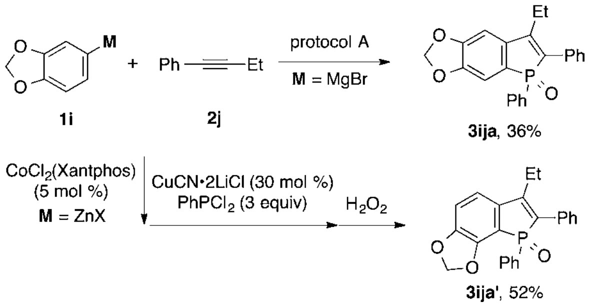
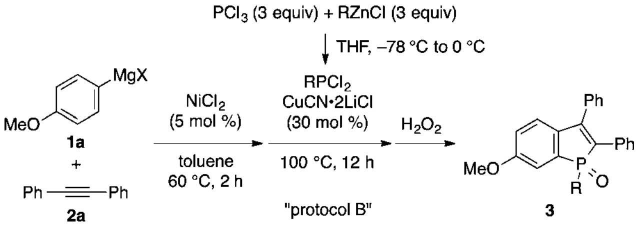


Table 1. Variation of the P Substituent[a]

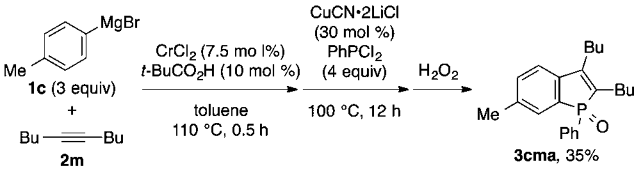


entry	R	product	yield (%)
1	4-MeOC$_6$H$_4$	**3aab**	47
2	4-Me$_2$NC$_6$H$_4$	**3aac**	51
3	4-FC$_6$H$_4$	**3aad**	47
4	*i*-Pr	**3aae**	54

[a] The reactions were performed using 0.6 mmol of **1a** and 0.5 mmol of **2a**.

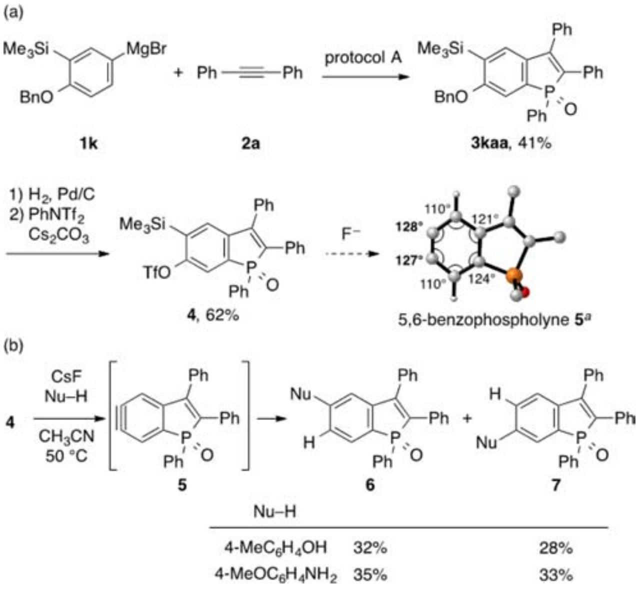
Besides the Ni-catalyzed reaction, other transition-metal-catalyzed arylmagnesiations can also be integrated into the present approach for benzophosphole synthesis. For example, the Cr-catalyzed arylmagnesation using *p*-tolyl Grignard reagent **1c** and 5-decyne (**2m**) developed by Yorimitsu and Oshima[13c] enabled the one-pot preparation of 2,3-dibutylbenzophosphole derivative **3cma**, albeit in a modest yield (Scheme 4). Such an alternative protocol would complement the Ni-catalyzed protocols because the Ni-catalyzed arylmagnesiation is not applicable to dialkylalkynes.[13d]

Scheme 4. Benzophosphole Synthesis Employing Cr-Catalyzed Arylmagnesiation



In comparison with existing approaches such as intramolecular cyclization,[3] the present benzophosphole synthesis enables facile preparation of benzophospholes variously substituted on the "benzo" moiety. We exploited this advantage to explore the reactivity of hitherto unknown 5,6-benzophospholyne species (Scheme 5). The silyl triflate precursor **4** was prepared by assembly of 3-trimethylsilyl-4-benzyloxyphenyl Grignard reagent **1k** and diphenylacetylene (**2a**) according to protocol A followed by deprotection of the benzyl group and triflation. Guided by the studies of Garg and Houk on the structure and reactivity of indolynes and other arynes,[15] we examined the structure of the 5,6-benzophospholyne species **5** to be generated from precursor **4** by a DFT calculation (B3LYP/6-31G(d)). The internal angles of the C≡C termini of **5** are very similar (θ_{CCC} = 128 and 127°), and there is only a small difference in the NPA charges at C5 (+0.04) and C6 (+0.03). These features suggest similar electrophilicities of the C5 and C6 positions. In line with this prediction, the addition of a nucleophile such as *p*-cresol or *p*-anisidine to **4** in the presence of CsF resulted in the formation of a nearly equimolar mixture of regioisomeric adducts **6** and **7** (Scheme 5b).

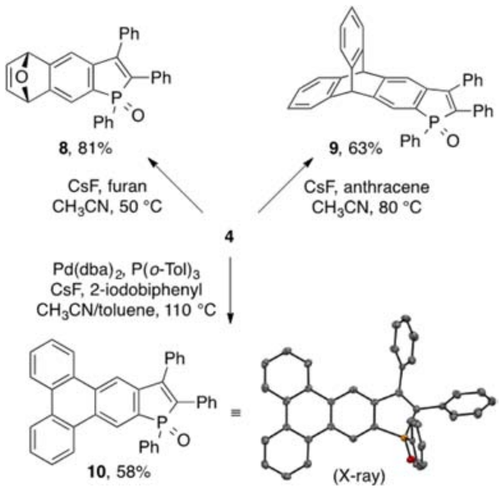
Scheme 5. Generation of and Nucleophilic Additions to 5,6-Benzophospholyne



[a] B3LYP/6-31G(d)-optimized structure (phenyl groups at the 1-, 2-, and 3-positions have been omitted for clarity).

5,6-Benzophospholyne **5** was amenable to a series of cycloaddition reactions (Scheme 6). The Diels–Alder reaction with furan proceeded efficiently to afford cycloadduct **8** in 81% yield (Scheme 6). Likewise, the reaction with anthracene furnished phosphole-embedded triptycene **9** in 63% yield.

Scheme 6. Cycloaddition Reactions of 5,6-Benzophospholyne



Furthermore, Pd-catalyzed annulation of **5** and 2-iodobiphenyl[16] afforded phosphole-embedded triphenylene **10**, the planar structure of which was confirmed by X-ray crystallographic analysis.

In conclusion, we have developed a one-pot multicomponent method for the construction of benzophosphole derivatives through the integration of transition-metal-catalyzed arylmagnesiation of an alkyne, trapping of the resulting alkenylmagnesium species with dichloroorganophosphine, and intramolecular phospha-Friedel–Crafts cyclization. The method allows for the streamlined and expeditious preparation of benzophospholes with various substituents on the P atom, the C2 and C3 atoms, and the benzo moiety, complementing the scope of our previous method based on the cobalt-catalyzed migratory arylzincation reaction. The flexibility of the present method with respect to the substitution pattern of the benzo moiety enabled facile access to 5,6-benzophospholyne. We anticipate that the present method will also pave the way for the investigation of hitherto unknown 4,5- and 6,7-benzophospholynes and thus allow for the synthesis of various polycyclic aromatic systems featuring benzophosphole moieties.[7c,8]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02950.

Experimental procedures and characterization data for new compounds (PDF)
Crystallographic data for **10** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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