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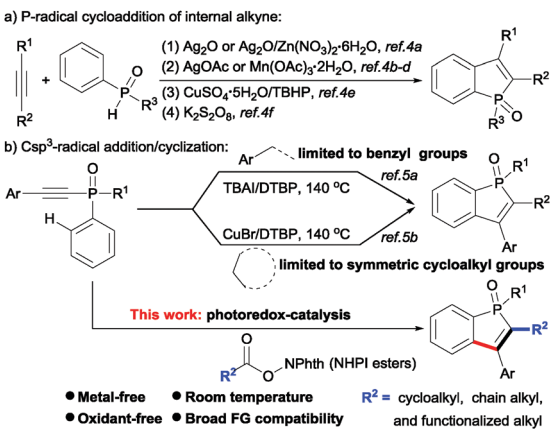
Photoredox-catalyzed decarboxylative alkylation/cyclization of alkynylphosphine oxides: a metal- and oxidant-free method for accessing benzo[*b*]phosphole oxides†

Lixin Liu,[a] Jianyu Dong,*[b] Yani Yan,[a] Shuang-Feng Yin,[a] Li-Biao Han[c] and Yongbo Zhou*[a]

By photoredox-catalysis, alkylation/aryl C–H cyclization of readily available alkynylphosphine oxides towards benzo[*b*]phospholes has been realized under metal- and oxidant-free conditions at room temperature. This reaction readily incorporates various functionalized alkyl groups into the benzo[*b*]phosphole skeletons, representing a mild and versatile tool for the preparation of valuable phosphole compounds.

As an important class of organophosphorus compounds, π-conjugated benzo[*b*]phospholes have received considerable attention due to their inherent unique electronic and photophysical properties and extensive applications as advanced organic optoelectronic materials and bioimaging probes.[1] Conventional synthetic approaches towards this class of organophosphorus compounds mainly rely on intramolecular cyclizations of *ortho*-phosphorus-functionalized internal alkynes in the presence of a stoichiometric strong base[2] and/or an expensive transition metal catalyst.[3] However, the cyclization precursors require complicated multistep syntheses, which make these procedures tedious and can decrease their functional group compatibility. Recently, as good alternatives, protocols based on intermolecular oxidative annulations of aryl secondary phosphine oxides with internal alkynes[4] and intermolecular oxidative addition/cyclization of alkynylarylphosphine oxides[5] have been developed, respectively (Scheme 1). However, these reactions are carried out under strong oxidant conditions (stoichiometric chemical oxidants and high temperature), and thus suffer from low functional group tolerance and/or a limited substrate scope.[6] In addition, transition metals are required in most of the cases, which are generally not easy to remove from this class of organophosphorus compounds, because they can ligate to a variety of metal ions.[7] Therefore, the development of mild procedures, especially oxidant-free conditions, for the general synthesis of benzo[*b*]phospholes is still highly desired.

Visible-light photoredox catalysis provides an attractive tool for the production of various reactive radicals for initiating radical reactions and assembly of diverse carbocyclic and heterocyclic skeletons.[8] In 2016, Lakhdar pioneered a photoredox-catalytic strategy for the preparation of benzo[*b*]phosphole oxides by intermolecular oxidative annulations (*N*-ethoxy-2-methylpyridinium tetrafluoroborate as the oxidant) of internal alkynes and secondary phosphine oxides at room temperature.[9] Alkyl *N*-hydroxyphthalimide (NHPI) esters are redox active and can accept an electron in a single electron transfer to form the corresponding alkyl radicals without the need of exotic oxidants under visible-light photoredox catalysis.[10,11] Inspired by these contributions, we envision that a cascade reaction including decarboxylation, alkyl radical addition, and aryl C–H cyclization could be achieved by mixing readily available alkynyldiphenylphosphine oxides[12] and NHPI esters under photoredox-catalysis conditions, and that benzo[*b*]phosphole oxides could be prepared in an attractive manner. Fortunately, we realized this strategy by extensively tuning the reaction parameters,



Scheme 1 Synthetic approaches to benzo[*b*]phosphole oxides.

[a] *State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China. E-mail: zhouyb@hnu.edu.cn*

[b] *Department of Educational Science, Hunan First Normal University, Changsha 410205, China. E-mail: djyustc@hotmail.com*

[c] *National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan*

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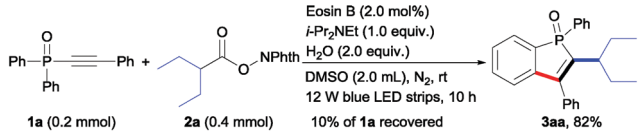


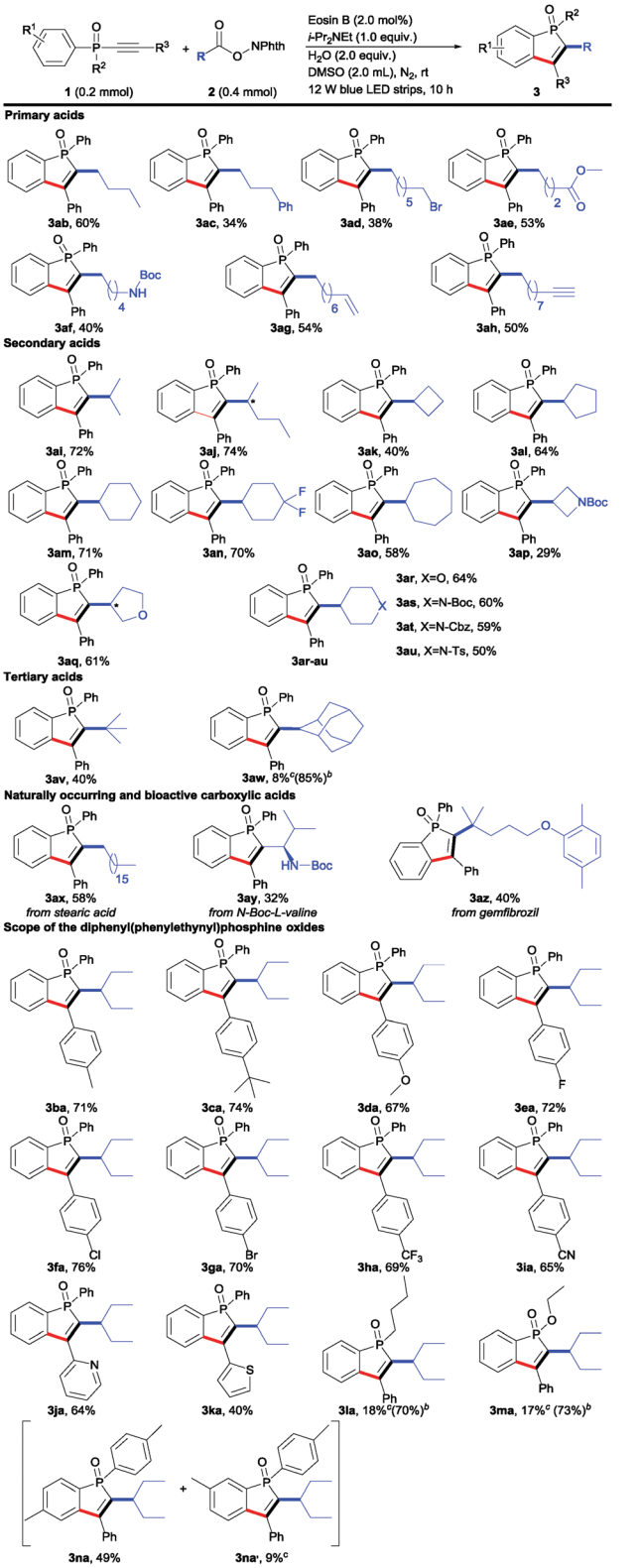
Scheme 2 Optimized reaction conditions.

such as photocatalysts, bases, solvents, and additives (for details, see the ESI†). Benzo[*b*]phosphole oxide **3aa** was obtained in 82% yield by the treatment of diphenyl(phenylethynyl)phosphine oxide (**1a**, 10% recovered) and 3-amyl NHPI ester **2a** in the presence of eosin B (2.0 mol%), *N*,*N*-diisopropylethylamine (i-Pr_2NEt, 1.0 equiv.), and H_2O (2.0 equiv.) in dimethylsulfoxide (DMSO) at room temperature under visible-light irradiation for 10 h (Scheme 2).

Herein, we report the details of the metal- and oxidant-free synthesis of alkyl functionalized benzo[*b*]phosphole oxides. As shown in Table 1, this decarboxylative alkylation/cyclization reaction exhibited a wide substrate scope and good functional group tolerance, producing various benzo[*b*]phosphole oxides in moderate to high yields. Primary alkyl NHPI esters derived from simple primary carboxylic acids bearing phenyl, bromine, ester, and amide groups were well suited for this reaction, giving the corresponding products (**3ab–af**) in synthetically useful yields (34–60%). Interestingly, long-chain alkyl groups containing terminal alkenyl and alkynyl groups, which are reactive radical acceptors, are also tolerated, producing the desired products in 54% (**3ag**) and 50% (**3ah**) yields, respectively. In addition to the primary alkyl NHPI esters, the scope of secondary alkyl NHPI esters was also broad. Acyclic secondary groups (**3aa**, **3ai**, and **3aj**; 82, 72, and 74% yields, respectively), alkyl cyclic groups (4- to 7-membered rings, **3ak–ao**, 40–71% yields), and various *N*- and *O*-heterocyclic alkyl groups (**3ap–au**, 29–64% yields) were all amenable to the alkylation/cyclization reaction. Sterically bulky alkyl groups lowered the yields of this transformation, which was probably due to the difficult addition of the alkyl radical to the C–C triple bond (*vide infra*). NHPI esters containing 5- and 6-membered rings gave higher yields than those achieved with those containing 4- and 7-membered rings, *e.g.*, **3ak** (40% yield) *vs.* **3am** (71% yield) and **3ap** (29% yield) *vs.* **3as** (60% yield). When *tert*-butyl *N*-(acyloxy)phthalimide was subjected to the reaction system, the reaction produced *tert*-butylated benzo[*b*]phosphole oxide **3av** in 40% yield, whereas the more sterically hindered *N*-(acyloxy)phthalimide derived from 1-adamantanecarboxylic acid only gave 8% ^{31}P NMR yield (**3aw**) with 85% of **1a** recovered.

In addition, aliphatic acids are widely encountered functionalities in bioactive compounds and biomass. We investigated the reactivity of *N*-(acyloxy)phthalimides derived from such sources as radical precursors. For example, NHPI esters from stearic acid (found in animal fats) and Boc-protected valine could be used as substrates to obtain the corresponding products in 58% (**3ax**) and 32% (**3ay**) yields, respectively. In addition, the NHPI ester derived from gemfibrozil (a drug used to lower lipid levels) was also compatible with this reaction system, providing the desired product (**3az**) in 40% yield.

Table 1 Substrate scope[a]



[a] Isolated yields. [b] The proportion of **1** recovered. [c] ^{31}P NMR yield using tributyl phosphate as an internal standard.

We then evaluated the substrate scope of alkynylphosphine oxides. As shown in Table 1, diphenyl(phenylethynyl)phosphine oxides substituted with alkyl (**3ba** and **3ca**), methoxy (**3da**), halogen (**3ea–3ga**), trifluoromethyl (**3ha**), and cyano (**3ia**) groups worked well to give the corresponding products in satisfactory yields (65–76%), regardless of the electronic effects of the substituents. Notably, the tolerance for halogens (Br and Cl) allows the further functionalization of the products for the preparation of more complex targets *via* stepwise coupling reactions. Heterocyclic substrates containing a pyridine ring or a thiophene ring were compatible with the decarboxylative alkylation/cyclization reaction and produced the desired heterocyclic products in moderate yields (**3ja**, 64% yield; **3ka**, 40% yield). In comparison, monophenyl alkynylphosphine oxides proceeded sluggishly under this photocatalytic system, and low yields of the desired products were observed (**3la**, 18% ^{31}P NMR yield; **3ma**, 17% ^{31}P NMR yield). When di-*p*-tolyl alkynylphosphine oxide was employed as the substrate, in addition to the desired benzo[*b*]phosphole oxide product (**3na**, 49% yield), the regioisomeric product (**3na′**) was also observed (19% ^{31}P NMR yield). This result demonstrates that the reaction probably proceeds through two pathways (*vide infra*).

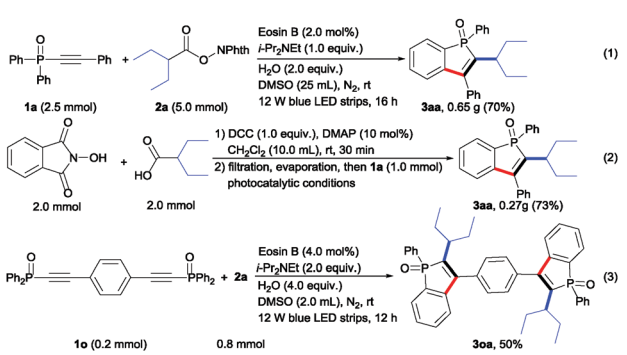
It is worth noting that the reaction proceeded with high selectivity. Alkyl radical rearrangement products were not found, even in the reactions of the primary alkyl NHPI esters (**2b–h**) and unsymmetrical secondary alkyl NHPI esters (**2j** and **2q**). The relatively low yields observed in some cases were due to the low conversion of the alkynylphosphine oxides.

To further extend the practicality of this photocatalytic radical addition/cyclization reaction, a gram-scale model reaction (2.5 mmol) was conducted under the standard reaction conditions and the desired product was obtained successfully (**3aa**) in 70% yield (Scheme 3, eqn (1)). In addition, a "one-pot" reaction of NHPI and 2-ethylbutyric acid was performed, and desired benzo[*b*]phosphole oxide **3aa** was produced in a good yield of 73% (Scheme 3, eqn (2)). These results demonstrate the synthetic value of the procedure in organic synthesis. In addition, the reaction of diyne **1o** with NHPI ester **2a** afforded bis(benzophosphole-3-yl)benzene skeleton **3oa** (50% yield), which has potential applications in organic photoelectric materials (Scheme 3, eqn (3)).

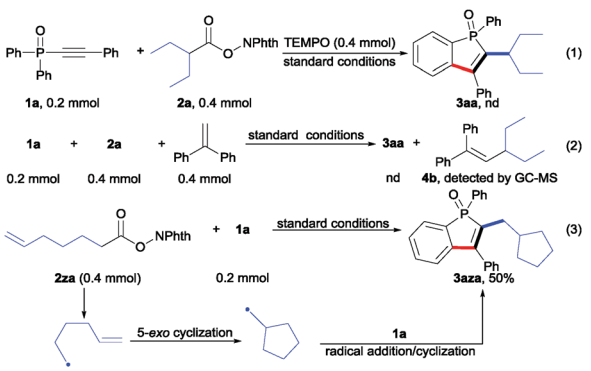
To elucidate the reaction mechanism, several control experiments were carried out under the standard conditions. First, when 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was added to the reaction mixture as a radical inhibitor, the reaction was completely suppressed (Scheme 4, eqn (1)). Furthermore, the radical scavenger, 1,1-diphenylethylene, could also block this reaction, and the radical adduct was observed (Scheme 4, eqn (2)). When NHPI ester **2za** containing a hex-1-ene moiety was subjected to the reaction conditions, product **3aza** was obtained in 50% yield, and this product was formed *via* an additional alkyl radical cyclization (Scheme 4, eqn (3)). These results suggested that radical intermediates were involved in the reaction. Fluorescence titration experiments with eosin B showed that the emission of EB* was quenched by the addition of the electron donor, i-Pr$_2$NEt, which proves that a single-electron transfer (SET) occurs between the two species (see the ESI,† Fig. S2 for details). Finally, the quantum yield (Φ) of the reaction was estimated by chemical actinometry, and a low value was observed (Φ = 1.43, see the ESI† for details), indicating that efficient radical chain processes were very unlikely to be involved in this mechanism.[13]

On the basis of the experimental results described above, and the literature precedents,[4,5,9,11f] a plausible mechanism for the reaction is illustrated in Scheme 5. Initially, the photocatalyst (PC) is photoexcited to its excited state (PC*), which is reductively quenched by the electron donor, i-Pr$_2$NEt, to give the corresponding radical anion (PC$^{\bullet-}$) with concomitant generation of i-Pr$_2$NEt$^{\bullet+}$. Then, the reduction of NHPI ester **2** by PC$^{\bullet-}$ affords the corresponding radical anion (**B**), regenerating PC. The splitting of the N–O bond of **B** together with subsequent elimination of CO_2 generates alkyl radical **C**. The selective intermolecular addition of alkyl radical **C** to the α-position of the P=O bond in alkynylphosphoryl compound **1** affords alkenyl radical **D** rather than **D′**. Finally, the intramolecular aryl C–H cyclization of radical **D** produces intermediates **E** (5-*exo*-ring) and **H** (*via* 4-*exo*-ring **F** and vinyl phosphorus radical **G**),[4,5,9] and subsequent SET and dehydrogenation generates the desired product (**3**).

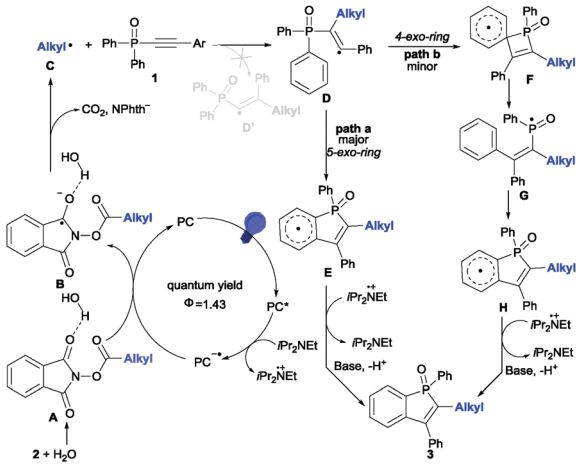
In summary, using photoredox catalysis, we have successfully developed a radical initiated cascade reaction of alkynylphosphoryl compounds for preparing functionalized benzo[*b*]phospholes. The reaction proceeds with high selectivity and produces a broad spectrum of alkyl benzo[*b*]phospholes in satisfactory yields without generating alkyl radical rearrangement products. The key to success is the photocatalytic generation of the alkyl radical from the NHPI ester along with its subsequent addition to the alkyne.



Scheme 3 Synthetic applications.



Scheme 4 Experimental probes of the reaction mechanism.



Scheme 5 Possible reaction mechanism.

Sterically bulky alkyl radicals add less efficiently to alkynes, and further studies are required to improve the reactivity of these substrates. The developed reaction is the first room temperature and oxidant-, strong base- and metal-free method for synthesizing these types of phosphole skeletons. Likely due to its very mild conditions, this reaction offers many advantages, such as simple operation, avoidance of metal contamination, high selectivity for the desired products, good functional group tolerance, and a broad scope of alkyl groups, especially those derived from naturally occurring carboxylic acids, making it valuable and practical in organic synthesis.

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Conflicts of interest

There are no conflicts to declare.

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