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ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C6GC01009A

Journal Name

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

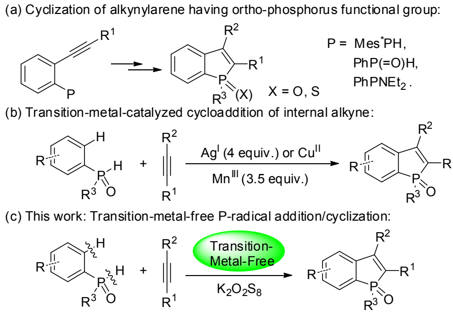
www.rsc.org/

$K_2S_2O_8$-mediated metal-free direct P-H/C-H functionalization: a convenient route to benzo[*b*]phosphole oxides from unactivated alkynes

Dumei Ma,[a] Weizhu Chen,[c] Gaobo Hu,[b] Yun Zhang,[b] Yuxing Gao,*[b] Yingwu Yin[a] and Yufen Zhao[b]

The first metal-free, facile and $K_2S_2O_8$-mediated radical addition/cyclization of unactivated alkynes with diarylphosphine oxides has been developed, affording a general and practical procedure to construct valuable benzo[*b*]phosphole oxides via sequential P-H/C-H functionalization.

Phosphorus-containing heterocycles has attracted much attention for synthetic chemists over the past few decades due to their wide applicability in organic synthesis, medicinal chemistry and material science.[1] Particularly, benzo[b]phosphole derivatives, the phosphorous analogue of indole, have attracted considerable attention as promising organic optoelectronic materials because of their unique physical and photoelectric properties.[2] Yet, the methods for the synthesis of these motifs are relatively lacking. Traditionally, benzo[b]phospholes were mainly obtained from alkynylarenes bearing ortho-phosphorus substituents via the intermolecular cyclization (Scheme 1a)[3] , which suffers from the requirement of the complicated multistep reactions for each cyclization precursor and a lack of functionality tolerance owing to using strong bases. Until recently, a few of novel and efficient methods for the synthesis of benzo[*b*]phosphole species including silver-[4] or manganese-[4a-b] mediated and copper-catalyzed[5] intermolecular cycloadditions of internal alkynes with phosphine derivatives (Scheme 1b), multicomponent approaches reported by Yoshikai et al.,[6] and our group's work on TBAI-catalyzed radical addition/cyclization of diaryl(arylethynyl)phosphine oxides with toluene derivatives,[7] have continuously emerged. Among them, transition-metal-catalyzed intermolecular cycloaddition of phosphine derivatives to internal alkynes has emerged as the most attractive and powerful approach for making benzo[*b*]phosphole oxides because this pathway is highly atom-economical and internal alkynes and diarylphosphine oxides as reaction partners are highly stable and readily available in a variety of substituted forms, making them convenient precursor for building compounds of wide substrate scope, however, these methods used a plenty of environmentally unfriendly Mn or Cu salts or noble Ag salts as catalysts, thus increasing the cost and restraining their applications. Therefore, the development of cheap, environmentally friendly and metal-free methods for the direct preparation of benzo[*b*]phosphole derivatives from readily available alkynes and diarylphosphine oxides is still desirable and essential.



Scheme 1 Synthetic methods of benzo[*b*]phospholes

Over the past several years, the development of transtition-metal-free transformations has become an active topic in organic synthesis[8] since metal-free catalyzed process is advantageous in terms of elimination of cost saving, metal toxicity and minimization of environmental pollution, and is regarded as an important subject in green chemistry. Such methodologies are extremely valuable as promising alternatives and beneficial complements to transition-metal-catalyzed processes. Particularly, the transition-metal-free direct C-H functionalization has emerged as one of the most important strategies for the preparation of a wide range of useful molecular frames in modern organic synthesis chemistry due to its avoidance of prefunctionalization of starting substrates and its remarkable advantages of both

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[a] Department of Chemical and Biochemical Engineering, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, Fujian, China
[b] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, Fujian, China. E-mail: gaoxingchem@xmu.edu.cn
[c] Third Institute of Oceanography, State Oceanic Administration, Xiamen 361005, Fujian, China

Electronic Supplementary Information (ESI) available: Experimental, spectral data and copies of spectra. See DOI: 10.1039/x0xx00000x

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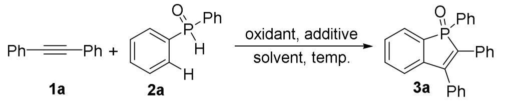
DOI: 10.1039/C6GC01009A

step- and atom-economy and environmental sustainability in industrial and green chemistry, and made significant progress.[9] On the other hand, the cheap, commercially available and nontoxic $K_2S_2O_8$ as catalyst is highly attractive for chemical synthesis from environmental and economic points of view. It is well known that $K_2S_2O_8$ can play as a radical initiator to produce sulfonyl radicals from sulfinates,[10] which could lead to the formation phosphorus-centered radicals followed by the radical reaction for the synthesis of organic phosphorus compounds.[11] However, to the best of our knowledge, the example of benzo[*b*]phosphole oxides formation via metal-free radical addition/cyclization of internal alkynes with diarylphosphine oxides has yet to be reported (Scheme 1c). As part of our on-going efforts to develop environmentally friendly new methods for the P-C bond formation,[12] herein, we first disclosed $K_2S_2O_8$-mediated metal-free oxidative radical addition/cyclization of unactivated alkynes towards the structurally diverse benzo[b]phosphole oxides via sequential P-H/C-H functionalization along with the formation of one C-C and one C-P bond. This metal-free strategy enables a simple, efficient and environment-benign access to structurally complex benzo[*b*]phosphole oxide frameworks of importance in material science through a simple one-pot process.

Table 1 Optimization of the reaction conditions[a]



Entry	Oxidant	Additive	Solvent	Temp (°C)/ Time (h)	Yield (%)[b]
1	$K_2S_2O_8$	-	dioxane	60/12	53
2	$K_2S_2O_8$	-	toluene	60/12	49
3	$K_2S_2O_8$	-	DMSO	60/12	24
4	$K_2S_2O_8$	-	C_2H_5OH	60/12	39
5	$K_2S_2O_8$	-	CH_3CN	60/12	60
6	$K_2S_2O_8$	-	CH_3CN	90/12	75
7	$\mathbf{K_2S_2O_8}$	**-**	$\mathbf{CH_3CN}$	**90/24**	**90**
8	$(NH_4)_2S_2O_8$	-	CH_3CN	90/24	69
9	$Na_2S_2O_8$	-	CH_3CN	90/24	51
10	oxone	-	CH_3CN	90/24	0
11	-	-	CH_3CN	90/24	0
12	$K_2S_2O_8$	pyridine	CH_3CN	90/24	56
13	$K_2S_2O_8$	AcOH	CH_3CN	90/24	58
14	$K_2S_2O_8$	TBAB	CH_3CN	90/24	0
15	$K_2S_2O_8$	-	CH_3CN	80/24	65
16	$K_2S_2O_8$	-	CH_3CN	100/24	50
17[c]	$K_2S_2O_8$	-	CH_3CN	90/24	83
18[d]	$K_2S_2O_8$	-	CH_3CN	90/24	60

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), oxidant (5 equiv.), additive (1 equiv.), solvent (2 mL), under Ar. [b] Isolated yields. [c] Using $K_2S_2O_8$ (6 equiv.). [d] Using $K_2S_2O_8$ (4 equiv.).

Our initial efforts focused on the model reaction of 1,2-diphenylethyne (**1a**) with diphenylphosphine oxide (**2a**) to optimize the reaction conditions (Table 1). To our delight, **1a** could react with **2a** in the presence of 5 equivalents of $K_2S_2O_8$ as the oxidant in 1,4-dioxane at 60 °C for 12 h to afford the desired product **3a** in 53% yield (entry 1). Encouraged by this result, the effect of solvents was detected, such as toluene, DMSO, ethanol and acetonitrile, which categorically approved acetonitrile as the most suitable choice (entries 2-5). When the reaction temperature was increased to 90 °C, the yield of **3a** was improved significantly (75% yield, entry 6). Gratifyingly, increasing the reaction time to 24 h led to an excellent yield of 90% (entry 7). To advance the process further, other oxidants such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$ and oxone were also investigated, with the finding that $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ gave unsatisfactory yields of 69% and 51%, respectively, and oxone was ineffective for the reaction (entries 8-10). Notably, no desired product was detected in the absence of $K_2S_2O_8$, revealing that $K_2S_2O_8$ was essential to achieve a high yield of product **3a**. (entry 11). Subsequently, we checked the effect of additives including pyridine, AcOH and TBAB (tetrabutyl ammonium bromide) and found that a sharp decrease of the yield was observed using pyridine and AcOH, but the addition of 1 equiv. of TBAB completely suppressed this reaction, demonstrating that the addition of the additive is less effective (entries 12-14). Increasing or decreasing the temperature from 90 °C gave rise to a significant decrease in reaction yield (entries 15-16). Similarly, an increase in the $K_2S_2O_8$ loading did not improve this reaction, and a low loading (4 equiv.) resulted in a decrease of the yield (entries 17-18).

With the optimized conditions in hand, the scope of this method was extended to the reaction of a wide range of alkynes with different diarylphosphine oxides. As shown in Table 2, various alkynes bearing different electron-withdrawing and electron-donating substituents were all efficiently reacted with diarylphosphine oxides via this novel metal-free $K_2S_2O_8$-mediated radical addition/cyclization reactions to afford diverse benzo[*b*]phosphole oxides with moderate to high yields (**3a-3s**), demonstrating that this protocol is a general and practical tool for the preparation of various valuable benzo[*b*]phosphole oxide motifs. Generally, both electron-rich and electron-deficient diarylacetylenes **1a-1i** were all suitable for this method, and the corresponding oxidative addition/cyclization products were obtained in moderate to excellent yields of 43-90% (**3a–3i**). Thus, a variety of substituents on the aromatic ring, such as methyl, ethyl, *t*-butyl, methoxyl, fluoro, chloro, bromo and trifluoromethyl groups, were all tolerated under the reaction conditions, revealing that electronic effects were not evident in this transformation. Notably, fluoro-, chloro- and bromo-substituted diarylacetylenes could be successfully converted into the desired products (**3e-3g**), which indicated the potential of this new procedure to allow access to highly functionalized targets by next coupling of halide products.[13] Encouraged by the above results, we next examined the oxidative addition/cyclization reactions of various asymmetrical phenylacetylenes with **2a**. It is worth noting

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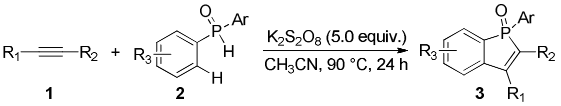
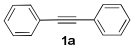
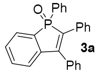
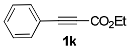
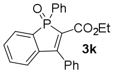
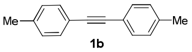
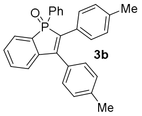
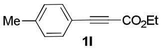
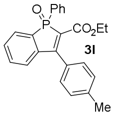
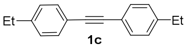
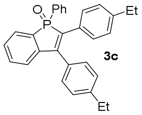
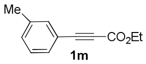
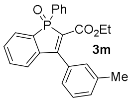
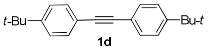
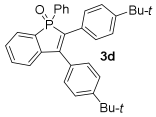
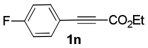
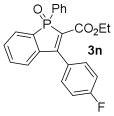
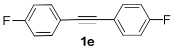
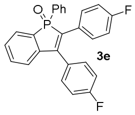
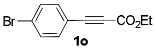
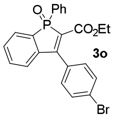
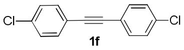
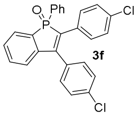
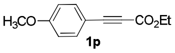
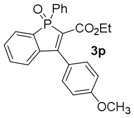
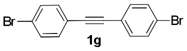
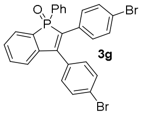
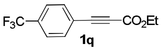
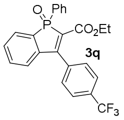
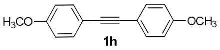
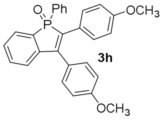
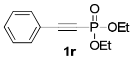
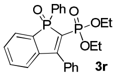
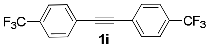
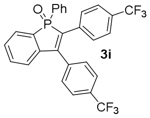
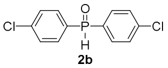
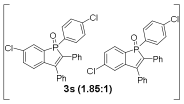
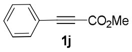
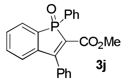
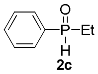
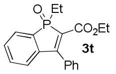
Table 2 $K_2S_2O_8$-mediated radical addition/cyclization of diarylphosphine oxides **2** with unactivated alkynes **1**[a]

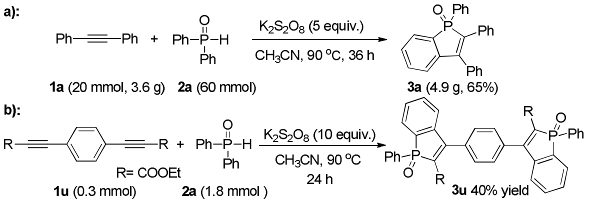


Entry	Alkyne **1**	Product **3**	Yield (%)[b]	Entry	Alkyne **1**	Product **3**	Yield (%)[b]
1	 1a	 3a	90	11	 1k	 3k	60
2	 1b	 3b	75	12	 1l	 3l	61
3	 1c	 3c	63	13	 1m	 3m	48
4	 1d	 3d	70	14	 1n	 3n	51
5	 1e	 3e	51	15	 1o	 3o	33
6	 1f	 3f	55	16	 1p	 3p	53
7	 1g	 3g	57	17	 1q	 3q	38
8	 1h	 3h	50	18	 1r	 3r	57
9	 1i	 3i	43	19	 2b	 3s (1.85:1)	61[c]
10	 1j	 3j	53	20	 2c	 3t	63

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), $K_2S_2O_8$ (1.5 mmol), CH_3CN (2mL), at 90 °C for 24 h under Ar. [b] Isolated yields. [c] Two regioisomers were generated and were not separated by column chromatography on silica gel owing to their very similar polarity. The ratio of two regioisomers of **3s** was determined by ^{31}P NMR analysis.

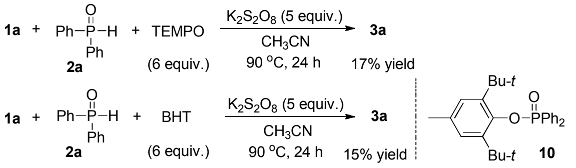
that various asymmetrical phenylacetylenes **1j-1s** reacted with **2a** or **2b** in a high regioselective manner to afford the 2-substituted 1,3-diphenyl-1H-phosphindole-1-ones **3j-3r** in moderate yields without the observation of other regioisomers by *in situ* ^{31}P NMR analysis. This result revealed that the phosphorus atom was installed at the less hindered position of alkynes preferentially. Interestingly, a series of aryllpropiolates (**1j-1q**) having different functional groups, such as methyl, fluoro, bromo, methoxyl and trifluoromethyl groups, still underwent a similar process to give the corresponding products **3j-3q**, albeit in somewhat low yields of **3o** and **3q**. Notably, steric hindrance significantly affected the reaction efficiency. For example, the ethyl 3-(p-tolyl)propiolate **1l** and meta-substituted counterpart **1m** afforded moderate yields of 61% and 48%, respectively, but sterically demanding ethyl 3-(o-tolyl)propiolate only gave a trace of product. Furthermore, diethyl (phenylethynyl)phosphonate **1r** is also a suitable reaction partner to extend the applicability of the present procedure. To gain more insight into the substrate scope, substituted secondary arylphosphine oxide **2b** was further evaluated. It was found that **2b** could also participate in this transformation, but a mixture of regioisomeric products (**3s**) were obtained as a result of a radical mechanism involving similar radical aryl migration rearrangement.[4,14] In addition, ethyl(phenyl)phosphine oxide **2c** smoothly reacted with **1k** and led to the corresponding product **3t** in a good yield.

To demonstrate the synthetic application of the present protocol, a gram-scale experiment was performed on **1a** (20 mmol, 3.6g) using **2a** under the optimal reaction conditions (Scheme 2a). The desired product **3a** was obtained in a good yield of 65% (**3a**, 4.9 g), revealing this method could be easily adopted for the large scale preparations with the high efficiency. In addition, as expected, **2a** could react with diyne **1u** to generate a bis(benzophosphole-3-yl)benzene framework, which is of interest for applications in thin-film photovoltaics and organic light-emitting diodes (Scheme 2b).[3a,15]



Scheme 2 Application studies

To understand the mechanism of the current reaction, the radical scavenger effect was examined by the reaction of **1a** with **2a**, and the addition of 6 equivalents of TEMPO or BHT as a radical scavenger dramatically suppressed this reaction (Scheme 3). Furthermore, the BHT adduct **10** was detected by the ESI-HRMS analysis. These results showed that the reaction probably proceeded via a free radical process.

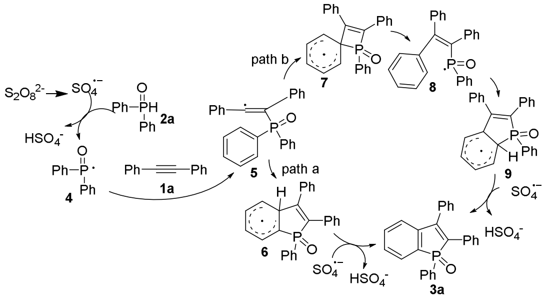


Scheme 3 Radical Trapping Study

Based on the above results and previous reports,[4,11] a plausible mechanism is proposed in Scheme 4. Initially, the homolysis of $K_2S_2O_8$ easily generated the $SO_4^{\cdot-}$ anion radical, which abstracted hydrogen from the P-H bond of **2a**, providing a phosphinoyl radical **4** and nontoxic HSO_4^- salt[11]. Then, the selective addition of the P-radical **4** to the triple bond of the alkyne **1a** afforded an alkenyl radical **5**. Finally, the radical **5** might undergo two pathways to give the desired product **3a** on the basis of the generation of two regioisomeric products via a similar process originally proposed by Miura and Duan.[4]

Conclusions

In conclusion, we have successfully developed the first efficient, $K_2S_2O_8$-mediated metal-free oxidative radical addition/cyclization of various unactivated alkynes with diarylphosphine oxides, affording rapid and environment-benign strategy for a structurally diverse array of benzo[*b*]phosphole oxides via sequential P-H/C-H functionalization under mild reaction conditions. Importantly, the use of commercially available, inexpensive and environmentally benign $K_2S_2O_8$ as oxidant represents a prominent advantage of the method. Most attractively, the present method avoids metals and other additives, and various valuable benzo[*b*]phosphole oxide moieties could be conveniently obtained in a simple one-step process. Therefore, the present protocol eliminates any possibility that residual heavy metal in the product would affect its performance when it is applied to organic electronic devices. In addition, the operational simplicity and environment-friendliness associated with this approach suggest its great potential for widespread application in the construction of important benzo[*b*]phosphole oxide frameworks in material science. Further mechanistic investigations and application researches will be pursued.



Scheme 4 Proposed mechanism

We are grateful for the financial support from the Chinese National Natural Science Foundation (21202135, 41576081) and the National Basic Research Program of China (2012CB821600).

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$K_2S_2O_8$-mediated metal-free direct P-H/C-H functionalization: a convenient route to benzo[*b*]phosphole oxides from unactivated alkynes

Dumei Ma, Weizhu Chen, Gaobo Hu, Yun Zhang, Yuxing Gao, Yingwu Yin and Yufen Zhao

A metal-free and $K_2S_2O_8$-mediated radical addition/cyclization of internal alkynes leading to benzo[*b*]phosphole oxides was developed, which eliminates residual heavy metal contamination in the product.