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COMMUNICATION

TBAI-Catalyzed Oxidative C-H Functionalization: A New Route to Benzo[*b*]phosphole Oxides

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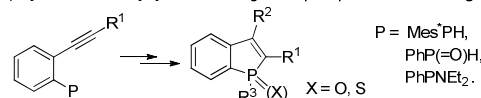
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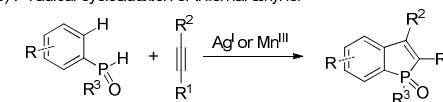
The first metal-free, efficient TBAI-catalyzed radical addition/cyclization of diaryl(arylethynyl)phosphine oxides with toluene derivatives has been developed, affording a general, one step approach to structurally sophisticated benzo[*b*]phosphole oxides via sequential C-H functionalization along with two new C-C bonds formation.

Benzo[*b*]phosphole derivatives, the phosphorous analogue of indole, have aroused the continuing strong interest for synthetic chemists over the past few decades owing to their unique physical and photoelectric properties with potential application in advanced organic optoelectronic materials.¹ However, the methods for the synthesis of these motifs are relatively scarce. The vast majority of these protocols rely on intramolecular cyclization of alkynylarenes having *ortho*-phosphorus substituents (Scheme 1a),² but their general use poses severe limitations owing to the requirement of the multistep synthesis for each cyclization precursor and poor tolerance of functional groups because of using strong bases. Until recently, two research groups independently developed a novel and efficient P-radical cycloaddition of internal alkynes for the preparation of benzo[*b*]phosphole oxides through using environmentally unfriendly Mn salts or noble Ag salts as catalysts (Scheme 1b).³ Very recently, Yoshikai and co-workers reported a modular approach to the synthesis of benzo[*b*]phosphole skeleton, which suffered from complicated multistep reactions and relatively lower yields, thus restraining its applications.⁴ Therefore, the development of convenient, metal-free catalyzed procedures to benzo[*b*]phosphole species from readily available starting substrates is still desirable.

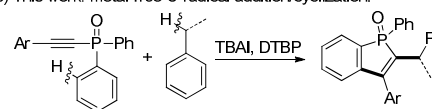
In recent years, direct activation or functionalization of unreactive C-H bonds for selective C-C and C-heteroatom bond formation through radical reactions has emerged as a fascinating and powerful tool in organic synthesis because of its avoidance of prefunctionalization of starting substrates and its remarkable potential for step economy and atom economy.⁵ Among these radical reactions, a variety of benzylic hydrocarbons have been served as reaction partners owing to their easily formed active benzylic radicals.⁶ Inspired on the

(a) Cyclization of alkynylarene having *ortho*-phosphorus functional group:

(b) P-radical cycloaddition of internal alkyne:



(c) This work: metal-free C-radical addition/cyclization:



Scheme 1. Synthetic methods of benzo[*b*]phosphole derivatives

recent report on the tandem radical addition/cyclization of alkenes with toluene derivatives,^{6g} a more synthetically valuable approach to benzo[*b*]phosphole would involve intermolecular addition/cyclization between alkynylphosphonates and toluene derivatives through successive cleavage of Csp³-H and Csp²-H bonds (Scheme 1c). Furthermore, recent numerous studies on direct functionalization of toluene⁷ and applying TBAI/peroxide as the catalyst system to initiate radical reactions⁸ were developed continuously. On the basis of these works and our continual interest in the development of the new procedures to organic phosphorus compounds,⁹ we herein reported the first facile and TBAI/DTBP-catalyzed radical addition/cyclization of various toluene derivatives with readily available diaryl(arylethynyl)phosphine oxides,¹⁰ providing a general, one step approach to structurally sophisticated benzo[*b*]phosphole oxide frameworks via sequential C-H functionalization along with the formation of two new C-C bonds, and to the best of our knowledge, there is no precedent for similar C-radical-induced benzo[*b*]phosphole-forming reactions.

Our initial efforts focused on the model reaction of diphenyl(phenylethynyl)phosphine oxide (**1a**) with toluene (**2a**) to optimize the reaction conditions (Table 1). Gratifyingly, using *tert*-butyl peroxide (DTBP, 3 equiv.) as the oxidant at 120°C for 30 h, the desired product **3a** was obtained in 40% yield (entry 1). Encouraged by this result, we further optimized the reaction conditions through adding pyridine as the additive and found that it

enhanced the product yield up to 55%, however, further increasing the loading of pyridine led to the yield reduction (entries 2-3). Further exploration suggested that a high yield of 82% was obtained when TBAI was employed as a catalyst (entry 4). Other catalysts such as KI, Bu₄NBr and Bu₄NCl were also investigated and it was found that KI could also improve the yield to 75%, but Bu₄NBr and Bu₄NCl gave unsatisfactory yields of 57% and 68%, respectively (entries 5-7). These results indicated that iodine ion plays a crucial role in achieving a high yield of product **3a**. Subsequent survey on the role of the base revealed pyridine as the most favored one to push the reaction forward (entries 4, 8-9). The effect of oxidants was also detected, and the results categorically approved DTBP as the most suitable choice and other oxidants like TBHP and H₂O₂ were less effective (entries 10-11). No product was observed in the absence of DTBP. An increase in the TBAI loading did not improve this reaction, and a low loading (10 mol%) led to a decrease of the yield (entries 12-13). The use of 0.5 equivalent of pyridine resulted in a significant decrease in reaction yield, and the yield could not be improved with increasing the loading of DTBP (entries 14-15). Finally, the effect of temperature was evaluated. To our delight, raising the temperature to 140 °C resulted in a higher yield of 88% (entry 16). Yet, further enhancing the reaction temperature to 160 °C gave rise to the yield reduction (entry 17).

Table 1. Optimization of the reaction conditions^a

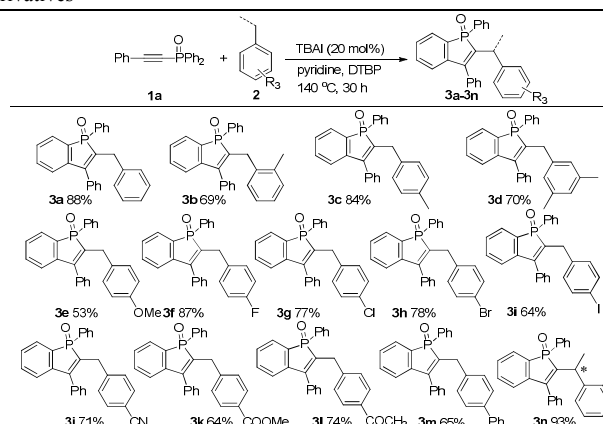
Entry	Catalyst	Oxidant	Additive	Yield(%) ^b
1	—	DTBP (3)	—	40
2	—	DTBP (3)	pyridine (1)	55
3	—	DTBP (3)	pyridine(1.5)	48
4	TBAI (20)	DTBP (3)	pyridine (1)	82
5	KI (20)	DTBP (3)	pyridine (1)	75
6	TBAB (20)	DTBP (3)	pyridine (1)	57
7	TBAC (20)	DTBP (3)	pyridine (1)	68
8	TBAI (20)	DTBP (3)	Et ₃ N (1)	48
9	TBAI (20)	DTBP (3)	K ₂ CO ₃ (1)	42
10	TBAI (20)	TBHP (3)	pyridine (1)	20
11	TBAI (20)	H ₂ O ₂ (3)	pyridine (1)	0
12	TBAI (30)	DTBP (3)	pyridine (1)	81
13	TBAI (10)	DTBP (3)	pyridine (1)	65
14	TBAI (20)	DTBP (3)	pyridin (0.5)	41
15	TBAI (20)	DTBP (5)	pyridine (1)	57
16 ^c	TBAI (20)	DTBP (3)	pyridine (1)	88
17 ^d	TBAI (20)	DTBP (3)	pyridine (1)	82

^aReaction conditions: **1a** (0.3 mmol), **2a** (1.5 mL), catalyst (mmol%), oxidant (equiv.), additive (equiv.), solvent (toluene), at 120 °C for 30 h, under Ar. DTBP = di-tert-butyl peroxide. TBHP = *tert*-butyl hydroperoxide 70% in water. H₂O₂ 30% in water. ^bIsolated yields. ^cAt 140 °C. ^dAt 160 °C.

With the optimized reaction conditions in hand (Table 1, entry 17), the substrate scope of this reaction was investigated. As shown in Table 2, diverse benzo[*b*]phosphole oxides can be conveniently and efficiently obtained by this novel metal-free TBAI-catalyzed radical addition/cyclization of **1a** with various toluene derivatives. Generally, both electron-rich and electron-deficient toluene derivatives were all suitable for this method, and the corresponding oxidative addition/cyclization products were obtained in moderate to excellent yields (Table 2, **3a–3n**). Notably, although xylenes (**2b** and **2c**) or mesitylene (**2d**) have more reactive positions, only mono-addition/cyclization products were observed (**3b–d**). Interestingly, fluoro-, chloro-, bromo- and iodo-substituted toluenes were also tolerated well to generate the desired products (**3f–3i**) in 64–87% yields. This result demonstrated the potential of this new procedure to allow access to highly functionalized targets by next coupling of halide products. More interestingly, the substrate **2l** having a reactive

carbonyl unit could also be compatible with this protocol, producing the desired benzo[*b*]phosphole oxide **3l** selectively in 74% yield without needing any protection of the carbonyl group. It is noticeable that ethylbenzene worked well in this process, thus leading to the desired racemization product **3n** in an excellent yield.

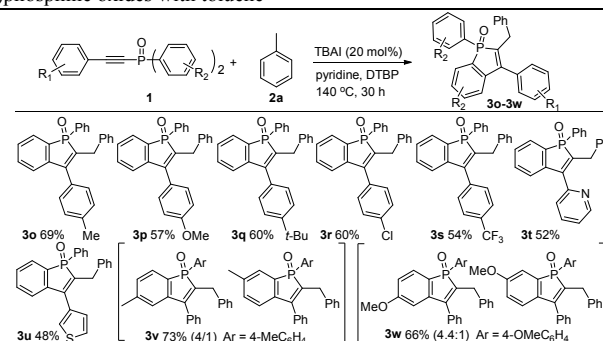
Table 2. TBAI-catalyzed radical addition/cyclization of **1a** with toluene derivatives^a



^a Reaction conditions: Bu₄NI (0.06 mmol), **1a** (0.3 mmol), **2** (1.5 mL), except for solid **2i** (2.52 g) and **2m** (1.53g), DTBP (0.9 mmol), pyridine (0.3 mmol), 140 °C, 30 h. Isolated yield.

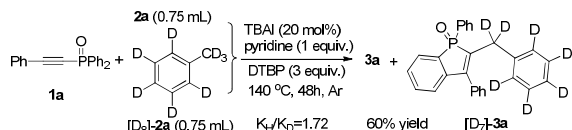
To gain more insight into the substrate scope, a variety of diaryl(arylethynyl)phosphine oxides were further evaluated (Table 3). It was found that various diaryl(arylethynyl)phosphine oxides containing both electron-donating and electron-withdrawing groups were all suitable reaction partners in this transformation, and generated the corresponding products (**3o–3s**) in moderate to good yields. Interestingly, heterocyclic substrates **1t** and **1u** could also participate in this reaction to produce the desired heterocyclic products (**3t–3u**) in moderate yields. It is worth noting that when **1v** and **1w** were employed, a mixture of regioisomeric products (**3v** and **3w**) were obtained as a result of a radical mechanism involving the rearrangement of a spirocyclic intermediate.³ Notably, this radical cyclization process is not common^{11a} and similar aryl migration rearrangement has been reported.^{11b}

Table 3. TBAI-catalyzed radical addition/cyclization of diaryl(phenylethynyl)phosphine oxides with toluene^a



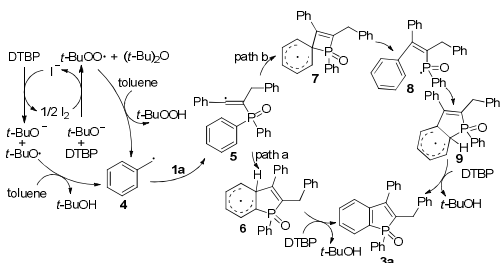
^a Reaction conditions: Bu₄NI (0.06 mmol), **1** (0.3 mmol), **2a** (1.5 mL), DTBP (0.9 mmol), pyridine (0.3 mmol), 140 °C, 30 h. Isolated yield.

To understand the mechanism of the current reaction, the kinetic isotope effect was examined by the reaction of deuterated toluene with **1a**, and K_H/K_D = 1.72 was observed (Scheme 2), indicating that the C-H bond cleavage on the methyl of toluene is not involved in the rate-limiting step.¹² Furthermore, it is noteworthy that the addition of 4 equivalents of BHT as a radical scavenger completely suppressed this reaction, thus showing the reaction likely to proceed by a SET process.



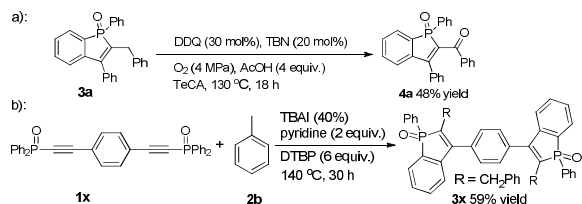
Scheme 2. The kinetic deuterium isotope effect

A plausible mechanism can be proposed based on these experimental results and previous reports (scheme 3).^{3,9b} Initially, the *tert*-butoxyl and *tert*-butylperoxyl radicals formed catalytically with the assistance of the iodide anion.^{8c-f} Then, these radicals trapped hydrogen from toluene to generate the benzyl radical **4**. Next, the selective addition of the C-radical to the α -position of the P=O bond in **1a** gave an alkenyl radical **5**. Finally, the radical **5** might undergo two pathways to produce the desired product **3a** on the basis of the generation of two regioisomeric products via a similar process originally proposed by Miura and Duan.³



Scheme 3. Proposed mechanism

To demonstrate the application of the present method, the oxidation reaction¹³ of **3a** with O₂ was conducted in the presence of DDQ and TBN (*tert*-butyl nitrite), affording a convenient protocol for the synthesis of a new type of 2-benzoyl benzo[*b*]phosphole oxides **4a**, which might be promising π -extended benzo[*b*]phosphole frameworks in organic electronics (Scheme 4a). In addition, as expected, toluene **2a** reacted with **1x** to generate a bis(benzophosphole-3-yl)benzene framework, which has interesting applications in organic light-emitting diodes and thin-film photovoltaics (Scheme 4b).^{1a,1b,2a}



Scheme 4. Application studies

In conclusion, we have successfully developed the first simple and efficient TBAI-catalyzed addition/cyclization of toluene derivatives with diaryl(arylethynyl)phosphine oxides, furnishing rapid access to a structurally diverse array of benzo[*b*]phosphole oxides via sequential Csp³-H/Csp²-H functionalization with remarkable functional group tolerance and good to excellent yields. From an organic synthesis point of view, the present method offers a new route to benzo[*b*]phosphole oxides and might open the door to new classes of functional benzo[*b*]phosphole oxides obtained through similar addition/cyclization of other C-, N-, O- and S-radicals with diaryl(arylethynyl)phosphine oxides. Importantly, this reaction is performed without the need of a transition-metal-catalyst, and various valuable products can be conveniently obtained in a one-pot process. In addition, an interesting aryl migration/cyclization on the P-atom was also observed. Further application researches and the addition/cyclization reaction of other radicals with diaryl(arylethynyl)phosphine oxides will be pursued.

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† Electronic Supplementary Information (ESI) available: general information, experimental procedures, copies of NMR spectra for products. See DOI: 10.1039/c000000x/

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TBAI-Catalyzed Oxidative C-H Functionalization: A New Route to Benzo[*b*]phosphole Oxides

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