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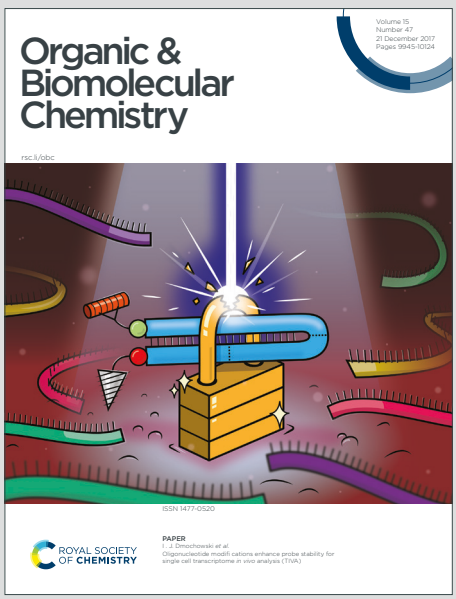

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COMMUNICATION

Additive-free coupling of bromoalkynes with secondary phosphine oxides to generate alkynylphosphine oxides in acetic anhydride

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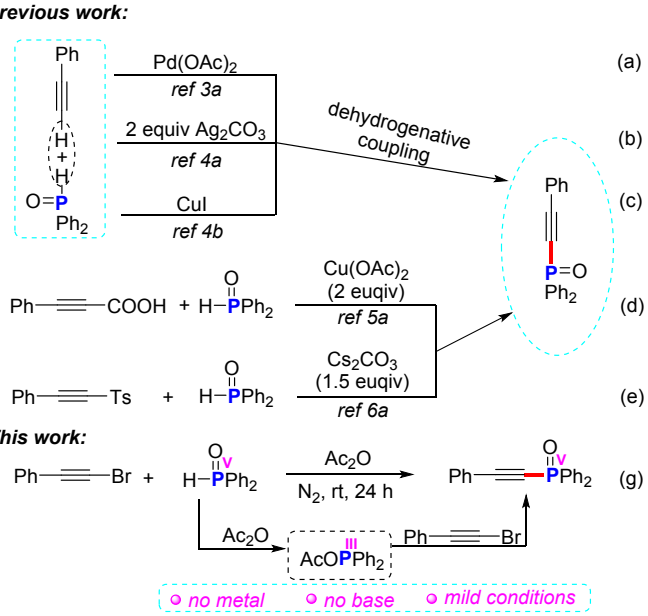
A coupling of bromoalkynes with secondary phosphine oxides was developed for the synthesis of alkynylphosphine oxides. This transformation was accomplished under additive-free conditions in acetic anhydride (Ac_2O). The reaction could be furnished with mild conditions, and a wide range of secondary phosphine oxides were obtained in good yields.

Direct construction of carbon-phosphorus (C–P) bonds is a shortcut strategy for the formation of organophosphorus compounds, which play important roles in the pharmaceutical and agrochemical industries. Among existing various phosphorus species, alkynyl-phosphorus compounds have been shown to be important precursors, due to their polar unsaturated bond, for the construction of functional organophosphorus derivatives.[1] Until now, different procedures have been developed to synthesize alkynylphosphoryl compounds.[2] The general method for their preparation is the cross-coupling of P(O)–H with terminal alkynes in the presence of transition metal catalysts (Scheme 1). For example, Han and Chen reported the Pd-catalyzed dehydrogenative coupling of terminal alkynes with H-phosphonates to generate alkynylphosphonates (Scheme 1a);[3] Lei and Zhao[4] achieved phosphorylation of terminal alkynes by employing Ag or Cu salts as a promoter or catalyst, respectively (Scheme 1b and 1c). Although the above dehydrogenative coupling can be carried out using terminal alkynes without prefunctionalization, such oxidative cross-coupling transformations cannot be workable without transition-metal catalysts and harsh reaction conditions.

As an effective and alternative strategy, heterosubstituted alkynes or alkyne derivatives have been used as candidate substrates for coupling with secondary phosphine oxides for the synthesis of phosphonoalkynes. For example, Yang and Wu used arylpropiolic acids to couple with H-phosphonates to afford alkynylphosphine oxides through the oxidative decarboxylative process (Scheme 1d);[5a] furthermore, alkynyl sulfones have also been used as potent alkynyl precursors to accomplish a similar C–P bond construction (Scheme 1e).[6] However, prominent deficiencies of the above methods still require a transition metal, large amount



Scheme 1 Different Routes to Phosphonoalkynes.

of base or complicated reaction conditions. Accordingly, the development of a simpler and more practical approach for the synthesis of phosphonoalkynes remains meaningful and interesting for chemists. Bromoalkynes are easily obtained from commercial terminal alkynes and *N*-bromosuccinimide (NBS) with a catalytic amount of $AgNO_3$, emerging as prominent synthetic precursors due to their good chemical reactivity in the reported organic transformations.[7,8] Therefore, we attempted the coupling reaction between bromoalkynes with secondary phosphine oxides under catalyst-free conditions, but no reaction was observed when the reaction was stirred in the classic solvents. To our delight, Ac_2O propelled the coupling of bromoalkynes with diarylphosphine oxide, and phosphonoalkynes were obtained with good chemoselectivity. Notably, in most reported works, the phosphorus valence remained unchanged during the formation of C–P bonds.[3-6] Conversely, this new protocol accomplished such transformations through an interesting procedure in acetic anhydride and had the advantages of simple reaction conditions to afford the desired coupling products in satisfactory yields with improving functional group tolerance (Scheme 1g). Herein, we report this facile platform for the synthesis of alkynylphosphine oxides from bromoalkynes with

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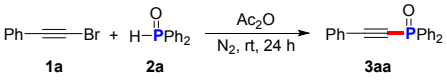
Table 1 Optimization of reaction conditions[a]



1a 2a 3aa

Entry	Solvent	Yield (%)[b]
1	Ac_2O	67[c]
2	Ac_2O	78[d]
3	Ac_2O	92
4	Ac_2O	81[e]
5	Ac_2O	76[f]
6	CH_3CN	NR
7	toluene	NR
8	THF	NR
9	DMSO	NR
10	DMF	NR
11	H_2O	NR

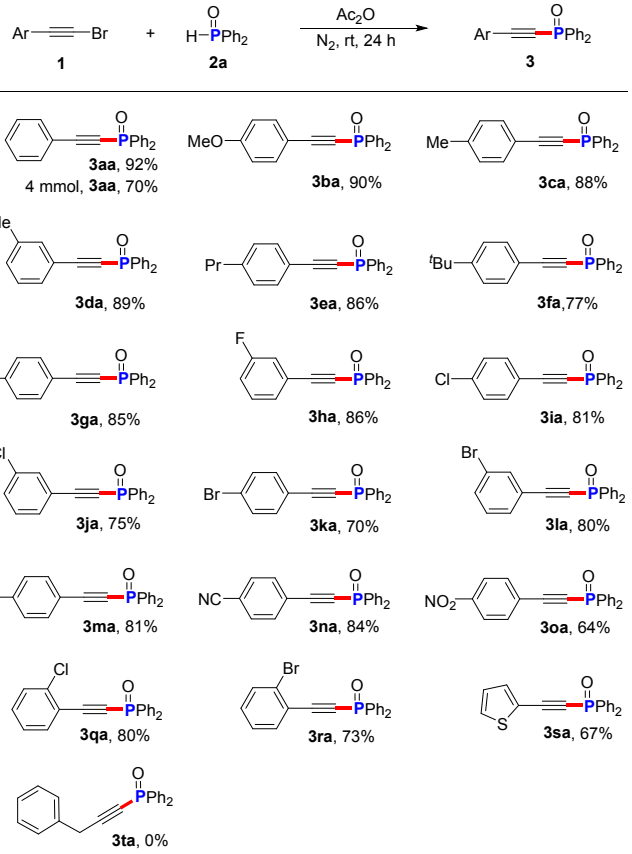
[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.60 mmol), solvent (1.0 mL) at room temperature under a N_2 atmosphere for 24 h. [b]Isolated yield. [c] Compound **2a** (0.2 mmol) was added. [d] Compound **2a** (0.4 mmol) was added. [e] The reaction was stirred under air. [f] The reaction was stirred under O_2. NR = no reaction.

secondary phosphine oxides under metal- and base-free conditions at room temperature in Ac_2O.

We commenced our work to optimize the cross-coupling reaction of phenylethynyl bromide **1a** and diphenylphosphine oxide **2a**, and the results are listed in Table 1. The model substrates **1a** and **2a** were stirred in Ac_2O at room temperature under a N_2 atmosphere for 24 h to afford the cross-coupling product **3aa** in 67% yield (entry 1, Table 1). The yield of **3aa** was improved with increasing amounts of **2a**, and 92% yield of **3aa** was obtained when 3.0 equiv. of **2a** was added in the reaction (entries 2 and 3, Table 1). The yield of **3aa** was slightly decreased when the reaction environment was changed from N_2 to air or O_2 (entries 4 and 5, Table 1). Further investigation of different solvents demonstrated that Ac_2O was an irreplaceable choice for the coupling reaction of **1a** and **2a**, and the efficiency of the reaction disappeared when the reaction was performed in CH_3CN, toluene, THF, DMSO, DMF and H_2O (entries 6–11, Table 1).

With the optimized conditions in our hands, the scope of the coupling of bromoalkynes with diphenylphosphine oxide (**2a**) was investigated. As shown in Scheme 2, all bromoalkynes (**1a**–**1s**) with different substituents on the phenyl ring reacted smoothly with **2a** to give the corresponding products (**3aa**–**3sa**) in 64–92% yield. The 1-bromo-2-arylacetylenes (**1**) with an electron-rich group, such as CH_3O, CH_3, ^{n}Pr, or ^{t}Bu on the *para*- or *meta*-position of the phenyl ring reacted with **2a** to afford the desired products (**3ba**–**3fa**) in 77–90% yields. The reactions of **1** with a weaker electron-poor group, including F, Cl or Br on the *para*- or *meta*-position of the phenyl ring, generated the corresponding coupling products (**3ga**–**3la**) in 70–86% yields. When a stronger electron-poor group, e.g., CF_3, CN or NO_2, was located at the para-position of the

Scheme 2 The scope of bromoalkynes[a,b]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), Ac_2O (1.0 mL) at room temperature under a N_2 atmosphere for 24 h. [b]Isolated yield.

benzene ring in the bromoalkynes **1**, the desired phosphonoalkyne products could be obtained with 81%, 84% and 64% yields, respectively, and no obvious electronic effects of the substituent were observed. Furthermore, *ortho*-substituted aromatic bromoalkynes, such as 1-(bromoethynyl)-2-chlorobenzene (**1q**) and 1-(bromoethynyl)-2-bromobenzene (**1r**) proceeded well in the reaction with **2a**, providing the corresponding products **3qa** and **3ra** in satisfactory yields, and no steric hindrance effect was found (**3qa** vs **3ia** and **3ja**; **3ra** vs **3ka** and **3la**). It should be noted that the heterosubstituted bromoalkyne 2-(bromoethynyl)thiophene (**1s**) reacted with **2a** to produce the anticipated product **3sa** in 67% yield. When the scope of substrate **1** was switched to an aliphatic substrate, e.g., 3-bromoprop-2-yn-1-yl benzene, no desired product was detected. When the model reaction was carried out on a gram-scale (4 mmol), a 70% yield of **3aa** was obtained.

Subsequently, the range of substrates was expanded to a variety of secondary phosphine oxides, and the detailed results are listed in Scheme 3. For the diaryl substituted phosphine substrates **2**, whether symmetrical electron-donating or electron-withdrawing groups were located on the aromatic rings, the couplings were comparable to give the desired alkynyl(diaryl)phosphine oxides (**3ab**–**3ah**) in 60%–80% yields. Using **2i**, which contained a dimethyl phenyl group, product **3ai** was afforded in 76% yield. Substrates **2**

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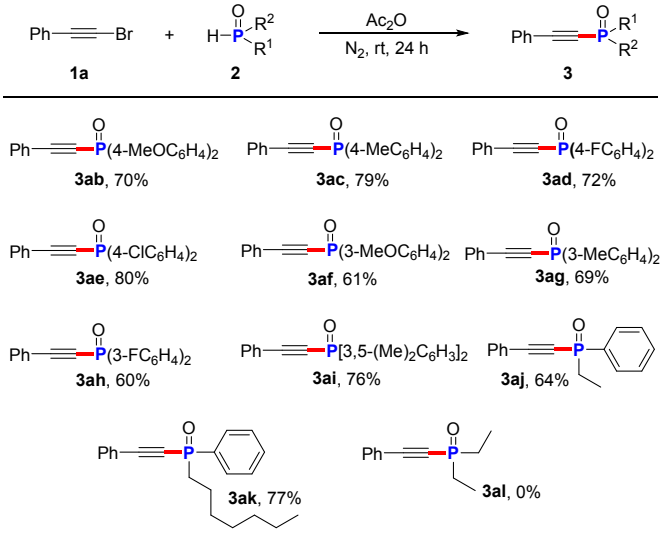
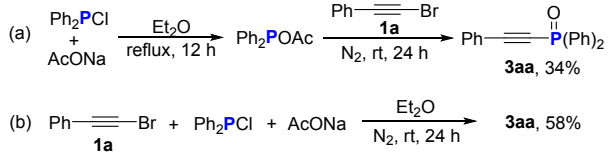
Scheme 3 The scope of the secondary phosphine oxides[a,b]



[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.60 mmol), Ac_2O (1.0 mL) at room temperature under a N_2 atmosphere for 24 h. [b]Isolated yield.

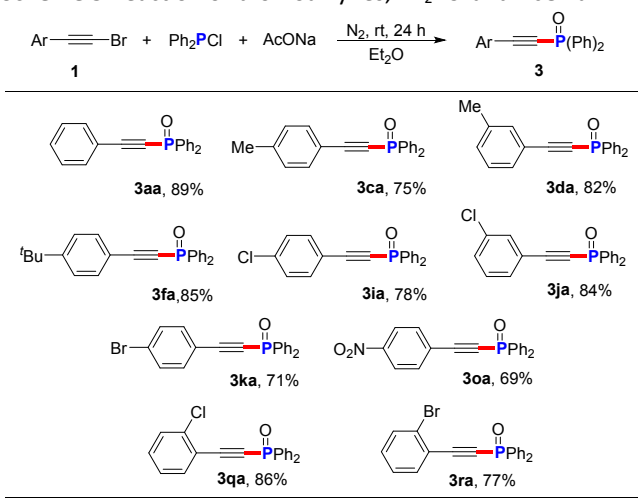
with unsymmetrical groups (one phenyl group and one aliphatic group) were also investigated and found to be suitable for the reaction, affording products **3aj** and **3ak** with 64% and 77% yields, respectively. However, when both the R^1 and R^2 groups in substrate **2** were changed to an aliphatic group, for example, when diethylphosphine oxide was involved in the reaction, the coupling reaction was unworkable.

From the obtained results in Table 1, Ac_2O plays an indispensable role during the formation of the coupling product. In addition, the yield of **3aa** improved with increasing amounts of Ac_2O (see SI for details), which confirmed the important role of Ac_2O and promoted us to speculate that the coupling reaction begins with the reaction of the diarylphosphine oxide and Ac_2O.[9] Consequently, the control experiments were conducted to elaborate the reaction clearly, as depicted in Scheme 4. First, the above speculation was verified by a previously reported work,[10] and the reaction with equiv. amounts of diarylphosphine oxide and Ac_2O to give the trivalent phosphine compound ($Ph_2P^{III}OAc$), which could be further reacted with **1a** to give the desired product **3aa** (Scheme 4a). Moreover, the coupling reaction could also be achieved via the reaction of equiv. amounts of **1a**, Ph_2PCl and AcONa (Scheme 4b). Subsequently, Ph_2PCl aroused our interest, and we attempted to converted different bromoalkynes **1** to their corresponding coupling products in the presence of Ph_2PCl and AcONa after quickly searching for the optimal conditions, as shown in Scheme 5. The results of Scheme 5 showed that a variety of bromoalkynes containing diverse substituents on



Scheme 4 Control experiments

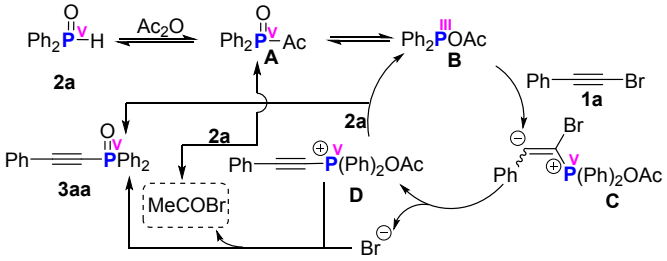
Scheme 5 Reaction of bromoalkynes, Ph_2PCl and AcONa[a,b]



[a]Reaction conditions: **1** (0.20 mmol), Ph_2PCl (0.6 mmol), AcONa (0.6 mmol), Et_2O (2 mL) at room temperature under a N_2 atmosphere for 24 h. [b]Isolated yield.

the phenyl ring could also be reacted with Ph_2PCl to be converted to the desired product in the presence of AcONa.

Based on the above mechanistic studies and previous reports, a possible mechanism is proposed in Scheme 6. A secondary phosphine oxide reacts with Ac_2O to generate intermediate **A**,[9] which can be converted to **B** via an equilibrium isomerization process. Next, intermediate **B** was added to bromoalkyne **1a** to give dipole intermediate **C**, which was followed by an elimination reaction to give intermediate **D**. Finally, **D** might lose an acetyl group in the presence of Br^- to afford the desired product **3aa** and concomitantly might generate acetyl bromide (MeCOBr). It should be noted that the key important intermediate **A** would be formed from the reaction of MeCOBr and **2a**.[11] To test this possibility, randomly selected bromoalkyne were examined, and the results are listed in Scheme 7. Bromoalkynes **1** containing different groups could react with diphenylphosphine oxide **2a** to afford the corresponding products **3aa**, **3da**, **3ja**–**3la** in good yield in the presence of MeCOBr, while heptyl(phenyl)phosphine oxide **2k** gave the desired product **3ak** in modest yield. Accordingly, the above results in Scheme 7 provide a direct evidence to support this possible pathway. On the other hand, intermediate **D** might also be transformed into **3aa** with the assistance of **2a** and concomitantly release intermediate **B** to further drive this coupling reaction. However, we cannot be sure which is the main pathway that forms the product.



Scheme 6 Proposed mechanism.

Scheme 7. Reaction of bromoalkynes, secondary phosphine oxides and MeCOBr[a,b]

Ar = C_6H_5	$R^1 = R^2 = C_6H_5$	**3aa**, 82%
Ar = 3-MeC_6H_4	$R^1 = R^2 = C_6H_5$	**3da**, 53%
Ar = 3-ClC_6H_4	$R^1 = R^2 = C_6H_5$	**3ja**, 75%
Ar = 4-BrC_6H_4	$R^1 = R^2 = C_6H_5$	**3ka**, 78%
Ar = 3-BrC_6H_4	$R^1 = R^2 = C_6H_5$	**3la**, 70%
Ar = C_6H_5	$R_1 = C_6H_5$, $R_2 = {}^nC_7H_{13}$	**3ak**, 40%

[a]Reaction conditions: **1** (0.20 mmol), secondary phosphine oxide (0.6 mmol), MeCOBr (0.60 mmol), MeCN (2.0 mL) at room temperature under a N_2 atmosphere for 24 h. [b]Isolated yield.

Conclusions

In conclusion, we have developed a convenient synthetic platform for the synthesis of alkynylphosphine oxides through the direct cross-coupling of bromoalkynes with secondary phosphine oxides without additive and harsh conditions. This facile and mild reaction was carried out under mild conditions in Ac_2O and generated a variety of alkynylphosphine oxides with good functional group tolerance.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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