Silver-Mediated Selective Oxidative Cross-Coupling between C−H/P−H: A Strategy to Construct Alkynyl(diaryl)phosphine Oxide

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S *Supporting Information*

ABSTRACT: A direct oxidative cross-coupling between terminal alkynes and secondary phosphine oxides was developed. This approach provides an efficient way to construct alkynyl di(phenyl) phosphine oxides from basic materials, and in this process, the silver salts act as a key promoter.

In terms of avoiding prefunctionalization of substrates, the direct oxidative coupling between two different C−H or heteroatom−H bonds is superior to the classical transition-metal-catalyzed coupling reactions, and it represents an ideal organic synthesis in modern chemical society.[1] In this emerging field, the highly efficient and selective oxidative cross-coupling reactions involving terminal alkynes are still challenging, since inevitable homocoupling of terminal alkynes negatively affects the reactions.[2] Very recently, the combination of terminal alkynes and silver salts has shown potential in the construction of interesting heterocycles in a selective manner, in which alkyne homocoupling product is successfully avoided,[3] thereby suggesting that the combination of terminal alkynes and silver salts does not tend to occur homocoupling of terminal alkynes. Undoubtedly, this method offers more possibilities for exploring oxidative cross-couplings involving terminal alkynes as the nucleophiles. Herein, we report the first silver-mediated oxidative cross-coupling between terminal alkynes and secondary phosphine oxide to construct alkynyl di(phenyl) phosphine oxides (Scheme 1).

Scheme 1. Silver-Mediated C−H/P−H Direct Oxidative Cross-Coupling
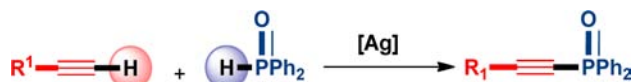
Alkynyl(diaryl)phosphine oxides are important precursors to synthesize various (P^O) or (P^N) bidentate ligands.[4] The traditional routes to alkynylphosphonates, such as the Michaelis−Arbuzov reaction and the Michaelis−Becker reaction, usually suffer from prefunctionalization of the starting materials and poor tolerance of functional groups.[5] Thus, it is still imperative to develop novel methods to improve the synthetical efficiency.[6] In 2009, Han and Zhao[6a] reported a copper-catalyzed oxidative coupling of alkynes with (iPrO)$_2$P-(O)H, which significantly simplified the process. However, secondary phosphine oxide Ph$_2$P(O)H was not tolerated to afford the corresponding product under their reaction conditions. Soon after, the groups of Yang and Liang[6d] and

Wu,[6e] respectively, realized the synthesis of alkynyl(diaryl)-phosphine oxides, but alkyne acid was employed instead of alkyne to react with Ph$_2$P(O)H. Recently, Zhao and Zhu further reported a Cu-catalyzed phosphorylation of terminal alkynes to achieve the synthesis of alkynyl(diaryl)phosphine oxides by adding the diphenylphosphine oxide to the reaction mixture dropwise, in which only one example was presented.[6g] Based on our continued interest in the development of terminal alkyne chemistry with silver salts, we envisioned that the direct oxidative coupling of terminal alkynes with Ph$_2$P(O)H might be generally achieved. This protocol would address the previous limitations and furnish a diverse collection of valuable alkynyl(diaryl)phosphine oxides from basic chemical materials.
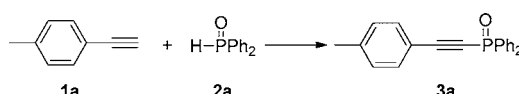
Our initial efforts focused on the reaction of 1-ethynyl-4-methylbenzene **1a** and diphenylphosphinoxide **2a** by using different silver(I) salts. To our delight, we found that the corresponding alkynyl(diaryl)phosphine oxides product was indeed obtained, albeit in low yields, when AgI, AgNO$_3$, Ag$_2$O, and Ag$_2$CO$_3$ were applied as the promoters (Table 1, entries 1−4). This interesting transformation encouraged us to further examine the feasibility of this direct oxidative cross-coupling.

After many efforts, the employment of Ag$_2$CO$_3$ (2.0 equiv) in DMSO at 120 °C was found to be the best reaction conditions for this direct C−H/P−H oxidative cross-coupling (Table 1, entry 8). Importantly, the reaction displayed high selectivity. Even though the two substrates were added in one pot, no terminal alkynes homocoupling and other byproducts were observed. Ag$_2$O could also provide the desired product in 17% yield, while AgI and AgNO$_3$ were totally ineffective (Table 1, entries 1−3). A lower amount of Ag$_2$CO$_3$ would afford lower yields (Table 1, entries 4 and 5). When the reaction temperature was decreased to 80 °C, the desired product could be obtained in only 47% yield (Table 1, entry 7). However, increasing the temperature did not improve the yield (Table 1, entries 9). The reaction could also proceed in other solvents, such as polar solvents DMF and DCE, albeit in lower yields (Table 1, entries 10 and 11). When toluene was used,

Table 1. Impact of Reaction Parameters on the Direct Oxidative Cross-Coupling[a]

entry	[Ag]	temp (°C)	solvent	yield[b] (%)
1	1.0 equiv of AgI	100	DMSO	trace
2	1.0 equiv of AgNO$_3$	100	DMSO	trace
3	1.0 equiv of Ag$_2$O	100	DMSO	17
4	1.0 equiv of Ag$_2$CO$_3$	100	DMSO	40
5	0.5 equiv of Ag$_2$CO$_3$	100	DMSO	16
6	2.0 equiv of Ag$_2$CO$_3$	100	DMSO	60
7	2.0 equiv of Ag$_2$CO$_3$	80	DMSO	47
8	**2.0 equiv of Ag$_2$CO$_3$**	**120**	**DMSO**	**70**
9	2.0 equiv of Ag$_2$CO$_3$	140	DMSO	68
10	2.0 equiv of Ag$_2$CO$_3$	120	DMF	51
11	2.0 equiv of Ag$_2$CO$_3$	120	DCE	43
12	2.0 equiv of Ag$_2$CO$_3$	120	toluene	trace
13[c]	2.0 equiv of Ag$_2$CO$_3$	120	DMSO	37

[a]The reaction was carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), 15 h, 3 mL of solvent, N$_2$. [b]Isolated yield. [c]The reaction was carried out under air.

only a trace amount product was obtained (Table 1, entry 12). The reaction could also proceed under air to generate the desired product, albeit in lower yield (Table 1, entry 13).

With the optimized conditions in hand, varied terminal alkynes **1** were found to be suitable reaction partners with diphenylphosphine oxide **2a** to provide the corresponding alkynyl(diaryl)phosphine oxides (Scheme 2). Both electron-withdrawing and electron-donating substituted groups or halogen groups at the aromatic ring of arylalkynes were well tolerated in the reactions, such as Me, OMe, Cl, Br, F, COEt, phenyl, n-pentyl, and n-butyl (Scheme 2, **3a–i,m–o**). Meanwhile, arylalkynes with substituents at the ortho, meta, or para position of the aromatic ring could react smoothly to afford the desired products in moderate to good yields. Terminal alkynes containing thiophene and pyridine moieties could also be employed to give the corresponding product in 54% and 52% yields, respectively (Scheme 2, **3j** and **3k**). Moreover, alkyl terminal alkynes were also found to be suitable reaction partners with diphenylphosphine oxide **2a** in the reaction. Aliphatic terminal alkynes, including those with cyclopropyl and tert-butyl, could also react with **2a** to afford the corresponding products in moderate yields (Scheme 2, **3t,u**). In addition, ethyl propiolate was also suitable for this reaction (Scheme 2, **3v**).

Varied secondary phosphine oxides are also tested to access the corresponding product. Various substituted groups at the aromatic ring of phosphine oxides could be introduced into the desired product, such as Cl, F, and Me (Scheme 2, **3p–r**). Ethyl phenylphosphinate could also react smoothly to afford the desired product in moderate yield (Scheme 2, **3s**). Unfortunately, under the current reaction conditions, (EtO)$_2$P(O)H could not afford the oxidative cross-coupling product (Scheme 2, **3w**).

The silver salts could be reused. An undisputable issue is the application of 2 equiv of Ag$_2$CO$_3$ in this reaction. It is well-known that Ag$_2$CO$_3$ is one of the most cost-effective silver sources; however, the cost and waste are still worth attempting to save.[3b] Actually, excess Ag$_2$CO$_3$ and all silver species after the reaction could be recycled conveniently by filtration and

**Scheme 2. Reactions of Alkynes 1 and Secondary Phosphine Oxides 2.**[a]
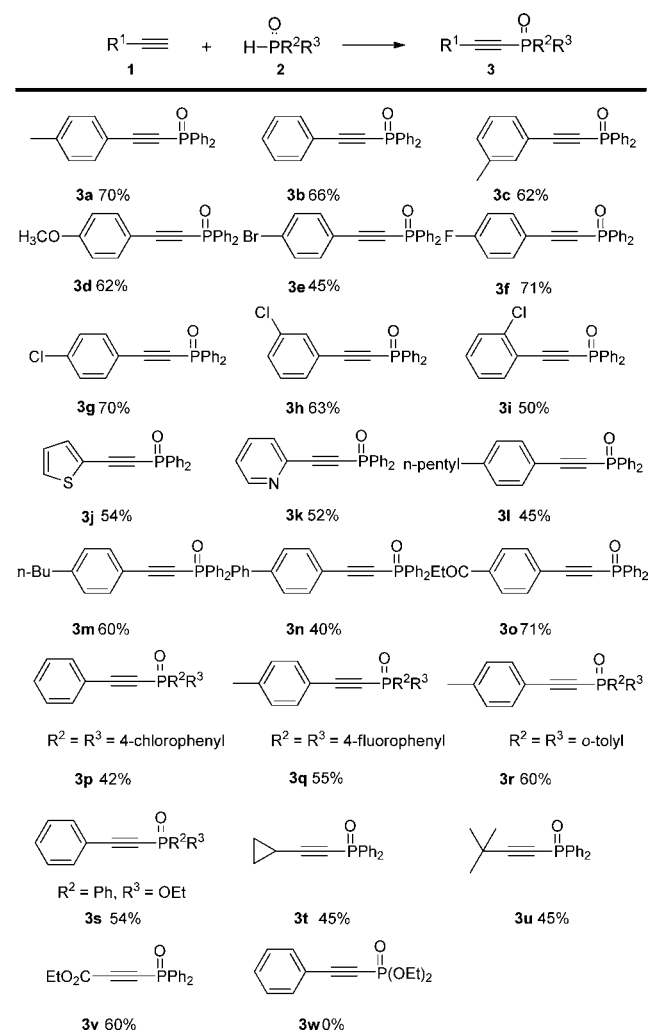
[a]Reactions of alkynes **1** and secondary phosphine oxides **2**. Reaction conditions: The reactions were carried out with **1** (0.3 mmol), **2** (0.2 mmol), Ag$_2$CO$_3$ (0.4 mmol), N$_2$, DMSO (3 mL), 120 °C, 15 h, isolated yield.
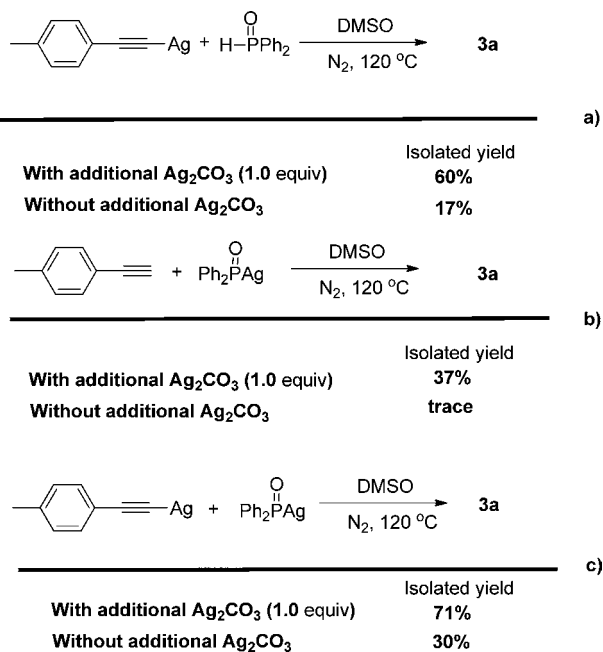
treatment with nitric acid and Na$_2$CO$_3$ (for the details of the Ag recovery experiment, see the Supporting Information). The regenerated Ag$_2$CO$_3$ could still promote this oxidative cross-coupling in comparable yield without loss of activity (Scheme 3).

To gain preliminary mechanistic information about this transformation, the prepared silver acetylide was reacted with **2a** under the standard conditions. As shown in Scheme 4a, in the presence of additional Ag$_2$CO$_3$, silver phenylacetylide could indeed react with **2a** and afford the desired product in 60%

Scheme 3. Recovery Experiments of Ag Salts
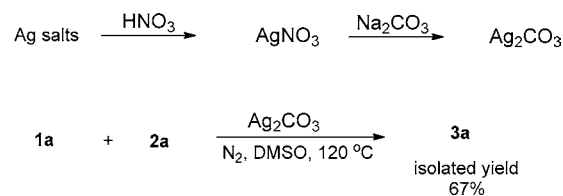
Scheme 4. (a) Reaction of 2a and Silver Phenylacetylide. (b) Reaction of 1a and (Ph)₂P(O)Ag. (c) Reaction of (Ph)₂P(O)Ag and Silver Phenylacetylide

	Isolated yield		a)
With additional Ag₂CO₃ (1.0 equiv)	60%		
Without additional Ag₂CO₃	17%		

	Isolated yield		b)
With additional Ag₂CO₃ (1.0 equiv)	37%		
Without additional Ag₂CO₃	trace		

	Isolated yield		c)
With additional Ag₂CO₃ (1.0 equiv)	71%		
Without additional Ag₂CO₃	30%		

yield. Without additional Ag_2CO_3, only 17% yield was obtained. The prepared $(Ph)_2P(O)Ag$ (for the preparation methods, see the Supporting Information) was also reacted with phenylacetylene. As shown in Scheme 4b, in the presence of additional Ag_2CO_3, the desired product could be obtained in 37% yield. Without additional Ag_2CO_3, only a trace amount of product was obtained. The stoichiometric reaction between $(Ph)_2P(O)Ag$ and silver phenylacetylide was also performed, and the corresponding product could be obtained in 30% yield (Scheme 4c); in the presence of additional Ag_2CO_3, 71% yield was obtained.

The putative mechanism of this silver-mediated C−H/P−H direct oxidative cross-coupling is outlined in Scheme 5. Initially,

Scheme 5. Proposed Mechanism
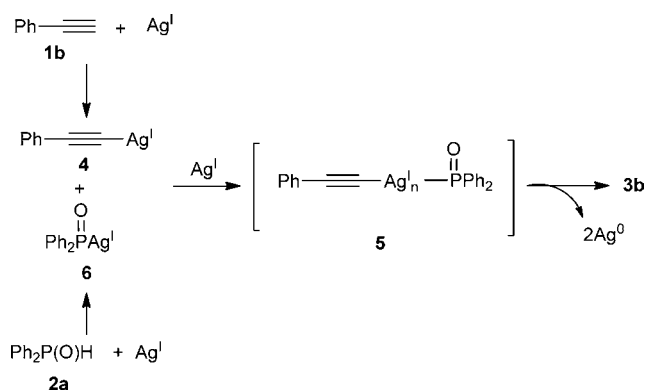
both silver acetylide complex **4** and (diphenylphosphoryl)silver **6** are formed by the reaction of terminal alkyne **1b** and diphenylphosphine oxide **2a** with Ag(I).[3a] Then, through the coordination of **6** and **4**,[7] the intermediate **5** is obtained (possibly aggregated with additional Ag,[8] Finally, silver-induced oxidative cross-coupling of **5** affords the product **3b** via two

single-electron oxidation. However, details of the mechanism are not clear at present. Our current efforts are focused on probing the mechanism of this oxidative transformation.

In summary, we have developed a novel silver-mediated highly selective oxidative C−H/P−H direct cross-coupling, which provided an efficient entry to the alkynyl(diaryl)-phosphine oxides in one step. From a synthetic point of view, this protocol represents an efficient way to alkynyl-(diaryl)phosphine oxides from basic starting materials. The combination of terminal alkynes and silver salts acts as a "dream ticket" for high selectivity in this oxidative C−H/P−H cross-coupling reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure, characterization data, and copies of ^1H, ^{13}C, and ^{19}P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.
Caution! The reaction apparatus should be placed behind blast shields to avoid safety issues.

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