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Copper-Catalyzed Direct Oxyphosphorylation of Alkynes with H-Phosphine oxides and Dioxygen: a Convenient Approach to β-Ketophosphine oxides

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Abstract

A simple and facile copper-catalyzed synthesis of β-ketophosphine oxides via direct oxyphosphorylation of alkynes with H-phosphine oxides and dioxygen has been developed under mild conditions without any base or cocatalyst. A radical reaction pathway for the formation of β-ketophosphine oxides is proposed. ^{18}O labeling experiment suggested that the carbonyl oxygen atom of β-ketophosphine oxides originated from dioxygen.

Graphical Abstract

KEYWORDS: β-ketophosphine oxides, copper-catalysis, alkynes, dioxygen, H-phosphine oxides

INTRODUCTION

Phosphorus-containing molecules exhibited a wide range of applications in organic synthesis,[1] medicinal chemistry,[2] and materials science.[3] In particular, β-ketophosphine oxides are extremely versatile intermediates, which can be used for various organic transformations toward many useful compounds such as olefins,[4] cyclopropanes,[5] and α, β-unsaturated ketones.[6] Furthermore, they can also serve as potential bidentate ligands and metal-extracting agents.[7] As a result, the synthesis of β-ketophosphine oxides has gained much attention.[8-12] The conventional synthetic methods usually relied on acylation of alkyl phosphine oxides with carboxylic acid derivatives by employing stoichiometric amounts of the hazardous organometallic reagents.[8] Alternative methods including the hydrolysis of enamine phosphine oxides,[9] base-promoted substitution reaction of hydrophosphoryl compounds with chloroacetophenone,[10] palladium-catalyzed hydration of alkynylphosphine oxides,[11] and copper-catalyzed C_{sp3}-H/P-H cross-coupling reaction of aryl ketone O-acetyl oximes with phosphine oxides have also been developed.[12] However, most of these methods suffered from limitations such as relatively harsh or complex reaction conditions, multistep reactions, preformed starting materials, toxic wastes, or requiring excess amounts of organometallic reagents.

Recently, the methods for the synthesis of β-ketophosphine oxides through the oxyphosphorylation of terminal alkynes and alkynylcarboxylic acids have been reported by several groups.[13-18] Zhao reported a $AgNO_3/CuSO_4$ co-catalyzed direct

oxyphosphorylation of terminal alkynes for the construction of β-ketophosphine oxides in the presence of $K_2S_2O_8$ (4.0 equiv) (Scheme 1, Eq (1)).[13] Song and He developed copper/iron co-catalyzed aerobic oxyphosphorylation of terminal alkynes and alkynyl carboxylic acids to access β-ketophosphine oxides in the presence of Et_3N (Scheme 1, Eq (2),(3)).[14,15] Tang reported a $CuSO_4 \cdot 5H_2O$-catalyzed coupling of alkynyl acids with H-phosphine oxides leading to β-ketophosphine oxides by using TBHP as the oxidant and $NH_3 \cdot H_2O$ as the base.[16] Wang described a novel method for the synthesis of β-ketophosphine oxides through the silver-catalyzed oxidative decarboxylative coupling of arylpropiolic acids with H-phosphine oxides.[17] Nevertheless, bimetallic catalysts, base, or stoichiometric amounts of oxidants such as $K_2S_2O_8$ and TBHP were inevitably used in above well-developed reaction systems. Herein, we wish to report a simple approach for the synthesis of β-ketophosphine oxides via copper catalyzed direct oxyphosphorylation of alkynes with H-phosphine oxides and dioxygen (Scheme 1, Eq (4)). The present reaction provides a convenient and efficient approach to various β-ketophosphine oxides in moderate to good yields with excellent functional group tolerance, which make it unnecessary for any metal co-catalyst or additives.

RESULT AND DISCUSSION

In an initial experiment, under an oxygen atmosphere, phenylacetylene (**1a**) and diphenylphosphine oxide (**2a**) were chosen as the model substrates to examine the catalytic activity of various transition metal complexes such as Cu, Ag, Au, Fe, Ni and Co salts in CH_3CN at 55 °C (Table 1, entries 1-11). Among various metals screened (5 mol%), copper salts especially CuCN was found to catalyze the formation of the desired

product **3aa**, albeit in low yield (Table 1, entry 5). The screening of a range of solvents showed that the reaction performed in DMSO was better than those in MeCN, THF, DME, DMF, toluene and 1,4-dioxane (Table 1, entries 5, 12-17). A low yield (33%) was obtained when the reaction was carried out at room temperature, and the best yield was obtained at 55 °C (Table 1, entries 17, 21-22). In addition, the proportion of the substrates also exerted the influences on the efficiencies. The optimal proportion of phenylacetylene (**1a**) to diphenylphosphine oxide (**2a**) was 1 : 2, and the decrease of the amount of **2a** (Table 1, entry 23) or increase of **1a** (Table 1, entry 24) would inhibit this transformation. Moreover, no desired product was observed in the absence of catalyst or dioxygen (Table 1, entries 25 and 26). After an extensive screening of the reaction parameters, the best yield of **3aa** (65%) was obtained by employing 5 mol% CuCN in DMSO at 55 °C under oxygen atmosphere (Table 1, entry 17).

With the optimized conditions in hand, the scope and limitations of this oxyphosphorylation reaction were investigated, with the results shown in Table 2. Generally, aromatic alkynes bearing both electron-rich and electron-poor groups on the aryl rings were all suitable for this process, producing the corresponding products in moderate to good yields (**3aa**-**3na**). It was found that this oxyphosphorylation was not significantly affected by the steric effect. The sterically congested *ortho*- or *meta*- methyl substituted aromatic alkynes could also be suitable for the reactions to deliver products (**3ea** and **3fa**) in good yields. Notably, various functional groups such as fluoro, chloro, bromo, ester, acetyl, cyano, and nitro groups were also found to be tolerated in this reaction to give the corresponding products (**3ga**-**3na**), which could be employed in

further transformations. Naphthyl alkyne such as 1-ethynylnaphthalene and heteroaryl alkyne such as 3-ethynylthiophene were also compatible with this reaction, providing the desired products in 60% and 54% yields, respectively (**3oa** and **3pa**). In addition, when internal alkyne such as 1-phenyl-1-propyne was employed in the present reaction system, the desired product **3qa** was obtained in 17% yield. Nevertheless, when aliphatic alkynes such as 3-cyclohexyl-1-proyne and 4-phenyl-1-butyne were used as the substrates, none of the corresponding products were obtained. The scope of this reaction was further expanded to other H-phosphine oxides, in addition to diphenylphosphine oxide (**2a**), other diarylphosphine oxides bearing electron-donating and electron-withdrawing groups could also be used in the reaction to give the expected products (**3ab**-**3ae**) in moderate yields.

A number of control experiments were performed to gain some insights into the reaction mechanism. Initially, the ^{18}O isotope-labeled product was obtained in 61% yield when isotope labeling experiment using $^{18}O_2$ was performed in the reaction of phenylacetylene (**1a**) and diphenylphosphine oxide (**2a**), indicating that the carbonyl oxygen atom of the β-ketophosphine oxide originated from dioxygen (Scheme 2).

Subsequently, the addition of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to model reaction completely inhibited the reactivity (Scheme 3). Furthermore, when the reaction of **2a** and TEMPO was performed in the absence of phenylacetylene (**1a**), a TEMPO-trapped compound (**4a′**) was obtained in 13% yield (Scheme 3). These results suggested that the present reaction should proceed through a radical pathway.

On the basis of above experiments and previous reports,[13-19] a tentative mechanism was proposed in the Scheme 4. Firstly, the reaction of Cu^{I} and O_2 would form Cu^{II}-(O^{2}·), which interacted with diphenylphosphine oxide **2a** leading to phosphonyl radical **4a** and Cu^{II}-(OOH).[19] Subsequently, the selective addition of the resulting phosphonyl radical **4a** to alkyne **1a** gave vinylradical **5a**.[13-15] Then, the reaction of vinylradical **5a** with Cu^{II}-(OOH) would lead to the formation of vinylperoxyl intermediate **6a**.[14] Next, the O-O bond of vinylperoxyl intermediate **6a** produced vinyloxy radical **7a** and hydroxyl radical ·OH. The coupling of hydroxyl radical ·OH with **4a** gave diphenylphosphinic acid **9a**.[13] Finally, vinyloxy radical **7a** would abstract the hydrogen of diphenylphosphine oxide **2a** to afford enolated phosphonate **8a**, which underwent tautomerization to yield the desired product **3aa**. [13-15]

Fortunately, the proposed vinylperoxyl intermediate **6a**, the diphenylphosphinic acid **9a**, and TEMPO-trapped radical **4a**, **5a**, **7a** were all detected by LC-MS analysis when TEMPO was added to the model reaction system after 2h (CuCN (5 mol%), DMSO (1 mL), 55 ^{o}C, O_2 (balloon)) (Fig. 1). The above results indicated that the proposed vinylperoxyl intermediate **6a** and radical **4a**, **5a**, **7a** should be involved in the present reaction system .

EXPERIMENTAL

All the reagents were bought from Alfa Aesar, TCI and J&K chemical companies. The products were purified by column chromatography using silica gel (200-300 mesh) and

aluminum oxide (neutral). ^{1}H NMR, ^{13}C NMR and ^{31}P NMR were recorded on a Bruker Avance 400 spectrometer. ^{1}H NMR were recorded on 400 MHz in $CDCl_3$ with TMS (tetramethylsilane) as internal standard, ^{13}C NMR were recorded on 100 MHz in $CDCl_3$ with TMS (tetramethylsilane) as internal standard and ^{31}P NMR were recorded on 162 MHz in $CDCl_3$ with H_3PO_4 (phosphoric acid) as internal standard. HRMS were performed on a Brucker Daltonics Bio-TOF-Q mass spectrometer by the ESI method and LC-MS were obtained on a Waters Acquity HPLC (PDA Detector) Quattor Premier XE triquadrupole mass spectrometer. IR spectra were obtained with a PerkinElmer Spectrum One FTIR Spectrometer. Melting points were obtained with a WRS-100 melting point apparatus.

General Procedure For Construction Of B-Ketophosphine Oxides

An oven-dried flask with the mixture of CuCN (0.025 mmol), alkynes **1** (0.5 mmol), H-phosphine oxides **2** (1.0 mmol) and DMSO (1.0 ml) was charged with O_2. The reaction mixture was stirred at 55 °C for 24 hours. After completion of the reaction, water (10 ml) was added and extracted with EtOAc (5.0 ml×3). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting mixture purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give the desired products **3**.

Spectral Data For The Product (Table 2, 3aa) [16,17]

2-(Diphenylphosphoryl)-1-Phenylethanone (3aa)

White solid; mp: 139.5-140.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99 – 7.97 (m, 2H), 7.83 – 7.78 (m, 4H), 7.55 – 7.50 (m, 3H), 7.48 – 7.39 (m, 6H), 4.14 (d, J = 15.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 192.9 (d, $J_{C\text{-}P}$ = 5.5 Hz), 137.1 (s), 133.7 (s), 132.3 (d, $J_{C\text{-}P}$ = 2.8 Hz), 132.0 (d, $J_{C\text{-}P}$ = 102.8 Hz), 131.2 (d, $J_{C\text{-}P}$ = 9.8 Hz), 129.3 (s), 128.7 (d, $J_{C\text{-}P}$ = 12.3 Hz), 128.6 (s), 43.4 (d, $J_{C\text{-}P}$ = 58.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 26.9 (s); IR (KBr) ν (cm^{-1}): 1682 (C=O), 1435 (P-Ph), 1178 (P=O); ESI HRMS calcd for $C_{20}H_{18}O_2P$ $[M+H]^+$ 321.1039, found 321.1039.

CONCLUSION

In conclusion, a simple and convenient method for the synthesis of β-ketophosphine oxides has been developed via copper-catalyzed direct oxyphosphorylation of alkynes with H-phosphine oxides and dioxygen. Preliminary mechanistic studies suggested that the present reaction might involve a radical process and the carbonyl oxygen atom of β-ketophosphine oxides came from the dioxygen. This simple reaction system is expected to expand the potential applications of β-ketophosphine oxides in the synthetic and pharmaceutical chemistry. Further studies of the detailed mechanism of this process and its application are underway in our laboratory.

SUPPLEMENTARY INFORMATION

Full experimental detail, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR spectra, melting point, HRMS and LC-MS for this article can be accessed in the "Supplementary Information" section of this article's webpage.

Supplementary information for this article can be accessed on the publisher's website.

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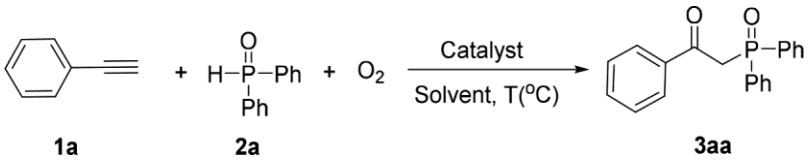
Table 1. Optimization of the reaction conditions[a]



1a 2a 3aa

Entry	Catalyst (mol%)	Solvent	T(°C)	Yield (%)[b]
1	$CuBr_2$ (5)	CH_3CN	55	trace
2	CuBr (5)	CH_3CN	55	23
3	CuF (5)	CH_3CN	55	24
4	CuI (5)	CH_3CN	55	17
5	CuCN (5)	CH_3CN	55	33
6	$Cu(AcO)_2$ (5)	CH_3CN	55	26
7	AuI (5)	CH_3CN	55	trace
8	$AgNO_3$ (5)	CH_3CN	55	26
9	$FeBr_3$ (5)	CH_3CN	55	trace
10	$NiCl_2$ (5)	CH_3CN	55	19
11	$Co(OAc)_2 \cdot 4H_2O$ (5)	CH_3CN	55	28
12	CuCN (5)	THF	55	30
13	CuCN (5)	DMF	55	33
14	CuCN (5)	DME	55	19
15	CuCN (5)	toluene	55	32
16	CuCN (5)	1,4-dioxane	55	29
17	**CuCN (5)**	**DMSO**	**55**	**65**
18	CuCN (2.5)	DMSO	55	58
19	CuCN (10)	DMSO	55	62
20	CuCN (20)	DMSO	55	56
21	CuCN (5)	DMSO	25	33
22	CuCN (5)	DMSO	80	53
23	CuCN (5)	DMSO	55	34[c]
24	CuCN (5)	DMSO	55	39[d]
25	--	DMSO	55	0
26	CuCN (5)	DMSO	55	0[e]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), Catalyst (2.5-20 mol%), Solvent (1.0 ml), O_2 (balloon), 24 h.

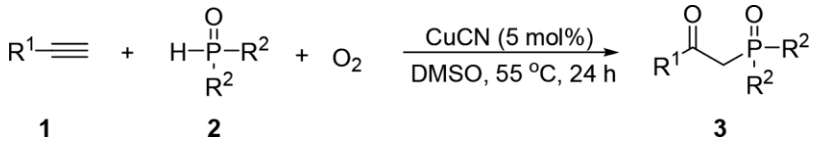
[b] Isolated yields based on **1a**.

[c] **1a** (0.5 mmol), **2a** (0.5 mmol).

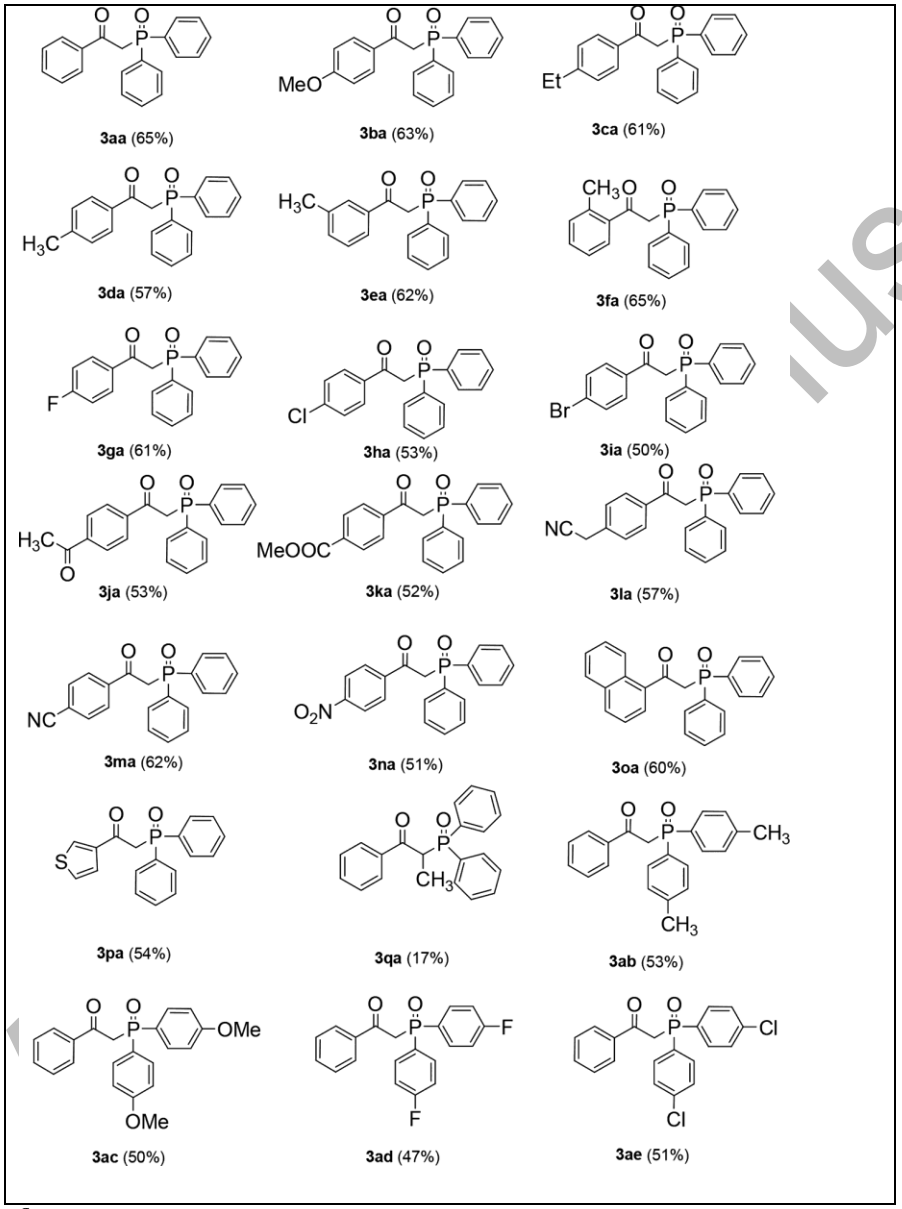
[d] **1a**(1.0 mmol), **2a** (0.5 mmol), isolated yields based on **2a**.

[e] under N_2.

Table 2. Copper catalyzed oxyphosphorylation of alkynes to form β-ketophosphine oxides.[a,b]



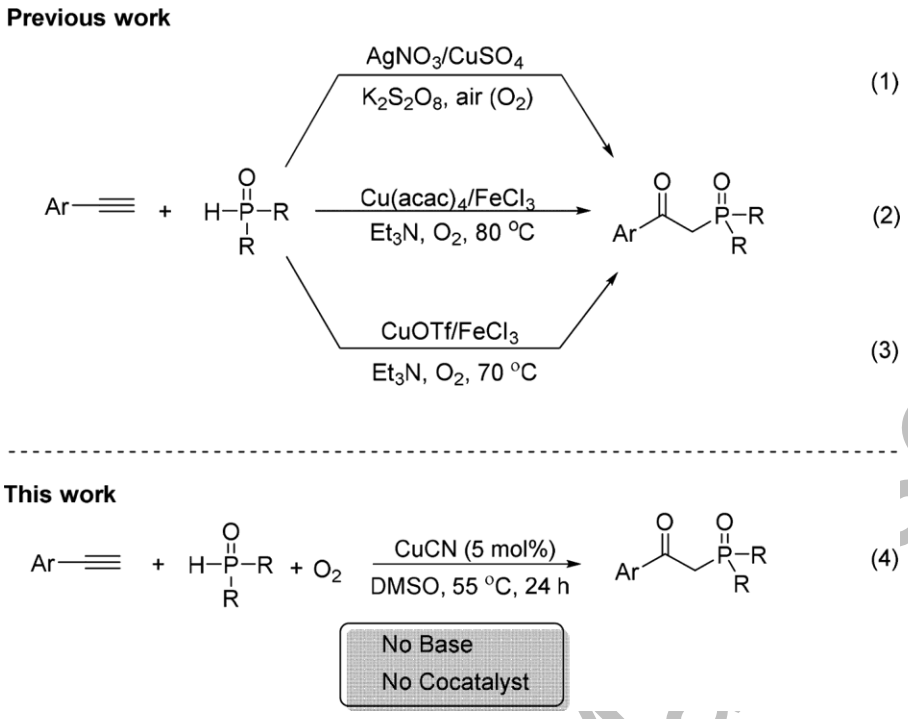
1 2 3



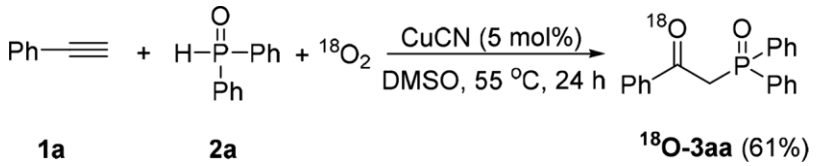
[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), CuCN (5 mol%), DMSO (1.0 ml), 55 °C, 24 h, O_2 (balloon).

[b] Isolated yields based on **1**.

Scheme 1. Synthesis of β-ketophosphine oxides via oxyphosphorylation of alkynes 14

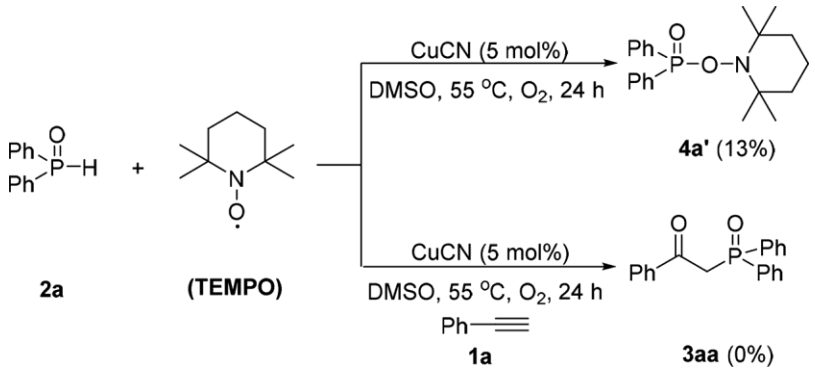


Scheme 2. Isotope labeling experiment 14



1a **2a** **^{18}O-3aa** (61%)

Scheme 3. Radical capture experiment 15



Scheme 4. Postulated reaction pathway 15

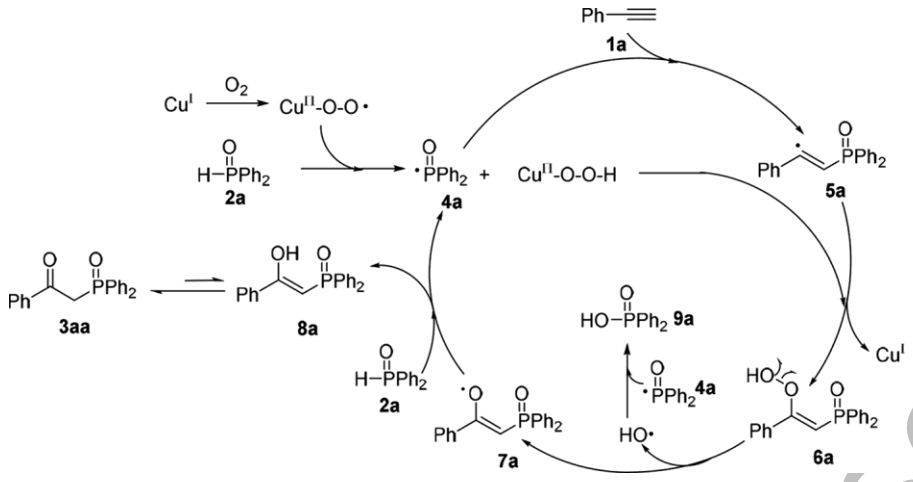


Figure 1. LC-MS spectrum of **6a**, **9a** , **3aa** and TEMPO-trapped **4a**, **5a**, **7a** 16