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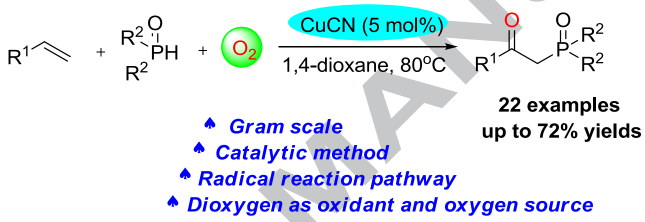

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Direct synthesis of β-ketophosphine oxides via copper-catalyzed difunctionalization of alkenes with H-phosphine oxides and dioxygen

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ABSTRACT

A simple copper-catalyzed direct difunctionalization of alkenes with H-phosphine oxides anddioxygen for the synthesis of β-ketophosphine oxides has been developed under mild conditions. The present protocol, which utilizes an inexpensive catalyst, readily available materials, and environmentally benign oxygen source, provides a convenient and cost-effective approach to construct various β-ketophosphine oxides.

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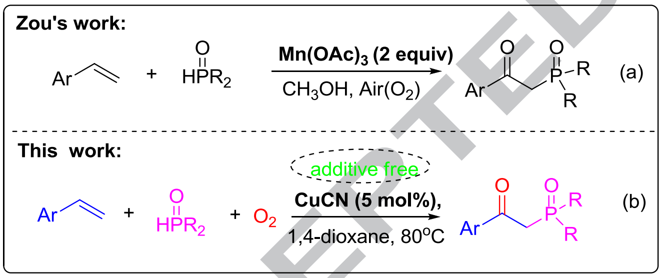
As an important class of phosphorus-containing compounds, β-ketophosphine oxides have drawn great attention of chemists because of their widely applications in organic synthesis.[1] Particularly, β-ketophosphine oxides can serve as the useful intermediates for the construction of olefins via well-known Wittig-Horner reaction.[2] In addition, they have also been used in the liquid-liquid extraction of metals due to their eminent metal-complexing abilities.[3] Traditionally, β-ketophosphine oxides are prepared by the acylation of alkylphosphine oxides with esters in the presence of *n*-BuLi,[4] hydrolysis of enaminephosphine oxides,[5] or KOH promoted the reaction of hydrophosphoryl compounds with chloroacetophenone.[6] However, all these methods suffer from limitations such as relatively harsh reaction conditions, tedious procedures, unreadily-available starting materials, or the use of excess amounts of organometallic reagents. In 2012, Gao and Xu reported an efficient $PdCl_2$-catalyzed hydration of alkynylphosphine oxides for the synthesis of β-ketophosphine oxides.[7] In 2015, Lei described copper-catalyzed radical/radical Csp^3-H/P-H cross-coupling reaction of aryl ketone *o*-acetyloximes with H-phosphine oxides leading to β-ketophosphine oxides in the presence of tricyclohexylphosphine.[8] Recently, some methods for the construction of β-ketophosphine oxides from terminal alkynes,[9] alkynylcarboxylic aids,[9bc,10] cinnamic acid,[11] ketones,[12] or enamides[13] have also been developed. Gracefully successive as these reactions could be, there is still a great demand for the development of new, convenient, and environmentally-benign methods to access β-ketophosphine oxides from simple and easily accessible starting materials.

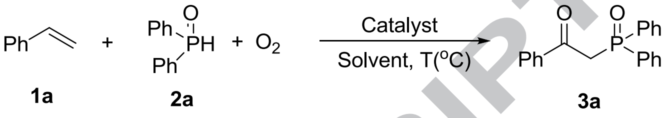


Scheme 1 Methods for the synthesis of β-ketophosphine oxides via oxyphosphorylation of alkenes .

Alkenes are inexpensive and easily accessible organic reactants and chemical feedstocks, which difunctionalization is one of the most powerful and reliable protocols for the construction of various useful and fascinating compounds.[14] In 2016, Zou and co-workers reported an efficient solvent-controlled $Mn(OAc)_3$-mediated radical oxyphosphorylation of alkenes leading to β-ketophosphine oxides, in which the phosphonyl radical is initiated by stoichiometric amounts of $Mn(OAc)_3$.[15] Nevertheless, the utilization of an excess amount of $Mn(OAc)_3$ (2 equiv) would lead to the generation of a large number of toxic wastes, which might limit their wide applications on a large scale in the synthetic and pharmaceutical chemistry. (Scheme 1, (a)). Recently, Zhao and Chen reported acetonitrile-dependent $CuSO_4$-catalyzed oxyphosphorylation of α,β-alkenyl carboxylic acids or alkenes with H-phosphonates leading to β-ketophosphonates.[16] Herein, we wish to report a simple and convenient method for the synthesis of β-ketophosphine oxides via CuCN (5 mol%) catalyzed direct difunctionalization of alkenes with H-phosphine oxides and dioxygen (Scheme 1, (b)), in which copper-activated dioxygen is essential for promoting this transformation. The present reaction, which can be effectively scaled up, provides a catalytic and attractive approach to various β-ketophosphine oxides in moderate to good yields with favorable functional group tolerance simply using inexpensive CuCN as a catalyst.

Table 1

Screening of the reaction conditions[a]



Entry	Catalyst (mol %)	Solvent	T(°C)	Yield(%)[b]
1	CuCl (5)	MeCN	60	45
2	CuI (5)	MeCN	60	37
3	CuBr (5)	MeCN	60	49
4	$CuCl_2$ (5)	MeCN	60	28
5	$CuBr_2$ (5)	MeCN	60	32
6	$Cu(OAc)_2$ (5)	MeCN	60	47
7	CuCN (5)	MeCN	60	53
8	CuCN (5)	THF	60	46
9	CuCN (5)	Toluene	60	32
10	CuCN (5)	1,4-dioxane	60	60
11	CuCN (5)	DCE	60	37
12	CuCN (5)	DME	60	38
13	CuCN (5)	DMSO	60	47
14	CuCN (5)	CH_3OH	60	36
15	CuCN (5)	1,4-dioxane	25	32
16	CuCN (5)	1,4-dioxane	40	48
17	CuCN (5)	1,4-dioxane	80	62
18	CuCN (5)	1,4-dioxane	100	57
19	CuCN(20)	1,4-dioxane	80	50
20	CuCN (10)	1,4-dioxane	80	59
21	CuCN (2)	1,4-dioxane	80	51
22	--	1,4-dioxane	80	12
23	**CuCN (5)**	**1,4-dioxane**	**80**	**72**[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (0-20 mol%), solvent (1 ml), 25-100°C, O_2 (balloon), 12h.

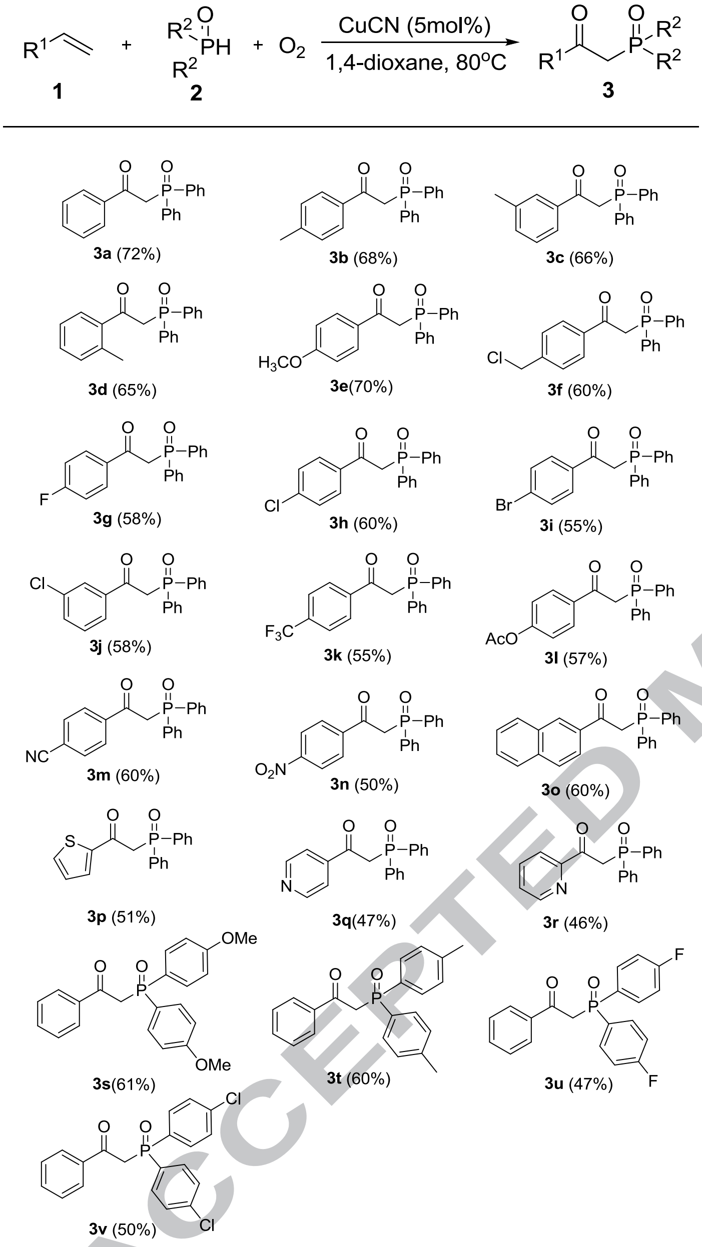
[b] Isolated yields based on **1a**.

[c] **1a** (0.5 mmol), **2a** (1.25 mmol).

Initially, styrene **1a** and diphenylphosphine oxide **2a** were chosen as model substrates to optimize the reaction conditions under oxygen atmosphere. Various transition-metal catalysts such as Cu, Fe, Co, Ag, Pd, Zn, In and Bi salts were screened in CH_3CN at 60°C (see Table S1, in the Supporting Information). To our delight, among the above metal salts examined, copper salts especially CuCN was found to be the most effective catalyst to give product **3a** in 53% yield in the absence of a base (Table 1, entry 7). Among the solvents tested, 1, 4-dioxane was shown to be more effective than the others such as CH_3CN, THF, toluene, DME, DCE, DMSO, and CH_3OH (Table 1, entries 7–14). The reaction temperature could also affect this transformation (Table 1, entries 10, 15–18). The desired product was only obtained in 32% yield when the model reaction was carried out at room temperature (Table 1, entry 15), and the reaction at 80°C gave the best result (Table 1, entry 17). Furthermore, the screening of catalyst loading found that 5 mol% of catalyst was the best choice and the reaction efficiency was slightly low with the decreasing or increasing of CuCN loading (Table 1, entries 19-21). Moreover, the desired product was isolated in only 12% yield when the reaction was conducted in the absence of copper catalyst (Table 1, entry 22). After a series of detailed investigations of the reaction parameters, we found that the best result (72% yield) was obtained when the reaction was carried out using 5 mol% of CuCN in 1,4-dioxane at 80 °C in the presence of 2.5 equiv. of **2a** (Table 1, entry 23).

Table 2

Results for copper-catalyzed synthesis of β-ketophosphine oxides from alkenes, H-phosphine oxides and dioxygen[a,b]



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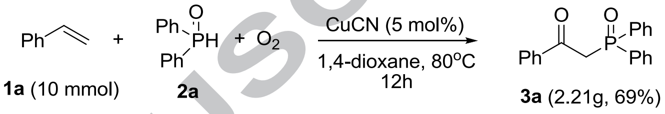
[a] Reaction conditions: **1** (0.5 mmol), **2** (1.25 mmol), CuCN (5 mol%), 1,4-dioxane (1 ml), 80°C, O_2 (balloon), 12 h.

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

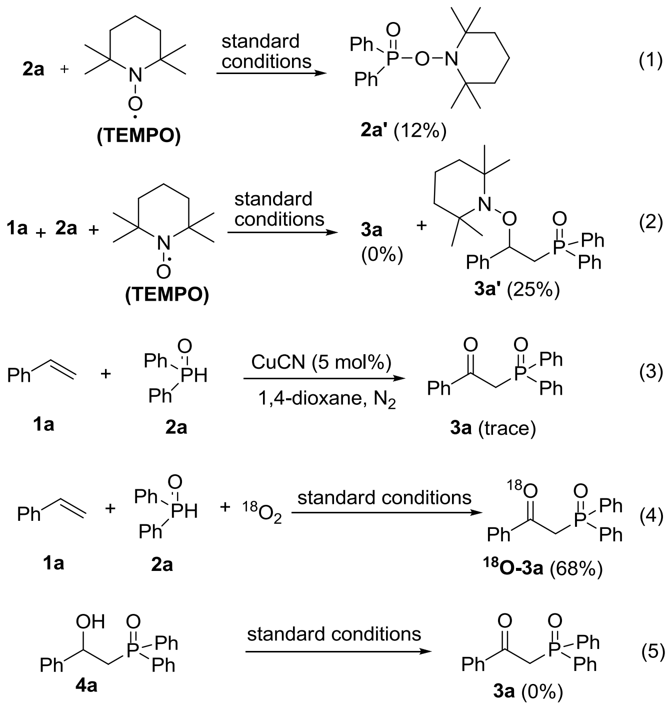
With the optimized condition in hand, we next examined the substrate scope of this transformation. Aromatic alkenes with both electron-donating and electron-withdrawing groups worked smoothly to afford β-ketophosphine oxides in moderate to good yields under the standard conditions, whereas the electron-withdrawing groups led to a negative effect on the yield (Table 2, **3a-3o**). Also, functional groups such as chloromethyl, halogen, acyloxy, cyano, and nitro groups (Table 2, **3f-3n**) were all well tolerated, whose corresponding products can be applied in further modifications. It was observed that 2-vinylnaphthalene was also tolerated to afford the product **3o** in 60% yield. Notably, heteroaromatic alkenes such as 2-vinylthiophene, 4-vinylpyridine, and 2-vinylpyridine could also be used in the reaction to give the expected products **3p-3r** in moderate yields. Nevertheless, when aliphatic alkenes such as 1-octene and 1-hexene were used as the substrates, only a trace amount of the desired products were obtained. With regard to the H-phosphine oxides, in addition to diphenylphosphine oxide **2a**, other diarylphosphine oxides bearing both electron-donating and electron-withdrawing groups were also compatible with this reaction to give the corresponding products in moderate yields (**3s-3v**).

Furthermore, the synthetic applicability of this method was investigated on a gram scale by using the model reaction between **1a** and **2a**. As shown in Scheme 2, the reaction could afford 2.21 g of **3a** in 69% yield without significant loss of its efficiency. Thus, this reaction could serve as a practical and efficient protocol to synthesize β-ketophosphine oxides.



Scheme 2 Gram scale reaction

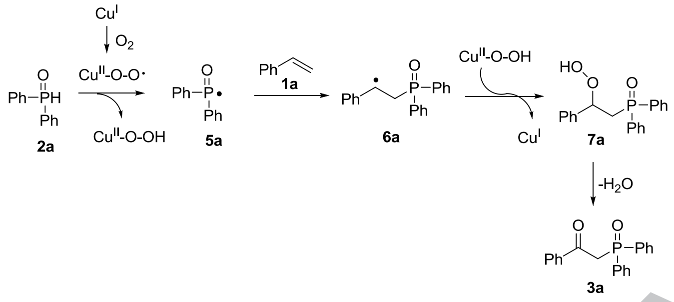
To gain some insights into this reaction mechanism, several control experiments were carried out as shown in Scheme 3. When the reaction of $H(O)PPh_2$ (**2a**) with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well-known radical scavenger) was performed under the standard conditions, TEPMO trapped compound **2a'** was detected (Scheme 3, Eq (1)). Furthermore, when TEMPO was added into the model reaction system, the reaction was completely inhibited and TEMPO trapped compound **3a'** was isolated in 25% yield (Scheme 3, Eq (2)). The above results suggested that the present reaction might involve a radical reaction pathway. Moreover, when the reaction was conducted under nitrogen atmosphere, only a trace amount of product **3a** was detected, indicating that dioxygen might play an



Scheme 3 Control experiments.

important role in the formation of β-ketophosphine oxide (Scheme 3, Eq (3)). To elucidate the origin of the carbonyl oxygen atom of β-ketophosphine oxides, ^{18}O labeling experiment was performed in the reaction of **1a** and **2a** (Scheme 3, Eq (4)). The experimental result shows that the carbonyl oxygen atom of β-ketophosphine oxide comes from dioxygen. In addition, the desired product **3a** was not obtained when β-hydroxyphosphine oxide **4a** was treated under the standard conditions, suggesting that *β*-hydroxyphosphine oxide should not be an intermediate in this reaction system (Scheme 3, Eq (5)).

Based on the above results and previous reports [9-13,15-17], a possible reaction pathway was proposed as shown in Scheme 4. Firstly, diphenylphosphine oxide **2a** was oxidized by copper-activated dioxygen to generate phosphonyl radical **5a** and Cu^{II}-OOH.[17] Subsequently, the resulting phosphonyl radical **5a** selectively added to alkene **1a** gave alkyl radical **6a**, which interacted with Cu^{II}-OOH to produce alkylperoxy **7a**. Finally, the elimination of water from alkylperoxy **7a** gave the desired product **3a**.[15,17]



Scheme 4 Postulated reaction mechanism.

In summary, we have developed a new and straightforward CuCN catalyzed method for the construction of a series of β-ketophosphine oxides from alkenes, H-phosphine oxides and dioxygen. The present protocol has the advantages of operation simplicity, high atom efficiency, as well as ready availability of materials and catalyst. Radical capture and isotope labeling experiments showed that this reaction might proceed through a radial process and carbonyl oxygen atom of β-ketophosphine oxides originated from dioxygen. Further studies of the detailed mechanism of this process and its application are underway in our laboratory.

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- Catalytic synthesis of β-ketophosphine oxides from alkenes and H-phosphine oxides
- Gram scale
- The carbonyl oxygen atom of β-ketophosphine oxides originated from dioxygen
- A radical process is proposed

18.