Catalyst-free direct difunctionalization of alkenes with H-phosphine oxides and dioxygen: A facile and green approach to β-hydroxyphosphine oxides

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Catalyst-free direct difunctionalization of alkenes with H-phosphine oxides and dioxygen: a facile and green approach to β-hydroxyphosphine oxides

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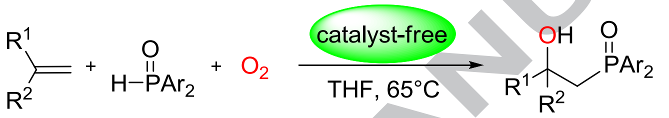
A simple and catalyst-free method has been developed for the construction of β-hydroxyphosphine oxides from alkenes and H-phosphine oxides in the presence of dioxygen under mild conditions.



18 examples
up to 86% yield

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Catalyst-free direct difunctionalization of alkenes with H-phosphine oxides and dioxygen: a facile and green approach to β-hydroxyphosphine oxides

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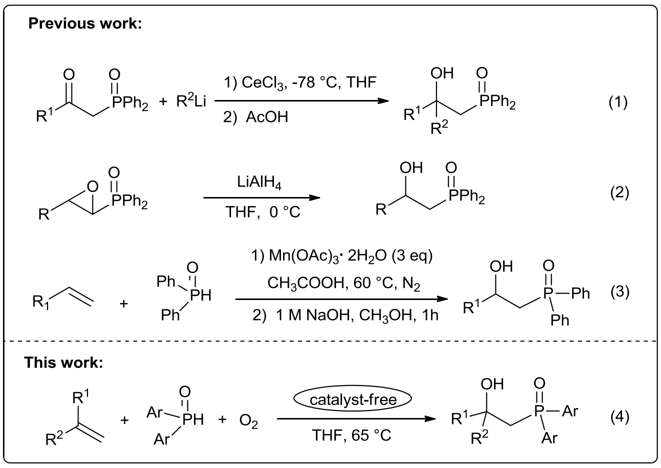
ABSTRACT

A simple and catalyst-free method has been developed for the construction of β-hydroxyphosphine oxides through direct difunctionalization of alkenes with H-phosphine oxides and dioxygen under mild conditions. Preliminary mechanistic studies indicated that the hydroxyl oxygen atom of β-hydroxyphosphine oxide originated from the dioxygen and the present reaction might involve a radical process.

Organophosphorus compounds are of great importance with regard to their widely applications in pharmaceutical industries,[1] functionalized materials,[2] and synthetic chemistry.[3] Particularly, β-hydroxyphosphine oxide compounds have elicited considerable synthetic interest of chemists because they can be employed as the key intermediates in Horner-Wittig reactions to construct various olefins with excellent stereocontrol.[4] Furthermore, β-hydroxyphosphine oxides can also serve as versatile precursors for various synthetically useful transformations.[5] Consequently, substantial efforts have been devoted to the construction of β-hydroxyphosphine oxides. Generally, β-hydroxyphosphine oxides are prepared by the nucleophilic addition of the anions of alkyl(diphenyl)phosphine oxide to carbonyl compounds,[6] the nucleophilic addition of organolithium reagents to α-diphenylphosphinoyl ketones (Scheme 1 Eq (1)),[7] and the reduction of a diphenylphosphinoyl ketones.[8] Alternative methods such as the oxidation of β-hydroxyphosphines with H_2O_2,[9] and ring opening of α, β-epoxy phosphane oxides with $LiAlH_4$ (Scheme 1 Eq (2))[10] have also been developed. However, almost all of these methods are inevitably accompanied with some problems such as the need of extra preparation steps for the active precursors, the use of excess amounts of organometallic reagents, relatively harsh reaction conditions, lack of functionality tolerance, and low atom economy. Therefore, there is still a great demand for the development of convenient, efficient, atom economical, and environmentally benign synthetic strategies to access β-hydroxyphosphine oxides.



Scheme 1. Synthetic routes to β-hydroxyphosphine oxides

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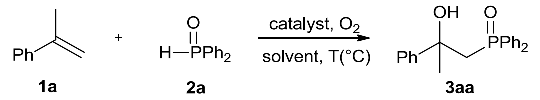
Recently, difunctionalization of alkenes has became as an extremely powerful protocol for the construction of many useful and fascinating organic compounds because it could provide an efficient way in the cascade formation of carbon-carbon and carbon-heteroatom bonds.[11] In 2014, Tang reported a $Mn(OAc)_3$-mediated radical oxidative phosphonation of alkenes with H-phosphine oxides leading to β-hydroxyphosphine oxides under nitrogen atmosphere (Scheme 1 Eq (3)).[12] Nevertheless, this well-developed reaction still require relatively complex reaction conditions and stoichiometric transition-metal catalysts. As part of our interest in the construction of important phosphorus compounds,[13] here, we wish to report a simple and catalyst-free process for the synthesis of β-hydroxyphosphine oxides via direct difunctionalization of alkenes with H-phosphine oxides and dioxygen (Scheme 1 Eq (4)).

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	T (°C)	Yield(%)[b]
1	$Fe(OAc)_2$	THF	65	60
2	CuF_2	THF	65	39
3	CuI	THF	65	40
4	$CuBr_2$	THF	65	trace
5	Ag_2CO_3	THF	65	41
6	$InCl_3$	THF	65	60
7	$CuSO_4$	THF	65	50
8	$NiCl_2$	THF	65	27
9	**--**	**THF**	**65**	**86**
10	--	DME	65	53
11	--	1,4-dioxane	65	83
12	--	CH_3CN	65	58
13	--	Toluene	65	57
14	--	DMF	65	46
15	--	EtOH	65	65
16	--	H_2O	65	0
17	--	THF	45	68
18	--	THF	25	49
19	--	THF	65	48[c]
20	--	THF	65	68[d]
21	--	THF	65	79[e]
22	--	THF	65	85[f]
23	--	THF	65	70[g]
24	--	THF	65	trace[h]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), catalyst (5 mol%), solvent (2 mL), O_2 (balloon), 12h.

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

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

[d] **1a** (0.5 mmol), **2a** (0.75 mmol).

[e] **1a** (0.5 mmol), **2a** (1.0 mmol).

[f] **1a** (0.5 mmol), **2a** (1.5 mmol).

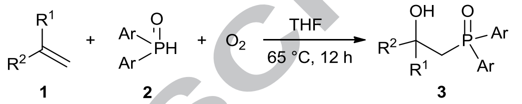
[g] under air.

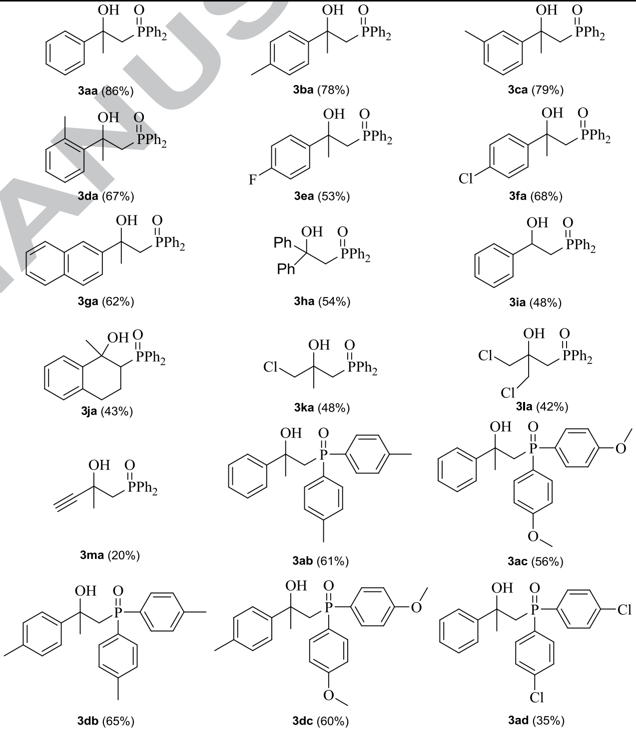
[h] under N_2.

In an initial experiment, under an oxygen atmosphere, α-methylsytrene **1a** and diphenylphosphine oxide **2a** were chosen as the model substrates to examine the catalytic activity of various transition metal complexes such as Fe, Cu, Ag, In, and Ni salts in THF at 65°C. Only low to moderate yields were obtained for the desired products when those metal catalysts were tested (Table 1, entries 1-8). The reaction in the absence of metal salt was subsequently investigated. To our delight, **3aa** was produced in 86% yield (Table 1, entry 9). The screening of a range of solvents under catalyst-free condition showed that the reaction performed in THF was better than those in DME, 1,4-dioxane, MeCN, toluene, DMF, and EtOH (Table 1, entries 9-15). Moreover, no conversion was observed when the reaction was performed separately in H_2O (Table 1, entry 16). Furthermore, the reaction efficiency was obviously low with the decreasing of reaction temperature or diphenylphosphine oxide loading (Table 1, entries 17-21). Notably, this oxyphosphorylation reaction could also proceed smoothly under the air atmosphere (Table 1, entry 23). In contrast, only a trace amount of **3aa** was detected when the reaction occurred in the absence of dioxygen (Table 1, entry 24). It indicates that dioxygen could play the key role in the formation of β-hydroxyphosphine oxide.

With the optimized conditions in hand, the substrate scope and limitations of this reaction were investigated (Table 2).

Table 2. Catalyst-free difunctionalization of alkenes with H-phosphine oxides and dioxygen leading to β-hydroxyphosphine oxides [a, b]



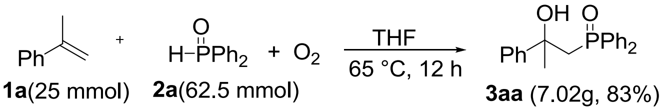


[a] Reaction conditions: alkene **1** (0.5 mmol), diarylphosphine oxide **2** (1.25 mmol), THF (2 mL), 65°C, O_2 (balloon), 12h.

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

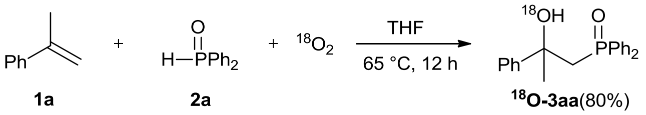
In general, α-methylsytrene and its derivatives which have electron-donating or electron-withdrawing groups on the aryl rings were suitable for this protocol, and the corresponding products were obtained in moderate to good yields (**3aa**-**3ga**). Notably, ethene-1,1-diyldibenzene and styrene were also compatible with this reaction, providing the corresponding products in 54% and 48% yields, respectively (**3ha** and **3ia**). In addition, when cyclic olefin such as 4-methyl-1,2-dihydronaphthalene was used as the substrate, the desired product was also obtained in 43% yield (**3ja**). Nevertheless, when aliphatic alkenes such as 3-chloro-2-methylprop-1-ene, 3-chloro-2-(chloromethyl)prop-1-ene, and 2-methylbut-1-en-3-yne were used as the substrates, the corresponding products were obtained in relatively low yields (**3ka**-**3ma**). With regard to the H-phosphine oxides, both electron-rich and electron-withdrawing diarylphosphine oxides were suitable for this protocol (**3ab**-**3ad**). In general, diarylphosphine oxides containing electron-rich groups showed the better activities than that bearing electron withdrawing groups. Unfortunately, none of the desired products were detected when diethyl phosphonate and ethyl phenylphosphinate were used as the substrates.

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 7.02g of **3aa** in 83% yield. Therefore, this reaction could serve as a practical and efficient protocol to access β-hydroxyphosphine oxides.



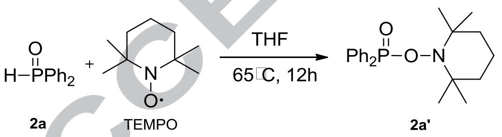
Scheme 2. Gram scale experiment

To gain clear mechanistic insight into the function of dioxygen, isotope labeling experiment using $^{18}O_2$ was performed in the reaction of α-methylsytrene **1a** with diphenylphosphine oxide **2a**, and the result indicated that the hydroxyl oxygen atom of β-hydroxyphosphine oxides originated from dioxygen (Scheme 3).



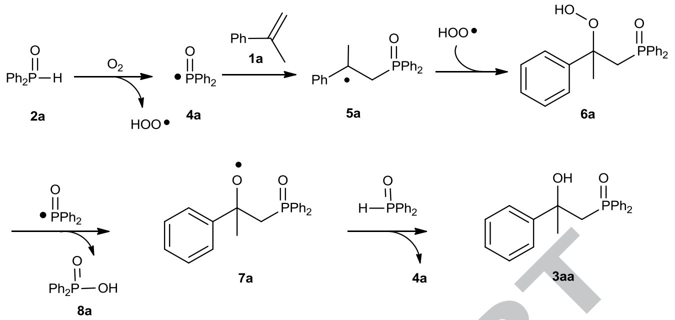
Scheme 3. Isotope labeling experiment

Considering that phosphorus radical species are easily formed from H-phosphine oxides in the presence of oxidant or transition metals,[14] we supposed a radical process might also be involved in the present difunctionalization reaction of alkenes. To support this assumption, a radical capture experiment was conducted. As shown in Scheme 4, a TEMPO-trapped compound **2a′** was isolated in 50% yield when the reaction of **2a** and TEMPO (2, 2, 6,6-tetramethyl-1-piperidinyloxy, a well-known radical-capturing species) was performed in the absence of α-methylsytrene **1a**. The result suggested that this oxyphosphorylation reaction of alkenes might involve a radical process.



Scheme 4. Radical capture experiment.

The detailed mechanism of the oxyphosphorylation reaction is still not clear at the present stage, however, based on our observations and previous reports,[15] a hypothesized reaction pathway of this oxyphosphorylation reaction was described in Scheme 5.



Scheme 5. Possible reaction pathway.

Initially, the oxidation of diphenylphosphine oxide with dioxygen would lead to the formation of phosphonyl radical **4a** and •OOH.[16] Subsequently, the resulting phosphonyl radical **4a** selectively added to alkene **1a** giving alkyl radical **5a**,[17] which interacted with •OOH species to form alkylperoxyl intermediate **6a**. Then, the interaction of alkylperoxyl intermediate **6a** with phosphonyl radical **4a** could produce alkyloxy radical **7a** along with the generation of diphenylphosphinic acid **8a**.[18] Finally, alkyloxy radical **7a** would abstract the hydrogen of diphenylphosphine oxide **2a** to give the desired product **3aa**.

LC-MS analysis technology was employed to investigate the possibility of the existence of phosphonyl radical **4a**, alkyl radical **5a**, alkylperoxyl intermediate **6a**, alkyloxy radical **7a** and diphenylphosphinic acid **8a** in the present reaction system. The reaction mixture was detected by LC-MS when the reaction of **1a**, **2a** and TEMPO was conducted under standard conditions (THF, 65°C, O_2) for 2h. As shown in Fig. 1, the $[M+H]^+$ ion peaks at m/z 219.0, 337.0, 352.8, 358.2, 475.9 and 491.9 for diphenylphosphinic acid **8a**, product **3aa**, alkylperoxyl intermediate **6a**, TEMPO-trapped phosphonyl radical **4a** TEMPO-trapped alkyl radical **5a** and alkyloxy radical **7a** were detected by LC-MS analysis, respectively. The above results indicated that the radical process should be involved in the present reaction system.

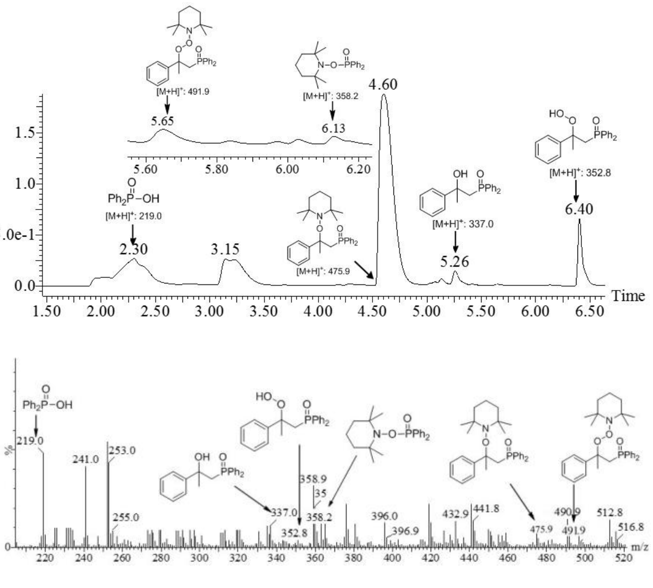


Figure 1. LC-MS spectrum of **6a, 8a, 3aa** and TEMPO-trapped **4a, 5a, 7a**.

In conclusion, a new and facile method has been developed for the synthesis of β-hydroxyphosphine oxide compounds via direct difunctionalization of alkenes with H-phosphine oxides and dioxygen. This methodology, which utilizes simple and readily available starting materials and catalyst-free conditions, provides a convenient and highly attractive route to various β-hydroxyphosphine oxides. Due to its simplicity, this protocol may have potential application in organic synthesis, and further studies of the detailed reaction mechanism and the potential synthetic applications are ongoing.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.****

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Highlights

- Catalyst-free approach to β-hydroxyphosphine oxides
- The hydroxyl oxygen atom of β-hydroxyphosphine oxide originated from dioxygen
- Key intermediates were detected by LC-MS analysis
- A radical process is proposed