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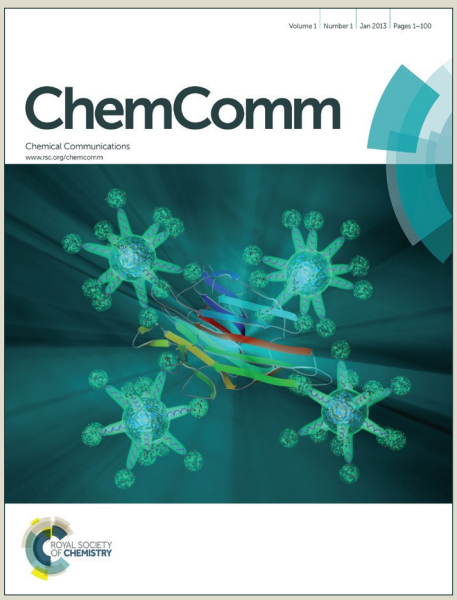


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# Dioxygen-induced oxidative activation of P-H bond: radical oxyphosphorylation of alkenes and alkynes toward β-oxy phosphonates

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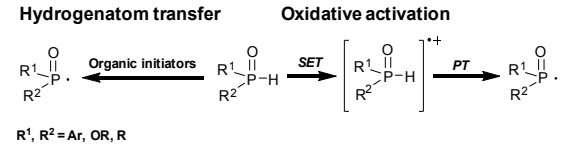
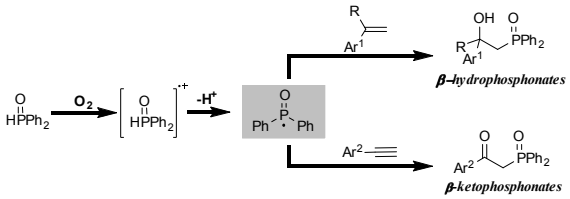
**The dioxygen-induced radical oxyphosphorylation of alkenes and alkynes is present while P-H bond was activated by molecular oxygen. Various β-oxy phosphonates could be facilely synthesized without assistance of any transition metals or extra organic initiators. Mechanistic studies showed that $HP(O)Ph_2$ act as a reductant to accelerate oxyphosphorylation.**

Reactions involving phosphorus-centered radicals play a vital role in the construction of π-conjugated materials, organophosphorus ligands and biologically active molecules.[1] Homolytic cleavage of P-H bonds is a common route to phosphorus-centered radicals. This process usually promoted by organic radical initiators such as azo compounds, peroxides and so on,[2] and known as hydrogen atom transfer process.[3] Another methods for the generation of phosphorus-centered radicals go through single electron oxidation of P-H compounds then lose the proton (Scheme 1).[4] This methods can be seen as "oxidative activation". In oxidative activation process, the decreases in the P-H bond dissociation energies (BDEs) are associated with acidities increases of radical cation derived from P-H compounds.[5] So the P-H bond was activated after oxidation process, and the oxidants mostly are metal salts such as sliver, iron and manganese salts. However, introduction of these transition metal salts often results in the residual catalysts and diverse by-products, limiting their applications in the chemical and pharmaceutical industries. Therefore, it is extraordinarily important to find greener and more sustainable oxidant to update these processes.




**Scheme 1.** Strategies for phosphorus-centered radical initiation.




**Scheme 2.** Synthesis of β-oxy phosphonates

As a result of its inherent features of environmental friendliness, cleanliness and sustainability,[6] radical reactions with dioxygen as the initiator have received increasing attentions.[7] Given the importance of organophosphorus compounds in organic synthesis, we questioned whether dioxygen could be also employed to initiate phosphinoyl radicals through oxidative activation process. Then generated phosphinoyl radicals further react with a variety of radical linkages such as alkenes and alkynes, furnish the valuable β-oxy phosphonates (Scheme 2).[8] Although β-oxy phosphonates are valuable synthons in synthetic community, the synthetic methods towards these compounds are quite limited, especially for green and sustainable ones.[8d, 9] Compared to the traditional synthetic methods of β-oxy phosphonates,[10] this protocol features synthetic simplicity and mild conditions, which would enable the potential application for academic community and pharmaceutical industry in the future.

To verify whether dioxygen could initiate phosphinoyl radicals through oxidative activation process, EPR experiment was performed to detect the phosphinoyl radical intermediate. As shown in Figure 1, when free radical spin trapping agent DMPO (5,5-dimethyl-1-pyrroline N-oxide) was mixed with diphenylphosphine oxide ($Ph_2POH$) under air atmosphere, an obvious EPR signal was identified, and assigned to stable

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radical **A** ($a_N$=14.0 G, $a_H$=17.8 G, $a_P$=36.7 G).[11] Suggested that phosphinoyl radical was generated, then quickly trapped by DMPO, formed the radical **A.** This result showed that phosphinoyl radicals could be induced by the dioxygen.

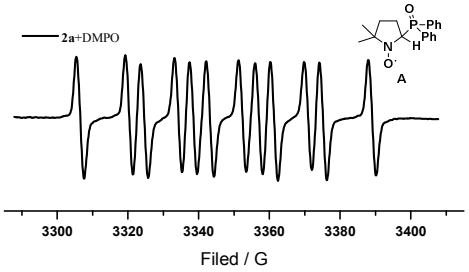
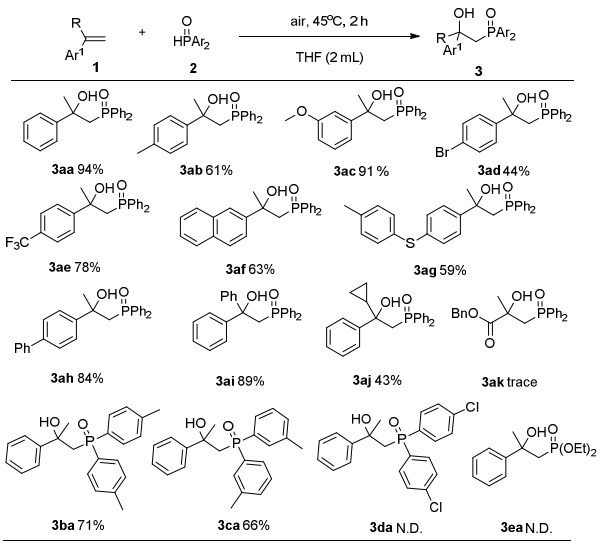



**Figure 1.** The electron paramagnetic resonance (EPR) spectra

Inspired by this result, the reaction of α-methylstyrene (**1a**) with 2-fold $Ph_2P(O)H$ (**2a**) was firstly performed under air atmosphere using THF (tetrahydrofuran) as solvent, giving 34% yield of the expected product **3aa** (for details, see Table S1, ESI†). A higher $Ph_2P(O)H$ loading proved to be optimal and 94% isolated yield could be obtained. While the decrease in the temperature inhibited the oxyphosphorylation reaction. Solvents proved to have huge influence in this radical oxyphosphorylation reaction. Conducting the reaction in DMF, DCE, $CH_3CN$, DMSO and toluene gave the product **3aa** in lower yield. Notably, just 18% yield could be obtained under oxygen atmosphere. And no product was detected when the reaction was performed under $N_2$ atmosphere. To probe the role of $O_2$, the model reaction between **1a** and **2a** under $N_2/^{18}O_2$ (4:1) was carried out. And the $^{18}O$-labeled product **3aa'** was isolated in 80% yield with 85% isotopic purity, indicating that molecular oxygen acted not only as initiator to induce the radical transformation but also as a terminal oxygen source introduced into final products (for details, see ESI†).

With the optimized condition in hand, we next explored the scope of the reaction between various α-methylstyrene and diphenyl phosphine oxides, and the results are summarized in Table 1. A series of α-methylstyrenes bearing both electron-donating groups (R= Me, OMe) and electron-withdrawing group (R= $CF_3$) furnished the desired tertiary β-hydrophosphonates in moderate to excellent yields (**3ab**-**3ac**, **3ae**). It is noteworthy that halogen (such as Br) group was well tolerated, which enabled a potential application in further functionalization (**3ad**). Additionally, a wide range of functional groups such as naphthyl (**3af**), thioether (**3ag**), and phenyl (**3ah**) were demonstrated to be tolerated in this protocol. 1,1-Diphenylethylene was also well applicable to give the desired product **3ai** in 89% yield. When submitting (1-cyclopropylvinyl)benzene to standard condition oxyphosphorylation product **3aj** was afforded in 43% yield. Aliphatic alkene generated **3ak** in trace amount of product with major hydrophosphorylation by-product. Moreover, the scope of phosphine oxides were also examined. *p*-Methyl substituted phosphine oxide and *m*-methyl substituted phosphine oxide could deliver the desired products with moderated yield of 71% and 66% respectively (**3ba**, **3ca**). Nevertheless, bis(4-chlorophenyl)phosphine oxide (**3da**) and diethyl phosphite (**3ea**) were not amenable to this procedure, probably owing to the higher oxidative potential.

**Table 1.** Radical oxyphosphorylation of alkenes[a]




[a] Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), **2** (0.6 mmol) in THF (2.0 mL) at 45 °C for 2 h under air, isolated yield.

To investigate the reaction mechanism, *in-situ* NMR was performed to monitor the reaction of **1a** and **2a** under the optimized conditions. The amount of **3aa** and byproduct $HOP(O)Ph_2$ increased steadily with decrease of **2a** during the reaction process. Meanwhile, an intermediate **V** firstly increased and then decreased with time going on (Figure 2, A), this intermediate **V** was proposed as β-peroxylphosphonates, it decreased due to reduction by $HP(O)Ph_2$. ESI-MS was further applied to verify β-peroxylphosphonate intermediate **V**. To our delight, a strong peak (m/z=353.30) was detected, which identified as $[\mathbf{V}+H]^+$. Besides, the over oxidative product $HOP(O)Ph_2$ (m/z=219.25) of **2a** was also detected (for details, see ESI†). To gain more information, the reaction was also monitored by *operando* IR spectroscopy. The kinetic profile clearly showed that $HOP(O)Ph_2$ and **3aa** increased proportionally (Figure 2, B). These results indicated that $HP(O)Ph_2$ served not only as phosphorus source but also as reductant, and the reduction of the intermediate **V** can accelerate the reaction.

On the basis of the aforementioned experimental results and previous reports,[12] a potential mechanism was proposed. As shown in scheme 3, radical cation **I** derives from **2a** through single electron transfer with dioxygen with the generation of superoxide radical anion at the same time.[13] Then radical cation **I** loses a proton to radical **II**, which further reacts with α-methylstyrene (**1a**) in a radical addition process to form the carbon-centered radical **III. III** reacts with dioxygen, produces an alkylhydroperoxy radical intermediate **IV**. And then the generated intermediate **IV** affords β-peroxylphosphonates **V** through hydrogen atom abstraction from **2a**. Finally,

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subsequent reduction of **V** by diphenylphosphine oxide gives the oxyphosphorylation product **3aa**.

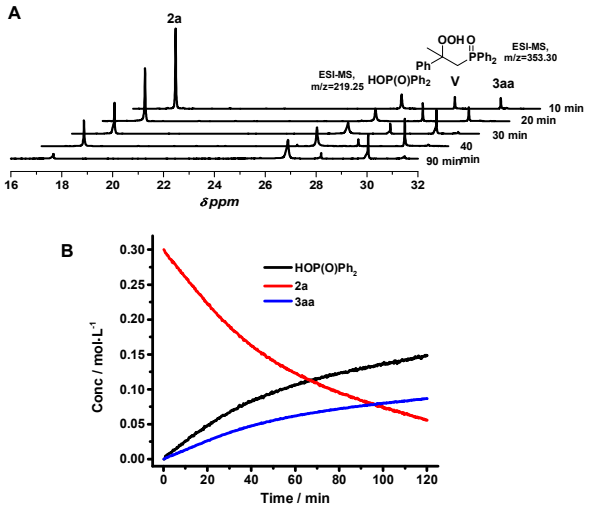
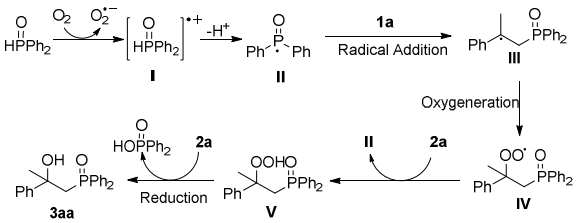



**Figure 2.** A) In situ NMR, reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol) in THF (2.0 mL) at 45 °C for different reaction time under air. B) The kinetic profile of the reaction of **1a** (0.4 mmol), **2a** (1.2 mmol) in THF (4.0 mL) at 45 °C under air.

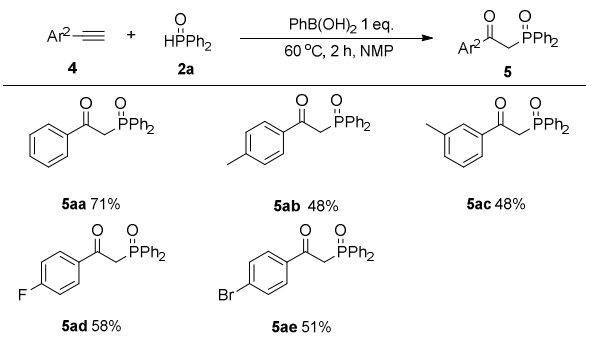



**Scheme 3.** Potential mechanism

With the better understanding of reaction mechanism, we turned to explore whether alkynes could be convert to β-ketophosphonates under this condition. The reaction of phenylacetylene **4a** with diphenylphosphine oxide **2a** was conducted under the foregoing condition, and 24% yield was obtained (for details, see Table S2, ESI†). Rising temprature and changing solvent slightly increased the yield to 30% yield. We considered the $O_2$ concentration might have great influence in this reaction, so when we increased oxygen concentration to 50%, an increased yield of 39% could be obtained. We speculated the generation of vinyl peroxide radical is difficult, which resulted in a low yield.[14] So we added phenylboronic acid to reduce the generated vinyl peroxide radical, forced the equilibrium to desired product in 71% isolated yield.[15] Besides, phenylboronic acid was oxidized to phenol in 93% GC yield.

Furthermore, reactions of the corresponding phenylacetylene derivatives was investigated, furnished corresponding ketones in moderated yields (**5ab**-**5ae**). *p*-Methyl and *m*-Methyl phenylacetylene gave the same 48% yield (**3ab**, **3ac**). Halogen substituents such as fluorine and bromine were also tolerated, giving the corresponding products in 58% and 51% yield (**5ad**, **5ae**), respectively.

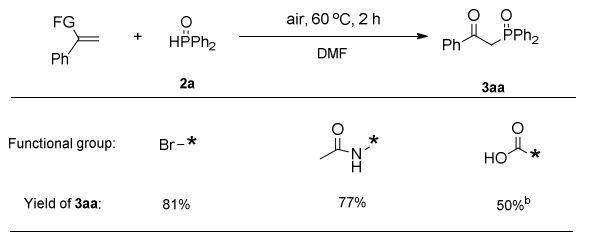
**Table 2.** Substrate scope of the radical oxyphosphorylation of various alkynes[a]




[a] Unless otherwise specified, all reactions were carried out using **4** (0.2 mmol), **2a** (0.6 mmol) in NMP (2.0 mL) at 60 °C for 2 h under a balloon of $O_2$:$N_2$ = 1:1, isolated yield.

Based on our proposed mechanism, we proposed if leaving group was introduced to α-position of styrene, β-ketophosphonates could also be obtained.[7d, 16] So we applied several α-substituted styrene derivatives to this protocol. To our delight, corresponding β-ketophosphonate **3aa** was obtained in moderate to excellent yields after simply changing the reaction temperature and solvent (Table 3). Intriguingly, $C_{vinyl}$-heteroatom bonds cleavage including C-Br and C-N were proven to be amenable to this protocol. Notably, decarboxylation which was deemed to need high energy was occurred under this mild condition due to ingenious substrate design. These transformations further highlight the synthetic utility of this method and broaden the scope of this reaction.

**Table 3.** Substrate scope of various substituted styrenes[a]




[a] Unless otherwise specified, all reactions were carried out using styrene (0.2 mmol), **2a** (0.6 mmol) in DMF (2.0 mL) at 60 °C for 2 h, isolated yield. [b] DCE (2.0 mL) instead of DMF (2.0 mL) for 5 h.

## Conclusions

In summary, we have disclosed an environmentally friendly radical oxyphosphorylation reaction without assistance of any transition metals or extra organic radical initiators. Various β-oxy phosphonates were facilely obtained with a wide range of functional group tolerance. EPR experiment showed that dioxygen could be employed to initiate phosphinoyl radicals through SET oxidative activation. Isotopic labeling experiment showed that the oxygen atom of hydroxyl comes from dioxygen. Mechanistic studies concluding *in-site* NMR and *operando* IR showed that diphenylphosphine oxide served not only as substrate but also as reductant. Besides, several kinds of alkynes and π-substituted styrene derivatives could also

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convert to β-ketophosphonates. Radical oxyphosphorylation of alkyne can be promoted by phenylboronic acid. Further studies on mechanistic details and expanding the substrate scope are currently underway in our laboratory.

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