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Recent advances in the construction of β-hydroxy phosphorus compounds *via* direct vicinal hydroxy-phosphorylation of alkenes

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ABSTRACT

β-Hydroxy phosphorus compounds are often encountered in numerous pharmaceuticals and bioactive molecules, and also of great importance as intermediates or building blocks in organic synthesis. Among various synthetic strategies developed, direct vicinal hydroxy-phosphorylation of easily accessible alkenes proves to be one of the most powerful and straightforward protocols to construct such privileged structures. In this review, we summarize the recent advances in the synthesis of titled compounds through the direct hydroxy-phosphorylation of alkene substrates using P(O)–H compounds, and underline the remaining challenges. This information would provide important and inspiring guidance for the researchers working in organophosphorus chemistry.

1. Introduction

The design and synthesis of structurally diverse organic molecules remain central goals in modern organic chemistry, driven by their pivotal roles in biological systems, material science, and drug discovery [1, 2]. Among these, organophosphorus compounds represent a particularly valuable class due to their unique reactivity and wide-ranging applications. Organophosphorus compounds, molecules containing P-C linkages, are widely present in numerous natural products, biologically active molecules and modern pharmaceutical compounds [3]. In this family of compounds, β-hydroxy phosphorus compounds (*e.g.*, β-hydroxy phosphonates, β-hydroxy phosphine oxides, β-hydroxy phosphinates) have attracted considerable attention from organic synthetic communities because of their diverse reaction patterns [4] and structural similarity to amino acids, hydroxyl carboxylic acids, or nucleoside analogues [5, 6]. Moreover, they also show various pharmacological and insecticidal activities (Scheme 1) [6, 7]. Due to wide importance of the titled compounds in organic, medicinal, and agrochemical chemistry, it is always interesting to develop efficient and straightforward synthetic strategies to prepare them form cheap and easily available starting materials [8].

In the last few decades, the direct vicinal difunctionalization of prevalent alkenes and alkynes has emerged as a powerful and viable strategy for rapidly increasing molecular complexity by installing two substituents across the C-C double/triple bonds within a single click [9-15]. In this class of reactions, hydroxy-functionalization of unsaturated hydrocarbons, which installs a unique functional group and a hydroxyl group at adjacent carbons in a one-pot process, offers a viable strategy for the selective synthesis of β-substituted alcohols [16, 17]. Along this line, recently, several elegant direct hydroxy-phosphorylation reactions using P(O)–H compounds were designed for efficient and concise synthesis of β-hydroxy phosphorus compounds (Fig. 1)

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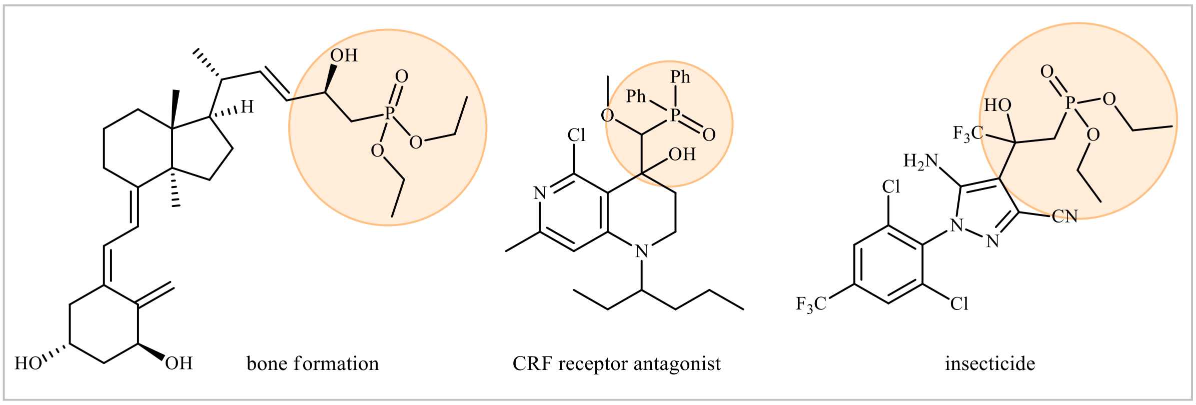


Scheme 1. Selected examples of biologically active β-hydroxy phosphorus compounds.

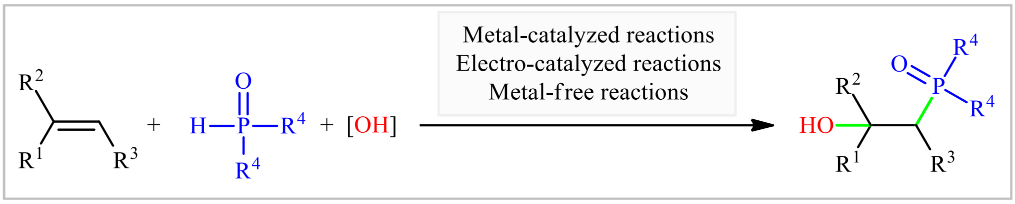


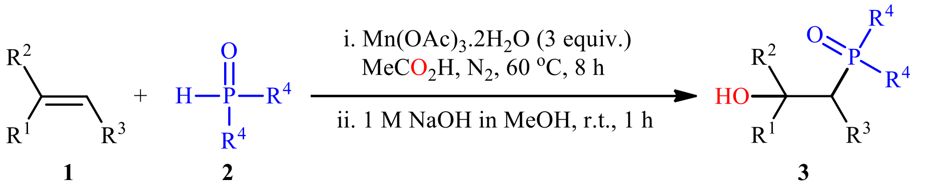
Fig. 1. Direct hydroxy-phosphorylation of alkenes with P(O)–H compounds.

High atom and step economy, easily available starting materials and operational simplicity were the advantages, mentioned for this promising synthetic strategy. To the best of our knowledge, a comprehensive review on this chemistry has not been reported in the literature to date. This study is an attempt to summarize the data available from the literature on the synthesis of β-hydroxy phosphorus compounds through the direct hydroxyphosp-orylation of alkenes using P(O)–H compounds as sources phosphoryl radicals. The content is categorized around the type of catalysis, including metal-free reactions, metal-catalyzed reaction, and electro-catalyzed reactions. Notably, herein, we will not speak on the oxy-phosphorylation reactions of unsaturated hydrocarbons, as it was recently highlighted by Bakhtiary *et al*. in their interesting paper entitled "Recent trends in the direct oxyphosphorylation of C-C multiple bonds" [18].

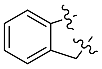
2. Metal-catalyzed/mediated reactions

Drawing inspiration from Taniguchi's work on the synthesis of β-hydroxyphosphonate derivatives by iron-catalyzed aerobic hydroxy-phosphorylation of corresponding alkenes using phosphorohydrazidates [$(RO)_2P(O)NHNH_2$] as radical precursors [19], the first general report on metal-mediated direct hydroxy-phosphorylation of alkene substrates with P(O)–H compounds was published by Tang and co-workers in 2014 [20]. By employing styrene and diisopropyl H-phosphonate as the model substrates, quite some oxidants (*e.g.*, $AgNO_3$, AgOAc, CuCl, $CuCl_2$, $Mn(OAc)_3{\cdot}2H_2O$, $Mn(acac)_3$, Bu_4NI + TBHP, $AgNO_3$ + $K_2S_2O_8$) and solvents (*e.g.*, MeCN, DMF, $MeCO_2H$, $EtCO_2H$, $^tBuCO_2H$) were screened, choosing eventually the $Mn(OAc)_3{\cdot}2H_2O$ as the most suitable oxidant and $MeCO_2H$ as the optimal solvent at 60 °C. On the basis of the optimal conditions, various terminal, internal, and 1,1-disubstituted alkenes **1** smoothly reacted with a series of P(O)–H compounds **2** (H-phosphonates and H-phosphine oxides) to generate desired β-hydroxy phosphorylated products **3** in poor to excellent yields, after methanolysis (Scheme 2). The results demonstrated that H-phosphonates afforded relatively higher yields compared to the H-phosphinates and the relative reaction rates of alkenes followed the order: electron-rich aromatic alkenes > benzylic alkenes > aliphatic alkenes ≥ strongly electron-poor aromatic alkenes. Unfortunately, the applicability of H-phosphinates [HP(O)(R)(OR')] was not investigated in this study. Notably, the authors demonstrated the scalability of their methodology since diisopropyl (2-hydroxy-2-phenylethyl)phosphonate could be obtained in 2.4 g scale in high yield of 84%. Furthermore, they highlighted the synthetic application of the prepared compounds as starting materials in the synthesis of β-ketophosphonates and β-benzoxyphosphonates *via* oxidation and Mitsonobu reaction, respectively.

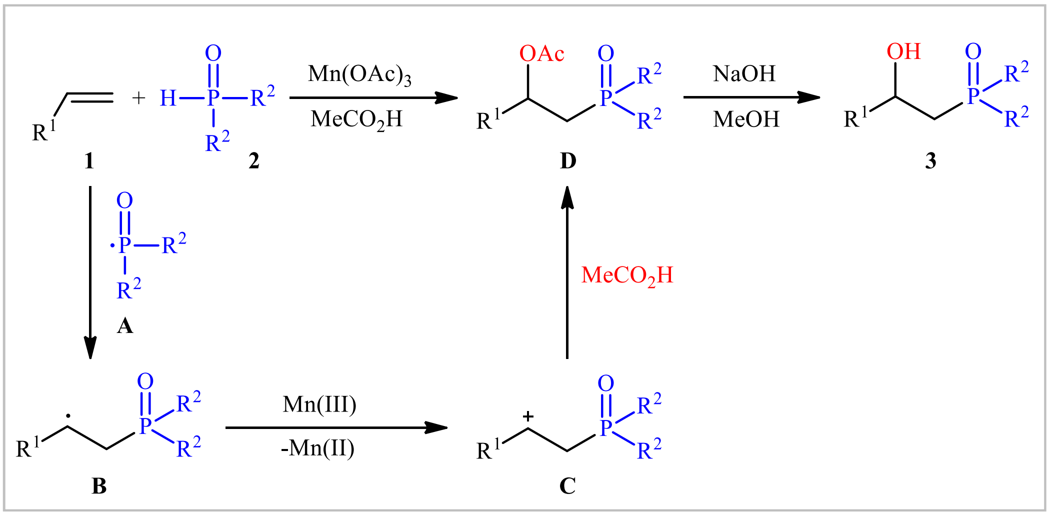
Based on the previous literature report and a series of control experiments, the authors proposed a possible mechanistic pathway for this hydrooxyphosphorylation which is outlined in Scheme 3. Initially, the reaction of P(O)–H compound **2** with Mn(III) salt generates phosphorus-centered radical **A**, which after addition to the alkene **1** with anti-Markovnikov selectivity affords the C-centered radical **B**. Subsequently, one-electron oxidation of the newly generated radical **B** by Mn(III) gives carbanion **C** that, after reaction with $MeCO_2H$ affords acetoxylated compound **D**. Shortly afterwards, the same strategy was applied by Zou and co-workers to the preparation of a diverse range of β-acetoxy-phosphonate from the corresponding styrene derivatives [21].



23 examples (25-90%)

R^1= ^{n}Bu, ^{n}Hex, Bn, Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-OMe-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-CN-C_6H_4, 3-NO_2-C_6H_4, 2-naphthyl, 2-thienyl
R^2= H, Me
R^3= H
R^1 + R^3= 
R^4= Ph, OEt, O^{n}Pr, O^{i}Pr, O^{n}Bu, OBn

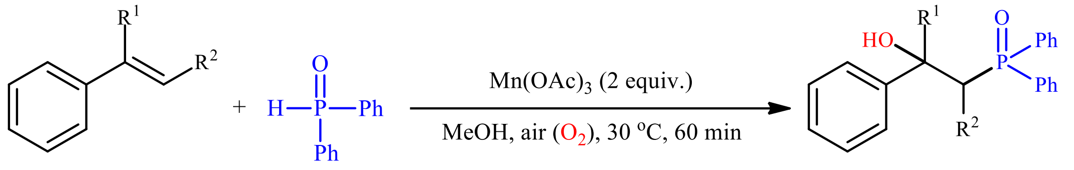
Scheme 2. Taniguchi's synthesis of β-hydroxy phosphorus compounds **3**.



Scheme 3. Plausible reaction mechanism for the formation of β-hydroxy phosphorus compounds **3**.

In a related investigation, Zou and colleagues disclosed that α- and β-substituted styrenes **4** in the treatment with diphenylphosphine oxide **5** in the presence of over-stoichiometric amounts of $Mn(OAc)_3$ in MeOH under aerobic conditions, underwent regioselective vicinal hydroxyphosphorylation to afford (2-hydroxy-2-phenylethyl)diphenylphosphine oxide derivatives **6** in good yields (Scheme 4) [22]. Surprisingly, when diphenylphosphine oxide was replaced by dimethylphosphite, the corresponding alkenylphosphonates were obtained as the sole products, without any β-hydroxy phosphorylated product. Noteworthy, under the identical conditions, α- and β-unsubstituted styrenes underwent selective oxyphosphorylation to yield the respective β-phosphorylated ketones in good yields. Therefore, although this protocol exhibits some novelties, the limited scope of both alkenes and P(O)–H compounds can be considered as a major drawback. According to the authors proposed mechanism, the hydroxyl group originated from air oxygen. Shortly after, Makino described that a similar oxy-phosphorylation can be effected with $Mn(acac)_2$ in the presence of pyridine as a base [23].

In another study, the same research group provided a further example of β-hydroxyphosphine oxides **9** synthesis from the corresponding styrene derivative **7** and diarylphosphine oxides **8** using their original reaction conditions (Scheme 5) [24]. Here, various α,β-unsubstituted as well as α- and β-substituted styrenes were compatible with the reaction condition and afforded the target products in synthetically useful

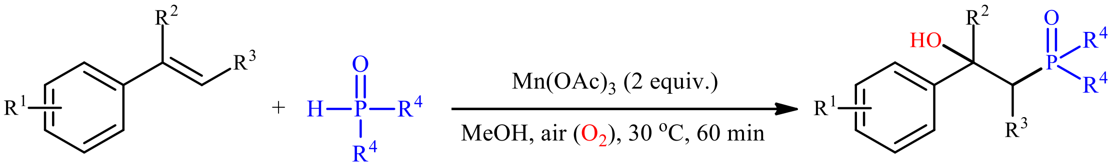


4 **5** **6**

R^1= H, Me, Ph
R^2= H, Me, Ph

4 examples (65-74%)

Scheme 4. $Mn(OAc)_3$-mediated hydroxyphosphorylation of α- and β-substituted styrenes **4** reported by Zou.



7 **8** **9**

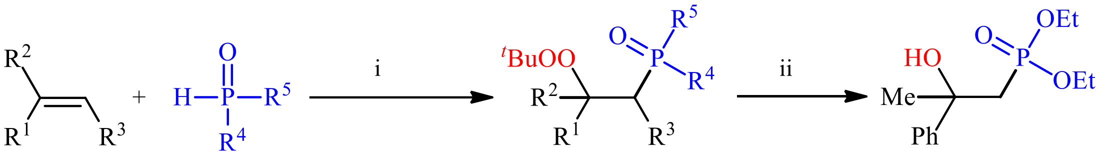
R^1= H, 4-NO_2, 2-Me, 2-OMe, 2-F, 2-Cl, 2-Br, 2-CF_3, 2-NO_2,
2-CN, 2-NHCOMe, 2,6-$(Cl)_2$, 2,3-$(CH=CH)_2$-
R^2= H, Me, Ph
R^3= H, Me
R^4= Ph, 4-OMe-C_6H_4

17 examples (25-74%)

Scheme 5. Zou's synthesis of β-hydroxyphosphine oxides **9**.

yields. In this study, the authors found some limitations in their protocol when they attempted to subject *o*-Ph, *o*-NH_2, *o*-CN, *m*-CF_3-substituted styrenes, cyclic styrene derivatives, and *N*-heteroaromatic alkenes to the reaction. In these cases, the desired products were obtained with extremely low yields or none at all.

In an interesting contribution in this field, Li and co-workers unfolded copper-catalyzed phosphorylation-peroxidation of alkenes **10** with P(O)-H compounds **11** and *tert*-butyl hydroperoxide (TBHP) to synthesize multisubstituted β-phosphoryl peroxides **12** under additive free conditions [25]. Both terminal and internal alkenes exhibited good applications in this protocol and afforded the target products in moderate to good yields (Scheme 6). The authors showed the peroxy group of the β-phosphoryl peroxides **3** could be easily converted to a hydroxyl group by the reduction over Pd/C in MeCN to form corresponding β-hydroxy phosphorus compounds **13** in almost quantitative yields. Later, various catalytic systems have been investigated in order to maximize the efficiency of this difunctionalization reaction [26-28].



10 **11** **12** **13**, (96%)

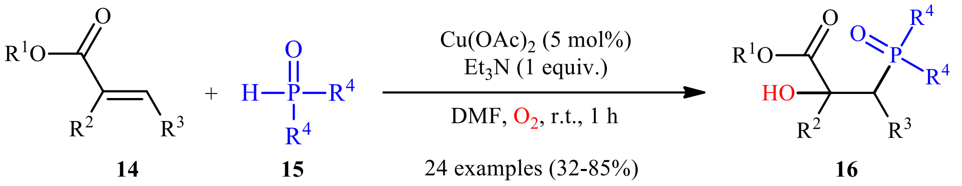
R^1= CO_2Me, $CO_2{}^tBu$, $CO_2{}^iPr$, Ph, 4-Me-C_6H_4,
4-Cl-C_6H_4, 4-F-C_6H_4, 1-naphthyl
R^2= H, Me, CH_2CO_2Me, Ph, 4-F-C_6H_4
R^3= H, Me, Ph
R^4= OEt
R^5= OEt, Ph

23 examples (45-87%)

i: $Cu(OAc)_2$ (10 mol%), MeCN, N_2, 60 °C, 3 h
ii: Pd/C (10 mol%), NH_4CO_2H (2 equiv.), MeCN, 50 °C, 3 h

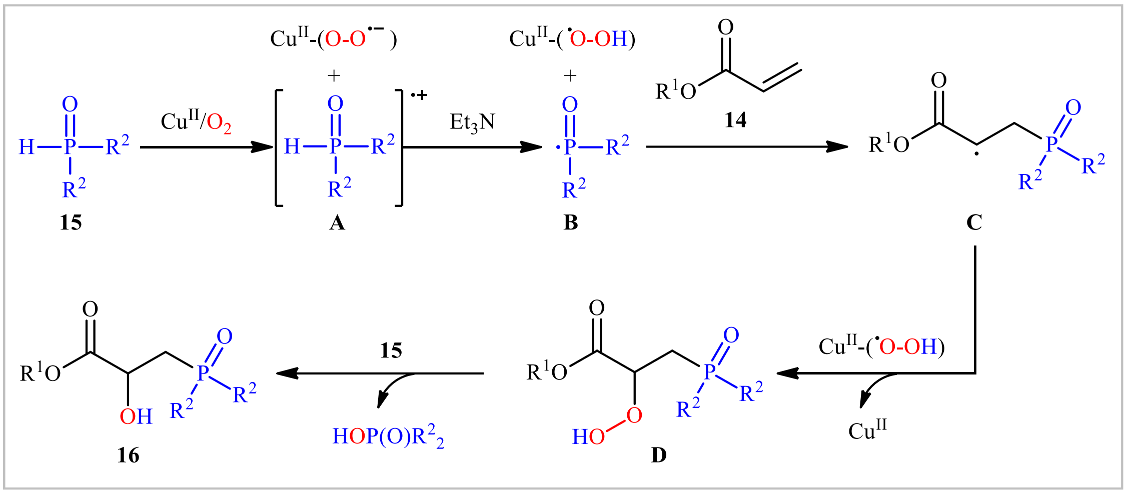
Scheme 6. Li's synthesis of β-hydroxy phosphorus compounds **13**.

In 2017, Zhang and Wei along with their co-workers developed an interesting Cu-catalyzed regioselective vicinal hydroxyphosphorylation of olefinic double bonds with P(O)-H compounds employing oxygen as the sole oxidant [29]. Using 5 mol% of Cu(OAc)2 as catalyst and 1 equiv. of Et3N as a base, a library of functionalized α,β-unsaturated esters 14 underwent regioselective hydroxyphosphorylation with H-phosphine oxides 15 to afford the corresponding β-hydroxyphosphine oxides 16 in fair to high yields within 1 h (Scheme 7). In this investigation, the authors demonstrated significant scope of α,β-unsaturated esters, but limited scope of the H-phosphine oxide substrate. Unfortunately, no comment was made by the authors regarding the applicability of H-phosphonates and H-phosphinates in this synthetic strategy. It should be mentioned that apart from α,β-unsaturated esters, other electron-deficient alkenes such as α,β-unsaturated amides, α,β-unsaturated ketones and α-CF3-substituted alkenes as well as various electron-rich alkenes were also well tolerated by this protocol. In addition, a gram-scale synthesis of β-hydroxyphosphine oxide was successfully performed under the standard reaction conditions (1.63 g, 73% yield). The authors proposed mechanistic pathway for this hydroxyphosphorylation reaction is depicted in Scheme 8. It consists of the following key steps: (i) single electron transfer from H-phosphine oxide 15 to copper(II) species in the presence of dioxygen to form the cation radical intermediate A and CuII_(OO•−) (superoxide) species; (ii) proton transfer from intermediate A to CuII_(OO•−) species to produce phosphorus radical B and CuII_(•OOH) (hydroperoxide) species; (iii) the addition of phosphorus radical B to α,β-unsaturated ester 14 to generate alkyl radical C; (iv) trapping of alkyl radical C by CuII_(•OOH) to access hydroperoxide intermediate D; and (v) reduction of hydroperoxide D by another molecule of H-phosphine oxide 15 to afford the desired product 16.



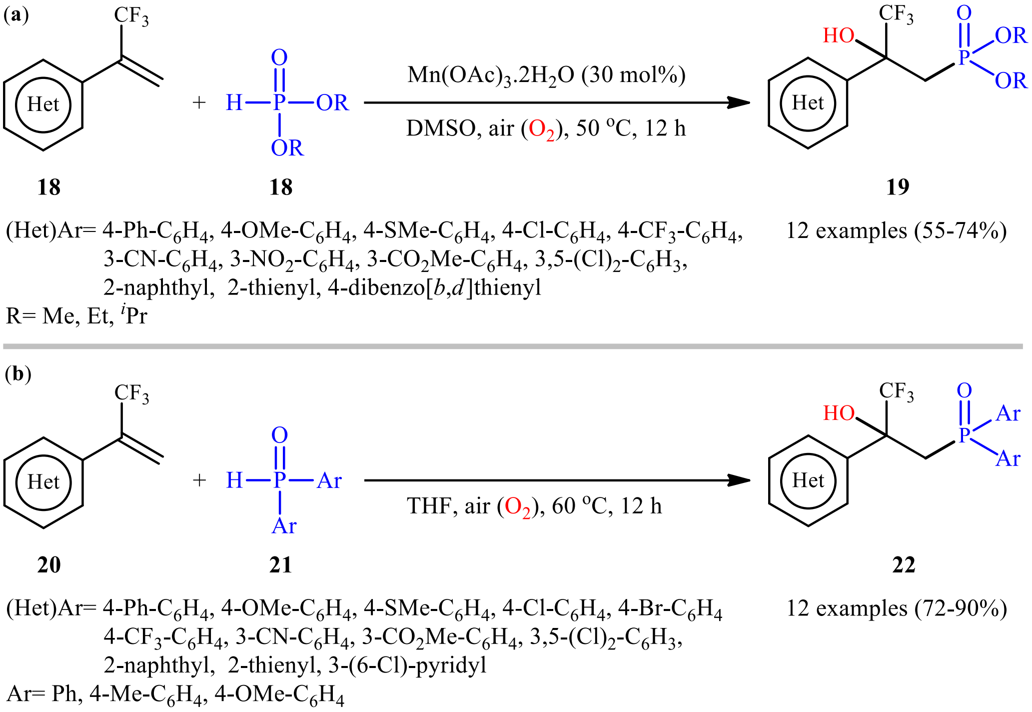
R^1= Me, Et, -CH$_2$-(3-OMe-C$_6$H$_4$)
R^2= Ph, 4-Me-C$_6$H$_4$, 4-OMe-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-SO$_2$Me-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$,
3-OMe-C$_6$H$_4$, 3-Br-C$_6$H$_4$, 2-Br-C$_6$H$_4$, 2-NO$_2$-C$_6$H$_4$, 3,4-(OMe)$_2$-C$_6$H$_3$, 3,5-(OMe)$_2$-C$_6$H$_3$,
2,4,5-(F)$_3$-C$_6$H$_2$, 1-naphthyl, 2-pyridyl, Bn, Me
R^1 + R^2= -(CH$_2$)$_2$-
R^3= H, Me
R^4= Ph, 4-Me-C$_6$H$_4$, 4-F-C$_6$H$_4$

Scheme 7. Zhang-Wei's synthesis of β-hydroxyphosphine oxides **16**.



Scheme 8. Proposed mechanism for the generation of β-hydroxyphosphine oxides **16**.

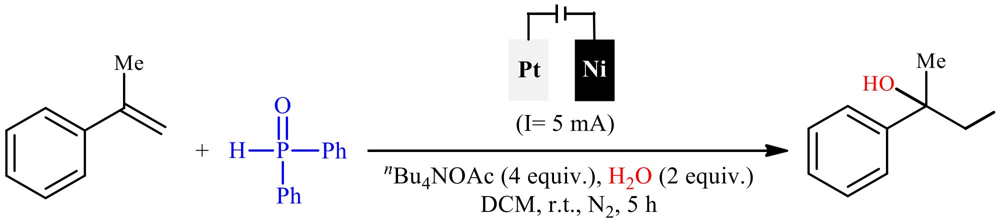
Recently, the research group of Zhang and Cao reported their results on the Mn-catalyzed hydroxyphosphorylation of α-trifluoromethy)styrenes **17** with H-phosphonates **18** [7]. Optimal conditions for this difunctionalization reaction were the use of Mn(OAc)$_3$·2H$_2$O (30 mol%) as the catalyst, air as the terminal oxidant, and DMSO as the solvent. The reaction proceeded cleanly at 50 °C and the desired β-hydroxy-β-CF$_3$-phosphonates **19** were obtained in modest to good yields (Scheme 9a). The reaction tolerated both electron-rich and electron-poor α-trifluoromethy)styrenes and a series of dialkyl phosphonates; nonetheless the reaction failed completely for *ortho*-substituted styrenes and dibenzyl/diaryl phosphonates. Noteworthy, Other manganese catalysts such as MnO$_2$, Mn(acac)$_3$, Mn$_2$O$_3$ and Mn(OAc)$_2$·4H$_2$O were also effective in this hydroxyphosphorylation reaction but gave lower yield of products. No desired product was obtained by replacing Mn(OAc)$_3$·2H$_2$O with Cu(OAc)$_2$, CuBr$_2$, Fe(OAc)$_3$, AgOAc, MnSO$_4$, and MnCl$_2$. In this work, the authors also demonstrated that a diverse range of β-hydroxy-β-CF_3-phosphine oxides **22** could be obtained in high yields (up to 90%) from the reaction of α-trifluoromethy)styrenes **20** with diaryl phosphine oxides **21** under catalyst- and additive-free conditions with the assistance of air (Scheme 9b).



Scheme 9. Zhang-Cao's synthesis of (a) β-hydroxy-β-CF_3-phosphonates **19; (b)** β-hydroxy-β-CF_3-phosphine oxides **22**.

3. Electro-catalyzed reactions

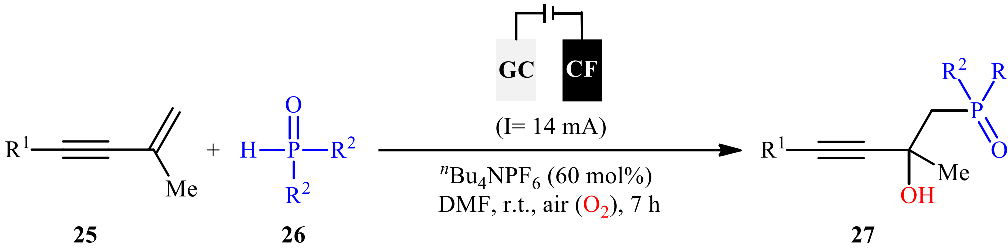
Zhang-Wen's research team recently achieved the electrochemical hydroxyphosphorylation of α-methylstyrene **23** with diphenylphosphine oxide **5** under catalyst- and oxidant-free conditions [30]. The reaction was conducted in an undivided cell assembled with a platinum plate as the anode and a nickel plate as the cathode under constant-current electrolysis at 5 mA cm^{-2} in anhydrous DMC using 2 equiv. of water as the oxygen donor at room temperature and afforded the target β-hydroxyphosphine oxide **24** in moderate yield of 55% (Scheme 10). Notably, when α-unsubstituted styrene derivatives were subjected to the same reaction conditions, the corresponding β-phosphorylated ketones were formed as the sole products (33 examples, 44-94%). These results clearly indicated that the presence of a substituent at the α-position of styrenes is crucial for the formation of β-hydroxyphosphine oxides by this protocol.



23 **5** **24**, (55%)

Scheme 10. Electrochemically enabled hydroxyphosphorylation of α-methylstyrene **23** reported by Zhang-Wen.

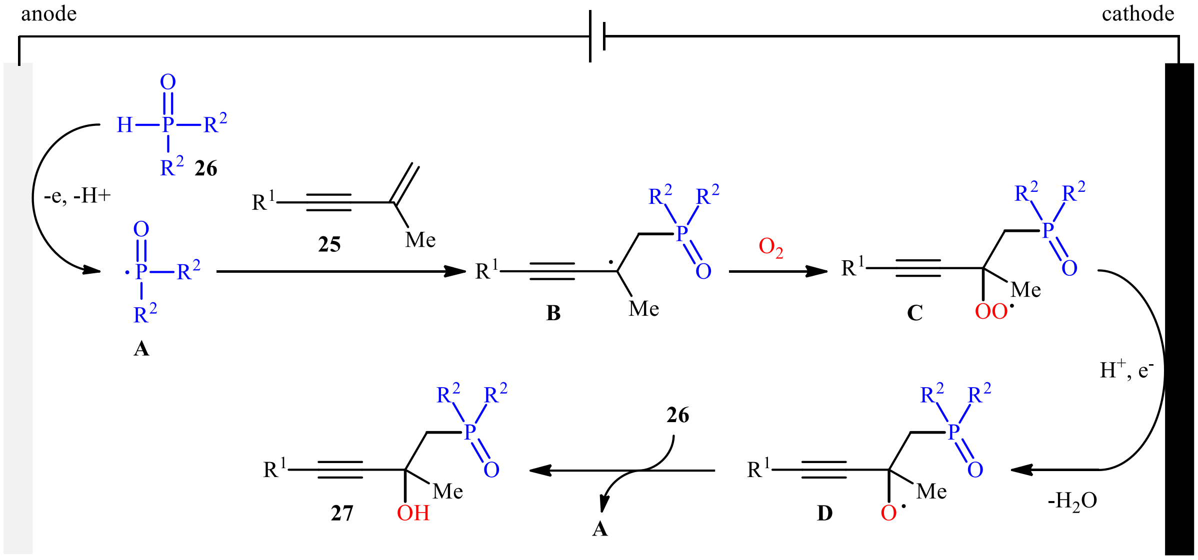
Very recently, Wu and Zhu along with their co-workers developed an elegant electrochemical hydroxyphosphorylation of 1,3-enynes **25** with various di(hetero)aryl phosphine oxides **26** under catalyst-free ambient conditions [31]. The reactions were conducted in an undivided cell under a constant current of 14 mA cm^{-2} with glassy carbon (GC) anode and copper foam (CF) cathode employing $^nBu_4NPF_6$ as the electrolyte and DMF as the solvent, which afforded the corresponding phosphinyl-substituted propargyl alcohols **27** in relatively poor to high yields (Scheme 11). The results indicated that 1,3-enynes bearing aryl rings in the alkyne terminus were high yielding compared to alkyl-substituted substrates and diaryl phosphine oxides gave higher yields than diheteroaryl ones. Unfortunately, neither dialkyl phosphine oxides nor β-hydroxy phosphonates could react in this system. In the plausible mechanistic pathway (Scheme 12), the authors suggested that this reaction proceeds *via* generation of P-centered radical **A** through electrochemical oxidation of phosphine oxide **26** at the anode surface. Next, radical **A** attacks the double bond of enyne **25** at sterically less hindered position to produce C-centered radical **B**, which after capturing molecular oxygen from air, produces peroxyl radical **C**. Subsequently, single-electron reduction of peroxyl radical **C** at the cathode leads to the formation of alkoxyl radical **D** along with the generation of H_2O through hydrogen abstraction. Finally, reduction of radical **D** by phosphine oxide **26** affords the observed product **27**.



27 examples (30-87%)

R^1= Ph, 4-Ph-C_6H_4, 4-OEt-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CN-C_6H_4, 4-CO_2Me-C_6H_4, 3-Me-C_6H_4, 3-Cl-C_6H_4, 2-Me-C_6H_4, 2-Cl-C_6H_4, 3-thienyl, CH_2CH_2OBn
R^2= Ph, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-OEt-C_6H_4, 4-Cl-C_6H_4, 3-OMe-C_6H_4, 2-Me-C_6H_4, 2,4-$(Me)_2$-C_6H_3, 3,5-$(Me)_2$-C_6H_3, 3,4-OCH_2O-C_6H_3, 2-naphthyl, 2-thienyl

Scheme 11. Wu-Zhu's synthesis of phosphinyl-substituted propargyl alcohols **27**.

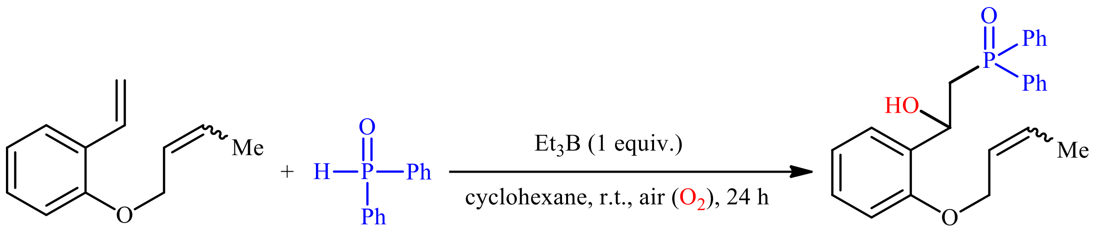


Scheme 12. Proposed mechanism for the reaction in Scheme 11.

4. Metal-free reactions

Compared to the metal-catalyzed vicinal hydroxy-phosphorylation reactions of alkenes, the analogues hydroxy-phosphorylation reactions under metal-free conditions are much less developed and all existed methods limited to the use of H-phosphine oxides as sources phosphoryl radicals. The first mention of the synthesis of β-hydroxyphosphine oxides through the direct hydroxy-phosphorylations of alkenes with H-phosphine oxides can be found in a 2008 paper by Parsons and co-workers [32]. In this study, they showed that treatment of 1-(but-2-en-1-yloxy)-2-vinylbenzene **28** with diphenylphosphine oxide **5** in the presence of stoichiometric amounts of Et_3B in cyclohexane under ambient conditions furnished the corresponding β-hydroxyphosphine oxide **29** in a poor yield of 13% (Scheme 13). Although only one low yield example was disclosed, this paper represents the first example of metal-free hydroxy-phosphorylation reactions.

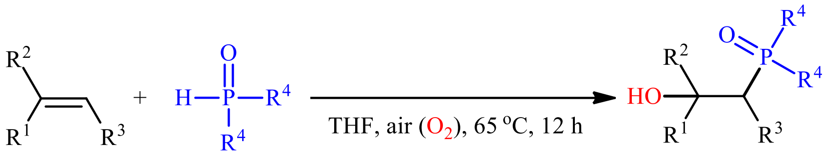
In 2016, Zhang-Wei's research team reported the synthesis of a library of β-hydroxyphosphine oxides **32** *via* direct hydroxyphosphorylation of corresponding alkenes **30** with diaryl phosphine oxides **31** under an air atmosphere without addition of any catalysts/additives [33]. The reactions carried out in THF at 65 °C, tolerated a series of sensitive functional groups, and provided the



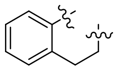
28 **5** **29**, (13%)

Scheme 13. Parsons's synthesis of β-hydroxyphosphine oxide **29**.

desired β-hydroxyphosphorylated products in poor to high yields (Scheme 14). The protocol was compatible with both terminal and internal alkenes and various diaryl phosphine oxides. The results demonstrated that aromatic alkenes afforded relatively better yields compared to aliphatic alkenes. On the other hand, electron-rich diaryl phosphine oxides gave higher yields of target products than electron-poor ones.

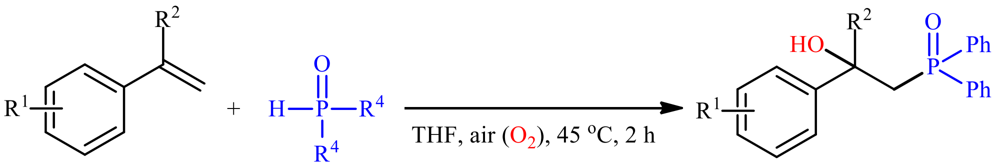


30 **31** **32**

R^1= Ph, 4-Me-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 3-Me-C$_6$H$_4$, 2-Me-C$_6$H$_4$, 2-naphthyl, CH$_2$Cl, acetylenyl   18 examples (20-86%)
R^2= H, Me, Ph, CH$_2$Cl
R^3= H
R^1 + R^3= 
R^4= Ph, 4-Me-C$_6$H$_4$, 4-OMe-C$_6$H$_4$, 4-Cl-C$_6$H$_4$

Scheme 14. Zhang-Wei's synthesis of β-hydroxyphosphine oxides **32**.

Shortly afterwards, Lei and co-workers provided further examples of β-hydroxyphosphine oxides **35** preparation *via* hydroxyphosphorylation of α-substituted styrene derivatives **33** with diaryl phosphine oxides **34** under Zhang-Wei's standard reaction condition (Scheme 15) [34]. However, when benzyl methacrylate (an aliphatic alkene) was employed under the identical conditions, only a trace amount of product with major hydrophosphorylation by-product were obtained. Unfortunately, diethyl phosphite did not take part in the reaction and therefore no other H-phosphonates were examined in the protocol. In this study, using the same scenario, the authors were able to synthesis of a series of β-phosphorylated ketones in moderate to good yields from the respective terminal alkynes and diphenylphosphine oxide.



33 **34** **35**

R^1= H, 4-Me, 4-Ph, 4-Br, 4-CF$_3$, 3-OMe, 4-S-(p-tolyl), 3,4-(CH=CH)$_2$ 12 examples (43-94%)
R^2= Me, ^{c}Pr, Ph
R^3= Ph, 4-Me-C$_6$H$_4$, 3-Me-C$_6$H$_4$

Scheme 15. Lei's synthesis of β-hydroxyphosphine oxides **32**.

5. Conclusion

The direct difunctionalization of alkenes is an efficient and useful method for concomitant introduction of two functional groups into the π system, and compounds with more structural complexity could be produced using this strategy. Hydroxy-phosphorylation of alkene substrates using P(O)–H compounds as sources phosphoryl radicals is one of the most promising difunctionalization reactions which allows rapid assembly of synthetically and biologically important β-hydroxy phosphorus compounds in an atom and step-economic manner from simple and easily accessible starting materials. Despite significant progress in recent years, several challenges remain in this field of expertise. For example, the scope of alkene substrates is largely limited to styrene derivatives and successful examples on the hydroxy-phosphorylation of aliphatic alkenes are rare. Moreover, the applicability of H-phosphinates as substrates has scarcely been investigated in this page of β-hydroxy phosphorus compounds synthesis. In addition, there is still no reported guideline for the synthesis of the titled compounds *via* hydroxy-phosphorylation of corresponding alkynes.

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