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Copper-catalyzed direct hydroxyphosphorylation of electron-deficient alkenes with H-phosphine oxides and dioxygen

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ABSTRACT

A copper-catalyzed direct hydroxyphosphorylation of electron-deficient alkenes with H-phosphine oxides and dioxygen is reported. The present reaction, proceeds under mild reaction conditions with good functional group tolerance, affording the facile and efficient synthesis of various β-hydroxyphosphine oxides in a scaled-up manner with moderate to good yields.

Phosphorus-containing molecules are valuable compounds, which have been widely used in organic synthetic chemistry,[1] pharmaceutical chemistry,[2] and materials science.[3] Among them, β-hydroxyphosphine oxide compounds have attracted increasing research interest from synthetic chemists, because they could not only act as the key synthetic intermediates in the well-known Horner–Wittig reaction,[4] but also serve as the versatile building blocks for the synthesis of various important products in organic chemistry.[5] Up to date, many synthetic strategies have been developed to construct β-hydroxyphosphine oxide scaffolds. Traditionally, β-hydroxyphosphine oxides have been prepared by the hydrogenation of β-ketophosphine oxides,[6] the nucleophilic addition of the anions of alkyl(diphenyl)phosphine oxides to carbonyl compounds,[7] and the nucleophilic addition of organolithium reagents to β-ketophosphine oxides.[8] Alternative procedures include the ring-opening reaction of epoxy compounds with phosphorus nucleophiles,[9] the ring-opening of α,β-epoxy phosphine oxides with $LiAlH_4$,[10] and the oxidation of β-hydroxyphosphines with H_2O_2.[11] However, almost all of these methods suffer from one or more drawbacks, such as relatively harsh reaction conditions, tedious procedures, lack of functionality tolerance, excess amounts of hazardous organometallic reagents, and low atom economy.

The difunctionalization of carbon-carbon unsaturated bonds is one of the powerful and attractive synthetic tools toward phosphorus-containing compounds.[12] In 2014, Tang and co-workers disclosed a new hydroxyphosphorylation of alkenes with H-phosphine oxides leading to β-hydroxyphosphine oxides in the presence of stoichiometric $Mn(OAc)_3{\cdot}2H_2O$ under nitrogen atmosphere (Scheme 1a).[13] Very recently, our group[14] and Lei group[15] independently developed dioxygen-induced direct hydroxyphosphorylation of alkenes under metal-free and heating conditions (Scheme 1b and c). These strategies are well suited for electron-rich alkenes, however, the hydroxyphosphorylation of electron-deficient alkenes with H-phosphine oxides has remained unexplored to date. As part of our continued interest in difunctionalization of alkenes and the construction of phosphorus-containing compounds,[14,16] herein, we wish to report a simple and practical copper-catalyzed direct hydroxyphosphorylation of electron-deficient alkenes with H-phosphine oxides and dioxygen at room temperature.

In order to realize the hydroxyphosphorylation of electron-deficient alkenes with H-phosphine oxides, initially, the reaction of ethyl 2-phenylacrylate (**1a**) and diphenylphosphine oxide (**2a**) was performed under the standard conditions of hydroxyphosphorylation of electron-rich alkenes according to previous reports.[14,15]

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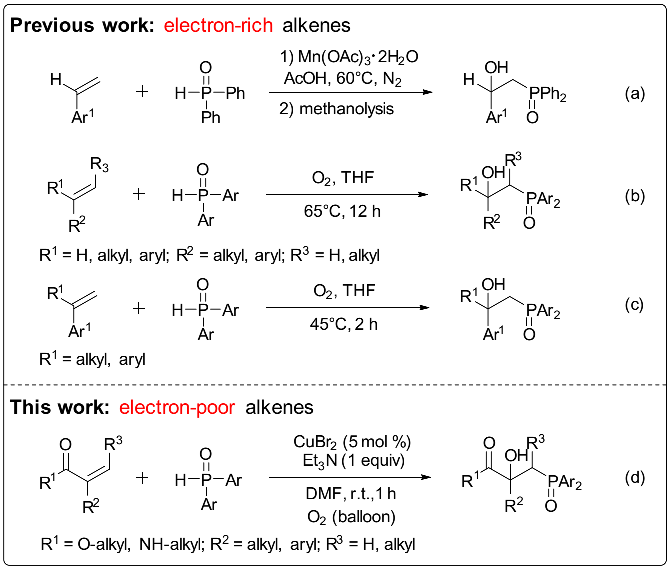
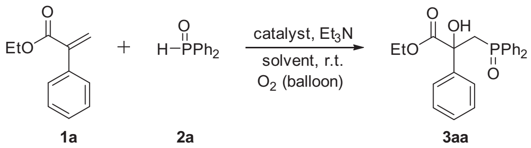


Scheme 1. Hydroxyphosphorylation of alkenes with H-phosphine oxides.

As shown in Table 1, only a trace amount of the hydroxyphosphorylation product β-hydroxyphosphine oxide (**3aa**) was detected at 45 °C or 65 °C (entry 1). To our delight, significantly improved reaction efficiency was obtained when $CuBr_2$ (5 mol%) and Et_3N (1 equiv) were introduced as the catalyst and base into the reaction at room temperature (entries 2 and 3). Furthermore, a range of reaction solvents were screened (entries 4–8), with *N*,*N*-dimethylformamide (DMF) being the superior for the formation of product **3aa** (73%). The effects of other catalysts, such as Cu, Fe, Ag, Pd, Au, In, Ni, and Ru salts, were also investigated and copper salts, especially $CuBr_2$, were found to be the best catalyst to afford the desired product **3aa** (entries 9–17). A relatively lower yields of **3aa** was obtained, when the loading of Et_3N was reduced to 0.1 equiv or 0.5 equiv, indicating that the stoichiometric amount of Et_3N is essential for this oxyphosphorylation (entries 18 and 19). It was noteworthy that this hydroxyphosphorylation reaction could also proceed smoothly even at 0 °C (entry 21), whereas the relatively lower yields were obtained under higher temperatures (entries 22 and 23). After a series of detailed investigations (Table 1 and the supplementary information), the best yield of **3aa** (73%) was obtained by employing **1a** (0.5 mmol), **2a** (1 mmol), $CuBr_2$ (5 mol%), and Et_3N (0.5 mmol) in DMF at room temperature under dioxygen atmosphere (Table 1, entry 6).

Upon optimization of the reaction conditions, the scope of this hydroxyphosphorylation reaction was evaluated. As demonstrated in Table 2, in general, 2-arylacrylate and its derivatives containing electron-rich or electron-poor groups on the aryl rings were suitable for this process to provide the corresponding products (**3aa**–**3qa**) in moderate to good yields. Various functional groups, such as methoxy, fluoro, chloro, bromo, nitro, and sulfonyl groups, were demonstrated to be well tolerated in this reaction, whose corre-

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	Et_3N(equiv)	Yield (%)[b]
1	–	THF	–	Trace[c,d]
2	$CuBr_2$	THF	–	Trace[e]
3	$CuBr_2$	THF	1	69
4	$CuBr_2$	$CHCl_3$	1	72
5	$CuBr_2$	1,4-Dioxane	1	72
6	**$CuBr_2$**	**DMF**	**1**	**73**
7	$CuBr_2$	EtOH	1	25
8	$CuBr_2$	AcOH	1	Trace
9	CuCl	DMF	1	72
10	CuCN	DMF	1	72
11	$FeCl_2$	DMF	1	11
12	AgF	DMF	1	Trace
13	$PdCl_2$	DMF	1	18
14	$AuCl_3$	DMF	1	ND
15	$InCl_3$	DMF	1	ND
16	$NiCl_2·6H_2O$	DMF	1	ND
17	$RuCl_3·H_2O$	DMF	1	ND
18	$CuBr_2$	DMF	0.1	41
19	$CuBr_2$	DMF	0.5	49
20	$CuBr_2$	DMF	1	70[f]
21	$CuBr_2$	DMF	1	62[g]
22	$CuBr_2$	DMF	1	61[h]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), catalyst (5 mol%), Et_3N (0.5 mmol), solvent (1 mL), O_2 (balloon), r.t., 1 h. ND = not detected.
[b] Isolated yields based on **1a**.
[c] **2a** (1.25 mmol), THF (2 mL), 65°C, 12 h.
[d] **1a** (0.2 mmol), **2a** (0.6 mmol), THF (2 mL), air, 45°C, 2 h.
[e] 12 h.
[f] 0 °C.
[g] 40 °C.
[h] 80 °C.