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Copper-Catalyzed Synthesis of α-Hydroxy Phosphonates from *H*-Phosphonates and Alcohols or Ethers

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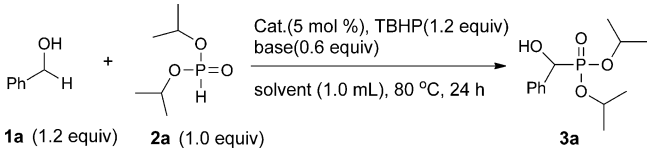
α-Hydroxy phosphonates have attracted considerable attention owing to their critical roles in anticancer drugs, plant growth regulators, and enzyme inhibitors.[1] The traditional way to synthesize α-hydroxy phosphonates is an addition reaction of monobasic phosphorus (the Pudovik reaction) or odorous trialkyl phosphite (the Abramov reaction) to an aldehyde or ketone.[2] Moreover, the reactions based on phosphonate derivatives such as oxidation of alkyl phosphonates[3] or reduction or addition of keto phosphonates[4] have also been found to be effective methods to form α-hydroxy phosphonates. Recently, great efforts have been made to develop metal-catalytic[5] or metal-free[6] syntheses of α-hydroxy phosphonates involving the condensation of *H*-phosphonates with carbonyls.

Catalytic functionalization of alcohols and ethers have garnered much interest owing to the ease of generating carbon–carbon[7] and carbon–heteroatom bonds.[8] Typical catalysts for this reaction are Ru,[9] Ir,[10] Pd,[11] Cu,[8a] and Fe[8c,12]; furthermore, it has been accomplished under transition-metal-free conditions.[13]Although many heteroatomic (oxygen, nitrogen) nucleophilic reagents are used in the alkylation catalyzed by these complexes, *H*-phosphonates as the substrates have not been investigated for the preparation of α-hydroxy phosphonates.

Herein, we present a facile method for the phosphonation of alcohols or ethers catalyzed by $CuCl_2$/TBHP (*tert*-butyl hydroperoxide) with moderate to good yields. Compared with aldehydes, the corresponding alcohols are readily available, highly stable, cheaper, and less toxic. The direct condensation of simple *H*-phosphonates with alcohols is found to be a more environmentally friendly route than reactions in which aldehydes and trivalent phosphorus compounds are used as reagents.

The α-hydroxyphosphonation reaction catalyzed by copper depends greatly on the reaction conditions. The scope and limitation of the reaction is illustrated in Table 1,

Table 1. Optimization of the reaction conditions.[a]



1a (1.2 equiv) **2a** (1.0 equiv) **3a**

Entry	Catalyst	Base	Solvent	Yield [%][b]
1	$CuCl_2$	K_2CO_3	EtOAc	49
2	$CuCl_2$	K_2CO_3	PhMe	28
3	$CuCl_2$	K_2CO_3	DMF	30
4	$CuCl_2$	K_2CO_3	DMSO	39
5	**$CuCl_2$**	**K_2CO_3**	**DCE**	**80**
6	$CuCl_2$	K_2CO_3	CH_3CN	46
7	**$CuCl_2$**	**K_2CO_3**	**1a**[d]	**82**
8	–	K_2CO_3	**1a**	n.d.[c]
9	$CuCl_2$	–	**1a**	n.d.
10	$CuCl_2$	$NaHCO_3$	**1a**	61
11	$CuCl_2$	Cs_2CO_3	**1a**	46
12	$CuCl_2$	K_3PO_4	**1a**	33
13	$CuCl_2$	*t*BuOK	**1a**	12
14	$CuCl_2$	Et_3N	**1a**	34
15	$CuCl_2$	Py	**1a**	<5
16	$CuCl_2$	DMAP	**1a**	40
17	$CuCl_2$	Na_2CO_3	**1a**	75
18	$Cu(OAc)_2$	Na_2CO_3	**1a**	40
19	$CuSO_4$	Na_2CO_3	**1a**	53
20	$CuBr_2$	Na_2CO_3	**1a**	23
21	CuO	Na_2CO_3	**1a**	40
22	CuCl	Na_2CO_3	**1a**	47
23	CuBr	Na_2CO_3	**1a**	63
24	CuI	Na_2CO_3	**1a**	19

[a] On a 1.0 mmol scale; [b] Yields determined by ^{31}P NMR spectrocopy; [c] n.d., not detected. [d] **1a** (1.0 mL) was used as the solvent.

with benzyl alcohol (**1a**) and diisopropyl *H*-phosphonate (**2a**) as selected substrates. The yield of **3a** was determined by ^{31}P NMR spectroscopy. Treament of **2a** (1.0 mmol, ^{31}P NMR: $\delta = 7.0$ ppm) with **1a** (1.2 mmol) in the presence of $CuCl_2$ (5 mol%) with TBHP (1.2 mmol) and K_2CO_3 (0.6 mmol) in 1,2-dichloroethane (DCE) at 80 °C for 24 hours produced diisopropyl α-hydroxybenzyl phosphonate (**3a**, ^{31}P NMR: $\delta = 19.5$ ppm) in 80% yield (Table 1,

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entry 5). No desired product was afforded without copper salt or base (entries 8, 9).

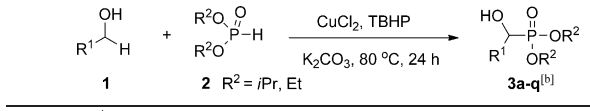
Subsequently, various reaction conditions, such as different catalysts, oxidants, bases, and solvents, were investigated for the catalytic reaction. Among the solvents tested, a good yield of the desired product **3a** was obtained using benzyl alcohol, one of the substrates, as a solvent (entry 7). Other solvents resulted in lower yields of **3a**; examples are ethyl acetate (49%) and acetonitrile (46%; see entries 1–4, 6). Under similar reaction conditions, K_2CO_3 gave the highest yield of product **3a**. Other bases such as K_3PO_4, Na_2CO_3, *t*BuOK, $NaHCO_3$, Cs_2CO_3, triethylamine, pyridine, and 4-dimethylaminopyridine (DMAP) were less effective, giving **3a** in low to moderate yields (entries 10–17). The choice of catalyst was also found to be crucial for the catalytic reaction. The best catalyst was $CuCl_2$ (entries 5, 7, and 17). $Cu(OAc)_2$, $CuSO_4$, $CuBr_2$, CuO, CuCl, CuBr, and CuI were catalytically less reactive in the model reaction (entries 18–24). TBHP exhibited a higher reactivity than other oxidants (see the Supporting Information). Reactions performed in air or under oxygen atmosphere did not lead to any detectable product as determined by ^{31}P NMR spectroscopy.

Next, we examined the reactions between various alcohols and phosphonates under the optimized conditions (Table 1, entry 5) to understand the scope of the reaction (Table 2). It was found that reactions of various benzyl alcohols with electron-donating and electron-withdrawing substitutents proceeded efficiently. Substituted benzyl alcohols with electron-donating methyl and methoxy groups on the benzene ring reacted with **2a** to provide products **3i** and **3j** in good yields. Benzyl alcohols with electron-withdrawing nitro and ester groups reacted with **2a** to provide products in slightly lower yields; for example, **3k** and **3l** were obtained in yields of 56% and 52%, respectively. This reaction is compatible with halogen substituents on the aromatic ring of benzyl alcohols **1**. Accordingly, 2-bromo-, 4-bromo-, and 4-chlorobenzyl alcohols reacted with diisopropyl *H*-phosphonate to give products **3c**, **3e**, and **3g** in 87%, 77%, and 82% yield, respectively. Compared to diethyl *H*-phosphonate and diisopropyl *H*-phosphonate, the former led to lower yields (**3d, 3f**, and **3h**) because it was easily oxidized to diethyl phosphate. With diphenylphosphine oxide, $Ph_2P(O)H$, no desired product was detected by ^{31}P NMR spectrocopy.

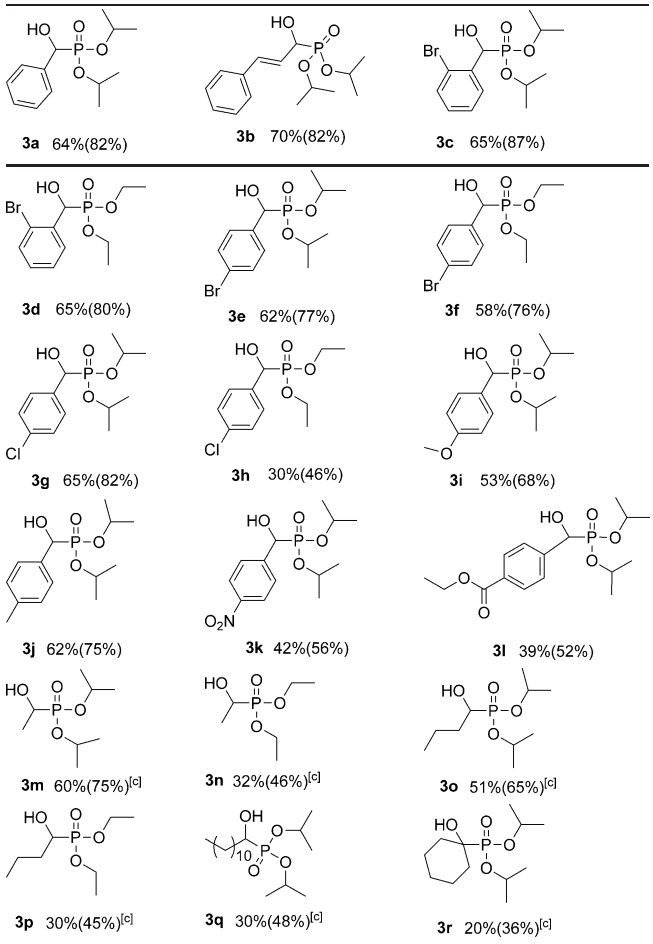
It is worth noting that aliphatic alcohols, such as ethanol, *n*-butanol, and 1-dodecanol, reacted with diisopropyl phosphonate to give the corresponding products in moderate to good yields. The isolated yield of the corresponding product decreased with increasing chain length in the normal primary aliphatic alcohols (**3m**–**3q**). A yield of 36% was obtained in the reaction of cyclohexanol (**3r**) and diisopropyl *H*-phosphonate, which was lower than that with the normal primary alcohols. We speculate that the steric hindrance and higher stability of alcohol affected the oxidation step of this tandem reaction.

Ether-containing molecules are abundant in natural products, pharmaceuticals, and materials. It is highly desirable to transfer the ether bond to other functionalized molecules in synthetic chemistry. Owing to the similar structure of the α-position (C–H) in ethers and in alcohols, we next examined the reactions of some ethers with *H*-phosphonates. Surprisingly, we found that the ring-opening of ethers such as THF afforded α-hydroxy phosphonate in 93% yield (Table 3, **4a**). Linear dialkyl ethers could also be applied to the present transformation (**4c**–**4f**), and two regioisomers were obtained when the substrates contained two ether bonds such as 1,2-dimethoxyethane and 1,2-diethoxyethane. The products **4c** and **4c′** were formed in 84% total yield with a ratio of 1:1 when 1,2-dimethoxyethane was used, while **4f** and **4f′** were obtained in 78% total yield with a ratio of 1:2 when 1,2-diethoxyethane was used. The latter result reflects the steric hindrance at C–H at the α-position in ethylene glycol dialkyl ethers. Meanwhile, when diethyl ether was reacted with diisopropyl *H*-phosphonate under the optimized reaction

Table 2. Synthesis of α-hydroxy phosphonates from alcohols and *H*-phosphonates.[a]

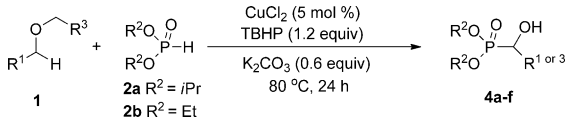


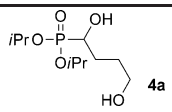
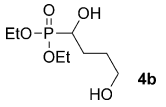
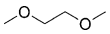
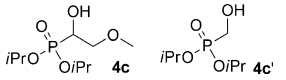
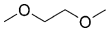
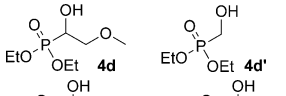
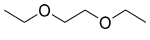
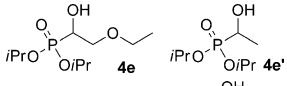
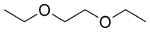
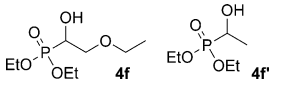
1 2 R² = *i*Pr, Et 3a-q[b]



[a] Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), K_2CO_3 (0.6 mmol), DCE (1.0 mL), TBHP (1.2 mmol), 80 °C, 24 h; [b] Isolated yields (^{31}P NMR yields in parentheses). [c] Na_2CO_3 and **1** (1.0 mL, used as the solvent) were used.

Table 3. Synthesis of α-hydroxy phosphonates from ethers and *H*-phosphonates.[a]

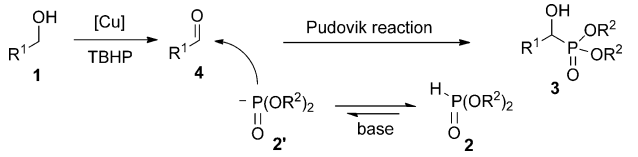


Ether	2	Product 4	4:4′	Yield [%]
	2a	 4a	–	72(93)
	2b	 4b	–	71(90)
	2a	 4c 4c′	1:1	62(84)
	2b	 4d 4d′	1:1	53(72)
	2a	 4e 4e′	1:2	46(63)
	2b	 4f 4f′	1:2	56(78)

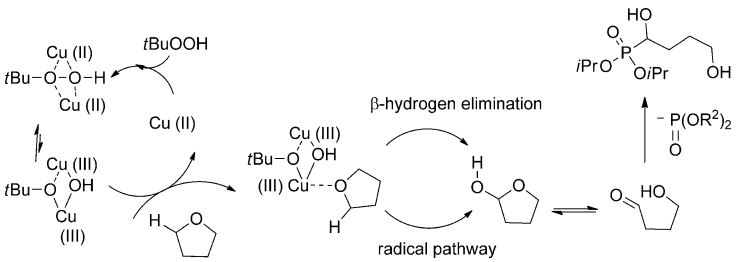
[a] Reaction conditions: **1** (1.0 mL), **2** (1.0 mmol), K_2CO_3 (0.6 mmol) and TBHP (1.2 mmol), sealed tube, 80 °C, 24 h. Isolated yields (^{31}P NMR yields in parentheses).

conditions, no desired product was detected owing to its relatively low boiling point. Unfortunately, propylene oxide, 1,4-dioxane, and tetrahydropyran showed very low reactivity under the same conditions.

The exact mechanism underlying the product formation remains unclear at present. However, on the basis of previous studies,[14] a plausible mechanism for this reaction is proposed as follows (Scheme 1): 1) Copper/TBHP-catalyzed oxidation of alcohol in situ generates an aldehyde (which was also detected by ^1H NMR spectroscopy in the reaction solution); and 2) a subsequent Pudovik reaction results in the formation of the α-hydroxy phosphonate. For the copper/TBHP-catalyzed synthesis of α-hydroxy phosphonate from tetrahydrofuran (Scheme 2), the rate of formation of **4a** was reduced by 10–20% when 1.5 equivalents of TEMPO was added to the reaction mixture. This result suggests that THF was converted into the hemiacetal via both β-hydrogen elimination and a radical pathway.



Scheme 1. Possible reaction mechanism for the synthesis of α-hydroxy phosphonates from alcohols and *H*-phosphonates.



Scheme 2. Possible reaction mechanism for the synthesis of α-hydroxy phosphonate from THF and *H*-phosphonate.

In summary, we report a simple method for the construction of a C–P bond by $CuCl_2$/TBHP-catalyzed functionalization of alcohols and ethers. The use of a green substrate and inexpensive catalyst as well as the fact that the procedure is simple make this approach valuable in synthetic chemistry. Further studies on the scope, mechanism, and synthetic applications of this reaction are currently under investigation.

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Keywords: alcohols · copper · ethers · *H*-phosphonates · α-hydroxy phosphonates

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