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Synthesis of Quaternary α-Hydroxy Phosphonates *via* Direct Hydroxylation of Phosphonate Compounds

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It was found for the first time that Cs_2CO_3 serves as highly efficient catalyst for the direct hydroxylation reactions of phosphonates under mild conditions. This reaction provides an efficient approach to quaternary α-hydroxy phosphonates, which possess intriguing biological activities and are widely used in many areas.

Keywords quaternary α-hydroxy phosphonates, molecular oxygen, direct hydroxylation

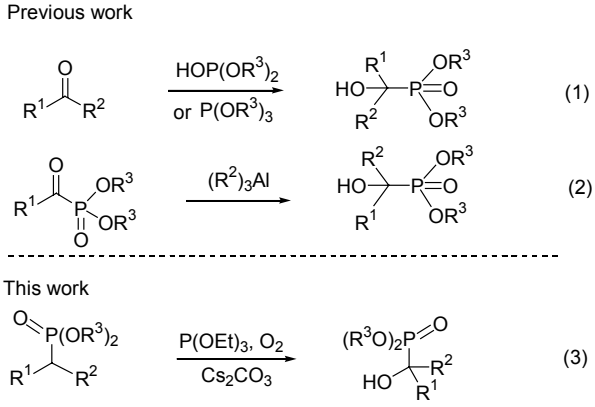
Introduction

Despite being a challenging process, direct C—H bond functionalization of unactivated sp^3-carbon atoms has received a great deal of attention in the last couple of decades. Notably, this process does not require the prefunctionalization of unactivated C(sp^3)—H bonds and the use of stoichiometric amounts of organometallic reagents, and thus is economically and ecologically favorable compared with the traditional approaches.[1] Within this reaction class, the direct hydroxylation of unactivated C(sp^3)—H bonds is of current research interest, and significant progress has been achieved in recent years.[2]

α-Hydroxy phosphonates, one important type of organic phosphoric compounds, possess intriguing biological activities and have gained widespread applications in many areas, including biological and pharmaceutical industries, due to their physical and structural similarity to biologically important phosphate esters.[3] Particularly, as analogues of quaternary α-hydroxy acids, the quaternary α-hydroxy phosphonates are of considerable value. Incorporation of α,α-disubstituted α-hydroxy phosphonates into peptides can alter their stabilization toward proteolysis as well as the conformation of the secondary structure of the corresponding proteins, which may give valuable information on enzymatic mechanisms.[4] Thus, the synthesis of quaternary α-hydroxy phosphonates has received increasing attention. Despite the numerous methods developed, the most atom-economic and straightforward method is the Pudovic reaction, *i.e.*, the nucleophilic addition of ketones with phosphites (Scheme 1, Eq. 1).[5] An alternative is reactions of acyl phosphonates with organoaluminum reagents at low temperature (Schemes 1, Eq. 2).[3f]

The use of molecular oxygen as an oxidant and oxygen-atom source for oxygen incorporation in organic synthesis has attracted considerable attention because of its atom-economical and environmentally benign character.[6] Although a significant number of transition-metal-catalyzed C—H hydroxylation reactions have been developed, practical and efficient C—H hydroxylation reactions with molecular oxygen as the oxidant and oxygen source are still desirable. Recently, Jiao and coworkers[7] reported a transition-metal-free Cs_2CO_3-catalyzed α-hydroxylation of carbonyl compounds with O_2 as the oxygen source. Based on our previous work related to dioxygen activation and using molecular oxygen as the terminal oxidant,[8] we set out to explore the use of molecular oxygen for the Cs_2CO_3-catalyzed direct hydroxylation of phosphonates to produce quaternary α-hydroxy phosphonates (Schemes 1, Eq. 3).

Scheme 1 Synthetic route to quaternary α-hydroxy phosphonates



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Experimental

Synthesis

Materials and equipment Reagents and solvents were obtained commercially and used as received. Cs_2CO_3 purity: 99.99%. IR spectra were recorded on an EQUINOX-55 spectrometer on a KBr matrix. ^1H NMR spectra were recorded on an Bruker-400 NMR spectrometer using TMS as an internal standard. GC-MS analyses were performed on a SHIMADZU QP2010. High resolution mass spectrometer (HRMS) spectra were recorded on a Bruker micrOTOF-Q II analyzer. 200－300 mesh silica gel was used for column chromatography.

Typical experimental procedure for the synthesis of title compounds An oven-dried Schlenk tube was charged with a magnetic stir-bar, phosphonates **1** (0.3 mmol), Cs_2CO_3 (0.06 mmol), $P(OEt)_3$ (0.45 mmol), DMSO (2 mL). The tube was sealed, and oxygen was purged through syringe. Reaction was stirred at 25 ℃ for 18－22 h. After the reaction was finished, the reaction mixture was diluted in 30 mL ethyl acetate, filtered on celite pad. The organic portion was washed with a saturated solution of brine (8 mL×3), dried (Na_2SO_4) and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired products **2**.

Dimethyl 1-hydroxy-1-phenylethylphosphonate (2a)[3f] ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59－7.55 (m, 2H), 7.40－7.28 (m, 3H), 4.41 (br, 1H), 3.71 (d, J=10.4 Hz, 3H), 3.58 (d, J=10.0 Hz, 3H), 1.79 (d, J=15.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.2 (d, J=0.8 Hz), 128.3 (d, J=2.0 Hz), 127.1 (d, J=2.6 Hz), 125.4 (d, J=4.1 Hz), 73.5 (d, J=159.7 Hz), 54.3 (d, J=7.3 Hz), 53.4 (d, J=7.4 Hz), 26.2 (d, J=3.2 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 26.21; IR (neat) v: 3251, 3031, 2921,1226, 1021, 990, 766 cm^{-1}; LRMS (EI 70 eV) m/z (%): 230 (M^+, 100); HRMS m/z (ESI) calcd for $C_{10}H_{16}O_4P$ $(M+H)^+$ 231.0787, found 231.0784.

Results and Discussion

We started our study by exploring the reaction between dimethyl 1-phenylethylphosphonate (**1a**) and molecular oxygen in the presence of PPh_3 (1.5 equiv.), Cs_2CO_3 (0.2 equiv.), at 25 ℃ in dimethylsufoxide (DMSO) for 20 h (Table 1, Entry 1). Gratifyingly, the desired quaternary α-hydroxy phosphonate (**2a**) was obtained in 67% yield. Different solvents were examined (Table 1, Entries 1－5). When 1,2-dichloroethane (DCE), benzene, and ethanol were used as solvents, no desired product **2a** was obtained. When DMF was used as the solvent, the desired product **2a** was obtained in 21% yield. It was found that Cs_2CO_3 was superior to other bases (Table 1, Entries 1, 6－10). The yield increased slightly when $P(OEt)_3$ was used instead of PPh_3 (Table 1, Entry 11). However, sodium *p*-toluenesulfinate only afforded the desired product **2a** in 12% yield (Table 1, Entry 12). Notably, the absence of Cs_2CO_3 resulted in no detectable amounts of α-hydroxy phosphonate **2a** (Table 1, Entry 13). Both $P(OEt)_3$ and O_2 are essential for reaction to take place (Table 1, Entries 14, 15). Interestingly, the reaction also proceeded well in the dark (Table 1, Entry 16). A moderate yield was achieved at a loading of 0.1 equiv. Cs_2CO_3 (Table 1, Entry 17). A lower amount of $P(OEt)_3$ would afford lower yields (Table 1, Entries 18, 19). Replacement of Cs_2CO_3 with $Cu(OAc)_2$, $Pd(OAc)_2$, $FeCl_3$, and Ag_2CO_3 did not give the desired quaternary α-hydroxy phosphonate **2a** (Table 1, Entries 18－21). The Fe, Ni, Pd, Cu, Ru, and Ag content in the Cs_2CO_3 used was less than δ=0.1, which indicated that this hydroxylation reaction is promoted by Cs_2CO_3 itself rather than catalyzed by trace metal impurities (ICP-MS analysis; see the Supporting Information).

Table 1 Optimization of reaction conditions[a]

Entry	Catalyst (0.2 equiv.)	Reducer (1.5 equiv.)	Solvent	Yield[b]/%
1	Cs_2CO_3	PPh_3	DMSO	67
2	Cs_2CO_3	PPh_3	DCE	0
3	Cs_2CO_3	PPh_3	PhH	0
4	Cs_2CO_3	PPh_3	DMF	21
5	Cs_2CO_3	PPh_3	EtOH	0
6	Na_2CO_3	PPh_3	DMSO	0
7	K_3PO_4	PPh_3	DMSO	trace
8	K_2CO_3	PPh_3	DMSO	trace
9	Et_3N	PPh_3	DMSO	0
10	CsOH	PPh_3	DMSO	trace
11	Cs_2CO_3	$P(OEt)_3$	DMSO	78
12[c]	Cs_2CO_3	–	DMSO	12
13	none	$P(OEt)_3$	DMSO	0
14[d]	Cs_2CO_3	$P(OEt)_3$	DMSO	0
15	Cs_2CO_3	none	DMSO	0
16[e]	Cs_2CO_3	$P(OEt)_3$	DMSO	71
17[f]	Cs_2CO_3	$P(OEt)_3$	DMSO	60
18[g]	Cs_2CO_3	$P(OEt)_3$	DMSO	66
19[h]	Cs_2CO_3	$P(OEt)_3$	DMSO	53
18	$Pd(OAc)_2$	$P(OEt)_3$	DMSO	0
19	$Cu(OAc)_2$	$P(OEt)_3$	DMSO	0
20	$FeCl_3$	$P(OEt)_3$	DMSO	0
21	Ag_2CO_3	$P(OEt)_3$	DMSO	0

[a] Reaction conditions: **1a** (0.3 mmol), Cs_2CO_3 (20 mol%), $P(OEt)_3$ (1.5 equiv.), solvent (2 mL), 25 ℃ in O_2 atmosphere for 20 h. [b] Isolated yield. [c] Sodium *p*-toluenesulfinate (0.45 mmol) was used. [d] Ar atmosphere (1 atm). [e] The reaction was carried out in the dark. [f] Cs_2CO_3 (10 mol%). [g] 1.2 equiv. of $P(OEt)_3$. [h] 1.0 equiv. of $P(OEt)_3$.

Next, we used the optimal conditions to extend the substrate scope by using a series of alternative phosphonates. As summarized in Table 2, the standard reaction conditions were found to be compatible with a wide

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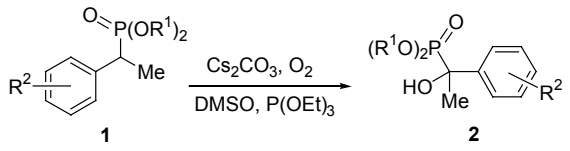
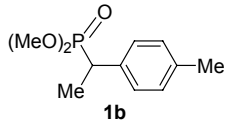
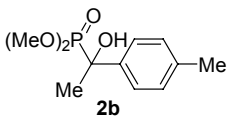
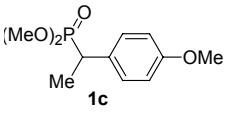
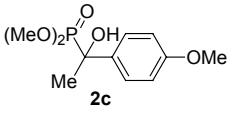
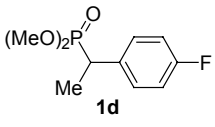
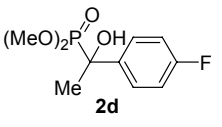
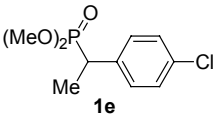
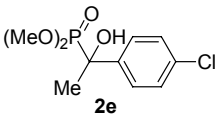
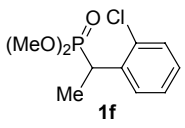
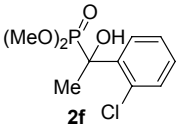
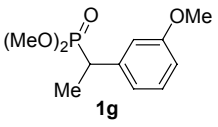
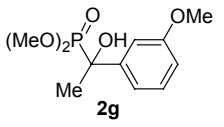
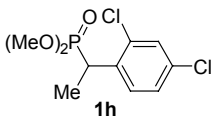
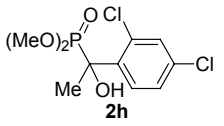
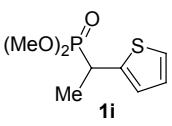
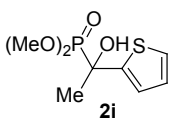
range of phosphonates **1**. These results showed that α-hydroxylation was realized in good yields irrespective of the nature and the position of the aryl substituents of the dimethyl benzylphosphonate (Table 2, Entries 1—6). Importantly, the polysubstituted phosphonate **1h** gave the desired product **2h** with a good yield (Table 2, Entry 7). Interestingly, replacement of a phenyl moiety by a 2-thienyl hardly affected the yield (Table 2, Entry 8), further extending the scope of this methodology. Gratifyingly, this direct hydroxylation protocol could also be applied to substrate **1j**, providing product **2j** in 61% yield (Table 2, Entry 9). Application of substrate **1k** with two phenyl groups, delivers the desired product in 67% yield (Table 2, Entry 10). Also, aliphatic phosphonates were viable for this reaction (Table 2, Entries 11—13).

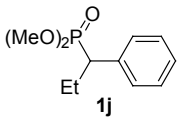
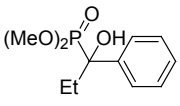
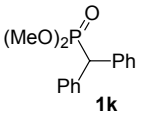
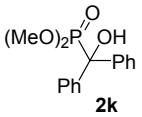
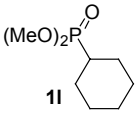
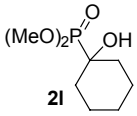
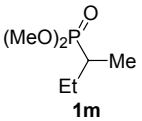
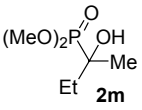
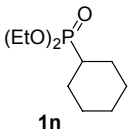
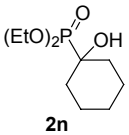
Table 2 Reaction scope of alkenes **1**[a]



1 **2**

Entry	Phosphonate	Product	Yield[b]
1	 **1b**	 **2b**	52%
2	 **1c**	 **2c**	60%
3	 **1d**	 **2d**	63%
4	 **1e**	 **2e**	58%
5	 **1f**	 **2f**	56%
6	 **1g**	 **2g**	71%
7	 **1h**	 **2h**	50%
8	 **1i**	 **2i**	66%

Continued

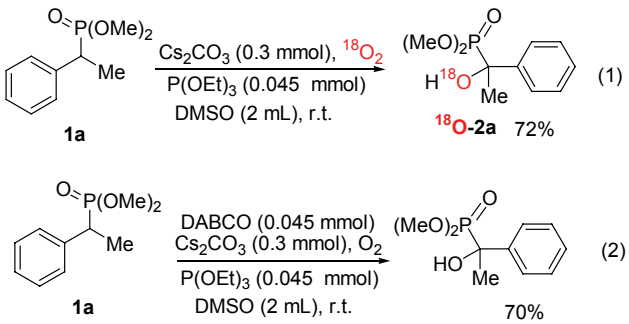
Entry	Phosphonate	Product	Yield[b]
9	 **1j**	 **2j**	61%
10	 **1k**	 **2k**	67%
11	 **1l**	 **2l**	73%
12	 **1m**	 **2m**	65%
13	 **1n**	 **2n**	51%

[a] Reaction conditions: **1** (0.3 mmol), Cs_2CO_3 (20 mol%), $P(OEt)_3$ (1.5 equiv.), DMSO (2 mL), 25 ℃ in O_2 atmosphere for 19—22 h. [b] Isolated yield.

To gain insight into the course of the reaction, we conducted a series of competition experiments. 1.0 equiv. of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a radical-trapping reagent, was added to the reaction mixture. The reaction was not inhibited, suggesting that no free radical intermediate was involved in the reaction. The results of ^{18}O labeling proved that the oxygen atom in the hydroxy group originates from molecular oxygen (Scheme 2). When the singlet oxygen inhibitor 1,4-diazabicyclo[2,2,2]octane (DABCO) was added to the model reaction, the desired quaternary α-hydroxy phosphonate **2a** was obtained in 70% yield. These results suggested that singlet molecular oxygen hardly participates in this transformation.[7]

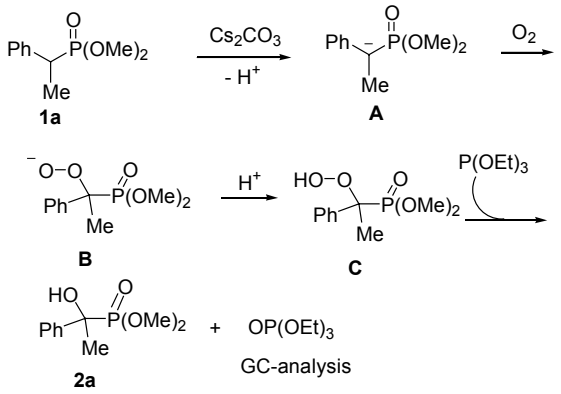
On the basis of these preliminary results and previous studies,[7] the catalytic cycle of this transformation

Scheme 2 Control experiments



was hypothesized as shown in Scheme 3. Carbanion **A** is initially generated from phosphonates **1a** with the aid of Cs_2CO_3. The resulting carbanion **A** is rapidly trapped by O_2 to give a superoxide anion **B** that in turn abstracts the hydrogen atom from phosphonates **1a** to form a superoxide **C**. Reduction of intermediate **C** by $P(OEt)_3$ would give the desired product **2a**.

Scheme 3 Plausible mechanism



Conclusions

In summary, we have developed a novel approach for the synthesis of quaternary α-hydroxy phosphonates which are highly valued chemicals and widely used in the chemical and pharmaceutical industries. The method advantageously enriches and complements the existing toolbox used by synthetic chemists, and allows a straightforward access to a wide range of functionalized products. In addition, molecular oxygen, the most environmentally friendly oxidant, was employed at a pressure of 1 atmosphere. Mechanistic, scope, and limitation studies of the reaction are in progress in our laboratory.

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