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C−H Hydroxylation of Phosphonates with Oxygen in [bmIm]OH To Produce Quaternary α-Hydroxy Phosphonates

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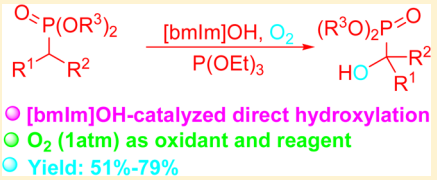
Supporting Information

ABSTRACT: A highly efficient and mild [bmIm]OH-catalyzed α-hydroxylation of phosphonates using O_2 as the oxygen source is described. The employment of ionic liquid under mild reaction conditions makes this transformation green and practical. Especially, this reaction provided a novel and convenient methodology for the construction of quaternary α-hydroxy phosphonates.



C−H bonds are ubiquitous in bioactive molecules, pharmaceuticals, natural products, and industrial materials. Although catalytic activation and subsequent functionalization of C−H bonds is very challenging, the formation of C−X (X = C, N, O, etc.) bonds by activation of C−H bonds is one of the most useful methods in organic synthesis, including the total synthesis of natural products.[1] This type of reaction is favorable, both economically and ecologically, when compared with more traditional approaches. Much current interest is focused on the direct hydroxylation of unactivated C(sp^3)−H bonds, and significant progress has been achieved in recent years.[2]

α-Hydroxy phosphonates, which have physical and structural similarities to biologically important phosphate esters, possess intriguing biological activities and have widespread applications in many areas, including the biological and pharmaceutical industries.[3] As analogues of quaternary α-hydroxy acids, quaternary α-hydroxy phosphonates, particularly, are of considerable value. Incorporation of α,α-disubstituted α-hydroxy phosphonates into peptides can alter the proteolytic stability of the peptides and can also alter the secondary structure of the corresponding proteins, which may give valuable information on enzymatic mechanisms.[4] The synthesis of quaternary α-hydroxy phosphonates has thus become a topic of great interest. Of the numerous methods that have been developed, the most straightforward and atom-economical approach is the Pudovic reaction, i.e., the nucleophilic addition of phosphites to ketones.[5] An alternative approach is the reaction of acyl phosphonates with organoaluminum reagents at low temperatures.[3f]

Over the past decades, ionic liquids (ILs) have been extensively studied and successfully applied in many areas, including organic synthesis, electrochemistry, materials chemistry, and chemical separations. ILs have distinct physical and chemical properties, which include low melting point, negligible vapor pressure, excellent solvating ability, and good recyclability.[6] There have been many reports describing the successful use of ILs as environmentally friendly or "green" solvents. ILs have also been used as catalysts or promoters in synthetic reactions, including Mannich reactions,[7] Friedel−Crafts reactions,[8] Knoevenagel condensations,[9] and Henry reactions.[10] ILs can be tailor-made for specific purposes by modifying the cations and anions, providing them with greater potential. To our knowledge, however, IL-catalyzed direct hydroxylation of phosphonates remains unknown. On the basis of our previous work on dioxygen activation and the use of molecular oxygen as the terminal oxidant,[11] we set out to explore the use of molecular oxygen for the IL-catalyzed direct hydroxylation of phosphonates (Scheme 1).[12] This reaction represents a rare example of direct hydroxylation of phosphonates and allows the highly regioselective preparation of quaternary α-hydroxy phosphonates.

We first investigated the IL-catalyzed aerobic oxidation of dimethyl 1-phenylethylphosphonate **1a** (0.3 mmol) in the presence of 1-*n*-butyl-3-methylimidazolium hydroxide ([bmIm]OH) (1.0 mmol) and $P(OEt)_3$ (2.0 equiv), at 25 °C under an O_2 atmosphere for 6 h. These conditions afforded the desired quaternary α-hydroxy phosphonate **2a** in 77% yield (Table 1, entry 1). We were surprised to find that the hydroxylation reaction also proceeded well in air (Table 1, entry 2). Other reagents, including PPh_3, $Na_2S_2O_3$, and $P(OMe)_3$, were tested and found to be less effective than $P(OEt)_3$ (Table 1, entries 3−5). The amount of $P(OEt)_3$ was found to influence the reaction; a good yield was achieved at a loading of 2.5 equiv $P(OEt)_3$ (Table 1, entries 6−8). Both $P(OEt)_3$ and O_2 are essential for the reaction to take place (Table 1, entries 9−10). No benefit was obtained by increasing the reaction time (Table 1, entry 11). Interestingly, the reaction also proceeded well in the dark (Table 1, entry 12).

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Scheme 1. Synthetic Route to Quaternary α-Hydroxy Phosphonates

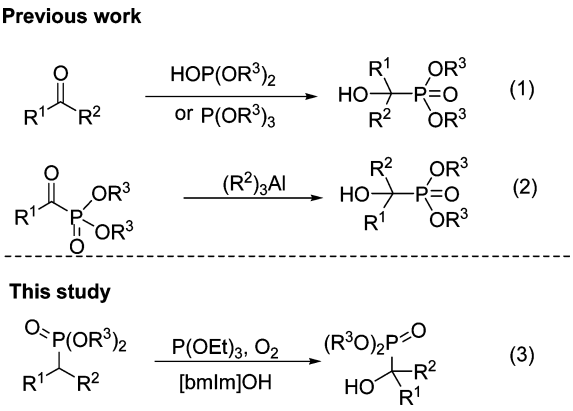
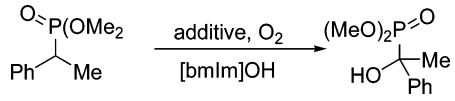


Table 1. Screening Optimal Conditions[a]

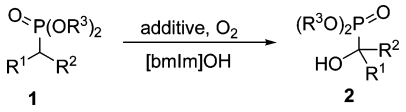


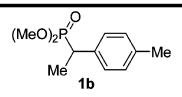
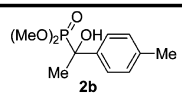
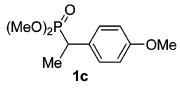
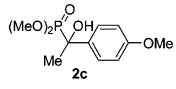
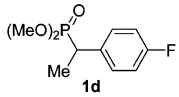
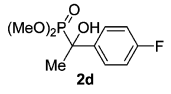
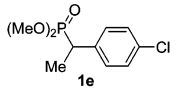
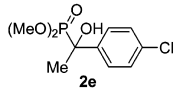
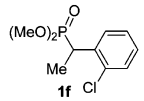
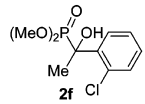
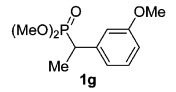
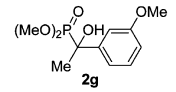
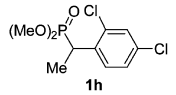
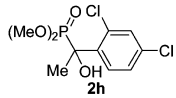
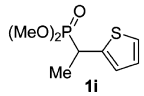
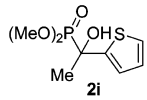
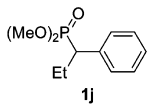
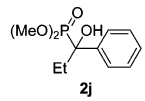
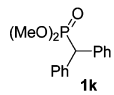
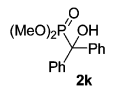
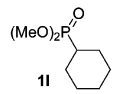
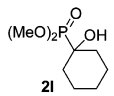
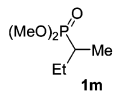
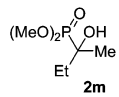
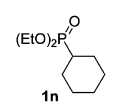
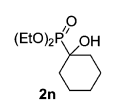
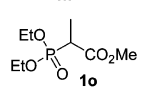
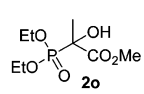
entry	additive	time	yield (%)[b]
1	$P(OEt)_3$	6 h	70
2	$P(OEt)_3$	6 h	59
3	PPh_3	6 h	62
4	$Na_2S_2O_3$	6 h	trace
5	$P(OMe)_3$	6 h	44
6[c]	$P(OEt)_3$	6 h	63
7[d]	$P(OEt)_3$	6 h	79
8[e]	$P(OEt)_3$	6 h	77
9	none	6 h	trace
10[f]	$P(OEt)_3$	6 h	0
11	$P(OEt)_3$	7 h	79
12[g]	$P(OEt)_3$	6 h	71

[a]Reaction conditions: **1a** (0.3 mmol), additive (2.0 equiv), [bmIm]-OH (1.0 mmol), 25 °C in O_2 atmosphere for 6 h. [b]Isolated yield. [c]$P(OEt)_3$ (1.5 equiv). [d]$P(OEt)_3$ (2.5 equiv). [e]$P(OEt)_3$ (3.0 equiv). [f]In Ar atmosphere. [g]The reaction was carried out in the dark.

With the standard reaction conditions defined, we next investigated the substrate scope of the reaction by employing a variety of phosphonates **1**. The standard reaction conditions were found to be compatible with a wide range of phosphonates **1** (Table 2). Several aromatic substituents, including Me, MeO, F, and Cl, were well-tolerated under the standard conditions; substituents at the ortho-, meta-, or para-positions had no distinct influence on the reaction. For example, substrates **1c** and **1g** with a MeO group were transformed into products **2c** and **2g** with similar yields. It is noteworthy that halogen groups, F and Cl, were compatible with the optimized reaction conditions, thereby enabling subsequent modifications at the halogenated positions (Table 2, entries **2d**–**2f**). Importantly, the polysubstituted phosphonate **1h** gave the desired product **2h** in good yield (Table 2, entry **2h**). The introduction of heterocyclic groups would make this methodology to be more useful for the preparation of pharmaceuticals and other commercially important materials (Table 2, entry **2i**). Gratifyingly, this direct hydroxylation protocol could also be applied to substrate **1j**, providing product **2j** in 74% yield. Reaction of substrate **1k**, with two phenyl groups, delivered the desired product in 62% yield

Table 2. Scope of Phosphonates[a,b]



entry	phosphonate **1**	product **2**	yield[b] (%)
1	 **1b**	 **2b**	70
2	 **1c**	 **2c**	64
3	 **1d**	 **2d**	61
4	 **1e**	 **2e**	56
5	 **1f**	 **2f**	54
6	 **1g**	 **2g**	60
7	 **1h**	 **2h**	51
8	 **1i**	 **2i**	77
9	 **1j**	 **2j**	74
10	 **1k**	 **2k**	62
11	 **1l**	 **2l**	58
12	 **1m**	 **2m**	70
13	 **1n**	 **2n**	56
14	 **1o**	 **2o**	51

[a]Reaction conditions: **1** (0.3 mmol), $P(OEt)_3$ (2.5 equiv), [bmIm]OH (1.0 mmol), 25 °C in O_2 atmosphere for 6 h. [b]Isolated yield.

(Table 2, entry **1k**). Satisfyingly, the reaction was also successful with aliphatic phosphonates (Table 2, entries **2l**–**2m**).

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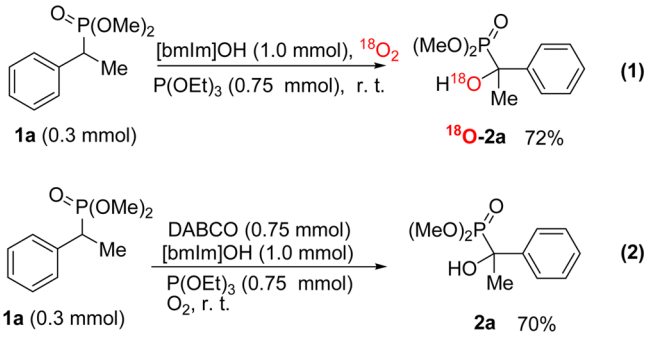
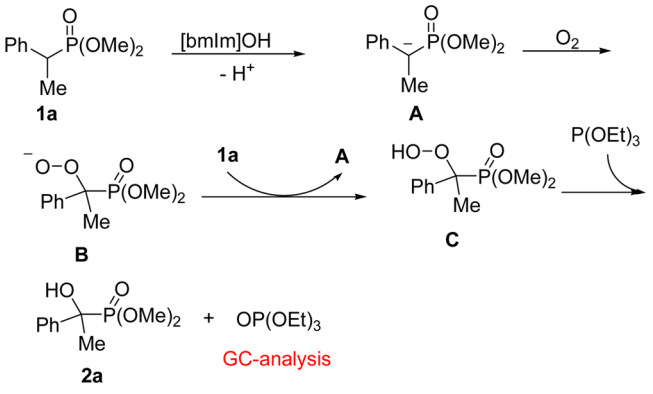
To gain an insight into the course of the reaction, we conducted a series of control experiments.[2j] Addition of a radical-trapping reagent, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (1.0 equiv), did not inhibit the reaction, suggesting that free radical intermediates are not involved. The results of ^{18}O labeling demonstrated that the oxygen atom in the hydroxy group originates from molecular oxygen. When a 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, suggesting little involvement of singlet molecular oxygen in the transformation (Scheme 2).[13]

Scheme 2. Experiments for Mechanistic Studies



On the basis of these preliminary results, and those of previous studies,[2j] we propose the catalytic cycle for this transformation shown in Scheme 3. Carbanion **A** is initially

Scheme 3. Possible Mechanism



generated from phosphonate **1a** in basic IL [bmIm]OH. The resulting carbanion **A** is rapidly trapped by O_2 to give superoxide anion **B** that, in turn, abstracts a hydrogen atom from phosphonate **1a** to form superoxide **C**. Reduction of intermediate **C** by $P(OEt)_3$ then gives the desired product **2a**. In summary, the procedure described, which uses a readily available ionic liquid, [bmIm]OH, provides an efficient and convenient procedure for direct hydroxylation of phosphonates with molecular oxygen, without a requirement for any other catalyst or organic solvent. This method offers marked improvements in terms of operational simplicity, reaction time, reaction conditions, general applicability, and good isolated yields of products. The procedure is also environmentally friendly, avoiding hazardous organic solvents and toxic catalysts, and using molecular oxygen, the "greenest" oxidant, at a pressure of 1 atm. The new process thus provides a practical and preferable, alternative to the existing procedures.

EXPERIMENTAL SECTION

Instrumentation and Chemicals. Reagents were obtained commercially and used as received. Solvents were purified and dried by standard methods. Substrates **1** were prepared according to the literature methods.[14] [bmIm]OH was prepared according to our previous reported method.[6e] All title products were characterized by infrared (IR), MS, ^1H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS). IR spectra were reported in frequency of the absorption (cm^{-1}). ^1H NMR spectra were recorded on 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard or 85% H_3PO_4 as external standard for ^{31}P NMR. Chemical shift values (δ) are given in ppm. Coupling constants (J) were measured in Hz. Mass spectra were obtained with ionization voltages of 70 eV. HRMS spectra were obtained by ESI on a TOF mass.

Typical Experimental Procedure for Synthesis of α-Hydroxy Phosphonates 2. An oven-dried Schlenk tube was charged with a magnetic stir-bar, phosphonates **1** (0.3 mmol), [bmIm]OH (1.0 mmol), and $P(OEt)_3$ (0.75 mmol). The tube was sealed, and oxygen was purged through syringe. The reaction was stirred at 25 °C for 6 h. After the reaction was finished, the reaction mixture was extracted with 30 mL of ethyl acetate. The extract was washed with brine, 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**. The ionic liquid left in the reaction vessel was rinsed with ether (2 mL) and dried under vacuum at 95 °C for 3.5 h to eliminate any water trapped from moisture and reused for subsequent reactions.

*Dimethyl 1-Hydroxy-1-phenylethylphosphonate (**2a**).*[15] Yield: 79%, 54.5 mg; ^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 cm^{-1}): 3251, 3031, 2921,1226, 1066, 1021, 990, 766; 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.

*Dimethyl 1-Hydroxy-1-p-tolylethylphosphonate (**2b**).*[15] Yield: 70%, 51.2 mg; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48 (dd, J = 8.0 Hz, J = 2.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.46 (br, 1H), 3.77 (d, J = 10.0 Hz, 3H), 3.63 (d, J = 10.0 Hz, 3H), 2.32 (d, J = 1.2 Hz, 3H), 1.83 (d, J = 15.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3 (d, J = 8.0 Hz), 136.4, 128.1, 125.2 (d, J = 4.2 Hz), 73.3 (d, J = 163.4 Hz), 54.1 (d, J = 7.7 Hz), 53.5 (d, J = 7.7 Hz), 25.7 (d, J = 3.3 Hz), 21.0; ^{31}P NMR (161 MHz, $CDCl_3$) δ: 26.64; IR (neat cm^{-1}): 3269, 2937, 1447, 1221, 1020, 941; LRMS (EI 70 ev) m/z (%): 244 (M^+, 100); HRMS m/z (ESI) calcd for $C_{11}H_{18}O_4P$ $(M + H)^+$ 245.0943, found 245.0939.

*Dimethyl 1-Hydroxy-1-(4-methoxyphenyl)ethylphosphonate (**2c**).*[15] Yield: 64%, 49.9 mg; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.43 (dd, J = 2.0 Hz, J = 8.0 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.69 (d, J = 10.0 Hz, 3H), 3.57 (d, J = 10.0 Hz, 3H), 1.76 (d, J = 15.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2 (d, J = 2.5 Hz), 132.1, 127.4 (d, J = 4.3 Hz), 113.4 (d, J = 2.0 Hz), 73.2 (d, J = 159.2 Hz), 55.4, 54.4 (d, J = 7.3 Hz), 53.2 (d, J = 7.3 Hz), 25.5 (d, J = 4.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 26.51; IR (neat cm^{-1}): 3313, 2988, 1561, 1451, 1233, 1041, 1014, 864. LRMS (EI 70 ev) m/z (%): 260 (M^+, 100); HRMS m/z (ESI) calcd for $C_{11}H_{18}O_5P$ $(M + H)^+$ 261.0893, found 261.0890.

*Dimethyl 1-(4-Fluorophenyl)-1-hydroxyethylphosphonate (**2d**).*[15] Yield: 61%, 45.4 mg; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60−7.53 (m, 2H), 7.04 (t, J = 10.0 Hz, 2H), 4.47 (br, 1H), 3.77 (d, J = 10.4 Hz, 3H), 3.64 (d, J = 10.4 Hz, 3H), 1.83 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6, 159.8, 159.1, 137.18, 137.15, 137.13, 137.12, 127.4, 127.39, 127.37, 127.32, 114.3, 114.1, 114.05, 114.03, 73.9 (d, J = 159.8 Hz), 54.7 (d, J = 7.6 Hz), 53.6 (d, J = 7.4 Hz), 26.1

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(d, J = 4.4 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 25.76; IR (neat cm^{-1}): 3401, 2992, 1500, 1426, 1221, 1125, 1067, 1023. LRMS (EI 70 ev) m/z (%): 248 (M^+, 100); HRMS m/z (ESI) calcd for $C_{10}H_{15}FO_4P$ $(M + H)^+$ 249.0693, found 249.0699.

*Dimethyl 1-(4-Chlorophenyl)-1-hydroxyethylphosphonate (**2e**).*[15] Yield: 56%, 44.3 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (dd, J = 2.0 Hz, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.49 (br, 1H), 3.69 (d, J = 10.0 Hz, 3H), 3.58 (d, J = 10.0 Hz, 3H), 1.71 (d, J = 15.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.1, 133.0 (d, J = 3.1 Hz), 128.6 (d, J = 2.2 Hz), 127.9 (d, J = 4.0 Hz), 73.1 (d, J = 159.5 Hz), 54.7 (d, J = 7.8 Hz), 53.5 (d, J = 7.6 Hz), 25.7 (d, J = 7.8 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 25.80; IR (neat cm^{-1}): 3411, 2962, 1487, 1226, 1073, 1027, 867. LRMS (EI 70 ev) m/z (%): 264 (M^+, 78); HRMS m/z (ESI) calcd for $C_{10}H_{15}ClO_4P$ $(M + H)^+$ 265.0397, found 265.0399.

*Dimethyl 1-(2-Chlorophenyl)-1-hydroxyethylphosphonate (**2f**).*[15] Yield: 54%, 42.8 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66−7.62 (m, 1H), 7.24 (dd, J = 1.2 Hz, J = 7.6 Hz, 1H), 7.19−7.14 (m, 2H), 4.46 (br, 1H), 3.68 (d, J = 10.4 Hz, 6H), 1.88 (d, J = 15.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.1 (d, J = 3.1 Hz), 131.8 (d, J = 5.3 Hz), 131.0 (d, J = 1.9 Hz), 129.4 (d, J = 3.5 Hz), 128.6 (d, J = 2.6 Hz), 126.3 (d, J = 1.7 Hz), 74.7 (d, J = 158.7 Hz), 54.4 (d, J = 7.0 Hz), 53.5 (d, J = 6.8 Hz), 25.3; ^{31}P NMR (161 MHz, $CDCl_3$) δ: 25.31; IR (neat cm^{-1}): 3381, 2949, 1448, 1402, 1225, 1118, 1054, 1037. LRMS (EI 70 ev) m/z (%): 264 (M^+, 86); HRMS m/z (ESI) calcd for $C_{10}H_{15}ClO_4P$ $(M + H)^+$ 265.0397, found 265.0400.

*Dimethyl 1-Hydroxy-1-(3-methoxyphenyl)ethylphosphonate (**2g**).*[16] Yield: 60%, 46.8 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31−7.28 (m, 1H), 7.23−7.19 (m, 2H), 6.88−6.85 (m, 1H), 4.44 (br, 1H), 3.87 (s, 3H), 3.79 (d, J = 10.4 Hz, 3H), 3.66 (d, J = 10.4 Hz, 3H), 1.81 (d, J = 15.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1 (d, J = 2.0 Hz), 142.3 (d, J = 1.2 Hz), 129.1 (d, J = 2.6 Hz), 118.7 (d, J = 4.6 Hz), 113.2 (d, J = 2.8 Hz), 110.9 (d, J = 4.3 Hz), 73.5 (d, J = 158.2 Hz), 55.7, 54.3 (d, J = 7.7 Hz), 53.2 (d, J = 7.7 Hz), 25.1 (d, J = 3.5 Hz); IR (neat cm^{-1}): 3291, 2921, 1441, 1231, 1129, 1044, 789; ^{31}P NMR (161 MHz, $CDCl_3$) δ: 25.99; IR (neat cm^{-1}): 3306, 2993, 1222, 1051, 1021, 771. LRMS (EI 70 ev) m/z (%): 260 (M^+, 100); HRMS m/z (ESI) calcd for $C_{11}H_{18}O_5P$ $(M + H)^+$ 261.0893, found 261.0898.

*Dimethyl 1-(2,4-Dichlorophenyl)-1-hydroxyethylphosphonate (**2h**).*[17] Yield: 51%, 45.6 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 6.4 Hz, 1H), 4.475(br, 1H), 3.69 (d, J = 10.4 Hz, 3H), 3.57 (d, J = 10.8 Hz, 3H), 1.85 (d, J = 15.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.3 (d, J = 4.4 Hz), 133.4 (d, J = 3.9 Hz), 132.5 (d, J = 2.0 Hz), 131.8 (d, J = 5.8 Hz), 129.9 (d, J = 3.1 Hz), 127.1 (d, J = 2.6 Hz), 73.4 (d, J = 161.9 Hz), 54.4 (d, J = 7.1 Hz), 53.6 (d, J = 7.4 Hz), 24.8 (d, J = 3.3 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 25.33; IR (neat cm^{-1}): 3284, 2960, 1469, 1247, 1108, 1053, 1019, 870. LRMS (EI 70 ev) m/z (%): 298 (M^+, 31); HRMS m/z (ESI) calcd for $C_{10}H_{14}Cl_2O_4P$ $(M + H)^+$ 299.0007, found 299.0011.

*Dimethyl 1-Hydroxy-1-(thiophen-2-yl)ethylphosphonate (**2i**).*[17] Yield: 77%, 54.5 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31−7.27 (m, 1H), 7.12−7.08 (m, 1H), 6.95−6.92 (m, 1H), 4.51 (br, 1H), 3.66 (d, J = 10.4 Hz, 3H), 3.58 (d, J = 10.4 Hz, 3H), 1.74 (d, J = 15.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.1, 142.3 (d, J = 10.1 Hz), 111.0, 108, 71.1 (d, J = 162.9 Hz), 54.3 (d, J = 7.5 Hz), 53.1 (d, J = 7.1 Hz), 23.1 (d, J = 2.8 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 24.67; IR (neat cm^{-1}): 3266, 2930, 1440, 1224, 1151, 1042, 1020, 862. LRMS (EI 70 ev) m/z (%): 236 (M^+, 100); HRMS m/z (ESI) calcd for $C_8H_{14}O_4PS$ $(M + H)^+$ 237.0350, found 237.0354.

*Dimethyl 1-Hydroxy-1-phenylpropylphosphonate (**2j**).*[16] Yield: 74%, 54.2 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52−7.49 (m, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.23−7.20 (m, 1H), 4.43 (br, 1H), 3.69 (d, J = 10.0 Hz, 6H), 2.61−2.27 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.7, 127.8 (d, J = 3.0 Hz), 127.0 (d, J = 3.3 Hz), 125.8 (d, J = 4.3 Hz), 75.7 (d, J = 158.6 Hz), 54.6 (d, J = 7.5 Hz), 53.1 (d, J = 7.3 Hz), 29.6 (d, J = 4.3 Hz), 9.1 (d, J = 8.9 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 25.29; IR (neat cm^{-1}): 3256, 2969, 1429, 1231, 1052, 1017, 827. LRMS (EI 70 ev) m/z (%): 244 (M^+, 100); HRMS m/z (ESI) calcd for $C_{11}H_{18}O_4P$ $(M + H)^+$ 245.0943, found 245.0944.

*Dimethyl Hydroxydiphenylmethylphosphonate (**2k**).*[17] Yield: 62%, 54.3 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J = 7.6 Hz, 4H), 7.37−7.31 (m, 4H), 7.23−7.20 (m, 2H), 4.51 (br, 1H), 3.71 (d, J = 10.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.4 (d, J = 1.4 Hz), 127.7 (d, J = 2.3 Hz), 127.0 (d, J = 3.1 Hz), 126.5 (d, J = 4.2 Hz), 75.8 (d, J = 254.6 Hz), 54.8 (d, J = 7.0 Hz), 53.4 (d, J = 7.8 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 23.53; IR (neat cm^{-1}): 3260, 2959, 1444, 1235, 1120, 1043, 761. LRMS (EI 70 ev) m/z (%): 292 (M^+, 100); HRMS m/z (ESI) calcd for $C_{15}H_{18}O_4P$ $(M + H)^+$ 293.0944, found 293.0947.

*Dimethyl 1-Hydroxycyclohexylphosphonate (**2l**).*[18] Yield: 58%, 36.2 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.48 (br, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 1.85 (t, J = 10.2 Hz, 2H), 1.68−1.31 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.8 (d, J = 164.0 Hz), 53.3 (d, J = 7.5 Hz), 31.1 (d, J = 2.8 Hz), 25.1, 19.7 (d, J = 11.3 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 26.43; IR (neat cm^{-1}): 3331, 2987, 1230, 1144, 1065, 1034, 1019. LRMS (EI 70 ev) m/z (%): 208 (M^+, 100); HRMS m/z (ESI) calcd for $C_8H_{18}O_4P$ $(M + H)^+$ 209.0945, found 209.0947.

*Dimethyl 2-Hydroxybutan-2-ylphosphonate (**2m**).*[15] Yield: 70%, 38.2 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.49 (br, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 1.85−1.81 (m, 1H), 1.69−1.62 (m, 1H), 1.33 (d, J = 15.6 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.3 (d, J = 161.2 Hz), 54.5 (d, J = 6.8 Hz), 53.1 (d, J = 5.9 Hz), 29.2 (d, J = 5.0 Hz), 21.5 (d, J = 4.4 Hz), 7.1 (d, J = 8.0 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 30.10; IR (neat cm^{-1}): 3300, 2939, 1452, 1227, 1132, 1057, 1020; LRMS (EI 70 ev) m/z (%): 182 (M^+, 100); HRMS m/z (ESI) calcd for $C_6H_{16}O_4P$ $(M + H)^+$ 183.0791, found 183.0797.

*Diethyl 1-Hydroxycyclohexylphosphonate (**2n**).*[19] Yield: 56%, 39.6 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.16−4.09 (m, 4H), 3.37 (br, 1H), 1.86 (t, J = 9.5 Hz, 2H), 1.68−1.60 (m, 5H), 1.52−1.49 (m, 2H), 1.31−1.27 (m, 6H), 1.20−1.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.7 (d, J = 163.9 Hz), 62.6 (d, J = 7.4 Hz), 31.4, 25.2, 20.0 (d, J = 11.0 Hz), 16.4 (d, J = 5.4 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 26.73; IR (neat cm^{-1}): 3310, 2983, 2911, 1371, 1232, 1133, 1050, 1026. LRMS (EI 70 ev) m/z (%): 236 (M^+, 100); HRMS m/z (ESI) calcd for $C_{10}H_{22}O_4P$ $(M + H)^+$ 237.1257, found 237.1261.

*Methyl 1-(Ethoxyphosphono)-1-hydroxyethanoate (**2o**).* Yield: 51%, 36.7 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.50 (br, 1H), 4.19−4.11 (m, 4H), 3.89 (s, 3H), 1.77 (d, J = 15.2 Hz, 3H), 1.33−1.29 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8 (d, J = 3.8 Hz), 79.9 (d, J = 139.3 Hz), 61.8 (d, J = 6.9 Hz), 61.6 (d, J = 7.4 Hz), 52.0 (d, J = 7.2 Hz), 16.2 (d, J = 3.2 Hz), 16.1 (d, J = 3.2 Hz), 11.7 (d, J = 5.9 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ: 23.33; IR (neat cm^{-1}): 3307, 2981, 1725, 1240, 1113, 1048, 1014. LRMS (EI 70 ev) m/z (%): 240 (M^+, 100); HRMS m/z (ESI) calcd for $C_8H_{18}O_6P$ $(M + H)^+$ 241.0767, found 241.0764.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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