Catalytic Aerobic Synthesis of Quaternary α-Hydroxy phosphonates via Direct Hydroxylation of Phosphonate Compounds

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(A) Materials and equipment

Reagents were obtained commercially and used as received. Solvents were purified and dried by standard methods. For substrates 1 were prepared according the literature methods.\textsuperscript{1} \textsuperscript{1}H NMR spectra were recorded on a Bruker-400 NMR spectrometer using TMS as an internal standard. Chemical shift values (\(\delta\)) are given in ppm. Coupling constants (\(J\)) were measured in Hz. 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.

(B) Typical experimental procedure

Typical experimental procedure for the synthesis of quaternary \(\alpha\)-hydroxy phosphonates

An oven-dried Schlenk tube was charged with a magnetic stir-bar, phosphonates 1 (0.3 mmol), CuCl\(_2\cdot\)2H\(_2\)O (0.045 mmol), NHPI (0.03 mmol), PPh\(_3\) (0.36 mmol), CH\(_3\)CN (2 mL), The tube was sealed, and oxygen was purged through syringe. Reaction was stirred at 100 °C for 8-10 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 \(\times\) 3), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired products 2.

(C) Labeling experiments

Reaction conditions: 1a (0.3 mmol), CuCl\(_2\cdot\)2H\(_2\)O (5 mol%), NHPI (10 mol%), CH\(_3\)CN (2.0 mL), 100 °C in \(^{18}\)O\(_2\) atmosphere (1 atm) for 10 h.

The HRMS spectra of 2a for the reaction under \(^{18}\)O\(_2\) (95%).
(D) Analytical data

Dimethyl 1-hydroxy-1-phenylethylphosphonate (2a): [2]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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\(_3\)) \(\delta\):
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\(_3\)) \( \delta \): 26.21; IR (neat cm\(^{-1}\)): 3251, 3031, 2921, 1226, 1021, 990, 766; LRMS (EI 70 ev) \( m/z \) (%): 230 (M\(^+\), 100); HRMS \( m/z \) (ESI) calcd for C\(_{10}\)H\(_{16}\)O\(_4\)P (M+H\(^+\)) 231.0787, found 231.0784.

**Dimethyl 1-hydroxy-1-p-tolylethylphosphonate (2b):**

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 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\(_3\)) \( \delta \): 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; IR (neat cm\(^{-1}\)): 3269, 2937, 1447, 1221, 1020, 941; \(^{31}\)P NMR (161 MHz, CDCl\(_3\)) \( \delta \): 26.64; LRMS (EI 70 ev) \( m/z \) (%): 244 (M\(^+\), 100); HRMS \( m/z \) (ESI) calcd for C\(_{11}\)H\(_{18}\)O\(_4\)P (M+H\(^+\)) 245.0943, found 245.0939.

**Dimethyl 1-hydroxy-1-(4-methoxyphenyl)ethylphosphonate (2c):**

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 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\(_3\)) \( \delta \): 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\(_3\)) \( \delta \): 26.51; LRMS (EI 70 ev) \( m/z \) (%): 260 (M\(^+\), 100); HRMS \( m/z \) (ESI) calcd for C\(_{11}\)H\(_{18}\)O\(_5\)P (M+H\(^+\)) 261.0893, found 261.0890.

**Dimethyl 1-(4-fluorophenyl)-1-hydroxyethylphosphonate (2d):**

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 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\(_3\)) \( \delta \): 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 (d, \( J = 4.4 \) Hz);
**Dimethyl 1-(4-chlorophenyl)-1-hydroxyethylphosphonate (2e):**

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta: 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 \text{ NMR (100 MHz, CDCl}_3) \delta: 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 \text{ NMR (161 MHz, CDCl}_3) \delta: 25.80; \text{ LRMS (EI 70 ev)} m/z (%): 264 (M^+ , 78); \text{ HRMS m/z (ESI) calcd for C}_{10}H_{15}ClO_4P (M+H)^+ 265.0397, found 265.0399.**

**Dimethyl 1-(4-acetylphenyl)-1-hydroxyethylphosphonate (2f):**

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta: 7.97 (dd, J = 7.2 Hz, J = 1.2 Hz, 2H), 7.29 (d, J = 7.2 Hz, 2H), 4.47 (br, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.61 (s, 3H), 1.78 (d, J = 15.2 Hz, 3H); ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta: 198.7, 138.0 (d, J = 4.4 Hz), 133.4 (d, J = 2.4 Hz), 129.0 (d, J = 2.6 Hz), 128.6 (d, J = 3.7 Hz), 73.6 (d, J = 157.3 Hz), 54.5 (d, J = 7.1 Hz), 53.5 (d, J = 7.2 Hz), 26.3, 24.6 (d, J = 3.3 Hz). ^{31}P \text{ NMR (161 MHz, CDCl}_3) \delta: 24.59; \text{ IR (neat cm}^{-1}): 3262, 2963, 1657, 1604, 1221, 1063, 1027, 979; \text{ LRMS (EI 70 ev) m/z (%): 272 (M^+ , 100); HRMS m/z (ESI) calcd for C}_{12}H_{18}O_5P (M+H)^+ 273.0893, found 273.0891.**

**Dimethyl 1-(2-chlorophenyl)-1-hydroxyethylphosphonate (2g):**

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta: 7.66-7.62 (m, 1H), 7.24 (dd, J = 1.2 Hz, J = 7.6 Hz, 1H), 7.19-7.14 (m, 2H), 4.46 (br, 1H), 3.68 (d, J = 10.4 Hz, 6H), 1.88 (d, J = 15.2 Hz, 3H); ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta: 137.1 (d, J = 3.1 Hz), 131.8 (d, J = 5.3 Hz), 131.0 (d, J = 1.9 Hz), 129.4 (d, J = 3.5 Hz), 128.6 (d, J = 2.6 Hz), 126.3 (d, J = 1.7 Hz), 74.7 (d, J = 158.7 Hz), 54.4 (d, J = 7.0 Hz), 53.5 (d, J = 6.8 Hz), 25.3; ^{31}P \text{ NMR (161 MHz, CDCl}_3) \delta: 25.31; \text{ LRMS (EI 70 ev) m/z (%): 264 (M^+ , 86); HRMS m/z} \]
Dimethyl 1-hydroxy-1-(3-methoxyphenyl)ethylphosphonate (2h): ³

¹H NMR (400 MHz, CDCl₃) δ: 7.31-7.28 (m, 1H), 7.23-7.19 (m, 2H), 6.88-6.85 (m, 3H), 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); ¹³C NMR (100 MHz, CDCl₃) δ: 159.1 (d, J = 2.3 Hz), 142.3 (d, J = 1.1 Hz), 129.1 (d, J = 1.8 Hz), 118.7 (d, J = 4.5 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 = 7.1 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; ³¹P NMR (161 MHz, CDCl₃) δ: 25.99; LRMS (EI 70 ev) m/z (%): 260 (M⁺, 100); HRMS m/z (ESI) calcd for C₁₁H₁₈O₅P (M+H)⁺ 261.0893, found 261.0898.

Dimethyl 1-(2,4-dichlorophenyl)-1-hydroxyethylphosphonate (2i): ⁴

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ³¹P NMR (161 MHz, CDCl₃) δ: 25.33; LRMS (EI 70 ev) m/z (%): 298 (M⁺, 31); IR (neat cm⁻¹): 3277, 2966, 1441, 1227, 1033, 853, 790; HRMS m/z (ESI) calcd for C₁₀H₁₄Cl₂O₄P (M+H)⁺ 299.0007, found 299.0011.

Dimethyl 1-hydroxy-1-(thiophen-2-yl)ethylphosphonate (2j): ⁴

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ³¹P NMR (161 MHz, CDCl₃) δ: 24.67; LRMS (EI 70 ev) m/z
%: 236 (M⁺, 100); HRMS m/z (ESI) calcd for C₈H₁₄O₄PS (M+H)⁺ 237.0350, found 237.0354.

![2k](image)

**Dimethyl 1-hydroxy-1-phenylpropylphosphonate (2k):**

$^1$H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) δ: 25.29; LRMS (EI 70 ev) m/z (%): 244 (M⁺, 100); HRMS m/z (ESI) calcd for C₁₁H₁₈O₄P (M+H)⁺ 245.0944, found 245.0944.

![2l](image)

**Dimethyl hydroxydiphenylmethylphosphonate (2l):**

$^1$H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) δ: 23.53; LRMS (EI 70 ev) m/z (%): 292 (M⁺, 100); HRMS m/z (ESI) calcd for C₁₅H₁₈O₄P (M+H)⁺ 293.0944, found 293.0947.

![2m](image)

**Dimethyl 1-hydroxycyclohexylphosphonate (2m):**

$^1$H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) δ: 26.43; LRMS (EI 70 ev) m/z (%): 208 (M⁺, 100); HRMS m/z (ESI) calcd for C₈H₁₈O₄P (M+H)⁺ 209.0945, found 209.0947.

![2n](image)

**Dimethyl 2-hydroxybutan-2-ylphosphonate (2n):**


\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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\(_3\)) \(\delta\): 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\(_3\)) \(\delta\): 30.10; IR (neat cm\(^{-1}\)): 3300, 2939, 1452, 1227, 1132, 1020; LRMS (EI 70 ev) \(m/z\) (%): 182 (M\(^+\), 100); HRMS \(m/z\) (ESI) calcd for C\(_6\)H\(_{16}\)O\(_4\)P (M+H)\(^+\) 183.0791, found 183.0797.

(EtO)\(_2\)POH

Diethyl 1-hydroxycyclohexylphosphonate (2o):

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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\(_3\)) \(\delta\): 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\(_3\)) \(\delta\): 26.73; LRMS (EI 70 ev) \(m/z\) (%): 236 (M\(^+\), 100); HRMS \(m/z\) (ESI) calcd for C\(_{10}\)H\(_{22}\)O\(_4\)P (M+H)\(^+\) 237.1257, found 237.1261.

(E) References


$^{1}H$ NMR of Compound 2a
$^{13}$C NMR of Compound 2a
$^1$H NMR of Compound 2b
\(^{13}\text{C} \text{NMR of Compound 2b}\)
$^{13}$C NMR of Compound 2c
$^1$H NMR of Compound 2d
$^{13}$C NMR of Compound 2d
"$^1$H NMR of Compound 2e"
$^{13}$C NMR of Compound 2e
\( ^1\text{H NMR of Compound 2f} \)
$^{13}$C NMR of Compound 2f
$^1$H NMR of Compound 2g
$^{13}$C NMR of Compound 2g
H NMR of Compound 2h
$^{13}$C NMR of Compound 2h
$^1$H NMR of Compound 2i
$^{13}$C NMR of Compound 2i
$^1$H NMR of Compound 2j
$^{13}$C NMR of Compound 2j
$^1$H NMR of Compound 2k
$^{13}$C NMR of Compound 2k
1H NMR of Compound 2
$^{13}$C NMR of Compound 21
$^1$H NMR of Compound 2m
$^{13}$C NMR of Compound 2m
$^1$H NMR of Compound 2n
$^{13}$C NMR of Compound 2n
$^1$H NMR of Compound 2o
$^{13}$C NMR of Compound 2o
$^{31}$P NMR of Compound 2a

$^{31}$P NMR of Compound 2b
$^{31}$P NMR of Compound 2c

$^{31}$P NMR of Compound 2d
$^{31}$P NMR of Compound 2c

$^{31}$P NMR of Compound 2f
$^{31}$P NMR of Compound 2g

$^{31}$P NMR of Compound 2h
$^{31}\text{P NMR of Compound 2i}$

$^{31}\text{P NMR of Compound 2j}$
$^{31}$P NMR of Compound 2k

$^{31}$P NMR of Compound 2l
$^{31}\text{P NMR of Compound 2m}$

$^{31}\text{P NMR of Compound 2n}$
$^{31}$P NMR of Compound 2o