Pd-Catalyzed Carbonylative Access to Aroyl Phosphonates from (Hetero)Aryl Bromides

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Supporting Information

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**General Method**

All reactions were setup using the commercially available COware two chamber system, with self-sealing PTFE/silicon septa. All purchased chemicals were used as received without further purification. Chemicals were purchased from Sigma-Aldrich. All Dry solvents were afforded by adding activated 4Å molecular sieves and purging rigorously with argon. HPLC grade solvents were purchased from Sigma-Aldrich. Flash chromatography was carried out on silica gel 60 (230–400 mesh). $^1$H NMR spectra were recorded at 400 MHz, $^{13}$C NMR spectra were recorded at 100 MHz, $^{19}$F NMR spectra were recorded at 376 MHz and $^{31}$P NMR spectra were recorded at 162 MHz on a Bruker Ascend 400 spectrometer. Chemical shifts were reported in ppm downfield to TMS ($\delta = 0$) and referenced to the solvent residual peak, using the following peak pattern abbreviations: br, broad; s, single; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; td, triplet of doublets. MS spectra were recorded on a LC TOF (ESI) apparatus.

**General procedure A: Phosphinocarbonylation of Aromatic Bromides.**

Chamber 1: In an argon filled glovebox, to chamber 1 of a COware two-chamber system, was added aryl bromides $^1$ (0.60 mmol), H-Phosphonate $^2$ (0.40 mmol), Pd(dba)$_2$ (11.6 mg, 0.02 mmol), XantPhos (11.6 mg, 0.02 mmol), dioxane (4.0 mL) and triethylamine (0.084 mL, 0.6 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. Chamber 2 (1.5 equiv CO): To chamber 2 of the two-chamber system was added 9-methylfluorene-9-carbonyl chloride (146 mg, 0.6 mmol), Pd(dba)$_2$ (17.4 mg, 0.03 mmol), HBF$_4$·$P(t$Bu)$_3$ (17.4 mg, 0.06 mmol), dioxane (4.0 mL) and triethylamine (0.168 mL, 0.12 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. The loaded two-chamber system was removed from the glovebox and stirred at 70, 80 or 90 °C for 16 h. After this period, the reaction was cooled to room temperature and filtrated through cotton to remove salt. The volatiles were removed under reduced pressure. The crude residue was subjected to flash column chromatography using pentane/ethyl acetate as eluent to afford the desired products 3. (Note: some aroylphosphonates are unstable on silica gel and brake down slowly during purification)

**diethyl (4-methoxybenzoyl)phosphonate (3a)**

Prepared according to procedure A at 90 °C; isolated as colorless liquid (86 mg, 79%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.29 (d, $J$=9.0 Hz, 2H), 6.98 (d, $J$=9.0 Hz, 2H), 4.31 – 4.23 (m, 4H), 3.90 (s, 3H), 1.38 (t, $J$=7.1 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 196.5 (d, $J$=174.1 Hz), 164.9, 132.5 (2C), 129.0 (d, $J$=65.3 Hz), 114.1 (2C), 63.8 (d, $J$=7.2 Hz, 2C), 55.6, 16.4 (d, $J$=5.8 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -0.71 (p, $J$=7.8 Hz). HRMS C$_{12}$H$_{17}$PO$_5$ [M+H]$^+$; calculated 273.0892, found: 273.0889.
diethyl (3-methoxybenzoyl)phosphonate (3b)

Prepared according to procedure A at 80 °C; isolated as colorless liquid (79 mg, 73%) using pentane/ethyl acetate (2:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.97 (ddd, $J$=7.6, 1.4, 1.0 Hz, 1H), 7.70 (dd, $J$=2.5, 1.6 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.19 (ddd, $J$=8.3, 2.7, 0.9 Hz, 1H), 4.33 – 4.24 (m, 4H), 3.86 (s, 3H), 1.39 (t, $J$=7.1 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 198.7 (d, $J$=175.6 Hz), 159.8, 136.8 (d, $J$=63.8 Hz), 129.9, 123.2, 121.9, 112.6 (d, $J$=2.9 Hz), 64.0 (d, $J$=7.2 Hz, 2C), 55.4, 16.4 (d, $J$=5.7 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = -1.32 (p, $J$=8.0 Hz). HRMS C$_{12}$H$_{17}$PO$_5$ [M+H]$^+$; calculated 273.0892, found: 273.0890.

diethyl (4-methylbenzoyl)phosphonate (3c)

Prepared according to procedure A at 90 °C; isolated as colorless liquid (81 mg, 80%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.19 (d, $J$=8.2 Hz, 2H), 7.32 (d, $J$=8.0 Hz, 2H), 4.28 (p, $J$=7.2 Hz, 4H), 2.44 (s, 3H), 1.39 (t, $J$=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 198.3 (d, $J$=174.0 Hz), 146.0, 133.3 (d, $J$=63.9 Hz), 130.0 (2C), 129.5 (2C), 63.9 (d, $J$=7.2 Hz, 2C), 21.93, 16.4 (d, $J$=5.7 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = -0.98 (p, $J$=7.9 Hz). HRMS C$_{12}$H$_{17}$PO$_4$ [M+H]$^+$; calculated 257.0943, found: 257.0940.

diethyl (4-(tert-butyl)benzoyl)phosphonate (3d)

Prepared according to procedure A at 90 °C; isolated as colorless liquid (82 mg, 69%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.23 (d, $J$=8.6 Hz, 2H), 7.54 (d, $J$=7.6 Hz, 2H), 4.29 (p, $J$=7.2 Hz, 4H), 1.40 (t, $J$=7.2 Hz, 6H), 1.36 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 198.3 (d, $J$=173.8 Hz), 158.8, 133.1 (d, $J$=63.8 Hz), 129.8 (d, $J$=1.7 Hz, 2C), 125.8 (2C), 63.9 (d, $J$=7.3 Hz, 2C), 35.3, 30.9 (3C), 16.4 (d, $J$=5.7 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -0.92 (p, $J$=7.9 Hz). HRMS C$_{15}$H$_{23}$PO$_4$ [M+H]$^+$; calculated 299.1412, found: 299.1412.
diethyl (4-(dimethylamino)benzoyl)phosphonate (3e)

![Chemical Structure of 3e]

Prepared according to procedure A at 90 °C; isolated as colorless liquid (104 mg, 92%) using pentane/ethyl acetate (1:1) as eluent. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.20 (d, \(J=9.2\) Hz, 2H), 6.65 (d, \(J=9.2\) Hz, 2H), 4.24 (p, \(J=7.2\), 4H), 3.08 (s, 6H), 1.36 (t, \(J=7.2\) Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 194.2 (d, \(J=170.8\) Hz), 154.4, 132.5 (d, \(J=2.5\) Hz, 2C), 124.2 (d, \(J=66.5\) Hz), 110.7 (2C), 63.5 (d, \(J=7.1\) Hz, 2C), 40.0 (2C), 16.4 (d, \(J=5.8\) Hz, 2C). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) (ppm) 0.72 (p, \(J=7.8\) Hz). HRMS C\(_{13}\)H\(_{20}\)PNO\(_4\) [M+H]\(^+\); calculated 286.1208, found: 286.1208.

diethyl (3,4-dimethoxybenzoyl)phosphonate (3f)

![Chemical Structure of 3f]

Prepared according to procedure A at 90 °C; isolated as slight yellow liquid (106 mg, 88%) using ethyl acetate as eluent. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.18 (dd, \(J=8.5, 1.9\) Hz, 1H), 7.67 (d, \(J=1.8\) Hz, 1H), 6.95 (d, \(J=8.5\) Hz, 1H), 4.27 (p, \(J=7.2\) Hz, 4H), 3.97 (s, 3H), 3.94 (s, 3H), 1.38 (t, \(J=7.2\) Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 196.6 (d, \(J=174.6\) Hz), 154.9, 149.2 (d, \(J=2.6\) Hz), 129.1 (d, \(J=66.1\) Hz), 126.7, 110.4, 110.3, 63.9 (d, \(J=7.2\) Hz, 2C), 56.2, 55.9, 16.4 (d, \(J=5.8\) Hz, 2C). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) (ppm) -0.72 (p, \(J=7.9\) Hz). HRMS C\(_{13}\)H\(_{19}\)PO\(_6\) [M+H]\(^+\); calculated 303.0997, found: 303.0997.

diethyl benzoylphosphonate (3g)

![Chemical Structure of 3g]

Prepared according to procedure A at 80 °C; isolated as colorless liquid (72 mg, 75%) using pentane/ethyl acetate (2:1) as eluent. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.30 – 8.26 (m, 2H), 7.68 – 7.62 (m, 1H), 7.55 – 7.49 (m, 2H), 4.36 – 4.22 (m, 4H), 1.39 (t, \(J=7.0\) Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 198.9 (d, \(J=175.1\) Hz), 135.5 (d, \(J=63.4\) Hz), 134.7, 129.8 (2C), 128.8 (2C), 64.1 (d, \(J=7.3\) Hz, 2C), 16.4 (d, \(J=5.7\) Hz, 2C). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) = -1.32 (p, \(J=7.9\) Hz). HRMS C\(_{11}\)H\(_{15}\)PO\(_4\) [M+H]\(^+\); calculated 243.0786, found: 243.0783.
diethyl (4-fluorobenzoyl)phosphonate (3h)

[Chemical structure image]

Prepared according to procedure A at 70 °C; isolated as yellow liquid (63 mg, 61%) using pentane/ethyl acetate (2:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.42 – 8.29 (m, 2H), 7.23 – 7.18 (m, 2H), 4.34 – 4.26 (p, $J$=7.2 Hz, 4H), 1.41 (t, $J$=7.2 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm) 197.3 (d, $J$=176.9 Hz), 166.7 (d, $J$=258.3 Hz), 132.8 (d, $J$=10.0 Hz, 2C), 132.1 (dd, $J$=64.7, 2.6 Hz), 116.2 (d, $J$=22.1 Hz, 2C), 64.1 (d, $J$=7.3 Hz, 2C), 16.4 (d, $J$=5.6 Hz, 2C). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm) -101.3 (m). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -1.73 (p, $J$=8.0 Hz). HRMS C$_{11}$H$_{14}$PFO$_4$ [M+H]$^+$; calculated 261.0692, found: 261.0690.

diethyl (4-chlorobenzoyl)phosphonate (3i)

[Chemical structure image]

Prepared according to procedure A at 70 °C; isolated as yellow liquid (68 mg, 62%) using pentane/ethyl acetate (2:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.16 (d, $J$=8.4 Hz, 2H), 7.42 (d, $J$=8.4 Hz, 2H), 4.21 (p, $J$=7.2 Hz, 4H), 1.31 (t, $J$=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 197.9 (d, $J$=177.6 Hz), 141.5, 133.9 (d, $J$=64.3 Hz), 131.2 (d, $J$=1.5 Hz, 2C), 129.2 (2C), 64.2 (d, $J$=7.3 Hz, 2C), 16.4 (d, $J$=5.7 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -1.73 (p, $J$=8.0 Hz). HRMS C$_{11}$H$_{14}$ClPO$_4$ [M+H]$^+$; calculated 277.0396, found: 277.0396.

diethyl (1,1'-biphenyl)-4-carbonylphosphonate (3j)

[Chemical structure image]

Prepared according to procedure A at 70 °C; isolated as yellow liquid (97 mg, 77% from ArBr or 86 mg, 68% from ArOTf) using pentane/ethyl acetate (3:2) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.28 (d, $J$=8.5 Hz, 2H), 7.66 (d, $J$=7.5 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.40 (t, $J$=7.3 Hz, 2H), 7.37 – 7.31 (m, 1H), 4.23 (p, $J$=7.2 Hz, 4H), 1.33 (t, $J$=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 198.4 (d, $J$=175.1 Hz), 147.4, 139.5, 134.3 (d, $J$=63.9 Hz), 130.5 (2C), 129.0 (2C), 128.6, 127.4 (2C), 127.3 (2C), 64.0 (d, $J$=7.2 Hz, 2C), 16.5 (d, $J$=5.7 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -1.15 (p, $J$=7.9 Hz). HRMS C$_{17}$H$_{19}$PO$_4$ [M+H]$^+$; calculated 319.1099, found: 319.1100.
diethyl (3-acetylbenzoyl)phosphonate (3k)

![Chemical structure of diethyl (3-acetylbenzoyl)phosphonate](diethyl_3-acetylbenzoyl_phosphonate.png)

Prepared according to procedure A at 70 °C; isolated as yellow liquid (56 mg, 50%) using pentane/ethyl acetate (2:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.78 (s, 1H), 8.51 – 8.47 (m, 1H), 8.25 – 8.21 (m, 1H), 7.63 (t, $J=7.8$ Hz, 1H), 4.35 – 4.24 (m, 4H), 2.66 (s, 3H), 1.40 (t, $J=7.1$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 198.6$ (d, $J=178.1$ Hz), 196.8, 137.6, 135.8 (d, $J=63.8$ Hz), 134.2, 133.7, 129.5 (d, $J=2.0$ Hz), 129.3, 64.2 (d, $J=7.3$ Hz, 2C), 26.6, 16.4 (d, $J=5.7$ Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -1.88 (p, $J=8.1$ Hz). HRMS C$_{13}$H$_{17}$PO$_5$ [M+H]$^+$; calculated 285.0892, found: 285.0891.

diethyl (1-naphthoyl)phosphonate (3l)

![Chemical structure of diethyl (1-naphthoyl)phosphonate](diethyl_1-naphthoyl_phosphonate.png)

Prepared according to procedure A at 80 °C; isolated as yellow liquid (88 mg, 76%) using pentane/ethyl acetate (2:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.92 (d, $J=8.6$ Hz, 1H), 8.87 (dd, $J=7.3$, 1.0 Hz, 1H), 8.12 (d, $J=8.2$ Hz, 1H), 7.93 (d, $J=8.1$ Hz, 1H), 7.72 – 7.65 (m, 1H), 7.61 (ddd, $J=11.0$, 9.3, 4.3 Hz, 2H), 4.61 – 4.05 (m, 4H), 1.41 (t, $J=7.2$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 201.2 (d, $J=172.6$ Hz), 135.4, 134.3 (d, $J=1.9$ Hz), 133.9 (d, $J=3.7$ Hz), 131.8 (d, $J=64.4$ Hz), 130.2 (d, $J=10.5$ Hz), 129.2, 128.7, 126.8, 125.4, 124.5, 64.1 (d, $J=7.4$ Hz, 2C), 16.4 (d, $J=5.8$ Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -1.22 (p, $J=7.8$ Hz). HRMS C$_{15}$H$_{19}$PO$_4$ [M+H]$^+$; calculated 293.0943, found: 293.0942.

diethyl (2-naphthoyl)phosphonate (3m)

![Chemical structure of diethyl (2-naphthoyl)phosphonate](diethyl_2-naphthoyl_phosphonate.png)

Prepared according to procedure A at 80 °C; isolated as yellow liquid (78 mg, 67%) using pentane/ethyl acetate (2:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 9.09 (s, 1H), 8.14 (dd, $J=8.6$, 0.9 Hz, 1H), 8.06 (d, $J=8.1$ Hz, 1H), 7.97 – 7.86 (m, 2H), 7.71 – 7.64 (m, 1H), 7.62 – 7.55 (m, 1H), 4.75 – 3.66 (m, 4H), 1.42 (t, $J=7.2$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 198.8 (d, $J=174.6$ Hz), 136.3, 134.1, 133.1 (d, $J=63.7$ Hz), 132.4, 130.3, 129.5, 128.8 (d, $J=1.4$ Hz), 127.8, 127.0, 123.4 (d, $J=4.2$ Hz), 64.1 (d, $J=7.2$ Hz, 2C), 16.4 (d, $J=5.8$ Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ (ppm) -1.23 (p, $J=7.8$ Hz). HRMS C$_{15}$H$_{17}$PO$_4$ [M+H]$^+$; calculated 293.0943, found: 293.0940.
diethyl (1-methyl-1H-indole-5-carbonyl)phosphonate (3n)

Prepared according to procedure A at 90 °C; isolated as yellow liquid (60 mg, 51%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.74 (d, J=1.2 Hz, 1H), 8.01 (dd, J=8.8, 1.2 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.05 (d, J=3.2 Hz, 1H), 6.59 (dd, J=3.2, 0.6 Hz, 1H), 4.28 – 4.14 (m, 4H), 3.74 (s, 3H), 1.31 (t, J=7.1 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ (ppm) 197.7 (d, J=171.0 Hz), 139.9, 130.8, 128.2 (d, J=64.8 Hz), 128.0, 126.5, 122.6 (d, J=3.9 Hz), 109.6, 104.0, 63.8 (d, J=7.2 Hz, 2C), 33.1, 16.4 (d, J=7.1 Hz, 6H).

$^{31}$P NMR (162 MHz, CDCl$_3$) δ (ppm) 0.04 (p, J=7.7 Hz).

HRMS C$_{14}$H$_{18}$PNO$_4$ [M+H]$^+$; calculated 296.1052, found: 296.1048.

diethyl (benzofuran-5-carbonyl)phosphonate (3o)

Prepared according to procedure A at 90 °C; isolated as yellow liquid (67 mg, 60%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.75 (d, J=1.5 Hz, 1H), 8.24 (dd, J=8.8, 1.7 Hz, 1H), 7.74 (d, J=2.2 Hz, 1H), 7.61 (d, J=8.8 Hz, 1H), 6.93 (dd, J=2.2, 0.9 Hz, 1H), 4.46 – 4.06 (m, 4H), 1.41 (t, J=7.0 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ (ppm) 198.1 (d, J=174.2 Hz), 158.3, 146.7, 131.3 (d, J=64.3 Hz), 127.8, 126.0 (d, J=2.9 Hz), 125.4, 112.1, 107.6, 64.0 (d, J=7.2 Hz, 2C), 16.4 (d, J=5.8 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) δ (ppm) -0.91 (p, J=7.9 Hz). HRMS C$_{13}$H$_{15}$PO$_5$ [M+H]$^+$; calculated 283.0735, found: 283.0735.

diethyl (thiophene-3-carbonyl)phosphonate (3p)

Prepared according to procedure A at 80 °C; isolated as yellow liquid (57 mg, 58%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.88 (dd, J=2.9, 1.1 Hz, 1H), 7.68 (dt, J=5.1, 1.0 Hz, 1H), 7.36 (ddd, J=5.0, 2.8, 2.1 Hz, 1H), 4.33 – 4.23 (m, 4H), 1.39 (t, J=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 192.1 (d, J=179.1 Hz), 140.9 (d, J=67.3 Hz), 138.6, 126.7, 126.5 (d, J=6.8 Hz), 64.2 (d, J=7.1 Hz, 2C), 16.4 (d, J=5.7 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) δ (ppm) -1.96 (p, J=7.9 Hz). HRMS C$_9$H$_{13}$PSO$_4$ [M+H]$^+$; calculated 249.0350, found: 249.0349.
diethyl (benzo[b]thiophene-3-carbonyl)phosphonate (3q)

Prepared according to procedure A at 90 °C; isolated as yellow liquid (48 mg, 41%) using pentane/ethyl acetate (1:1) as eluent. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ (ppm) 9.50 (s, 1H), 8.75 (d, J=8.2 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.51 – 7.44 (m, 1H), 4.32 (p, J=7.2 Hz, 4H), 1.42 (t, J=7.2 Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ (ppm) 192.6 (d, J=177.0 Hz), 145.8 (d, J=4.1 Hz), 139.4 (d, J=3.1 Hz), 135.9 (d, J=12.6 Hz), 134.2 (d, J=68.6 Hz), 126.4, 126.1, 125.2, 122.3, 64.1 (d, J=7.1 Hz, 2C), 16.4 (d, J=5.7 Hz, 2C). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) δ (ppm) -2.50 (p, J=7.9 Hz). HRMS C\(_{13}\)H\(_{15}\)PSO\(_4\) [M+H]\(^+\); calculated 299.0507, found: 299.0505.

dibutyl (4-methoxybenzoyl)phosphonate (3r)

Prepared according to procedure A at 90 °C; isolated as colorless liquid (104 mg, 80%) using pentane/ethyl acetate (1:1) as eluent. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ (ppm) 8.27 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.3 Hz, 2H), 4.18 (dd, J=12.8, 6.3 Hz, 4H), 3.88 (s, 3H), 1.74 – 1.63 (m, 4H), 1.40 (dd, J=15.0, 7.4 Hz, 4H), 0.91 (t, J=7.4 Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ (ppm) 196.6 (d, J=174.0 Hz), 164.8, 132.4 (d, J=1.9 Hz, 2C), 129.1 (d, J=65.1 Hz), 114.1 (2C), 67.4 (d, J=7.5 Hz, 2C), 55.5, 32.4 (d, J=5.8 Hz, 2C), 18.6 (2C), 13.5 (2C). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) δ (ppm) -0.58 (p, J=7.1 Hz). HRMS C\(_{16}\)H\(_{25}\)PO\(_5\) [M+H]\(^+\); calculated 329.1518, found: 329.1513.

diisopropyl (4-methoxybenzoyl)phosphonate (3s)

Prepared according to procedure A at 90 °C; isolated as colorless liquid (105 mg, 88%) using pentane/ethyl acetate (1:1) as eluent. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ (ppm) 8.36 – 8.27 (m, 2H), 6.98 (d, J=8.9, 1.0 Hz, 2H), 4.87 – 4.76 (m, 2H), 3.90 (s, 3H), 1.38 (dd, J=6.1, 3.9 Hz, 12H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ (ppm) 197.3 (d, J=175.8 Hz), 164.7, 132.5 (d, J=1.8 Hz, 2C), 129.1 (d, J=65.2 Hz), 114.0 (2C), 72.9 (d, J=7.3 Hz, 2C), 55.5, 24.0 (m, 4C). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) δ (ppm) -2.11 (t, J=7.3 Hz). HRMS C\(_{14}\)H\(_{22}\)PO\(_5\) [M+H]\(^+\); calculated 301.1205, found: 301.1203.
**13C-labelled diethyl (4-methoxybenzoyl)phosphonate (13C-3a)**

Prepared according to procedure A at 90 °C; isolated as colorless liquid (85 mg, 78%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.33 – 8.22 (m, 2H), 6.97 (d, $J$=8.5 Hz, 2H), 4.26 (p, $J$=7.2 Hz, 4H), 3.88 (s, 3H), 1.37 (t, $J$=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 196.6 (d, $J$=174.0 Hz, $^{13}$C), 164.9, 132.5 (2C), 129.0 (dd, $J$=65.1, 52.7 Hz), 114.1 (d, $J$=4.5 Hz, 2C), 63.8 (d, $J$=7.2 Hz, 2C), 55.6, 16.4 (d, $J$=5.7 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) δ (ppm) -0.62 (dp, $J$=173.9, 7.8 Hz). HRMS C$_{11}$H$_{17}$PO$_5$ [M+H]$^+$; calculated 274.0925, found: 274.0924.

**13C-labelled diethyl (4-(dimethylamino)benzoyl)phosphonate (13C-3e)**

Prepared according to procedure A at 90 °C; isolated as colorless liquid (102 mg, 90%) using pentane/ethyl acetate (1:1) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.29 – 8.13 (m, 2H), 6.65 (d, $J$=8.6 Hz, 2H), 4.24 (p, $J$=7.2 Hz, 4H), 3.09 (s, 6H), 1.36 (t, $J$=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 194.3 (d, $J$=170.8 Hz, $^{13}$C), 154.4, 132.6 – 132.5 (m, 2C), 124.2 (dd, $J$=66.5, 57.7 Hz), 110.7 (d, $J$=4.5 Hz, 2C), 63.5 (d, $J$=7.1 Hz, 2C), 40.0 (2C), 16.4 (d, $J$=5.8 Hz, 2C). $^{31}$P NMR (162 MHz, CDCl$_3$) δ (ppm) 0.73 (dp, $J$=170.8, 7.7 Hz). HRMS C$_{12}$H$_{20}$NPO$_4$ [M+H]$^+$; calculated 287.1242, found: 287.1241.

**Diethyl (difluoro(phenyl)methyl)phosphonate (4)***

Diethyl benzoylphosphonate 3g (121.1mg, 0.5 mmol) and (diethylamino)sulfur trifluoride (DAST) (0.3 mL, 2 mmol) were stirred together at 0 °C under an argon atmosphere. The reaction was warmed to ambient temperature over 1 h and continued to stir for 20 h. The reaction mixture was then cooled again to 0 °C and added to a 25% solution of NaHCO$_3$ in H$_2$O (5 mL). The resulting suspension was stirred for 15 min, 7.5 mL of H$_2$O was added, and the aqueous phase was extracted with 3 portions of DCM. The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (pentane/ethyl acetate = 1/1) to afford the title compound as a light yellow oil (72 mg, 55%). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.62-7.60 (m, 2H), 7.49-7.42 (m, 3H), 4.25-4.08 (m, 4H), 1.30 (t, $J$=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 132.6 (td, $J$=21.9, 13.7 Hz), 130.8 (d, $J$=1.6 Hz), 128.4 (d, $J$=1.0 Hz, 2C), 126.2 (td, $J$=7.0, 2.2 Hz, 2C), 118.1 (td, $J$=261.6, 216.9 Hz), 64.8 (d, $J$=6.7 Hz, 2C), 16.3 (d, $J$=5.6 Hz, 2C). $^{19}$F
diethyl (1-hydroxy-3-oxo-1-phenylbutyl)phosphonate (5)$^4$

To a stirred solution of diethyl benzoylphosphonate 3g (121 mg, 0.5 mmol) and dry acetone (2.0 mL) was added L-proline (29 mg, 0.25 mmol) at room temperature. The reaction mixture was stirred at this temperature for 24 h and then quenched by few drops of water. The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined extracts were washed with brine solution, dried over Na$_2$SO$_4$, and evaporated to give the crude product. The crude product was purified by column chromatography over silica gel (ethyl acetate) to afford the title compound as a white solid (138.0 mg, 92%).$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.59-7.57 (m, 2H), 7.35-7.23 (m, 3H), 5.10 (d, $J = 17.6$ Hz, 1H), 4.16-4.08 (m, 2H), 3.88-3.80 (m, 1H), 3.70-3.62 (m, 1H), 3.34-3.31 (m, 2H), 2.10 (s, 3H), 1.28 (t, $J = 6.4$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 209.7 (d, $J = 12.6$ Hz), 139.5, 128.2 (d, $J = 2.7$ Hz, 2C), 127.7 (d, $J = 3.0$ Hz), 125.9 (d, $J = 4.3$ Hz, 2C), 75.3 (d, $J = 165.8$ Hz), 63.8 (d, $J = 7.4$ Hz), 63.5 (d, $J = 7.8$ Hz), 47.7 (d, $J = 2.8$ Hz), 32.2 (d, $J = 1.9$ Hz), 16.4 (d, $J = 5.5$ Hz), 16.2 (d, $J = 5.5$ Hz). $^{31}$P NMR (CDCl$_3$, 162 MHz) $\delta$ (ppm) 20.22. HRMS C$_{13}$H$_{21}$O$_3$P [M+Na$^+$]; calculated 301.1205, found 301.1204.

diethyl ((2,2-dimethylhydrazono)(phenyl)methyl)phosphonate (6)$^5$

To a solution of dimethylhydrazine (41 mg, 0.7 mmol) in glacial acetic acid (0.5 mL), benzoylphosphonate 3g (121 mg, 0.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was neutralized with Na$_2$CO$_3$ aqueous solution, extracted with ethyl acetate, and the combined extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to afford the title compound as a colourless oil (105 mg, 74%).$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.37-7.28 (m, 5H), 4.14-4.06 (m, 4H), 2.80 (s, 6H), 1.26 (t, $J = 7.2$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 135.4 (d, $J = 22.5$ Hz), 133.5 (d, $J = 238.4$ Hz), 129.2 (d, $J = 4.3$ Hz, 2C), 128.0 (d, $J = 1.7$ Hz), 127.8 (2C), 62.4 (d, $J = 6.1$ Hz, 2C), 46.8 (2C), 16.2 (d, $J = 6.5$ Hz, 2C). $^{31}$P NMR (CDCl$_3$, 162 MHz) $\delta$ (ppm) 12.60. HRMS C$_{13}$H$_{21}$N$_2$O$_3$P [M+H$^+$]; calculated 285.1368, found 285.1369.
diethyl (2-oxo-1,2-diphenylethyl) phosphate (7)\(^6\)

\[
\begin{align*}
\text{3g} & \quad \text{P} \quad \text{Et} \quad \text{CHO} + 30 \% \text{KCN} \\
\text{DMF} & \quad \text{7} \\
\text{P} \quad \text{Et} \quad \text{Et}
\end{align*}
\]

Benzaldehyde (29 mg, 0.275 mmol) was added into a mixture of diethyl benzoylephosphonate 3g (61 mg, 0.25 mmol) and potassium cyanide (4.8 mg, 0.075 mmol) in 1.0 mL DMF. The reaction mixture was stirred under argon at room temperature for 6 h. Then the reaction mixture was extracted with ether, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 1/1) to afford the title compound as a colourless oil (71 mg, 81\%).\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.92 (d, \(J = 8.4\), 2H), 7.52-7.34 (m, 8H), 6.63 (d, \(J = 8.0\), 1H), 4.23-4.13 (m, 2H), 3.95-3.86 (m, 2H), 1.32 (t, \(J = 8.0\) Hz, 3H), 1.14 (t, \(J = 8.0\) Hz, 3H).\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 193.7 (d, \(J = 4.5\) Hz), 134.9 (d, \(J = 5.5\) Hz), 134.4, 133.5, 129.3, 129.1 (2C), 129.0 (2C), 128.6 (2C), 128.1 (2C), 80.1 (d, \(J = 4.8\) Hz), 64.3 (d, \(J = 5.9\) Hz), 64.0 (d, \(J = 6.2\) Hz), 16.1 (d, \(J = 6.9\) Hz), 15.8 (d, \(J = 7.1\) Hz). \(^31\)P NMR (CDCl\(_3\), 162 MHz) \(\delta\) (ppm) -1.88. HRMS C\(_{18}\)H\(_{21}\)O\(_3\)P [M+H\(^+\)]; calculated 349.1205, found 349.1205.

diethyl (hydroxy(phenyl)methyl)phosphonate (8)\(^7\)

\[
\begin{align*}
\text{3g} & \quad \text{P} \quad \text{Et} \quad \text{Et} + \text{PMe}_3 (1 \text{ eq}) \\
\text{THF, r.t.} & \quad \text{8} \\
\text{P} \quad \text{Et} \quad \text{Et}
\end{align*}
\]

To a solution of diethyl benzoylephosphonate 3g (121 mg, 0.5 mmol) in 0.5 mL THF, trimethylphosphine (38 mg, 0.5 mmol) was added under argon. The reaction mixture was stirred at room temperature for 2 h. Then the reaction solution was concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (DCM/MeOH = 30/1) to afford the title compound as a white solid (85.0 mg, 70\%).\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.48-7.47 (m, 2H), 7.35-7.28 (m, 3H), 5.00 (d, \(J = 11.2\) Hz, 1H), 4.63 (s, 1H), 4.06-3.93 (m, 4H), 1.24 (t, \(J = 7.2\) Hz, 3H), 1.19 (t, \(J = 7.2\) Hz, 3H).\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 136.8 (d, \(J = 1.8\) Hz), 128.2 (d, \(J = 2.3\) Hz, 2C), 128.0 (d, \(J = 3.3\) Hz), 127.1 (d, \(J = 5.7\) Hz, 2C), 70.8 (d, \(J = 158.2\) Hz), 63.0 (d, \(J = 7.3\) Hz), 62.8 (d, \(J = 6.8\) Hz), 16.4 (d, \(J = 3.6\) Hz), 16.3 (d, \(J = 2.0\) Hz). \(^31\)P NMR (CDCl\(_3\), 162 MHz) \(\delta\) (ppm) 21.47. HRMS C\(_{13}\)H\(_{17}\)O\(_3\)P [M+Na\(^+\)]; calculated 267.0762, found 267.0758.

References

1. A detailed description of how to use the COware two chamber system can be found on the www.sytracks.com.
NMR Spectrum

3a
3c
3i
3k
3n

[Chemical structure and NMR spectrum images]
3r
$^{13}$C-3a