Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Functional Bisphosphonate Synthesis for the Development of New Anti-Resorption Bone Drug Candidates

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General

^{1}H NMR, $^{31}P\{^{1}H\}$ NMR, $^{13}C\{^{1}H\}$ NMR spectra were run on:
Bruker Avance 300 spectrometer operating at 300, 122, 75 MHz, respectively, at 298 K.
Bruker Avance 400 spectrometer operating at 400, 162, 101 MHz, respectively, at 298 K.
δ values are reported in ppm relative to $Si(CH_3)_4$ or 85% H_3PO_4.

EI-MS analyses were performed on a GC Trace GC 2000 coupled with a quadrupole MS Thermo Finnigan Trace MS with *Full Scan* method. Experimental conditions are reported in the following table.

Experimental conditions for GC-MS analyses	
Capillary column:	HP5-MS 30 m, 0.25 mm x 0.25 μm
Initial T, °C:	80°C for 5 min
Rate, °C/min:	30°C/min
Final T, °C:	280°C for 30 min
Injector T (split), °C:	280°C
Gas carrier flow, mL/min.	0.8 mL/min
Injected volume, μL	0.8-1 μL
Solvent delay, min.	4 min.
Mass range, amu:	35-500 amu
Detector voltage, V:	350 V
Interface T, °C	280°C
Source T, °C:	200°C

Low resolution mass spectra (LRMS) were recorded on a Finningan LCQ Deca XP Max mass spectrometer coupled to electrospray ionisation source (ESI) in positive or negative mode.

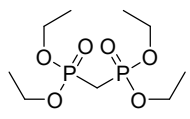
Column chromatography was performed on 230-400 mesh silica, thin layer chromatography was carried out on 20 cm x 20 cm ALUGRAM® Xtra SIL G/UV_{254} MACHEREY-NAGEL.

HPLC analyses were performed on a Hewlett Packard Series 1100 G1311A QuatPump at reported conditions.

Synthesis and characterization of BP intermediates and products

Methylenebisphosphonate tetraethyl ester (MBP)

The sodium ethoxide solution was prepared by addition of metal sodium (5 g, 220 mmol) in portions to ethanol (130 mL). Diethyl phosphite (220 mmol) was then added with stirring to the sodium ethoxide solution, continuing for 1 h at room temperature and the mixture was concentrated on a rotary evaporator. The residue was dissolved with 10 mL of methylene chloride (156 mmol) and the mixture was stirred 2 weeks at room temperature. The mixture was washed with brine and the methylene chloride phase was dried with sodium sulphate and concentrated on a rotary evaporator. The residue was distilled at reduced pressure to give MBP in 54% yield.



MBP

^{1}H NMR (400 MHz, $CDCl_3$)δ 4.20 – 4.00 (m, 8H), 2.39 (t, *J* = 21.0 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 12H) ppm.

^{31}P {1H}-NMR (162 MHz, $CDCl_3$) δ 19.38 (s, 2P) ppm.

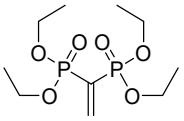
^{13}C {1H}-NMR (101 MHz, $CDCl_3$) δ 62.62 (t, *J* = 3.0 Hz), 25.43 (t, *J* = 136.9 Hz), 16.36 (d, *J* =

3.2 Hz) ppm.

EI-MS (70 eV) m/z: 288 $[M]^+$, 261 $[M -CH_2CH_3]^+$, 233 $[M -2(CH_2CH_3)]^+$, 205 $[M -3(CH_2CH_3)]^+$.

Vinylidenebisphosphonate tetraethyl ester (VBP)

Paraformaldehyde (3,18 g, 106mmol) and diethylamine (21mmol) were combined in 60 mL of methanol and the mixture was warmed until clear. The heat was removed and MBP (20mmol) was then added. The mixture was refluxed for 24 h, then was concentrated under vacuum. Toluene (30mL) was added and the solution again concentrated. This last step was repeated to ensure complete removal of methanol from the intermediate which was obtained as a clear liquid. The residue was re-dissolved in toluene (30 mL), treated with 15,2 mg of pTSA (0,09 mmol) and refluxed through a Dean-Stark trap for 18 h. The sample was concentrated in vacuo, dissolved in CH_2Cl_2, washed twice with H_2O, dried with Na_2SO_4, and concentrated in vacuum to give VBP higher than 90% yield.



VBP

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, *J* = 37.8, 33.8 Hz, 2H), 4.23 – 4.03 (m, 8H), 1.33 (t, *J* = 7.1 Hz, 12H) ppm.

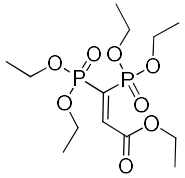
^{31}P {1H}-NMR (162 MHz, $CDCl_3$) δ 13.05 (s, 2P) ppm.

^{13}C {1H}-NMR (101 MHz, $CDCl_3$) δ 149.29 (s), 132.17 (t, *J* = 166.6 Hz), 62.78 (t, *J* = 2.8 Hz), 16.38 (t, *J* = 3.3 Hz) ppm.

EI-MS (70 eV) m/z: 300 $[M]^+$, 273 $[M -CH_2CH_3]^+$, 245 $[M -2(CH_2CH_3)]^+$, 217 $[M -3(CH_2CH_3)]^+$.

General procedure for synthesis of the bi-substituted alkylidene bisphosphonates

A flame-dried 50 mL round bottom flask with magnetic stir bar was charged with MBP (3 mmol), 40 mL of CH_2Cl_2 and 3 mmol of glyoxylate. 12 mmol of NEt_3 was added to the solution under inert atmosphere and the mixture was then cooled down to 0°C. 3 mmol of $TiCl_4$ were added dropwise to the flask and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was concentrated under vacuum and the formed oily solid was partially dissolved with ethyl acetate. The organic phase was filtered on silica bed, concentrated under reduced pressure and purified by column chromatography using 95/5 ethyl acetate/acetone mixture as eluent.



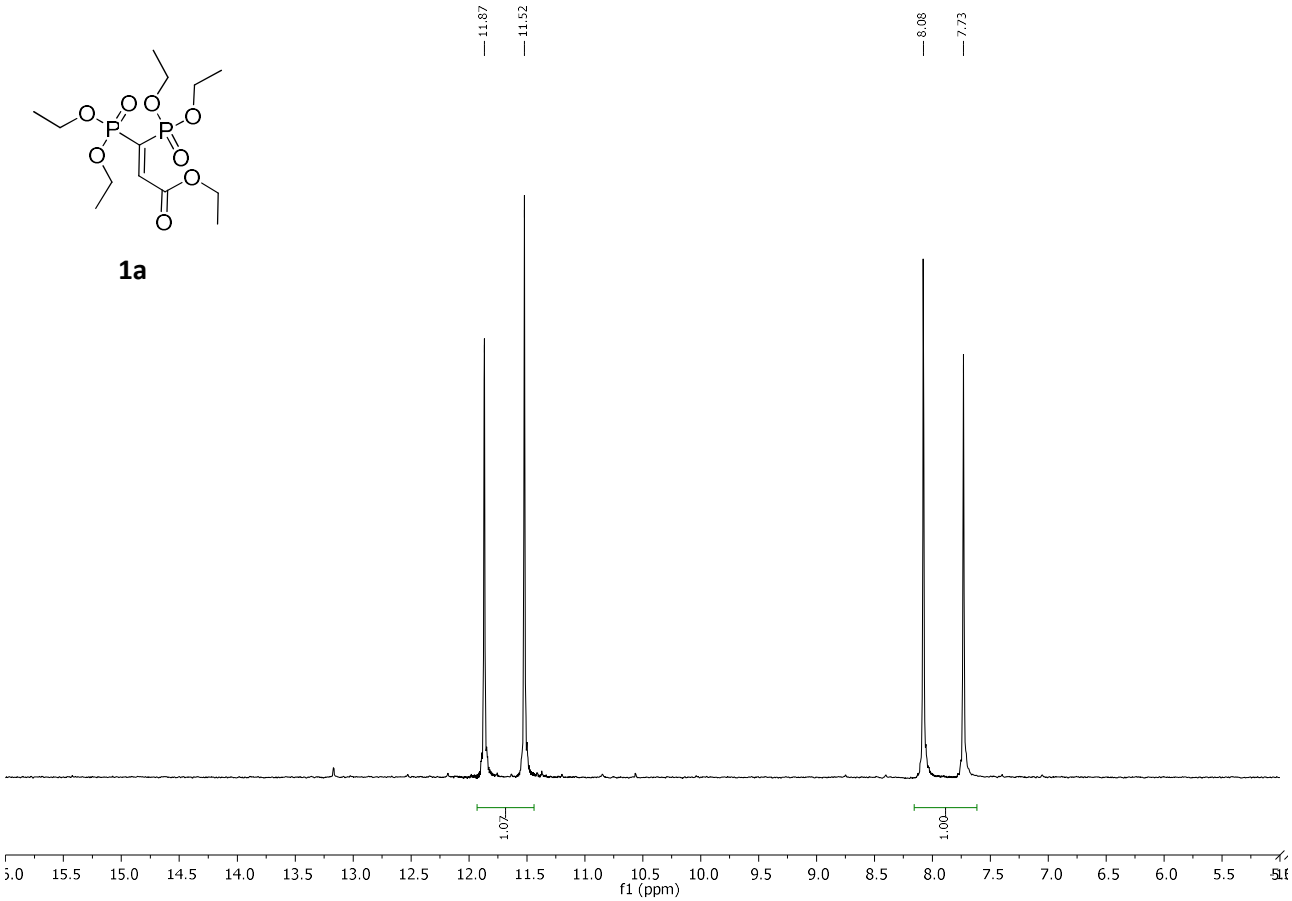
1a

Yield 90%

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.48 (dd, J=44.4, 27.7 Hz, 1H), 4.33 (q, J=7.2 Hz, 2H), 4.27-4.12 (m, 8H), 1.42-1.32 (m, 15H) ppm.

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 11.69 (d, J=42.2 Hz, 1P), 7.90 (d, J=42.2 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$): δ 165.67 (dd, J=27.1, 11.3 Hz), 150.55 (s), 14.37 (s), 129.29 (dd, J=164.3, 162.1 Hz), 63.45 (dd, J=10.7, 5.8 Hz), 62.39 (s), 60.80 (s), 16.67 (dd, J=6.4, 4.2 Hz), 14.61 (s), 14.37 (s) ppm.



1a

Figure S1. ^{31}P $\{^{1}H\}$-NMR (122 MHz, $CDCl_3$) spectrum of **1a** at 298K.

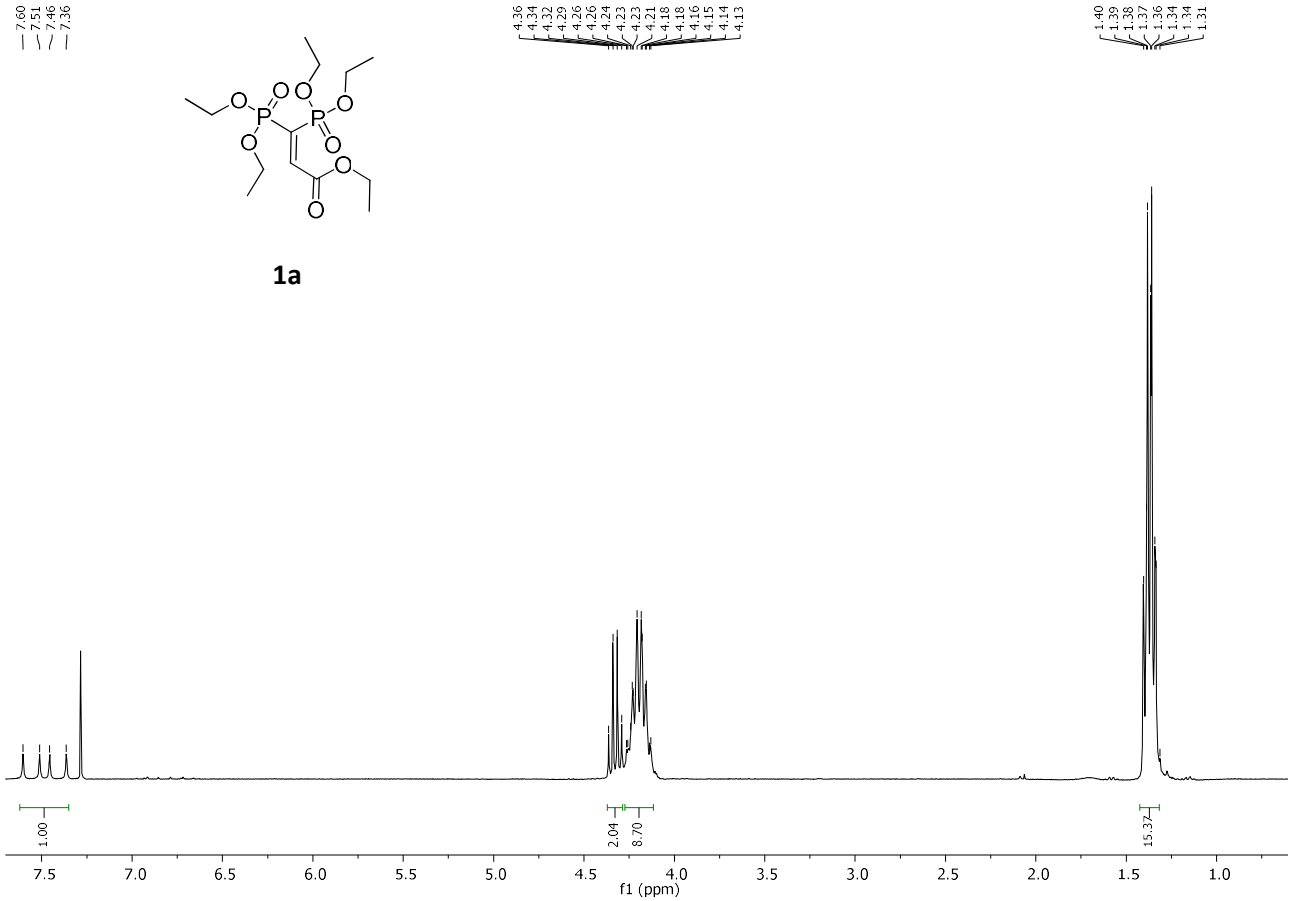


Figure S2. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **1a** at 298K.

EI-MS, m/z: 327 [M^+-OCH_2CH_3], 299 [M^+-COOEt], 271 [M^+-CH_2CH_3-CH_2CH_3+H^+], 235 [M^+-$PO(OEt)_2$].

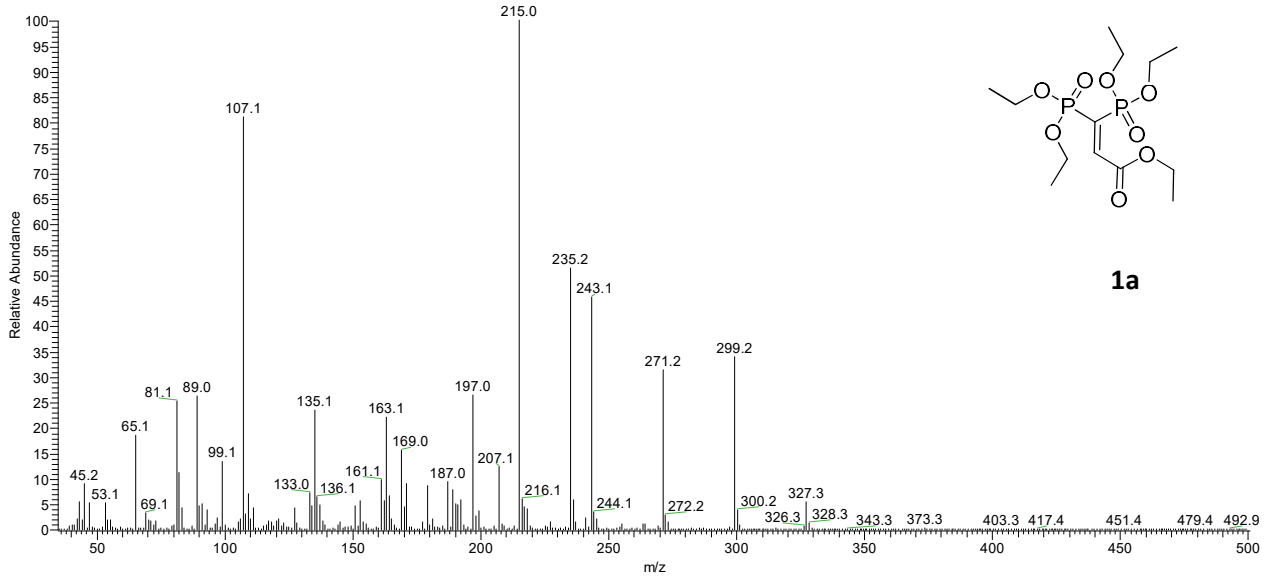
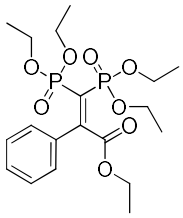


Figure S3. EI-MS spectrum of **1a**.

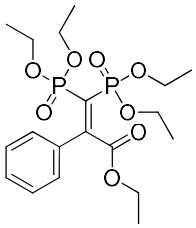


1b

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.48 (dd, J=6.7, 3.0 Hz, 2H), 7.40-7.34 (m, 3H), 4.32-4.17 (m, 6H), 4.00-3.87 (m, 2H), 3.86-3.73 (m, 2H), 1.39 (t, J=7.1 Hz, 6H), 1.26 (t, J=7.1 Hz, 3H), 1.08 (t, J=7.1 Hz, 6H) ppm.

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 11.28 (d, J=44.5 Hz, 1P), 10.13 (d, J=44.5 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$): δ 168.02 (dd, J=26.8, 12.5 Hz), 164.18 (s), 136.30 (dd, J=19.6, 9.6 Hz), 130.04 (s), 128.48 (s), 128.20 (s), 122.71 (dd, J=167.5, 159.9 Hz), 63.36 (d, J=5.2 Hz), 62.85 (d, J=6.4 Hz), 62.62 (s), 16.68 (d, J=6.4 Hz), 16.41 (d, J=6.5 Hz), 14.24 (s) ppm.



1b

Figure S4. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **1b** at 298K.

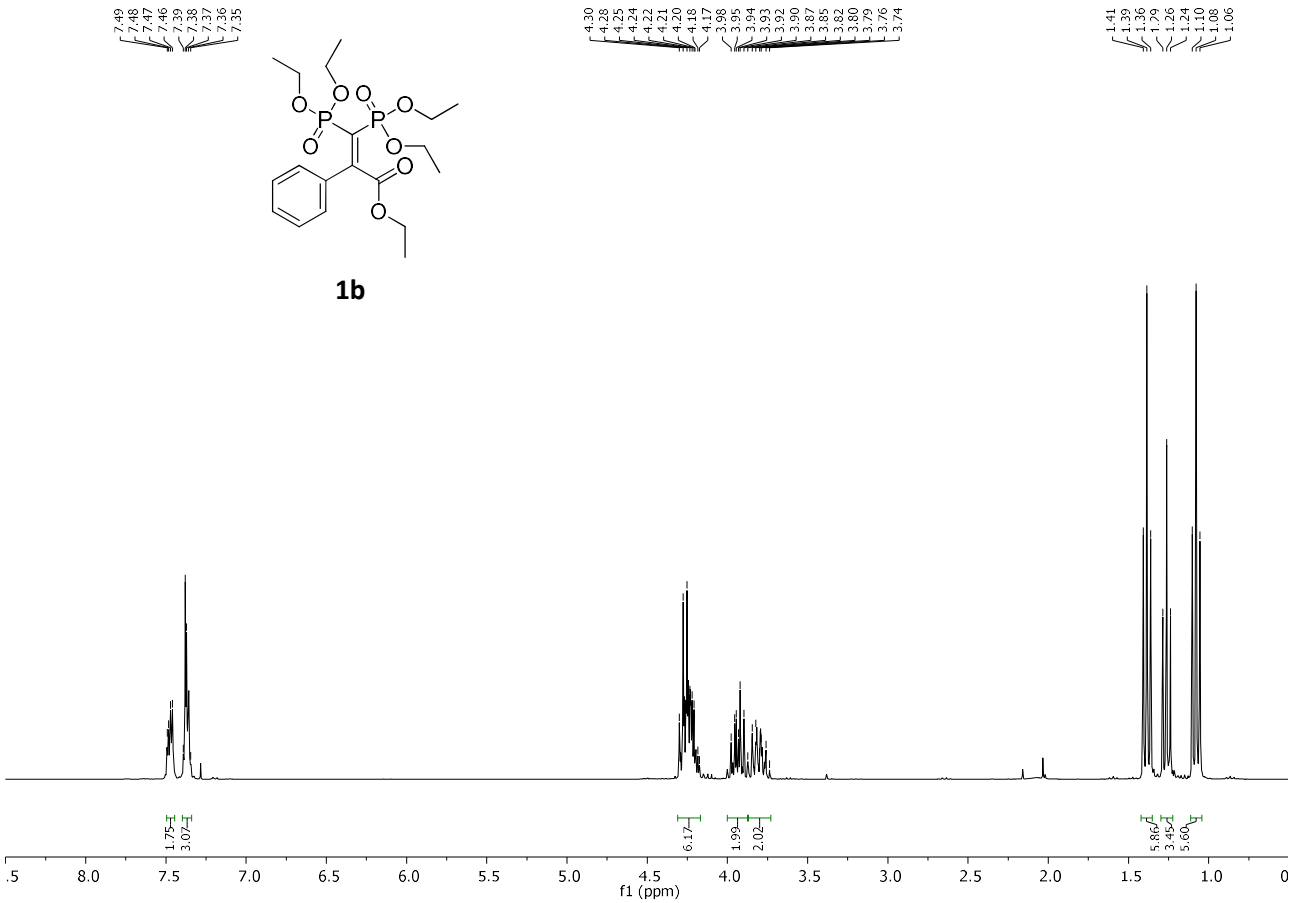


Figure S5. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **1b** at 298K

EI-MS, m/z: 448 [M^+], 403 [M^+-OEt], 375 [M^+-COOEt], 311 [M^+-$PO(OEt)_2$] 267 [M^+-$PO(OEt)_2$-OEt+H], 239 [M^+-$PO(OEt)_2$-COOEt+H].

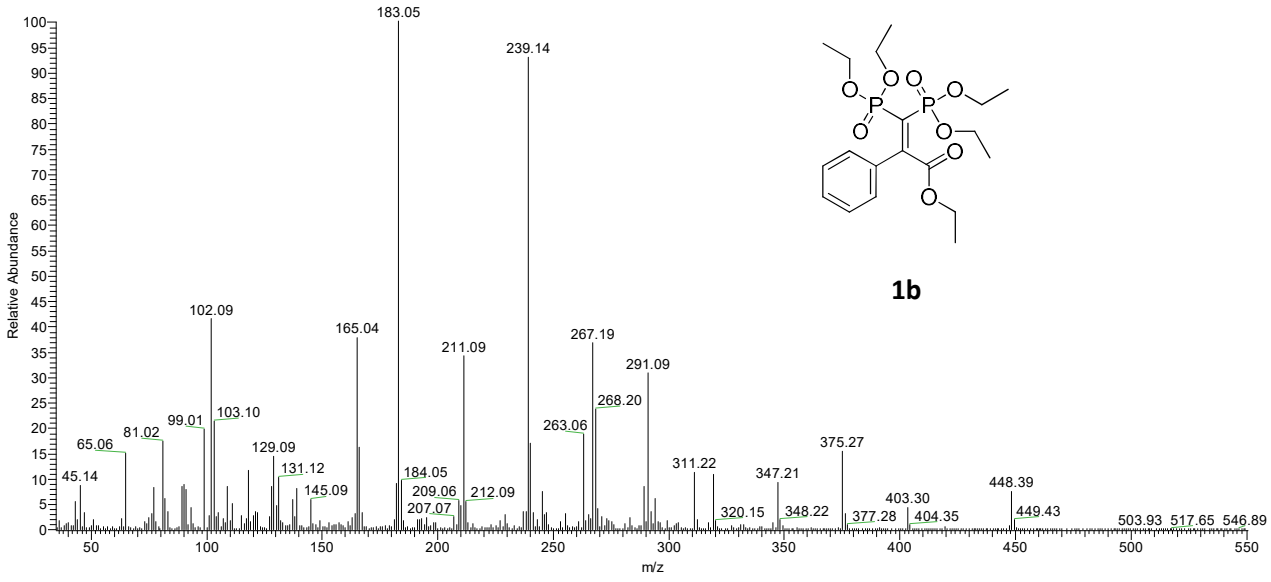


Figure S6. EI-MS spectrum of **1b**.

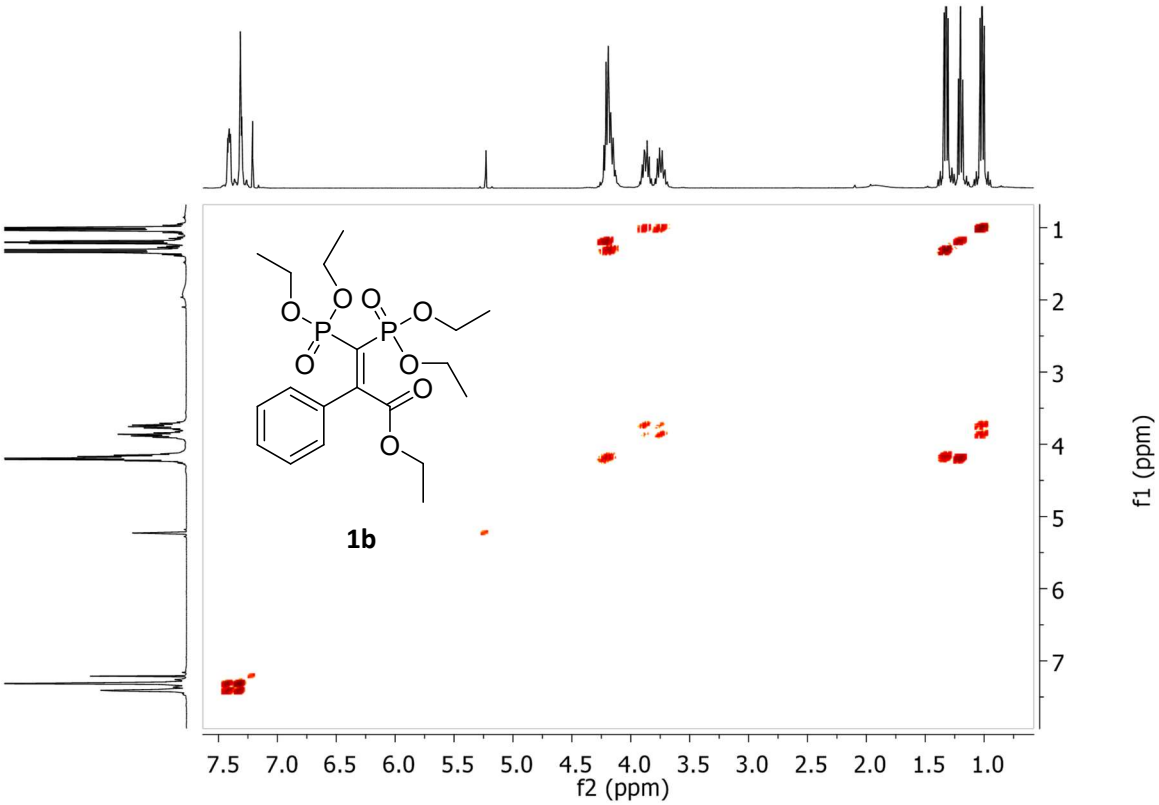


Figure S7. 2D-NMR COSY of **1b** at 298K.

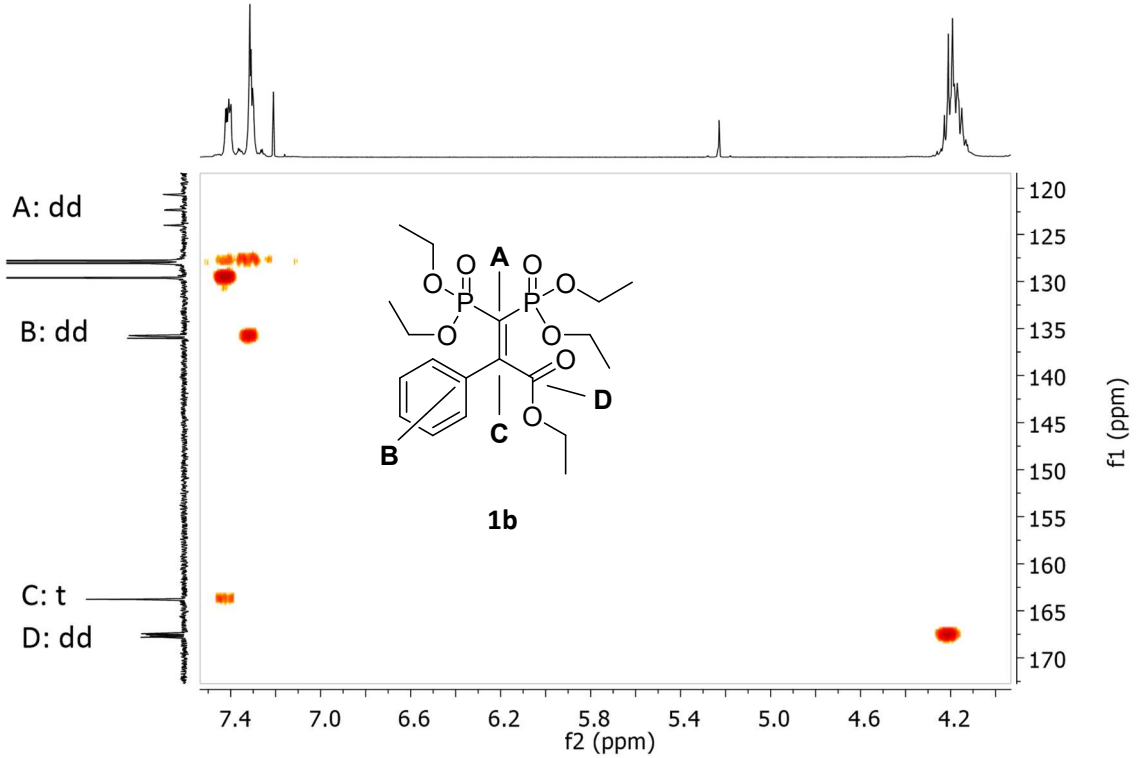
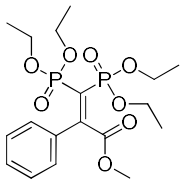


Figure S8. 2D-NMR HMBC of **1b** at 298K.

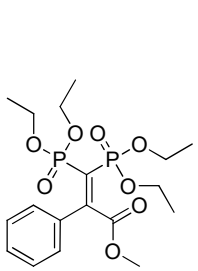


1c

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49 (dd, J=6.7, 3.0 Hz, 2H), 7.41-7.36 (m, 3H), 4.32-4.19 (m, 6H), 4.00-3.90 (m, 2H), 3.81 (s, 3H), 1.40 (t, J=7.0 Hz, 6H), 1.09 (t, J=7.0 Hz, 6H) ppm.

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 11.23 (d, J=44.2 Hz, 1P), 9.89 (d, J=44.2 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$): δ 168.54 (dd, J=25.8, 13.2 Hz), 163.99 (s), 136.47-135.79 (m), 128.54 (s), 130.16 (s), 128.23 (s), 123.25 (t, J=164.5 Hz), 63.46 (s), 62.89 (d, J=3.0 Hz), 53.6 (s), 16.54 (dd, J=21.0, 3.7 Hz), 14.60 (s) ppm.



1c

Figure S9. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **1c** at 298K.

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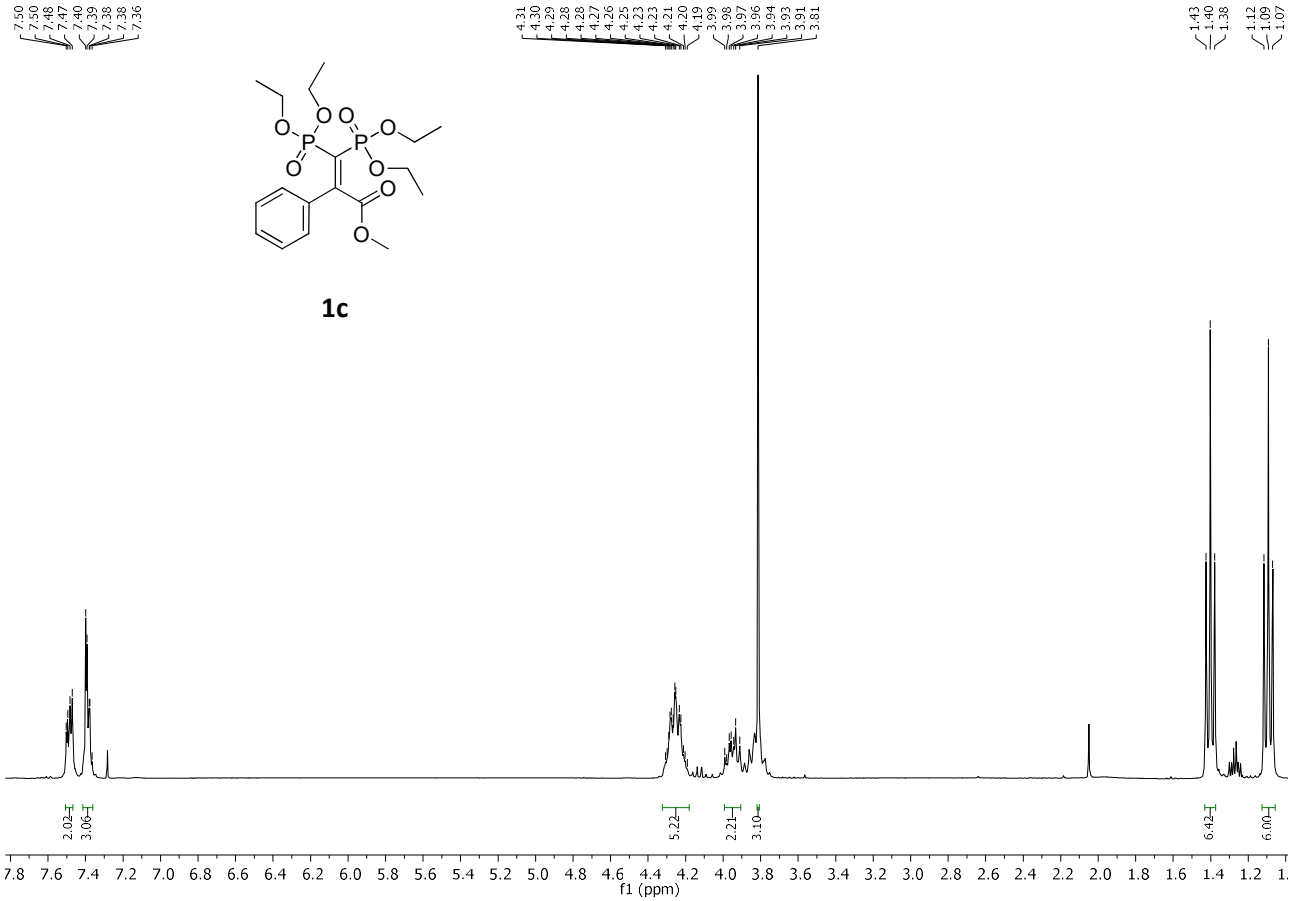


Figure S10. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **1c** at 298K.

EI-MS, m/z: 434 [M^+], 403 [M^+-OMe], 375 [M^+-COOMe], 297 [M^+-PO(OEt)$_2$], 239 [M^+-COOMe-PO(OEt)$_2$].

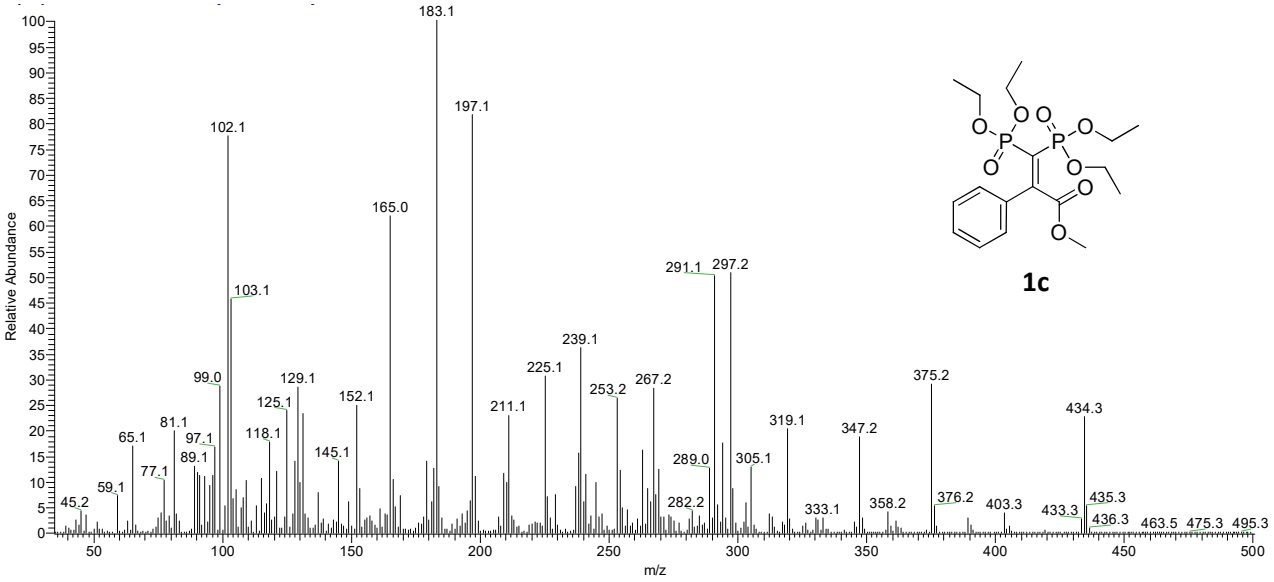
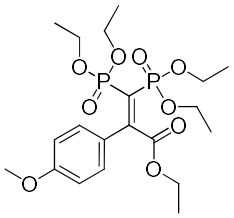


Figure S11. EI-MS spectrum of **1c**.

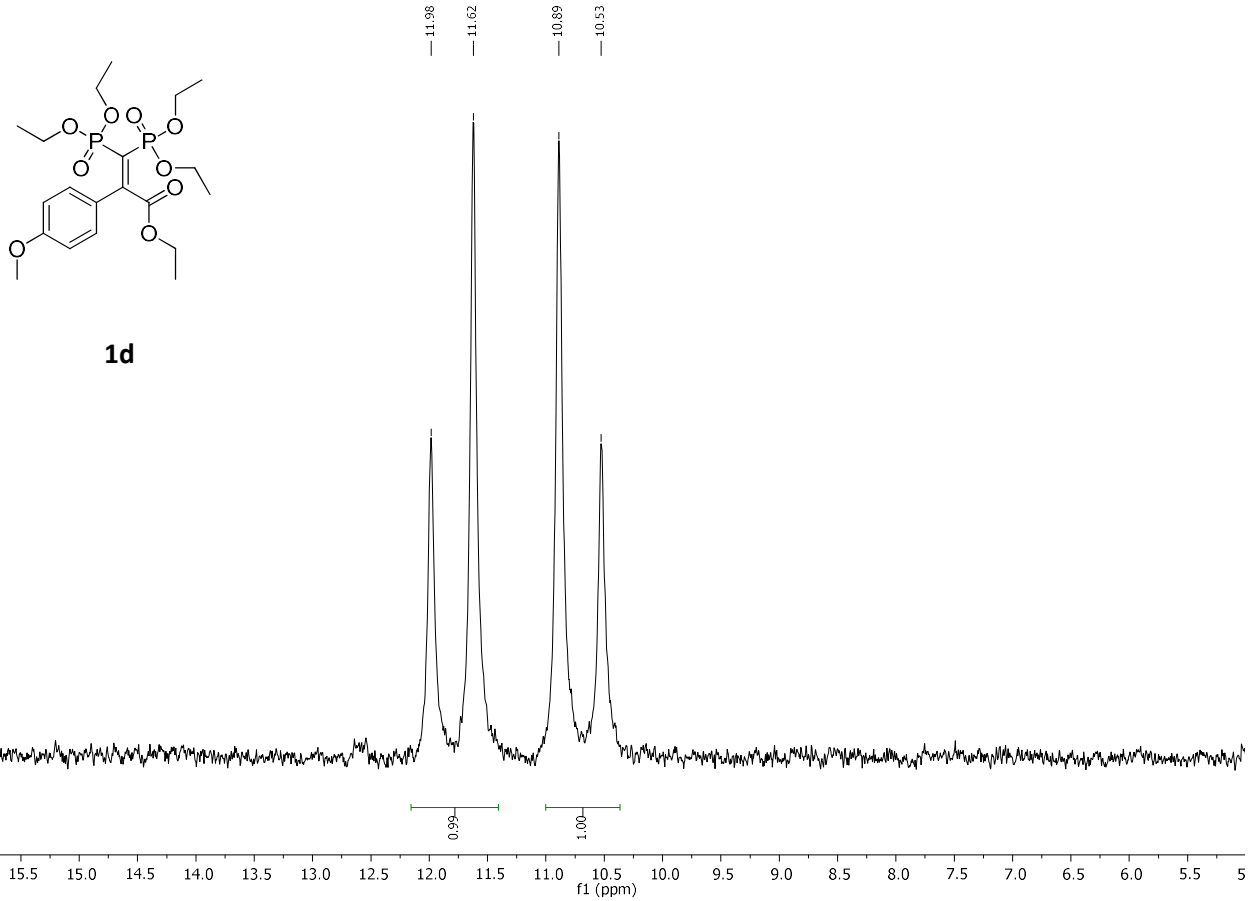


1d

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J=8.8 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H), 4.35-4.18 (m, 8H), 4.02-3.92 (m, 2H), 3.84 (s, 3H), 1.40 (t, J=7.1 Hz, 6H), 1.30 (t, J=7.1 Hz, 3H), 1.13 (t, J=7.1 Hz, 6H) ppm.

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 11.80 (d, J=44.1 Hz, 1P), 10.71 (d, J=44.1 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$): δ 171.0 (s), 167.82 (dd, J=26.7, 12.3 Hz), 163.67 (s), 160.92 (s), 130.19 (s), 129.78 (s), 127.89 (dd, J=20.0, 9.8 Hz), 120.53 (dd, J=167.7, 160.8 Hz), 114.11 (s), 113.40 (s), 62.73 (d, J=5.1 Hz), 62.33 (d, J=6.3 Hz), 62.06 (s), 60.25 (s), 55.19 (s), 20.91 (s), 16.15 (d, J=6.4 Hz), 15.91 (d, J=6.5 Hz), 14.07 (s), 13.74 (s) ppm.



1d

Figure S12. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **1d** at 298K.

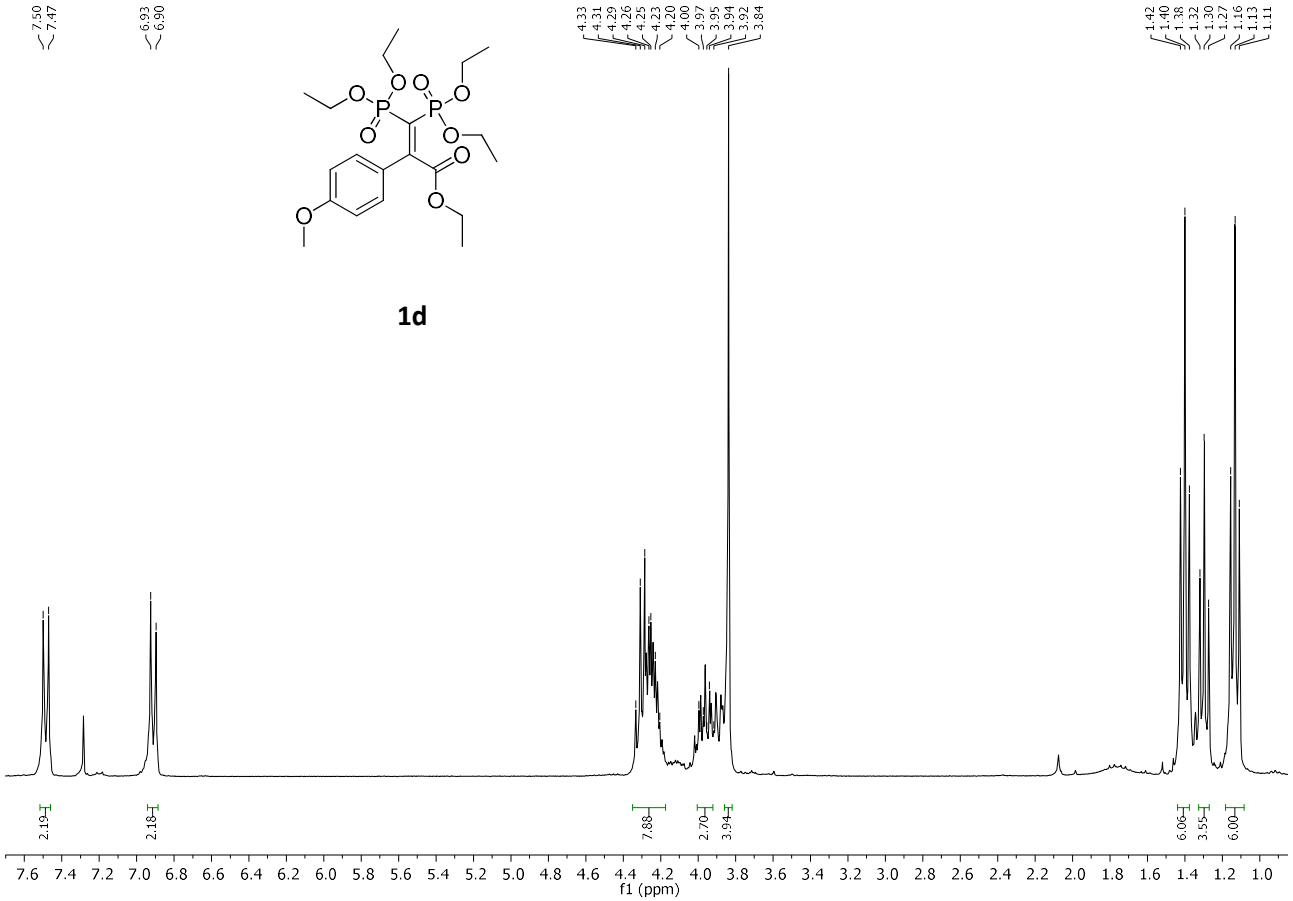


Figure S13. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **1c** at 298K.

EI-MS, m/z: 478 [M^+], 433 [M^+-OEt], 405 [M^+-COOEt], 341 [M^+-$(PO(OEt)_2]$], [297 [M^+-$(PO(OEt)_2$-OEt-H], 269 [M^+-$(PO(OEt)_2$-COOEt-H].

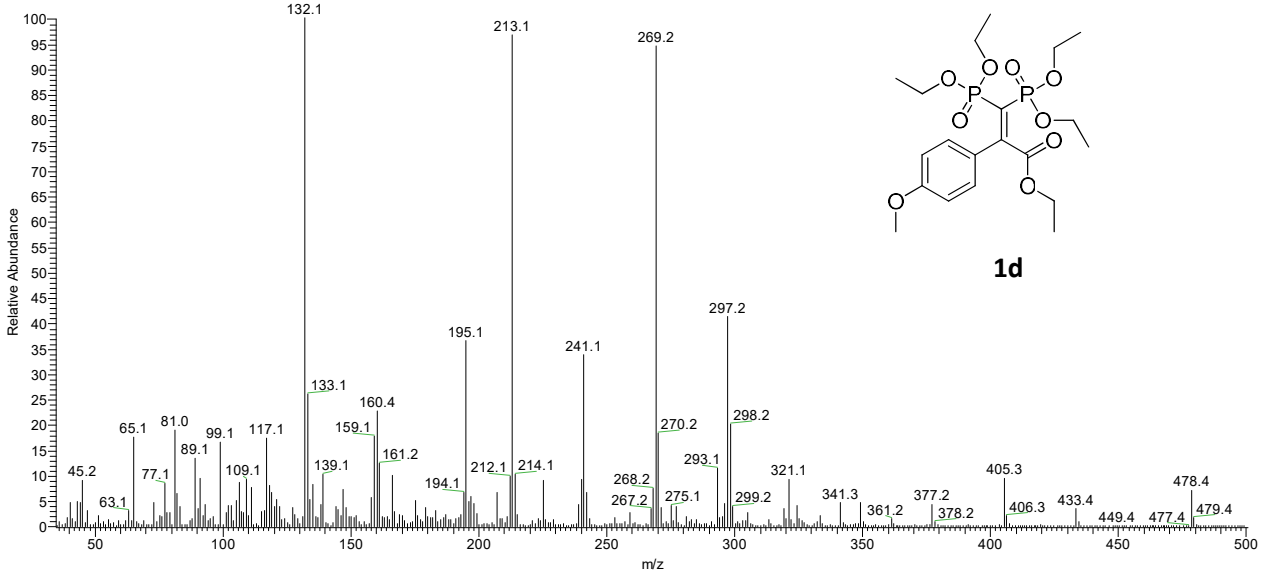
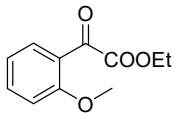


Figure S14. EI-MS spectrum of **1d**.

The synthesis of the aryl-keto esters **6e-6j** below reported was carried out following the procedure reported in the literature.[1,2]

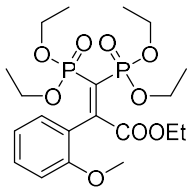


6e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.02 (td, *J* = 7.8, 0.8 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C {^{1}H}-NMR(76 MHz, $CDCl_3$) δ 187.06 (s, *J* = 66.7 Hz), 165.75 (s, *J* = 44.4 Hz), 160.73 (s, *J* = 56.6 Hz), 136.83 (s), 131.08 (s), 123.15 (s, *J* = 14.1 Hz), 121.70 (s), 112.51 (s), 62.18 (s), 56.42 (s), 14.55 (s) ppm.

EI-MS, (70 eV) m/z: 208 [M]$^{+}$, 135 [M -COOEt]$^{+}$.



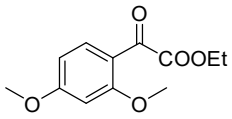
1e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H), 6.88 (dd, *J* = 8.3, 0.7 Hz, 1H), 4.35 – 4.21 (m, 6H), 4.14 – 4.04 (m, 1H), 4.03 – 3.95 (m, 1H), 3.94 – 3.83 (m, 1H), 3.81 (s, 3H), 3.73 – 3.59 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 6H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.26 – 1.15 (broad signal, 3H), 1.02 (broad signal, 3H) ppm.

^{31}P {^{1}H}-NMR(162 MHz, $CDCl_3$) δ 12.45 (d, *J* = 46.3 Hz, 1P), 11.99 (d, *J* = 46.3 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 167.75 (d, *J* = 38.5 Hz), 161.37 (s, *J* = 11.2 Hz), 156.99 (d, *J* = 6.2 Hz), 132.15 (s), 131.92 (s), 126.72 – 126.19 (m), 128.11 – 123.39 (m), 120.88 (s, *J* = 21.8 Hz), 111.04 (s, *J* = 18.2 Hz), 63.46 (s), 62.90 (d, *J* = 23.9 Hz), 62.33 (s, *J* = 8.0 Hz), 56.01 (s, *J* = 16.7 Hz), 16.78 – 16.56 (m), 16.43 (s), 14.30 (s) ppm.

EI-MS, (70 eV) m/z: 478 [M]$^{+}$, 447 [M -OMe]$^{+}$, 433 [M -OEt]$^{+}$, 405 [M -COOEt]$^{+}$.

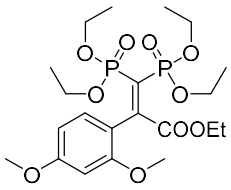


6f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 1H), 6.60 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 4H) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 185.48 (s), 167.18 (s), 166.38 (s), 162.77 (s), 133.29 (s), 116.37 (s), 107.22 (s), 98.61 (s), 61.97 (s), 56.39 (s), 56.16 (s), 14.58 (s) ppm.

EI-MS, (70 eV) m/z: 238 [M]$^{+}$, 165 [M -COOEt]$^{+}$.



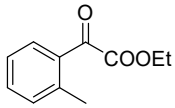
1f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 1H), 6.51 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 4.33 – 4.17 (m, 7H), 4.15 – 3.93 (m, 3H), 3.81 (s, *J* = 4.5 Hz, 3H), 3.75 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 6H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.22 – 0.99 (m, 6H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 13.02 (d, *J* = 46.7 Hz, 1P), 12.67 (d, *J* = 46.5 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 167.72 (dd, *J* = 23.4, 14.6 Hz), 163.11 (s), 160.91 (s), 158.15 (s), 133.64 (s), 123.84 (dd, *J* = 168.0, 163.0 Hz), 118.87 (dd, *J* = 17.6, 11.4 Hz), 104.28 (s), 98.44 (s), 62.96 (d, *J* = 4.5 Hz), 62.52 (s), 61.91 (s), 55.51 (d, *J* = 7.1 Hz), 16.28 (d, *J* = 5.2 Hz), 16.04 (s), 13.93 (s) ppm.

EI-MS, (70 eV) m/z: 508 $[M]^+$, 477 $[M - OMe]^+$, 463 $[M - OEt]^+$, 435 $[M - COOEt]^+$.

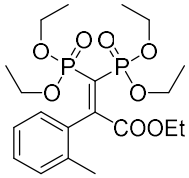


6g

^{1}H NMR (300 MHz, CDCl3) δ 7.72 – 7.67 (m, 1H), 7.53 – 7.45 (m, 1H), 7.36 – 7.28 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C {1H}-NMR (75 MHz, CDCl3) δ 189.22 (s), 165.06 (s), 141.74 (s), 134.07 (s), 132.78 (s, *J* = 5.0 Hz), 132.67 (s), 131.1 (s), 126.34 (s), 62.67 (s), 21.85 (s, *J* = 10.3 Hz), 14.51 (s, *J* = 62.3 Hz) ppm.

EI-MS, (70 eV) m/z: 192 $[M]^+$, 119$[M - COOEt]^+$, 91 $[M - COCOOEt]^+$.



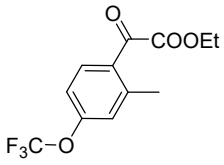
1g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 1H), 7.20 – 7.14 (m, 1H), 4.31 – 4.17 (m, 6H), 3.96 – 3.83 (m, 2H), 3.83 – 3.70 (m, 1H), 3.67 – 3.56 (m, 1H), 2.39 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.16 – 1.07 (m, 6H).

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 12.00 (d, *J* = 46.4 Hz, 1P), 11.13 (d, *J* = 46.6 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 167.19 (dd, *J* = 27.3, 12.3 Hz), 164.01 (s), 135.63 (dd, *J* = 17.8, 10.2 Hz), 135.59 (s), 130.01 (s), 128.83 (s), 127.93 (t, *J* = 1.6 Hz), 125.26 (s), 124.23 (dd, *J* = 168.9, 157.9 Hz), 63.02 (d, *J* = 5.2 Hz), 62.92 (d, *J* = 5.0 Hz), 62.40 (d, *J* = 6.5 Hz), 62.32 (d, *J* = 6.4 Hz), 62.06 (s), 19.89 (s), 16.31 (d, *J* = 3.3 Hz), 16.25 (d, *J* = 3.4 Hz), 16.15 (d, *J* = 6.1 Hz), 13.82 (s) ppm.

EI-MS, (70 eV) m/z: 462 $[M]^+$, 447 $[M - Me]^+$, 417 $[M - OEt]^+$, 389 $[M - COOEt]^+$, 325 $[M - PO(OEt)_2]^+$.

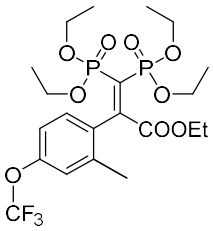


6h

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 4.44 (q, *J*= 7.1 Hz, 2H), 2.62 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 187.28 (s), 164.08 (s), 152.54 (s), 144.43 (s), 134.29 (s), 129.71 (s), 123.73 (s), 120.33 (q, *J* = 259.2 Hz), 117.33 (s), 62.54 (s), 21.51 (s), 14.03 (s) ppm.

EI-MS, (70 eV) m/z: 276 $[M]^+$, 203 $[M - COOEt]^+$, 191 $[M - OCF_3]^+$, 175 $[M\ COCOOEt]^+$.



1h

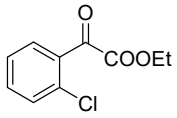
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 7.03 (d, *J* = 7.0 Hz, 2H), 4.29 – 4.17 (m, 6H), 3.98 – 3.86 (m, 2H), 3.86 – 3.75 (m, 1H), 3.74 – 3.65 (m, 1H), 2.41 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 6H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.12 (dt, *J* = 8.7, 7.1 Hz, 6H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 11.49 (d, *J* = 45.3 Hz, 1P), 10.80 (d, *J* = 45.3 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 166.88 (dd, *J* = 26.8, 12.4 Hz), 162.32 (s), 149.37 (d, *J* = 1.8 Hz), 138.32 (s), 134.22 (dd, *J* = 19.2, 9.6 Hz), 129.47 (s), 125.32 (dd, *J* = 168.0, 158.2 Hz), 122.22 (s), 120.41 (q, *J* = 257.4 Hz), 117.62 (s), 63.12 (d, *J* = 5.2 Hz), 63.02 (d, *J* = 5.1 Hz), 62.54 (d, *J* = 6.6 Hz), 62.47 (d, *J* = 6.5 Hz), 62.26 (s), 20.02 (s), 16.29 (d, *J* = 3.4 Hz), 16.23 (d, *J* = 3.6 Hz), 16.06 (d, *J* = 5.8 Hz), 13.79 (s) ppm.

^{19}F {^{1}H}-NMR (376 MHz, $CDCl_3$) δ -57.71 (s, 3F) ppm.

EI-MS, (70 eV) m/z: 546 $[M]^+$, 501 $[M - OEt]^+$, 473 $[M - COOEt]^+$, 461 $[M - OCF_3]^+$, 409 $[M - PO(OEt)_2]^+$.

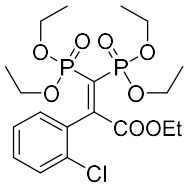


6i

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.47 – 7.37 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C {^{1}H}-NMR(75 MHz, $CDCl_3$) δ 186.60 (d, *J* = 13.3 Hz), 163.20 (s), 134.39 (s), 131.72 (s), 130.66 (s), 127.58 – 127.09 (m), 62.90 (s), 13.96 (s) ppm.

EI-MS, (70 eV) m/z: 212 [M, Cluster 1 Chloro] $^+$, 139 [M -COOEt, Cluster 1Chloro] $^+$, 111 [M -COCOOEt, Cluster 1 Chloro] $^+$.

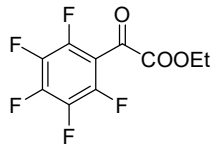


1i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 1H), 7.33 – 7.27 (m, 1H), 4.32 – 4.19 (m, 6H), 4.09 – 3.98 (m, 2H), 3.95 – 3.87 (m, 1H), 3.74 – 3.64 (m, 1H), 1.39 (td, *J* = 6.9, 1.8 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 11.37 (d, *J* = 43.8 Hz, 1P), 10.64 (d, *J* = 43.8 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 166.26 (dd, *J* = 26.2, 12.1 Hz), 160.28 (d, *J* = 2.2 Hz), 135.35 (dd, *J* = 19.7, 9.7 Hz), 131.95 (s), 130.63 (s), 130.26 (s), 129.35 (s), 126.59 (dd, *J* = 166.3, 158.1 Hz), 126.45 (s), 63.21 (t, *J* = 5.2 Hz), 62.90 (d, *J* = 6.2 Hz), 62.39 (d, *J* = 6.4 Hz), 62.33 (s), 16.28 (d, *J* = 6.3 Hz), 16.18 (d, *J* = 6.3 Hz), 16.06 (d, *J* = 6.2 Hz), 13.79 (s) ppm.

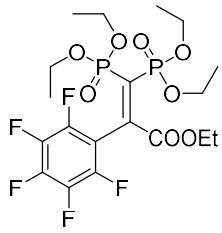


6j

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 178.14 (s), 160.56 (s), 147.99 – 147.39 (m), 146.63 – 146.01 (m), 144.56 – 143.87 (m), 143.15 – 142.42 (m), 139.90 – 139.17 (m), 136.48 – 135.74 (m), 110.85 (t, *J* = 16.2 Hz), 63.77 (s), 13.85 (s) ppm.

EI-MS, (70 eV) m/z: 268 $[M]^+$, 195 $[M - COOEt]^+$, 167 $[M - COCOOEt]^+$.



1j

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 – 4.11 (m, 6H), 4.09 – 3.95 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 6H), 1.27 – 1.19 (m, 9H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 9.12 (t, *J* = 36.3 Hz, 2P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 165.00 (dd, *J* = 20.3, 16.0 Hz), 148.09 (s), 144.68 (s), 142.63 – 141.78 (m), 140.50 (s), 139.12 – 138.39 (m), 136.70 – 135.77 (m), 131.60 (t, *J* = 158.2 Hz), 63.58 – 63.41 (m), 63.28 – 63.07 (m), 62.92 (s), 16.31 – 16.03 (m), 13.74 (s) ppm.

^{19}F {^{1}H}-NMR (376 MHz, $CDCl_3$) δ -137.98 – -138.53 (m), -152.17 (t, *J* = 20.9 Hz), -161.64 – -162.06 (m) ppm.

EI-MS, (70 eV) m/z: 538 $[M]^+$, 493 $[M - OEt]^+$, 465 $[M - COOEt]^+$.

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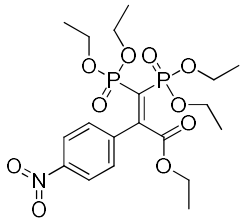
11 p-nitrophenyl glyoxylate is commercially available and was used as received (Sigma Aldrich).

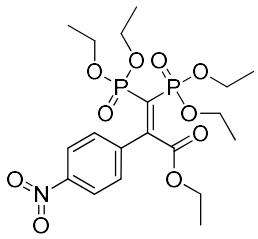


1k

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.25 (d, J=8.8 Hz, 2H), 7.64 (d, J=8.8 Hz, 2H), 4.32-4.19 (m, 6H), 4.05-3.87 (m, 4H), 1.41 (t, J=7.1 Hz, 6H), 1.28 (t, J=7.1 Hz, 3H), 1.16 (t, J=7.1 Hz, 6H) ppm.

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 9.17 (d, J=40.9 Hz, 1P), 9.95 (d, J=40.9 Hz, 1P) ppm.

^{13}C {^{1}H}- NMR (75 MHz, $CDCl_3$) δ 167.05 (dd, *J* = 25.9, 12.7 Hz), 161.40 (s), 148.66 (s), 142.74 (dd, *J* = 19.8, 10.0 Hz), 129.24 (s), 125.30 (dd, *J* = 165.0, 160.0 Hz), 123.64 (s), 63.65 (d, *J* = 5.2 Hz), 63.21 (d, *J* = 6.3 Hz), 63.14 (s), 16.70 (d, *J* = 6.1 Hz), 16.55 (d, *J* = 6.1 Hz), 14.22 (s) ppm.



1k

Figure S15. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **1k** at 298K.

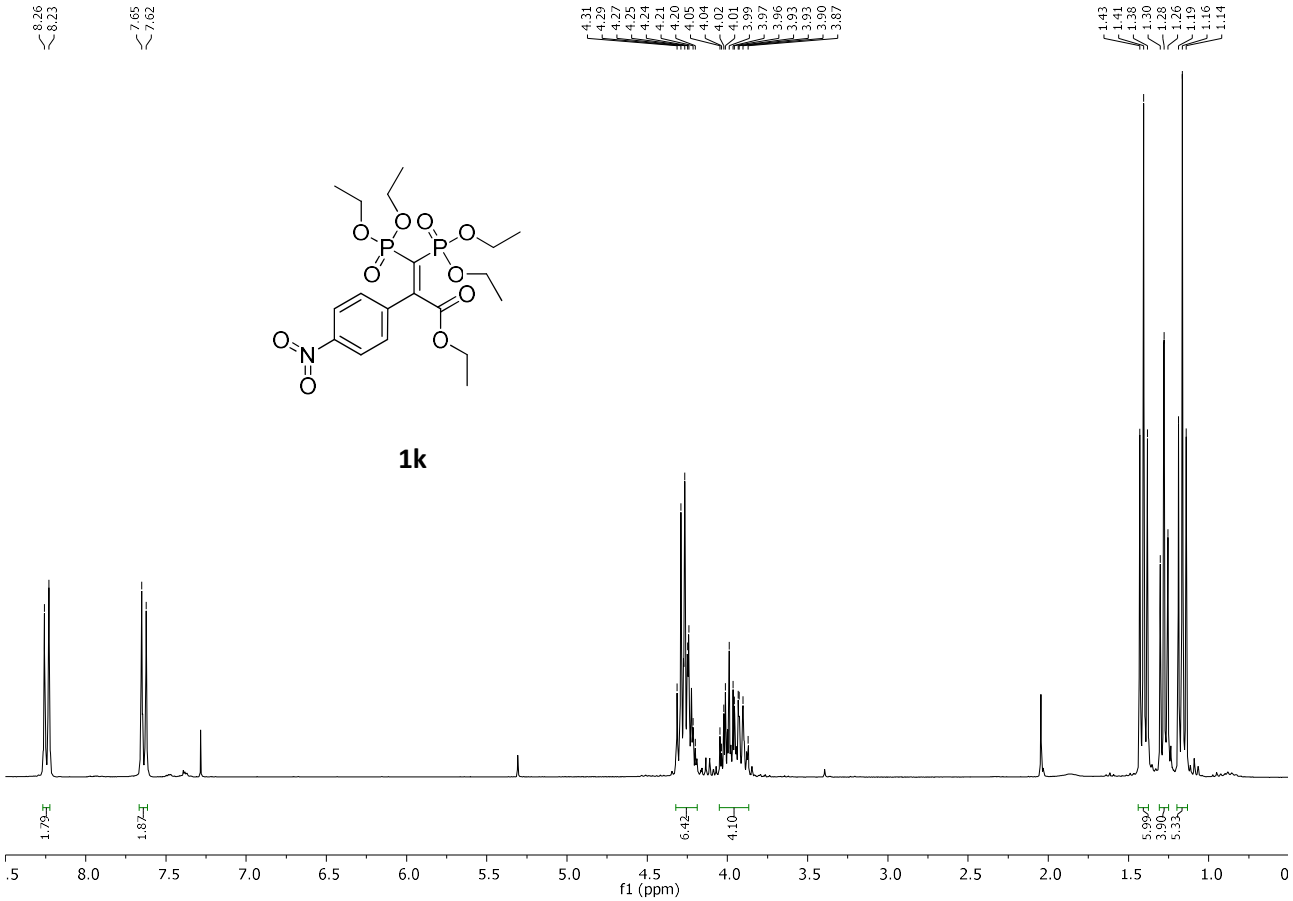


Figure S16. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **1k** at 298K.

EI-MS, m/z: 493[M^+], 448 [M^+-OEt], 420 [M^+-COOEt], 392 [M^+-COOEt-Et+H], 356 [M^+-PO(OEt)$_2$], 284 [M^+-COOEt-PO(OEt)$_2$].

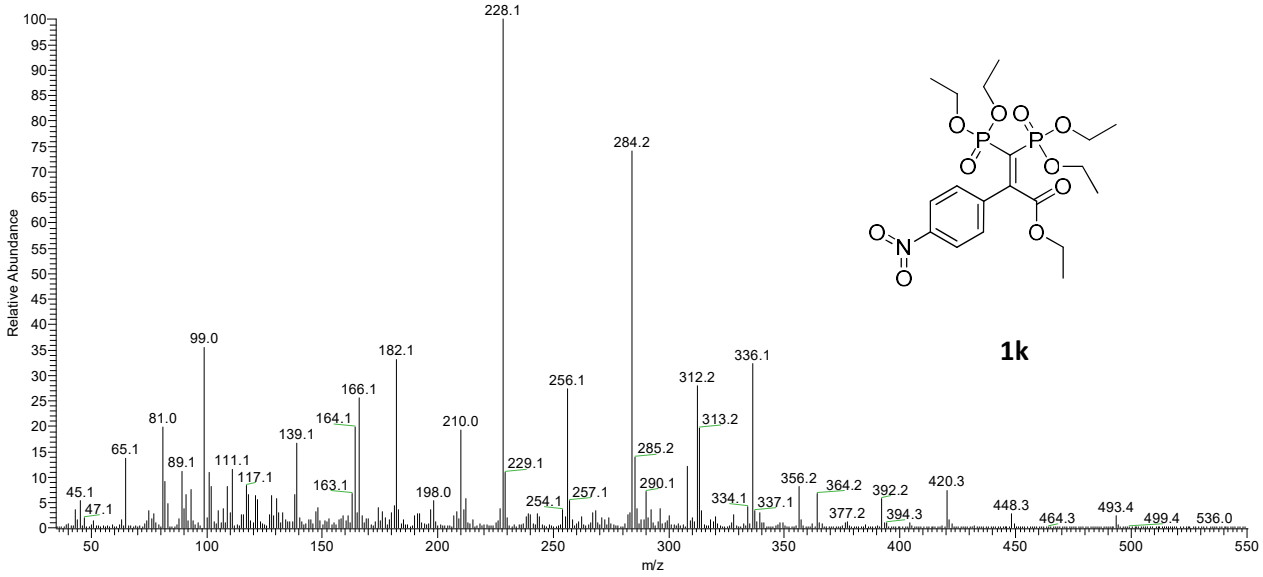
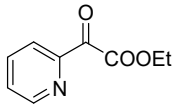


Figure S17. EI-MS spectrum of **1k**.

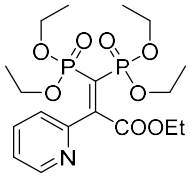


11

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.7 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 187.79 (s), 165.41 (s), 150.36 (s), 149.90 (s), 137.33 (s), 128.36 (s), 123.45 (s), 62.27 (s), 14.16 (s) ppm.

EI-MS, (70 eV) m/z: 179 $[M]^+$, 150 $[M -Et]^+$, 106 $[M -COOEt]^+$, 78 $[M -COCOOEt]^+$.



1l

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.74 – 7.70 (m, 2H), 7.31 – 7.26 (m, 4H), 4.34 – 4.20 (m, 6H), 4.18 – 4.04 (m, 2H), 4.03 – 3.89 (m, 4H), 1.40 – 1.35 (m, 6H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.10 (td, *J* = 7.1, 0.5 Hz, 6H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 12.09 (d, *J* = 42.1 Hz, 1P), 11.09 (d, *J* = 42.2 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 166.78 (dd, *J* = 26.4, 12.4 Hz), 161.36 (s), 154.44 (dd, *J* = 22.1, 10.4 Hz), 149.13 (s), 136.20 (s), 125.03 (s), 124.33 (dd, *J* = 164.9, 159.4 Hz), 124.01 (s), 63.15 (d, *J* = 5.3 Hz), 62.75 (d, *J* = 6.4 Hz), 62.45 (s), 16.27 (d, *J* = 6.6 Hz), 16.01 (d, *J* = 6.7 Hz), 13.81 (s) ppm.

EI-MS, (70 eV) m/z: 449 $[M]^+$, 434 $[M -Me]^+$, 404 $[M -OEt]^+$, 376 $[M -COOEt]^+$, 312 $[M -PO(OEt)_2]^+$.

General Procedure for Pd/C Hydrogenation of Bi-Substituted VBP Precursors.

In a vial equipped with magnetic stirring bar 100 mg of bi-substituted VBP precursor, 5 mL of non-anhydrous MeOH and 20% mol of Pd (with respect to VBP precursor) of Pd/C 5% w/w catalyst were added.

The system was closed under inert atmosphere and H_2 (1 atm) was bubbled overnight. The solution was filtered, and the solvent removed under reduced pressure. The crude was purified by TLC chromatography using 8/2 ethyl acetate/acetone as eluent.

The purified raceme product was eluted by cellulose-2 chiral HPLC in isocratic condition in order to optimize a enantiomeric separation method. Elution times of enantiomer are reported (in parenthesis elution time of non-hydrogenated VBP precursor).

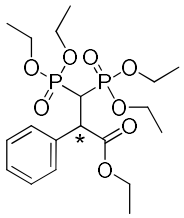
Enantioselective hydrogenation attempts

Autoclave reactions

Three empty/nitrogen cycles were performed in a test tube equipped with a magnetic stirring bar. The catalyst, the chiral ligand and 1 mL of degassed toluene were introduced under stirring. The mixture was left under stirring for few minutes after which the BP precursor was added (substrate: metal: ligand = 500: 1: 2). The test tube prepared was inserted into the autoclave, three empty/nitrogen cycles were performed, and the autoclave was then loaded with H_2 at the requested pressure and temperature. The reaction was run for the requested time, then the autoclave was vented, and the mixture analyzed by GC-MS and NMR.

Vial reaction

In a vial equipped with a magnetic stirring bar 10 mg of substrate, 0.5 mL of cyclohexane and 20% of mol (with respect to the substrate) of quinine thiourea or quinidine thiourea were introduced. After complete dissolution, three equivalents of $NaBH_4$ were added and the mixture was left to react for 2 hours. At the end the mixture was analyzed by NMR and the enantioselectivity was assessed by HPLC on chiral column.



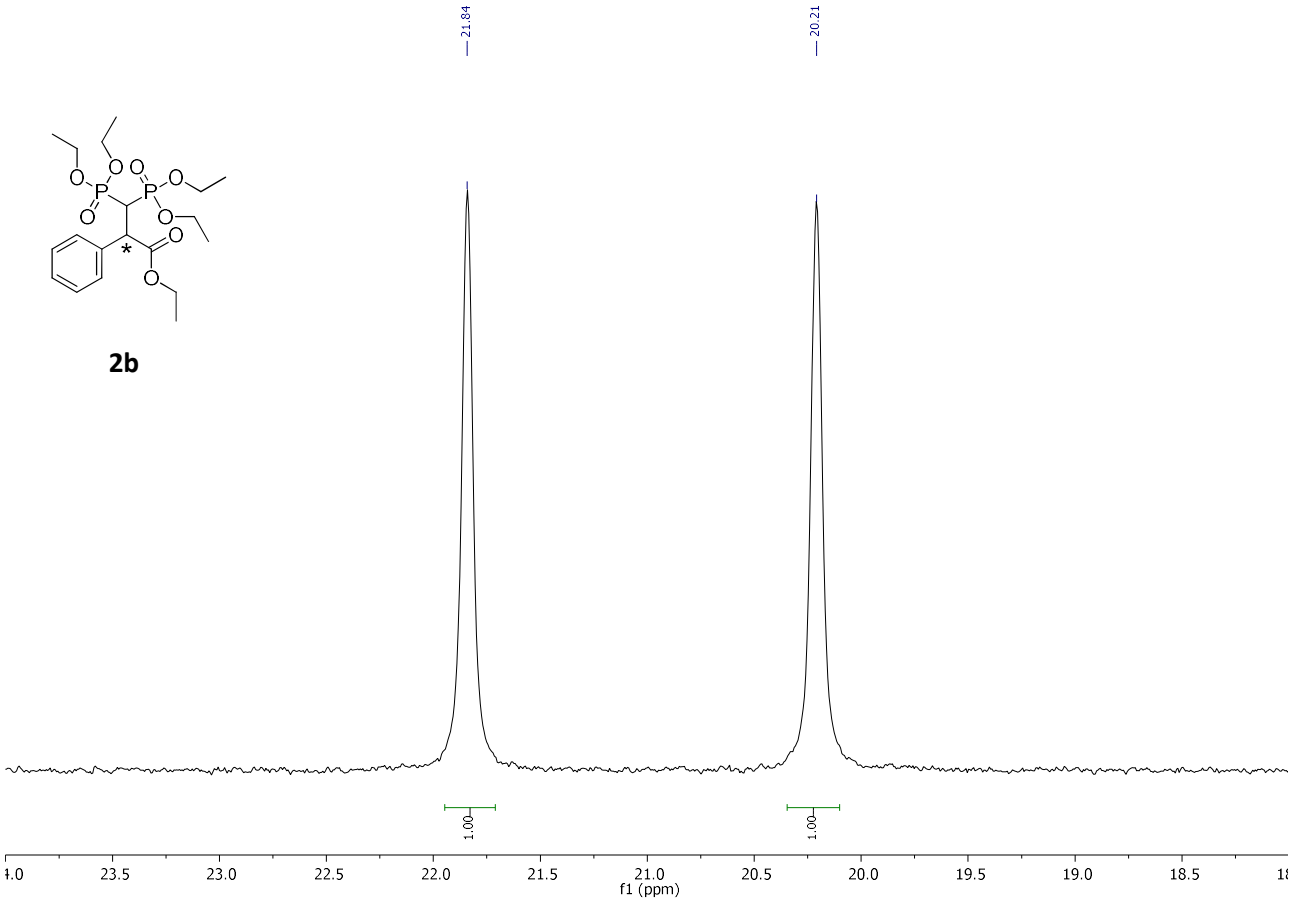
2b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.30 – 7.22 (m, 3H), 4.29 – 4.05 (m, 7H), 3.96 – 3.74 (m, 3H), 3.61 – 3.45 (m, 2H), 1.34 (td, *J* = 7.1, 3.2 Hz, 6H), 1.19 – 1.10 (m, 6H), 1.06 (t, *J* = 7.1 Hz, 3H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$): δ 20.21 (s, 1P), 21.84 (s, 1P) ppm

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 172.17 (dd, *J* = 18.5, 3.0 Hz), 135.55 (dd, *J* = 14.3, 4.0 Hz), 129.90 (s), 127.95 (s), 127.80 (s), 63.20 (d, *J* = 6.6 Hz), 62.68 (d, *J* = 6.7 Hz), 62.34 (d, *J* = 6.9 Hz), 61.97 (d, *J* = 6.7 Hz), 61.40 (s), 49.60 – 49.07 (m), 40.72 (dd, *J* = 136.1, 127.8 Hz), 16.45 – 16.23 (m), 16.13 (d, *J* = 0.9 Hz), 16.07 (d, *J* = 1.4 Hz), 13.88 (s) ppm.

Elution time: 23'-31'(11’), isopropanol/n-hexane 2/8



2b

Figure S18. ^{31}P $\{^{1}H\}$-NMR (162 MHz, $CDCl_3$) spectrum of **2b** at 298K.

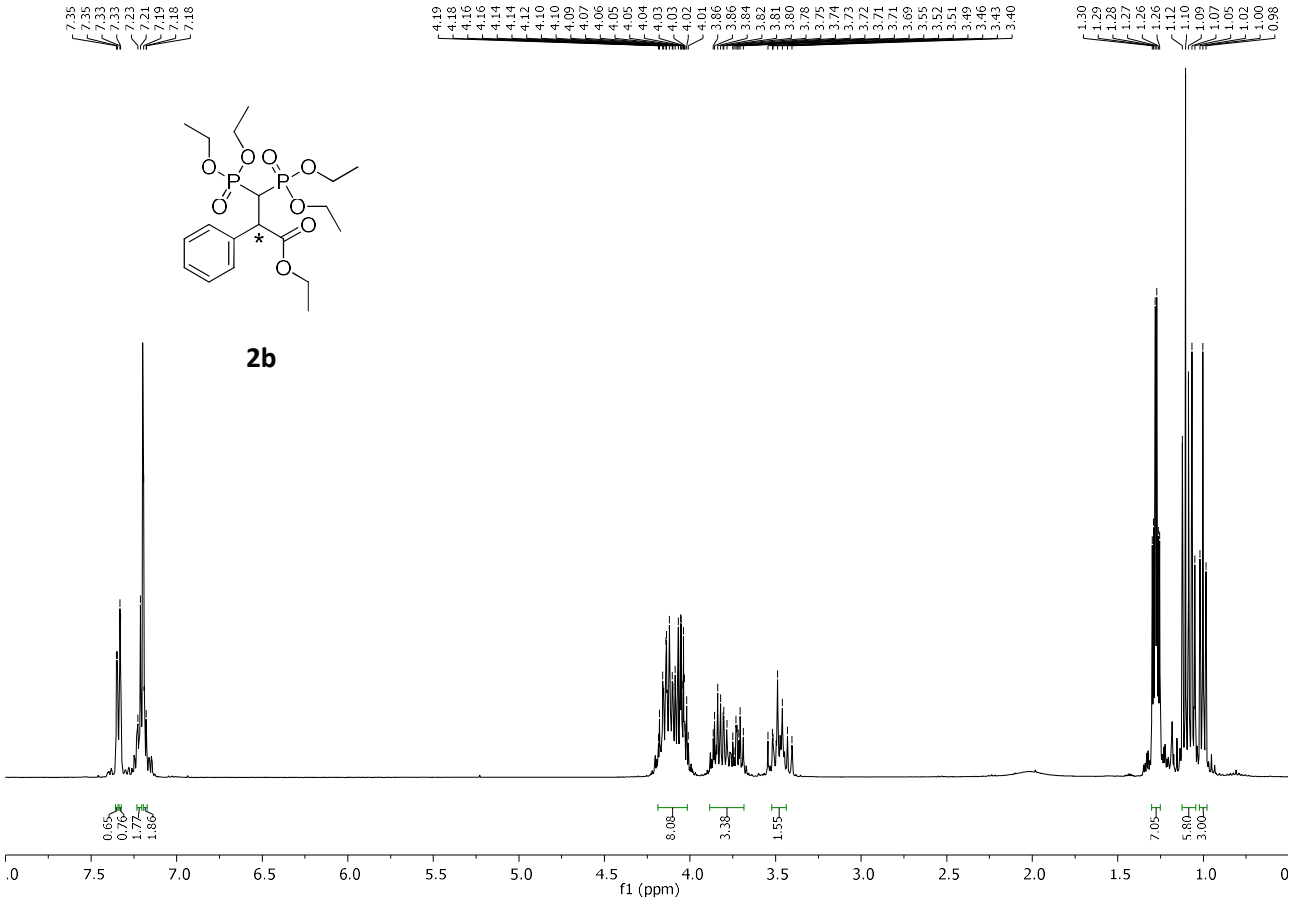


Figure S19. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2b** at 298K**.**

EI- MS, m/z: 450 [M^+], 405 [M^+-(OEt)], 376 [M^+-COOEt-H], 313 [M^+-$PO(OEt)_2$], 269 [M^+-$PO(OEt)_2$-OEt], 241 [M^+-$PO(OEt)_2$-COOEt].

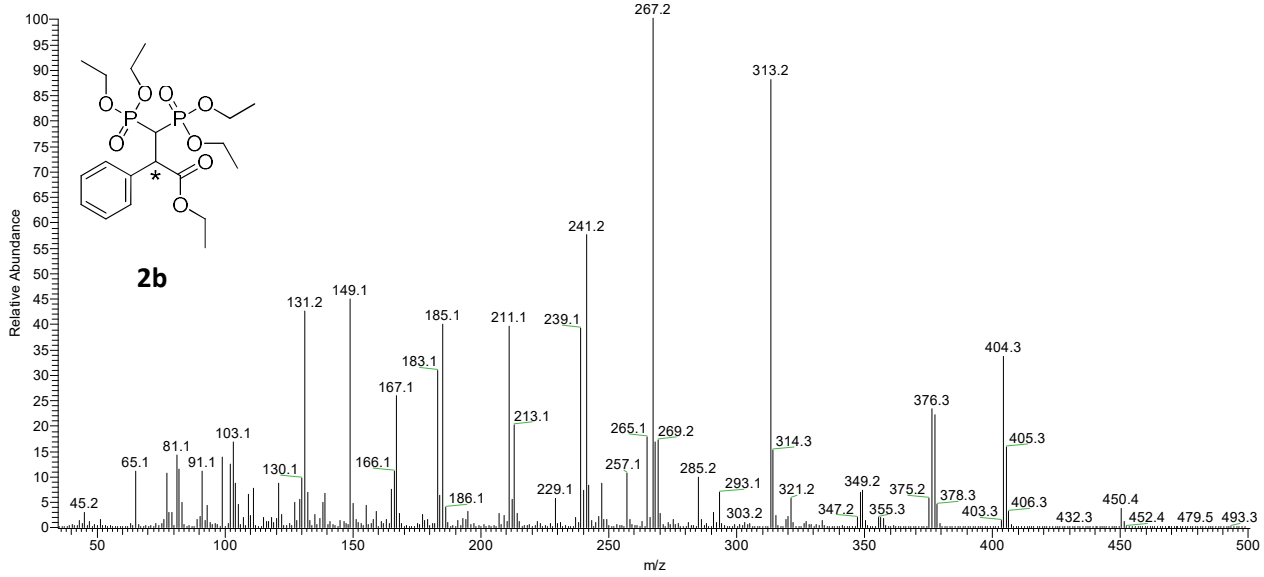
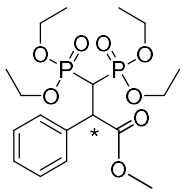


Figure S20. EI-MS spectrum of **2b**.



2c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.33 (d, J=1.5 Hz, 1H), 7.20 (d, J=1.2 Hz, 2H), 7.22 (s, 1H), 4.20 – 4.04 (m, 5H), 3.90 – 3.77 (m, 2H), 3.75 – 3.64 (m, 1H), 3.60 (s, 3H), 3.56 – 3.38 (m, 2H), 1.28 (td, *J* = 7.1, 2.0 Hz, 6H), 1.07 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.1 Hz, 3H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 21.74 (d, *J* = 3.2 Hz, 1P), 20.05 (d, *J* = 3.2 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$): 172.91 (dd, *J* = 18.7, 3.0 Hz), 135.39 (dd, *J* = 14.2, 4.0 Hz), 129.88 (s), 128.02 (s), 127.89 (s), 63.23 (d, J=6.6 Hz), 62.68 (d, J=6.6 Hz), 62.34 (d, J=6.9 Hz), 61.95 (d, J=6.7 Hz),), 52.59 (s), 49.50 – 49.19 (m), 40.84 (dd, J=136.3, 127.7 Hz), 29.70 (s), 16.33 (dd, J=9.2, 6.2 Hz), 16.13 (s), 16.06 (s), ppm.

Elution time: 102', 116'(40'), isopropanol/n-hexane 2/8

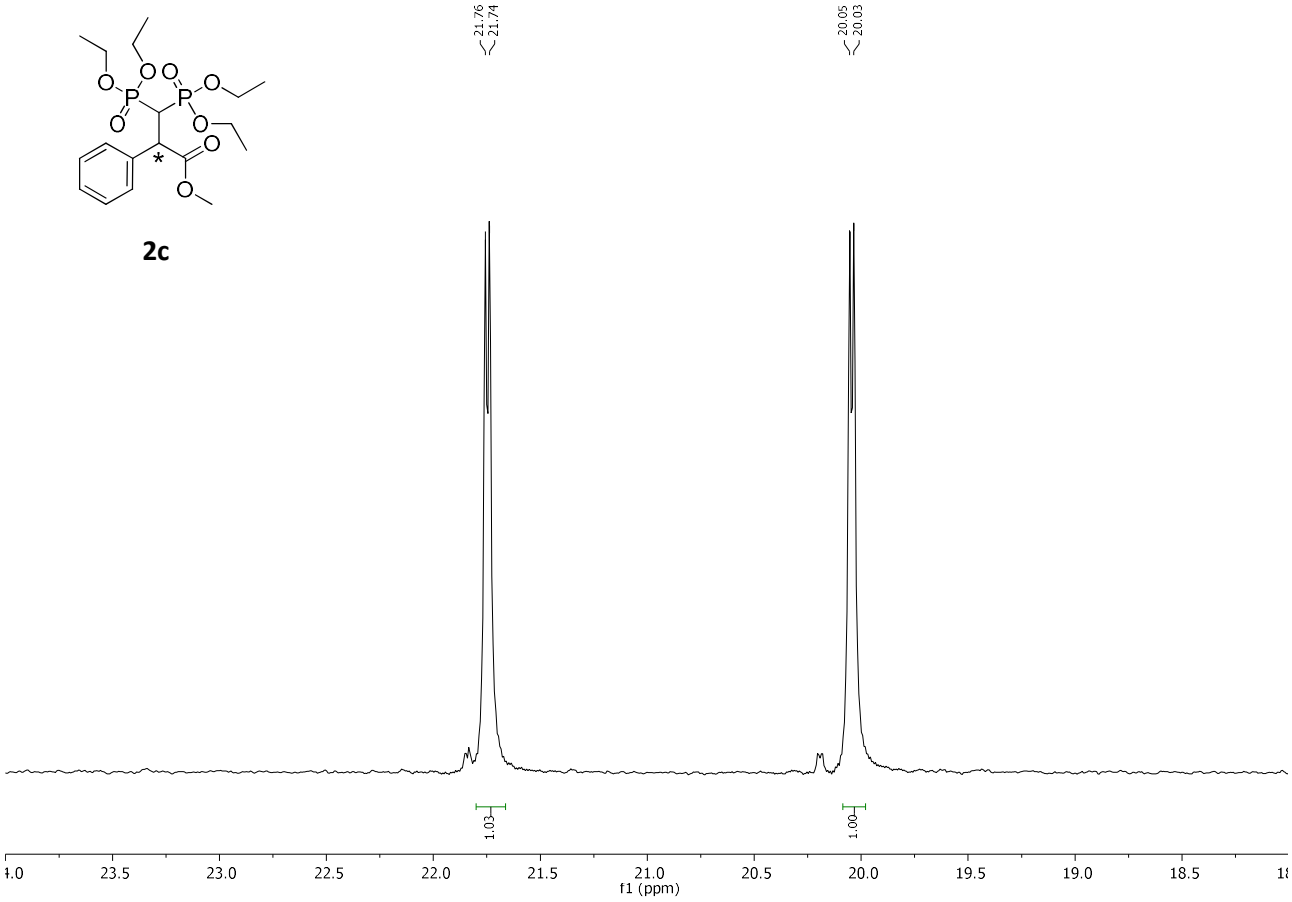


Figure S21. ^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) spectrum of **2c** at 298K.

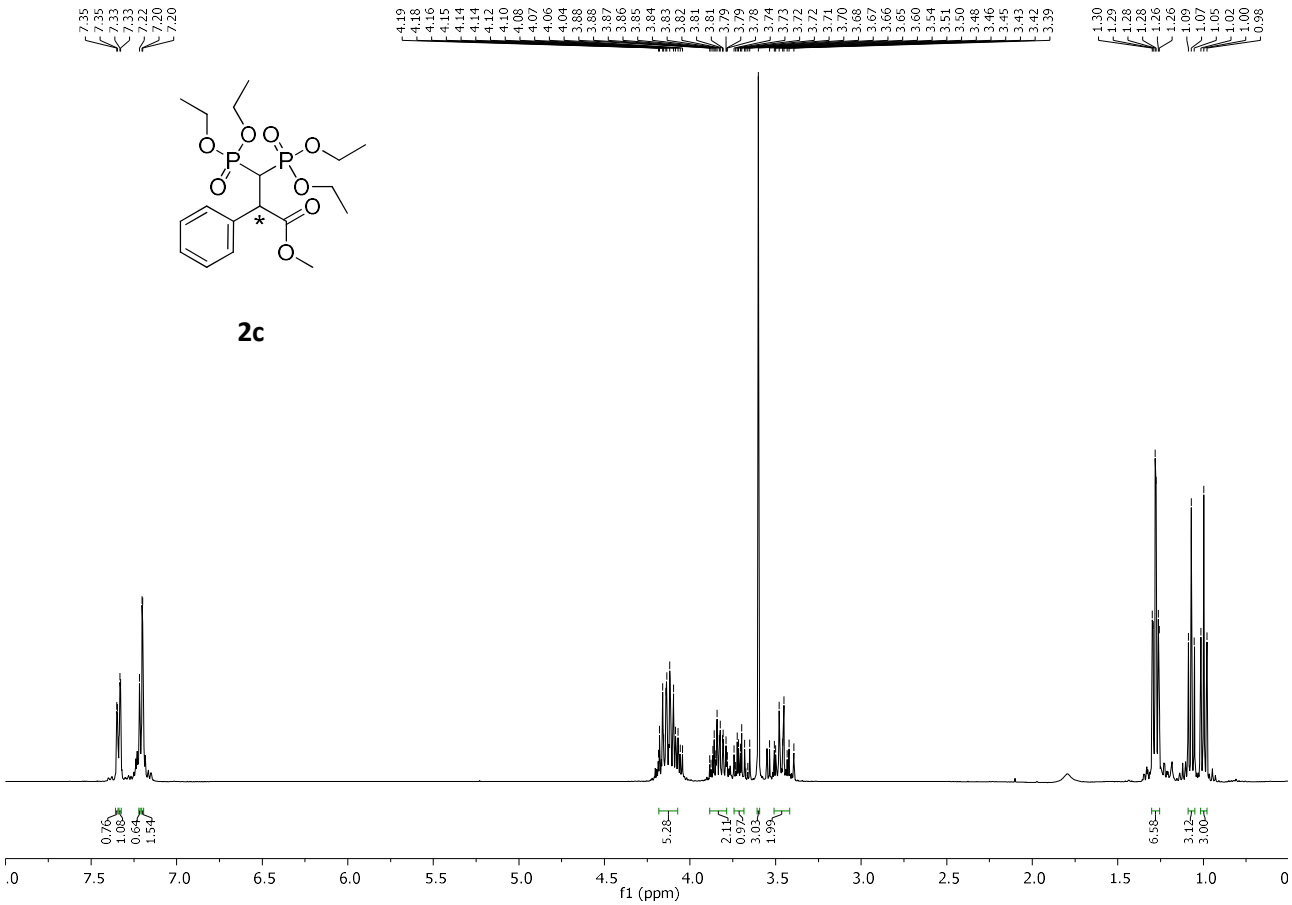


Figure S22. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2c** at 298K.

EI-MS, (70 eV) m/z: 436 $[M]^+$, 405 $[M-OMe]^+$, 404 $[M-Ome-H]^+$, 377 $[M-COOMe]^+$, 299 $[M-PO(OEt)_2]^+$, 268 $[M-PO(OEt)_2–OMe-H]^+$.

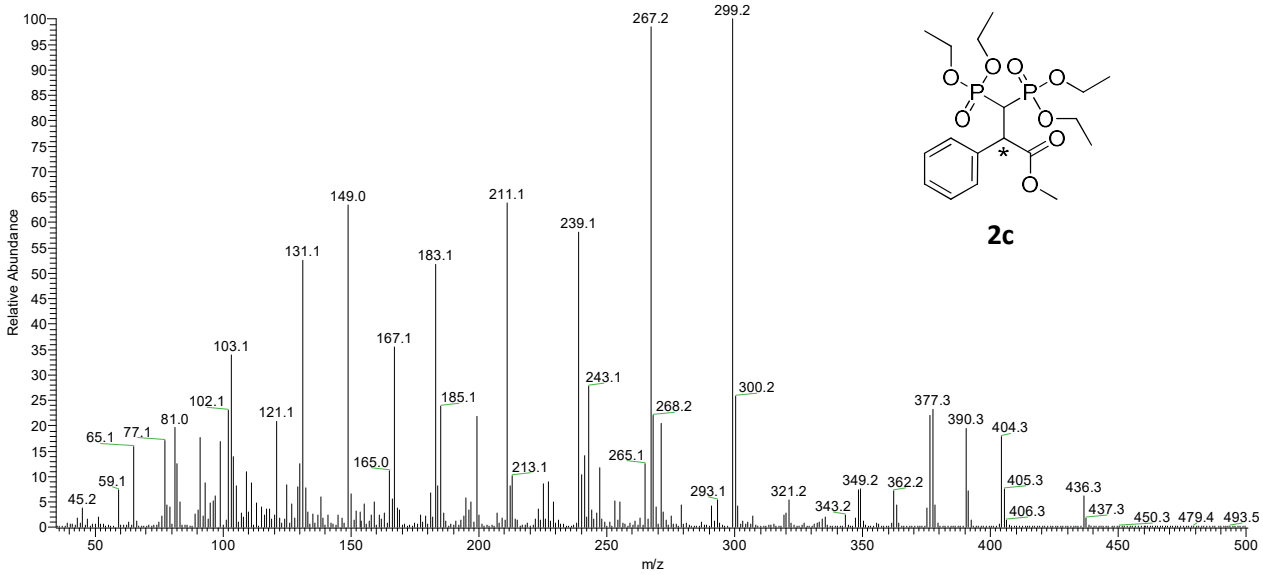
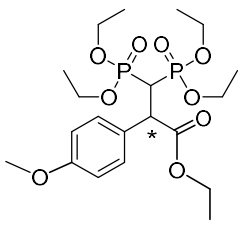


Figure S23. EI-MS spectrum of **2c**.



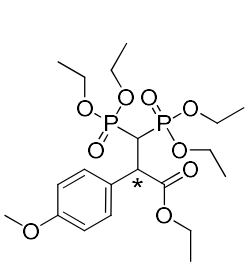
2d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.7 Hz, 2H), 6.74 (d, J=8.7 Hz, 2H), 4.16-4.00 (m, 6H), 3.90-3.73 (m, 6H), 3.71 (s, 3H), 3.58-3.53 (m, 1H), 3.44 (d, J=10.8 Hz, 1H), 1.27 (td, J=7.1, 3.4 Hz, 6H), 1.10 (q, J=7.0 Hz, 6H), 1.03 (t, J=7.1 Hz, 3H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$): δ 21.89 (d, *J* = 2.9 Hz, 1P), 20.35 (d, *J* = 2.9 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 172.36 (dd, J=18.3, 3.1 Hz), 159.24 (s), 131.00 (s), 127.58 (d, J=4.1 Hz), 127.44 (d, J=4.1 Hz), 113.31 (s), 63.12 (d, J=6.6 Hz), 62.23 (d, J=6.7 Hz), 62.33 (d, J=6.9 Hz), 61.99 (d, J=6.7 Hz), 61.33 (s), 55.23 (s), 40.72 (dd, J=136.2, 127.6 Hz), 29.70 (s), 16.42-16.24 (m), 16.14 (d, J=6.5 Hz), 13.91 (s) ppm.

Elution time: 68', 79' (40'), isopropanol/n-hexane 2/8



2d

Figure S24. ^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) spectrum of **2d** at 298K.

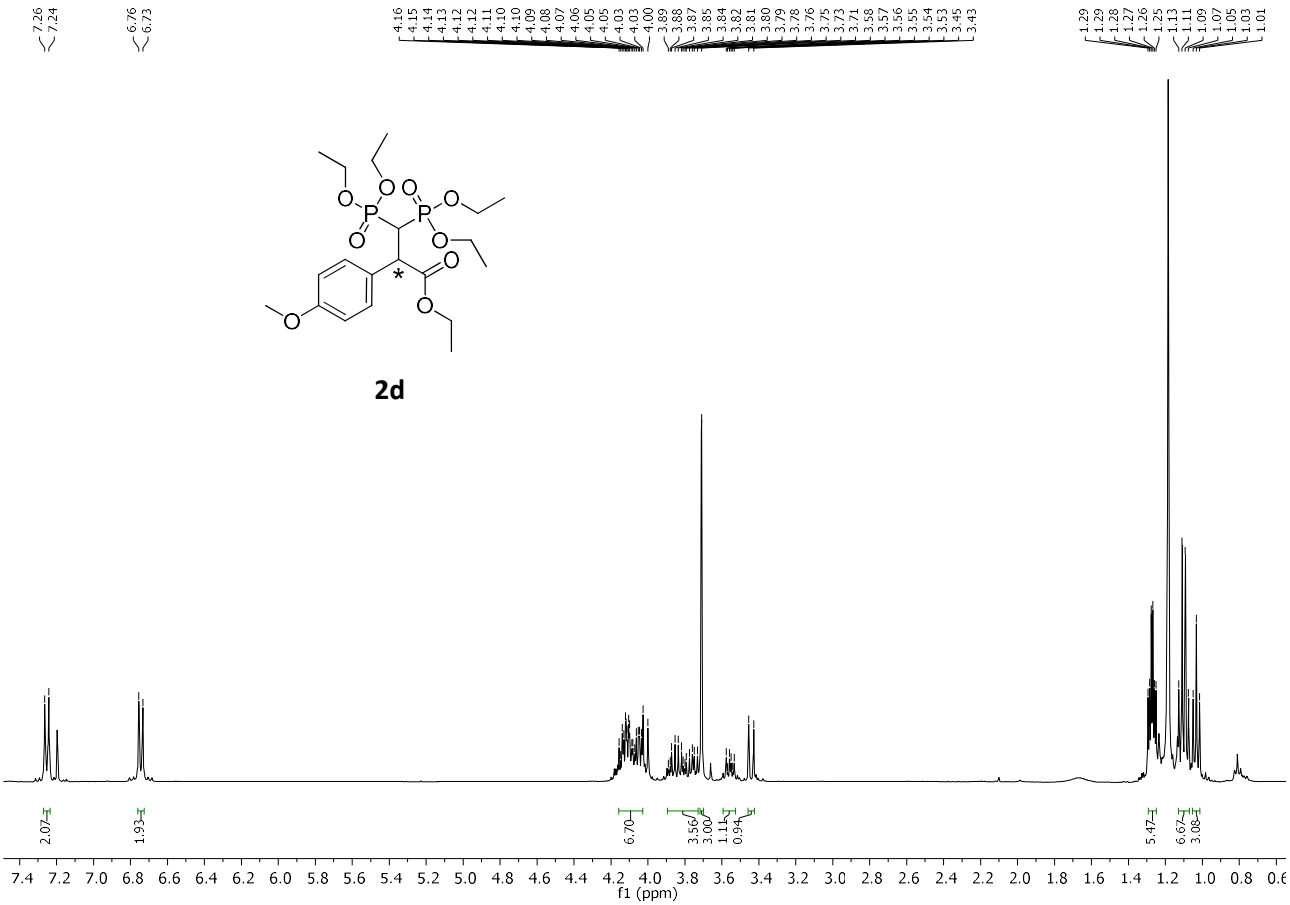


Figure S25. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2d** at 298K.

EI-MS, (70 eV) m/z: 480 $[M]^+$, 435 $[M\text{-}OEt]^+$, 407 $[M\text{ -}COOEt]^+$, 343 $[M\text{ -}PO(OEt)_2]^+$, 298 $[M\text{ -}PO(OEt)_2\text{–}OEt\text{-}H]^+$, 270 $[M\text{-}PO(OEt)_2\text{–}COOEt\text{-}H]^+$.

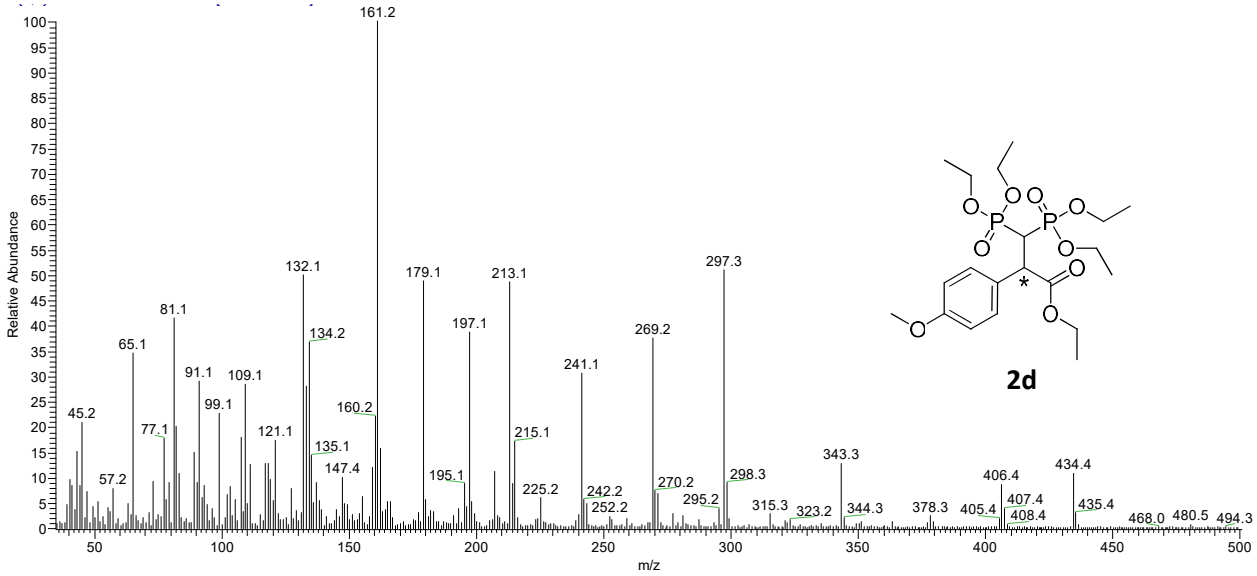


Figure S26. EI-MS spectrum of **2d**.

2e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 6.82 (td, *J* = 7.5, 1.0 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 4.67 (ddd, *J* = 14.1, 9.8, 6.1 Hz, 1H), 4.21 – 3.99 (m, 6H), 3.89 – 3.79 (m, 3H), 3.78 (s, 3H), 3.72 – 3.63 (m, 1H), 3.56 (td, *J* = 23.8, 9.9 Hz, 1H), 1.26 (td, *J* = 7.1, 3.0 Hz, 6H), 1.13 – 1.05 (m, 9H) ppm.

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) δ 21.03 (d, *J* = 0.8 Hz, 1P), 19.60 (d, *J* = 0.8 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 172.19 (dd, *J* = 16.3, 2.7 Hz), 157.49 (s), 130.69 (s), 128.89 (s), 124.20 (dd, *J* = 12.4, 5.1 Hz), 120.00 (s), 110.73 (s), 63.15 (d, *J* = 6.5 Hz), 62.54 (d, *J* = 6.7 Hz), 62.23 (d, *J* = 6.7 Hz), 61.18 (s), 55.68 (s), 41.42 (t, *J* = 2.7 Hz), 39.64 (dd, *J* = 135.6, 129.2 Hz), 16.47 – 16.01 (m), 13.95 (s).

EI-MS, (70 eV) m/z: 480 $[M]^+$, 343 $[M - PO(OEt)_2]^+$, 407 $[M - COOEt]^+$.

Elution time: 26', 53' (18'), isopropanol/n-hexane 2/8

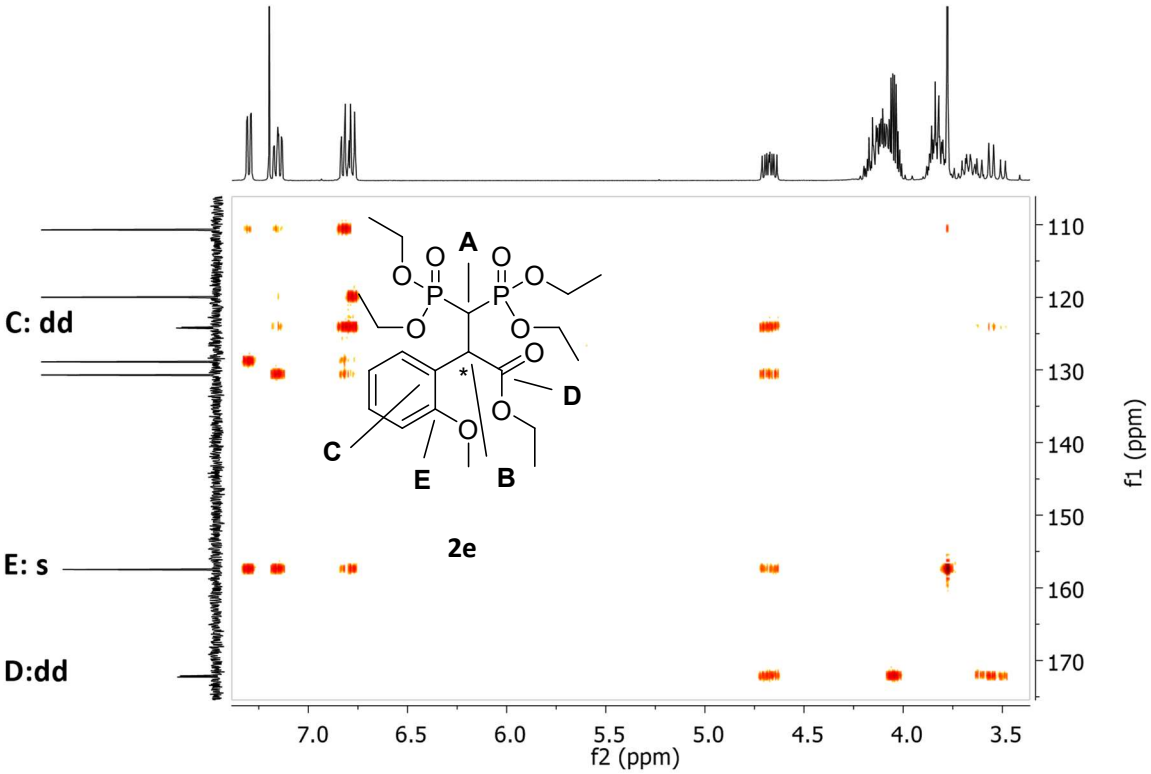


Figure S27. 2D-NMR HMBC spectrum of **2e** at 298K.

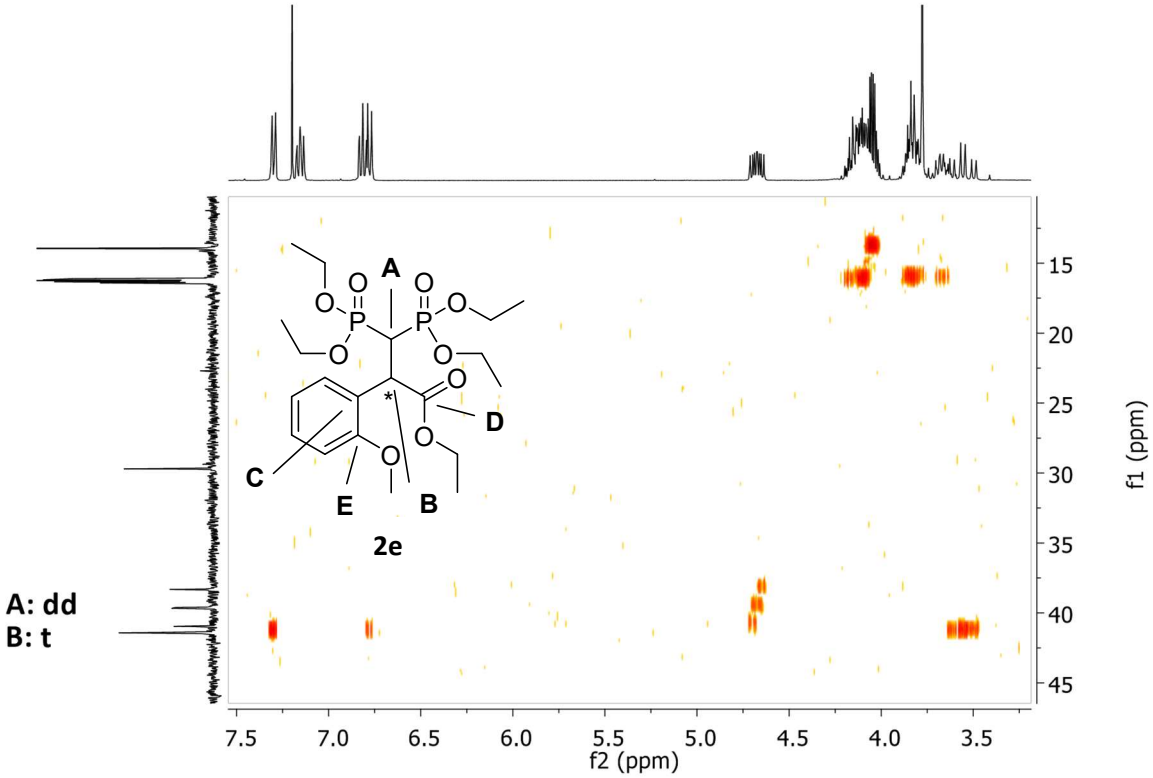


Figure S28. 2D-NMR HMBC spectrum of **2e** at 298K.

2f

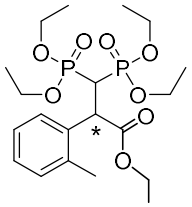
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.41 – 6.34 (m, 2H), 4.61 (ddd, *J* = 13.9, 9.9, 6.0 Hz, 1H), 4.26 – 4.02 (m, 6H), 3.96 – 3.81 (m, 4H), 3.79 (s, *J* = 8.4 Hz, 3H), 3.75 (s, 3H), 3.60 (td, *J* = 23.6, 9.7 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 6H), 1.17 – 1.10 (m, 9H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 22.48 (s. 1P), 21.07 (s, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 172.32 (dd, *J* = 16.4, 2.5 Hz), 160.40 (s), 158.46 (s), 131.31 (s), 116.52 (dd, *J* = 12.8, 5.1 Hz), 103.97 (s), 98.31 (s), 63.20 (d, *J* = 6.2 Hz), 62.60 (d, *J* = 6.6 Hz), 62.36 (d, *J* = 6.4 Hz), 61.12 (s), 55.65 (s), 55.30 (s), 40.88 (s), 39.57 (dd, *J* = 128.3, 121.5 Hz), 29.70 (s), 16.51 – 16.06 (m), 13.99 (s) ppm.

EI-MS, (70 eV) m/z: 510 $[M]^+$, 464 $[M - OEt - H]^+$, 373 $[M - PO(OEt)_2]^+$.

Elution time: 27’, 40’ (21’), isopropanol/n-hexane 2/8



2g

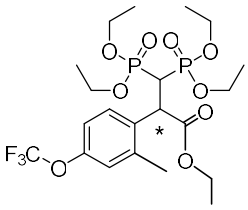
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 1H), 7.16 – 7.08 (m, 3H), 4.42 (td, *J* = 11.1, 3.6 Hz, 1H), 4.31 – 4.15 (m, 4H), 4.14 – 4.01 (m, 2H), 3.99 – 3.84 (m, 2H), 3.75 – 3.65 (m, 1H), 3.57 (td, *J* = 22.6, 11.5 Hz, 1H), 3.44 – 3.31 (m, 1H), 2.51 (s, 3H), 1.36 (td, *J* = 7.1, 1.6 Hz, 6H), 1.15 (q, *J* = 7.3 Hz, 6H), 1.03 (t, *J* = 7.1 Hz, 3H).

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 22.25 (d, *J* = 4.0 Hz, 1P), 20.90 (d, *J* = 4.0 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 172.75 (dd, *J* = 20.0, 1.5 Hz), 137.71 (s), 134.13 (dd, *J* = 14.8, 4.0 Hz), 130.50 (s), 129.01 (s), 127.66 (s), 125.56 (s), 63.34 (d, *J* = 6.5 Hz), 62.75 (d, *J* = 6.7 Hz), 62.48 (d, *J* = 6.9 Hz), 62.01 (d, *J* = 6.7 Hz), 61.39 (s), 44.08 (t, *J* = 2.8 Hz), 40.41 (dd, *J* = 137.0, 127.1 Hz), 20.28 (s), 16.55 (d, *J* = 6.1 Hz), 16.44 (d, *J* = 6.2 Hz), 16.30 (d, *J* = 2.9 Hz), 16.24 (d, *J* = 2.6 Hz), 13.99 (s) ppm.

EI-MS, (70 eV) m/z: 464 $[M]^+$, 419 $[M\text{-}OEt]^+$, 391 $[M\text{ -}COOEt]^+$, 327 $[M\text{ -}PO(OEt)_2]^+$.

Elution time: 21', 27' (8'), isopropanol/n-hexane 2/8



2h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 1H), 7.02 – 6.94 (m, 2H), 4.40 (td, *J* = 11.0, 3.9 Hz, 1H), 4.30 – 4.16 (m, 4H), 4.15 – 4.05 (m, 2H), 4.01 – 3.87 (m, 2H), 3.79 – 3.68 (m, 1H), 3.61 – 3.39 (m, 2H), 2.53 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 6H), 1.20 – 1.12 (m, 6H), 1.04 (t, *J* = 7.1 Hz, 3H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 21.81 (d, *J* = 3.6 Hz, 1P), 20.68 (d, *J* = 3.6 Hz, 1P) ppm

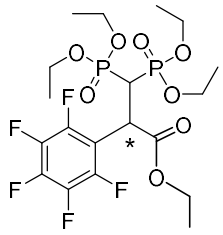
^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 172.40 (dd, *J* = 19.5, 1.7 Hz), 148.45 (dd, *J* = 3.3, 1.6 Hz), 140.12 (s), 133.02 (dd, *J* = 14.9, 4.1 Hz), 130.59 (s), 122.59 (s), 120.61 (d, *J* = 256.9 Hz), 117.83 (s), 63.46 (d, *J* = 6.6 Hz), 62.83 (t, *J* = 6.5 Hz), 62.05 (d, *J*= 6.8 Hz), 61.62 (s), 43.72 (t, *J* = 2.5 Hz), 40.41 (dd, *J* = 137.0, 127.5 Hz), 20.40 (s), 16.54 (d, *J* = 6.0 Hz), 16.43 (d, *J* = 6.2 Hz), 16.26 (d, *J* = 6.2 Hz), 16.14 (d, *J* = 6.1 Hz), 13.99 (s) ppm.
^{19}F {^{1}H}-NMR (376 MHz, $CDCl_3$) δ -57.73 (s) ppm.

EI-MS, (70 eV) m/z: 548 $[M]^+$, 503 $[M\text{ -}OEt]^+$, 475 $[M\text{ -}COOEt]^+$, 411 $[M\text{ -}PO(OEt)_2]^+$.

Elution time: 6', 8' (4'), isopropanol/n-hexane 2/8

The **2i** product as not formed therefore no characterization is provided.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (ddd, *J* = 13.8, 10.5, 3.1 Hz, 1H), 4.30 – 4.13 (m, 6H), 4.08 – 3.94 (m, 4H), 3.72 (td, *J* = 23.0, 10.5 Hz, 1H), 1.36 (td, *J* = 7.0, 4.9 Hz, 6H), 1.25 – 1.17 (m, 9H) ppm.



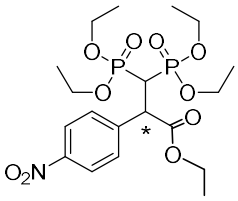
2j

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 20.86 (d, *J* = 6.8 Hz, 1P), 19.09 (d, *J* = 6.8 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 168.88 (d, *J* = 15.9 Hz), 147.72 – 147.22 (m), 145.26 – 144.73 (m), 142.72 – 142.22 (m), 139.18 – 138.09 (m), 136.44 – 135.82 (m), 63.71 (d, *J* = 6.6 Hz), 63.10 (dd, *J* = 8.0, 6.8 Hz), 62.87 (d, *J* = 6.7 Hz), 62.42 (s), 38.13 (s), 37.44 (dd, *J* = 134.0, 129.5 Hz), 16.51 (d, *J* = 6.0 Hz), 16.41 (d, *J* = 6.2 Hz), 16.07 (t, *J* = 6.0 Hz), 14.01 (s) ppm.

^{19}F {^{1}H}-NMR (376 MHz, $CDCl_3$) δ -138.01 – -138.22 (m), -152.25 (t, *J* = 20.9 Hz), -161.69 – -161.89 (m) ppm.

EI-MS, (70 eV) m/z: 540 $[M]^+$, 495 $[M - OEt]^+$, 467 $[M - COOEt]^+$, 403 $[M - PO(OEt)_2]^+$.

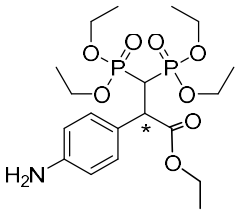


2k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 4.27 – 4.08 (m, 7H), 4.07 – 3.81 (m, 3H), 3.68 – 3.48 (m, 2H), 1.35 (td, *J* = 6.9, 3.5 Hz, 8H), 1.19 (t, *J* = 7.1 Hz, 6H), 1.13 (t, *J* = 7.1 Hz, 3H) ppm.

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$): δ 22.05 (d, *J* = 2.5 Hz, 1P), 20.49 (d, *J* = 2.5 Hz, 1P) ppm. (**2k'**)

^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 20.79 (d, *J* = 2.6 Hz, 1P), 19.22 (d, *J* = 2.6 Hz, 1P) ppm. (**2k**)



2k'

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 172.63 (dd, *J* = 18.7, 2.7 Hz), 146.17 (s), 130.92 (s), 125.50 – 125.05 (m), 114.66 (s), 111.93 (s), 63.19 (d, *J* = 6.6 Hz), 62.68 (d, *J* = 6.6 Hz), 62.37 (d, *J* = 6.8 Hz), 62.11 (d, *J* = 6.7 Hz), 61.33 (s), 48.86 – 48.47 (m), 40.83 (dd, *J* = 136.4, 127.0 Hz), 16.46 (t, *J* = 6.6 Hz), 16.31 (d, *J* = 2.3 Hz), 16.25 (d, *J* = 2.6 Hz), 14.04 (s) ppm.

Elution time: 118', 141' (15'), isopropanol/n-hexane 2/8

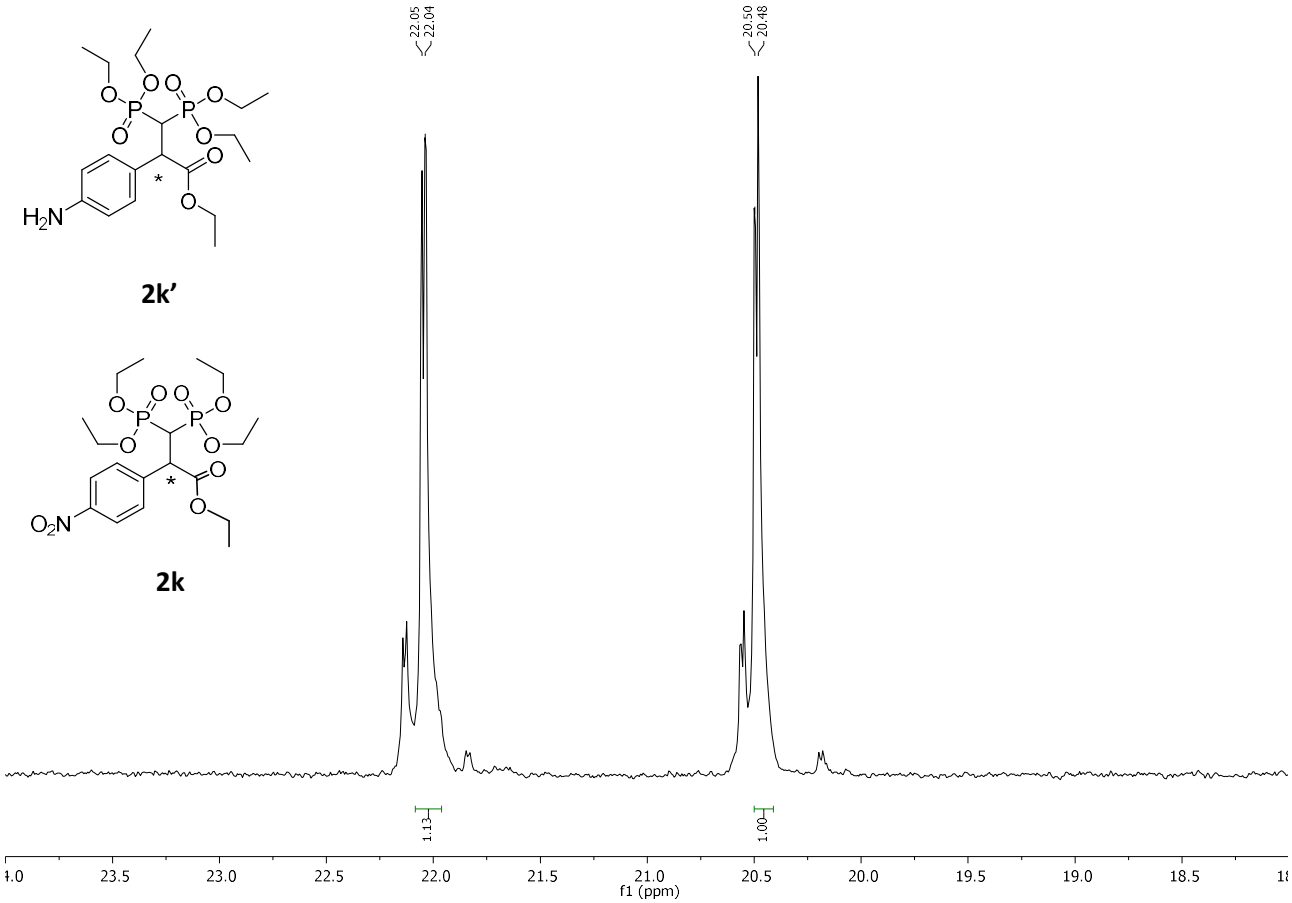


Figure S29. ^{31}P $\{^{1}H\}$-NMR (162 MHz, $CDCl_3$) spectrum of **2k** and **2k'** at 298K.

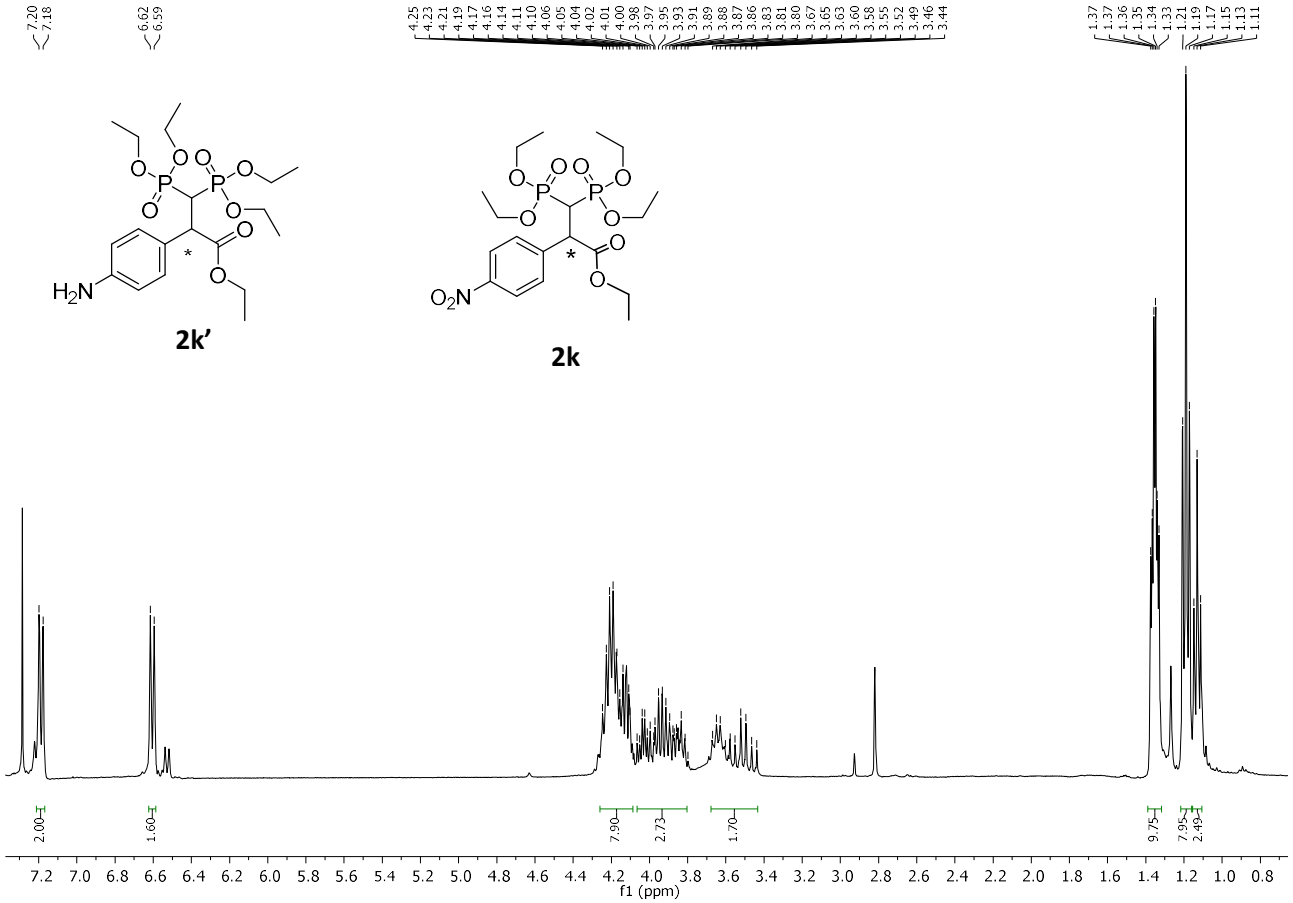


Figure S30. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2k** and **2k'** at 298K.

EI-MS, (70 eV) m/z: 465 $[M]^+$, 419 $[M\text{-}OEt\text{-}H]^+$, 391 $[M\text{-}COOEt\text{-}H]^+$, 328 $[M\text{-}PO(OEt)_2]^+$, 283 $[M\text{-}PO(OEt)_2\text{–}OEt\text{-}H]^+$, 255 $[M\text{-}PO(OEt)_2\text{–}COOEt\text{-}H]^+$.

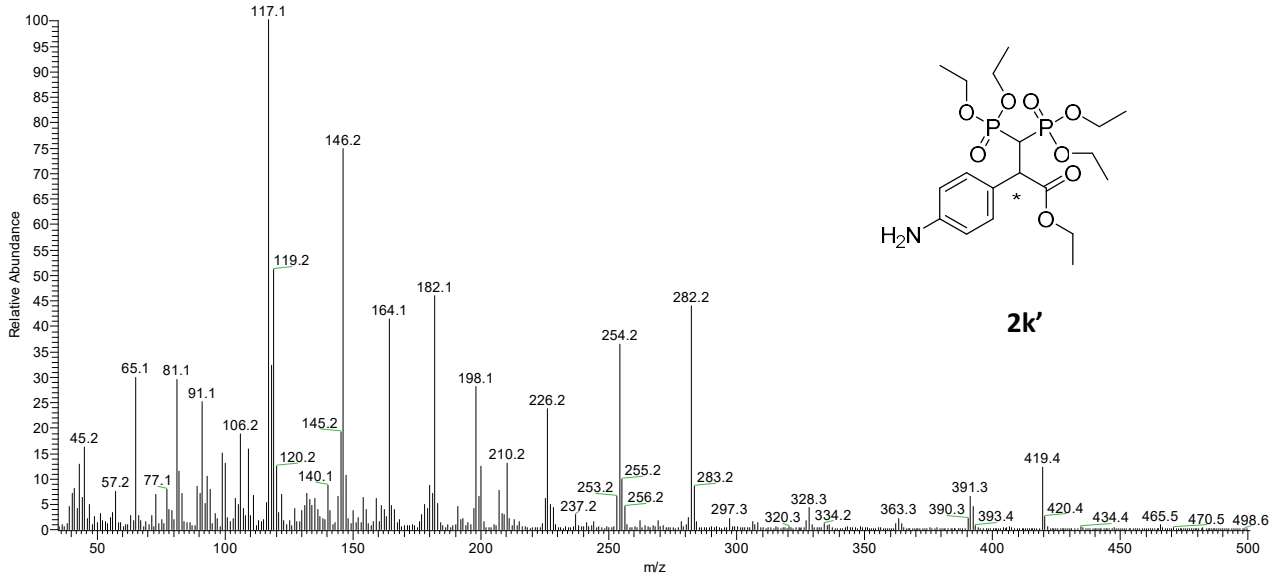
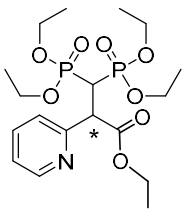


Figure S31. EI-MS spectrum of **2k'**.



2l

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.8, 1.8, 0.8 Hz, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.18 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 4.37 (ddd, *J* = 11.6, 10.0, 7.6 Hz, 1H), 4.27 – 4.13 (m, 6H), 4.08 – 3.98 (m, 1H), 3.96 – 3.88 (m, 1H), 3.87 – 3.71 (m, 3H), 1.36 – 1.29 (m, 6H), 1.22 – 1.09 (m, 9H) ppm.

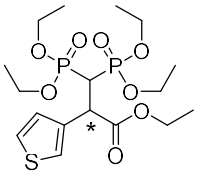
^{31}P {^{1}H}-NMR (162 MHz, $CDCl_3$) δ 21.63 (d, *J* = 3.2 Hz, 1P), 20.44 (d, *J* = 3.2 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 170.90 (dd, *J* = 18.0, 6.1 Hz), 148.95 (s), 136.22 (s), 125.09 (s), 122.51 (s), 63.11 (d, *J* = 6.5 Hz), 62.77 – 62.51 (m), 62.09 (d, *J* = 6.9 Hz), 61.51 (s), 16.37 (d, *J* = 6.1 Hz), 16.28 (d, *J* = 6.2 Hz), 16.12 (dd, *J* = 6.3, 4.8 Hz), 13.95 (s) ppm.

EI-MS, (70 eV) m/z: 451 $[M]^+$, 406 $[M - OEt]^+$, 378 $[M - COOEt]^+$, 314 $[M - PO(OEt)_2]^+$.

General procedure for catalytic addition of boronic acids to substituted VBP

In a vial equipped with magnetic stirring bar, 100 mg of **1a** (0.33 mmol), 2 mL of anhydrous toluene, 12 mg of $Cu(OTf)_2$ (10 mol% with respect to **1a**) were added followed by 1.5 equivalents of boronic acid with respect to **1a**. The vial was thermostatted at 70°C for 18h under vigorous stirring. Subsequently, the mixture was diluted with 5 mL of dichloromethane, the organic phase was extracted with a saturated aqueous solution of EDTA and washed with water. The product of the reaction was isolated by means of preparative TLC with 6:4 n-hexane:acetone eluent and was characterized with ^{1}H, ^{31}P NMR analysis.



3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.19 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.14 (dd, *J* = 5.0, 1.3 Hz, 1H), 4.33 (dd, *J* = 20.1, 9.9 Hz, 1H), 4.24–4.10 (m, 6H), 4.03–3.87 (m, 3H), 3.82–3.72 (m, 1H), 3.50 (td, *J* = 23.4, 9.6 Hz, 1H), 1.33 (td, *J* = 7.1, 4.6 Hz, 6H), 1.24–1.14 (m, 9H) ppm.

^{31}P {1H}-NMR (162 MHz, $CDCl_3$) δ 21.48 (d, *J* = 2.4 Hz, 1P), 20.24 (d, *J* = 2.4 Hz, 1P) ppm.

^{13}C {1H}-NMR (101 MHz, $CDCl_3$) δ 171.75 (dd, *J* = 15.5, 5.3 Hz), 135.38 (dd, *J* = 13.5, 4.7 Hz), 128.91 (s), 125.08 (s), 124.34 (s), 63.08 (d, *J* = 6.7 Hz), 62.68 (d, *J* = 6.6 Hz), 62.48 (d, *J* = 6.8 Hz), 62.09 (d, *J* = 6.7 Hz), 61.50 (s), 44.54 (t, *J* = 3.0 Hz), 40.75 (dd, *J* = 136.0, 128.9 Hz), 16.32 (t, *J* = 6.1 Hz), 16.21 (d, *J* = 0.5 Hz), 16.14 (d, *J* = 0.9 Hz), 13.94 (s) ppm.

EI-MS, (70 eV) m/z: 456 $[M]^+$, 410 $[M - OEt - H]^+$, 382 $[M - COOEt - H]^+$, 319 $[M - PO(OEt)_2]^+$.

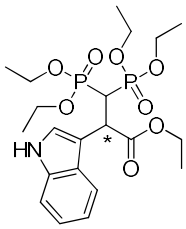
General procedure for catalytic addition of indoles to substituted VBP

Catalytic tests in organic solvent

In a vial equipped with magnetic stirring bar 0.3 mmol of substituted VBP, 2 mL of anhydrous 1,2-dichloroethane was added followed by 12 mg of $Cu(OTf)_2$ (10 mol% with respect to BP) and 1.5 equivalents of indole with respect to BP. The vial was thermostatted at 70°C for 18h under vigorous stirring. Subsequently, the mixture was diluted with 5 mL of dichloromethane, the organic phase was extracted with a saturated aqueous solution of EDTA and washed with water. The product of the reaction was isolated by means of preparative TLC (conditions reported for each compounds) and characterized with ^{1}H, ^{31}P ^{13}C and EI-MS analyses.

Catalytic tests in water

In a vial equipped with magnetic stirring bar 100 mg of substituted VBP (0.3 mmol), 2 mL of distilled water, 100 mg of sodium dodecylsulfate (SDS) were added followed by 12 mg of $Cu(OTf)_2$ (10 mol% with respect to BP) and 1.5 equivalents of indole with respect to BP. The vial was thermostatted at 70°C for 18h under vigorous stirring. Subsequently, the mixture was diluted with 5 mL of ethyl acetate and the organic phase was extracted with a saturated aqueous solution of EDTA and washed with water. The product of the reaction was isolated by preparative TLC with 6/4 n-hexane/acetone eluent and was characterized with ^{1}H, ^{31}P and EI-MS analyses.



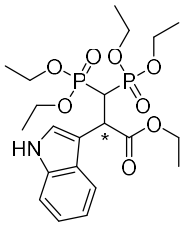
4aa

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1H) 7.76 (d, J=7.3 Hz, 1H), 7.35-7.27 (m, 2H), 7.17-7.06 (m, 2H), 4.51 (ddd, J=11.6, 9.9, 7.8 Hz, 1H), 4.28-4.04 (m, 6H), 3.97-3.64 (m, 4H), 3.46-3.38 (m, 1H), 1.32 (t, J=7.1 Hz, 6H), 1.16 (t, J=7.1 Hz, 3H), 1.05 (t, J=7.1 Hz, 3H), 0.86 (t, J=7.1 Hz, 3H) ppm

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 20.70 (d, *J* = 2.4 Hz, 1P), 19.42 (d, *J* = 2.4 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$): δ 172.22 (dd, *J* = 16.8, 3.2 Hz), 136.32 (s), 126.92 (s), 126.07 (s), 121.48 (s), 119.93 (s), 119.25 (s), 111.43 (s), 108.84 (dd, *J* = 14.3, 4.9 Hz), 63.09 (d, *J* = 6.6 Hz), 62.73 (d, *J* = 6.7 Hz), 62.60 (d, *J* = 7.0 Hz), 62.02 (d, *J* = 6.9 Hz), 61.34 (s), 41.41 (s), 40.11 (dd, *J* = 137.3, 127.9 Hz), 16.37 (t, *J* = 5.6 Hz), 16.07 (d, *J* = 6.5 Hz), 15.67 (d, *J* = 6.7 Hz), 14.01 (s) ppm.

Elution mixture: Ethyl Acetate/Acetone 8/2



4aa

Figure S32. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **4aa** at 298K.

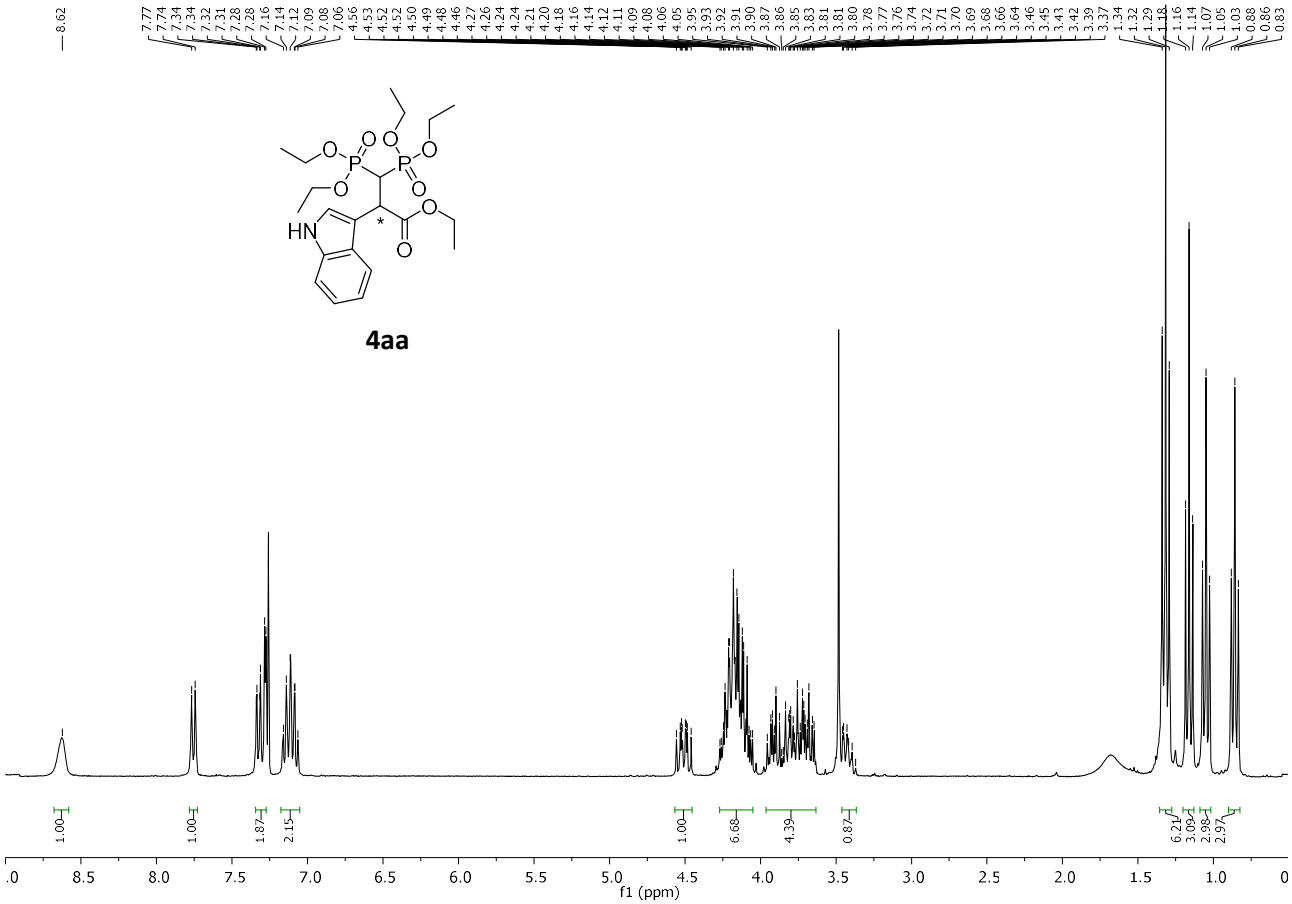


Figure S33. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4aa** at 298K.

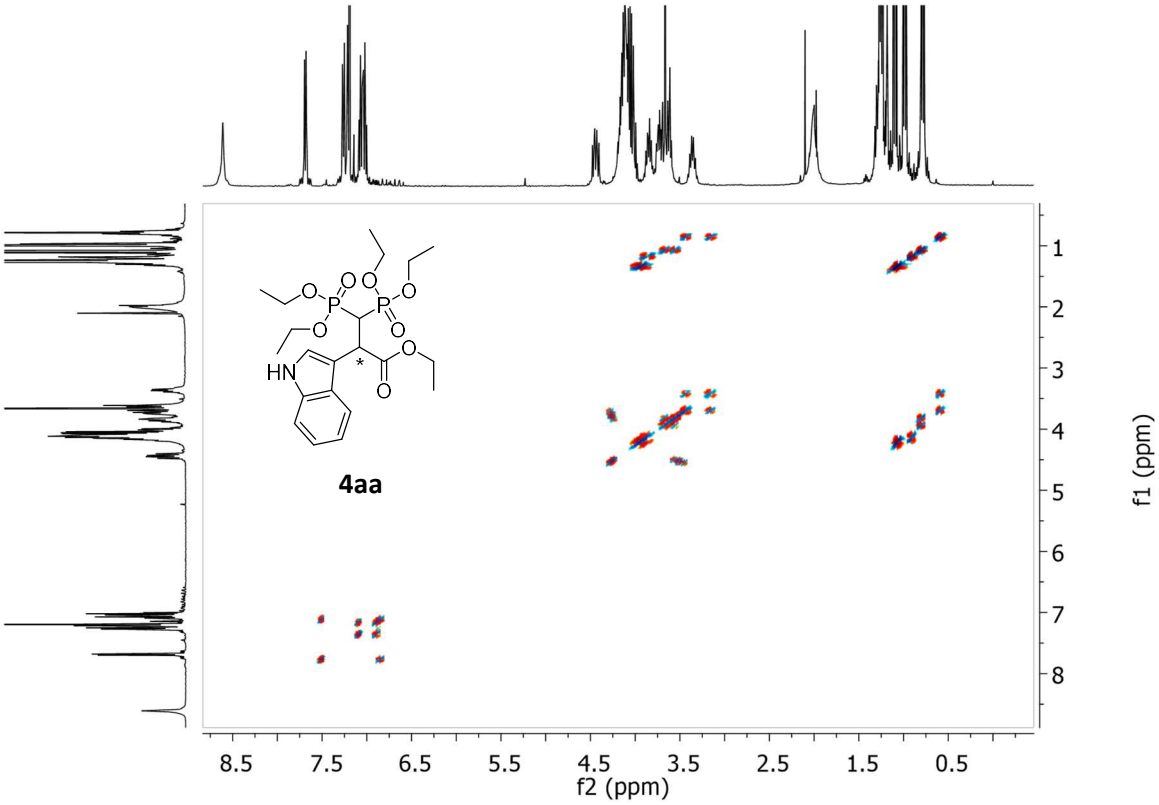


Figure S34: 2D-NMR COSY spectrum of **4aa** at 298K.

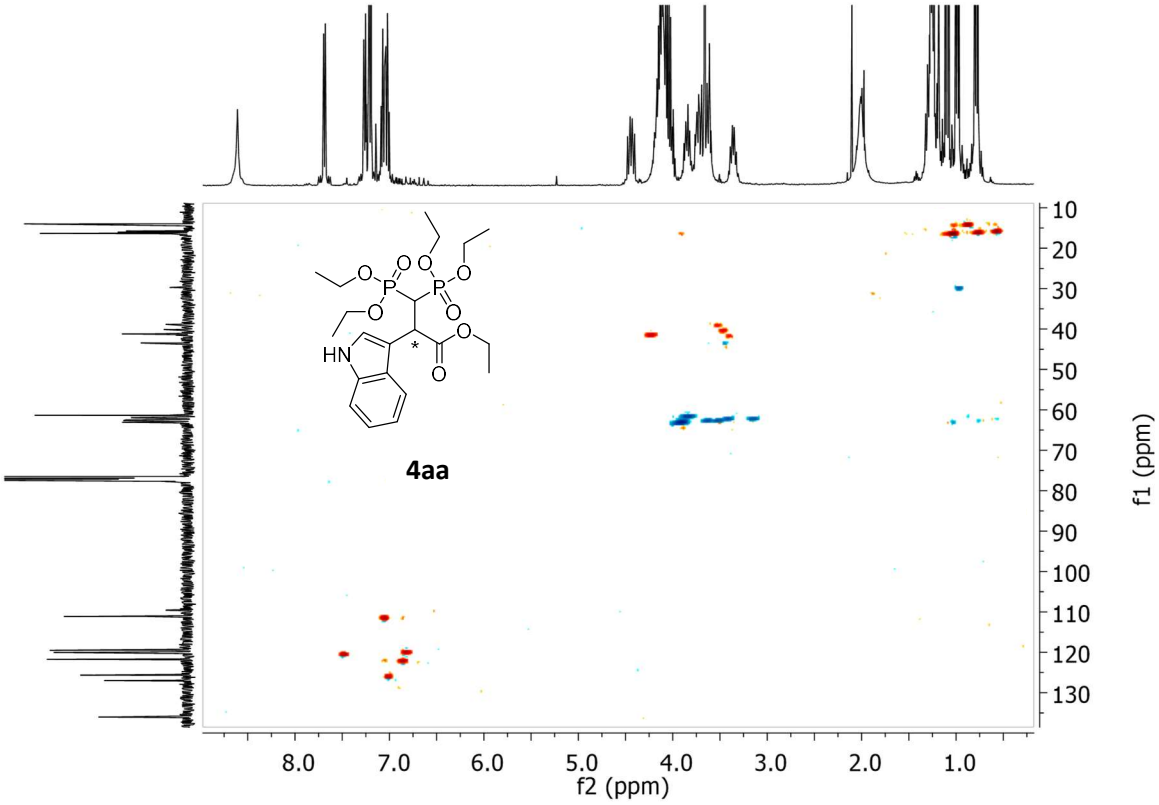


Figure S35: 2D-NMR HSQC spectrum of **4aa** at 298K.

EI-MS, (70 eV) m/z: 489 [M^+], 444 [M^+-OEt], 306 [M^+-$PO(OEt)_2$-OEt-H], 278 [M^+-$PO(OEt)_2$-COOEt-H].

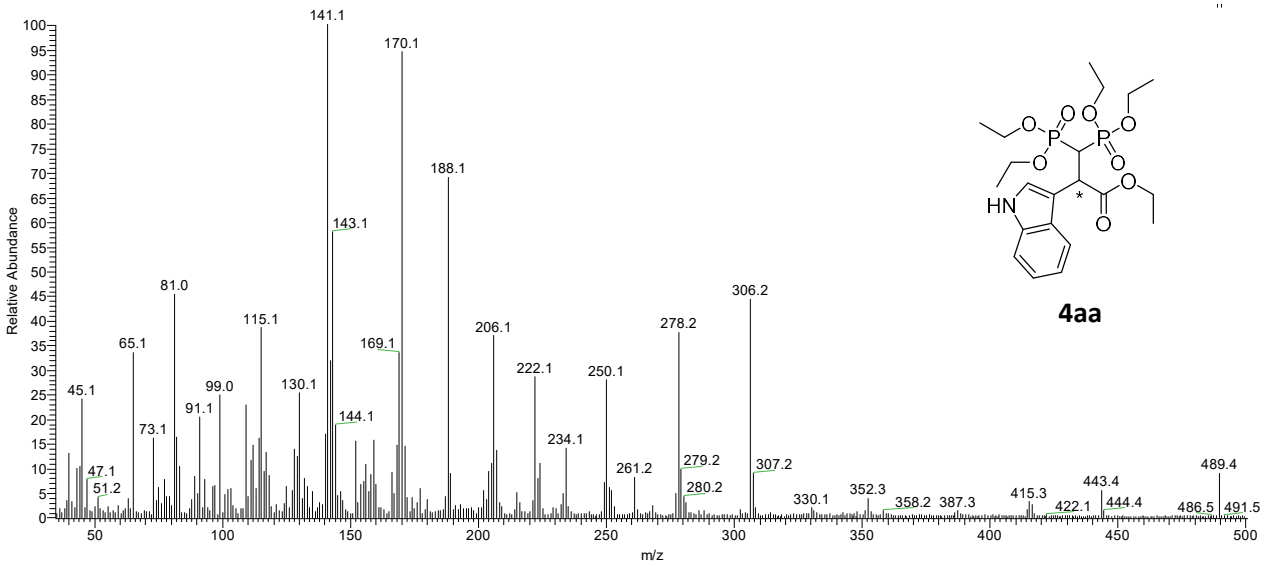
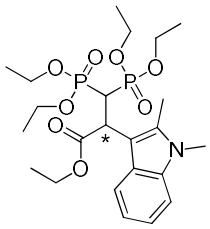


Figure S36. EI-MS spectrum of **4aa.**



4ab

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J=7.5 Hz, 1H), 7.21 (d, J=7.7 Hz, 1H), 7.15-7.01 (m, 2H), 4.43 (ddd, J=11.7, 11.0, 2.6 Hz, 1H), 4.37-4.19 (m, 4H), 4.14 (ddd, J=14.3, 9.0, 5.4 Hz, 2H), 4.03 (ddd, J=15.2, 11.2, 7.6 Hz, 2H), 3.95-3.75 (m, 2H), 3.66 (s, 3H), 3.46 (ddd, J=13.9, 7.0, 2.6 Hz, 1H), 2.50 (s, 3H), 1.40 (td, J=7.1, 2.4 Hz, 6H), 1.16 (t, J=7.1 Hz, 3H), 1.01 (t, J=7.1 Hz, 3H), 0.65 (t, J=7.0 Hz, 3H) ppm

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 21.34 (d, J=2.2 Hz, 1P), 19.65 (d, J=2.2 Hz, 1P) ppm

^{13}C {^{1}H}-NMR (101 MHz, $CDCl_3$) δ 171.87 (d, *J* = 19.8 Hz), 136.81 (s), 136.47 (s), 127.26 (s), 120.53 (s), 120.16 (s), 119.24 (s), 108.48 (s), 104.89 (dd, *J* = 16.8, 4.4 Hz), 63.25 (d, *J* = 6.6 Hz), 62.68 (d, *J* = 6.6 Hz), 62.41 (d, *J* = 6.9 Hz), 61.66 (d, *J* = 7.0 Hz), 61.25 (s), 41.27 (s), 39.04 (dd, *J* = 138.6, 125.6 Hz), 29.81 (s), 16.54 (dd, *J* = 9.5, 6.1 Hz), 16.06 (d, *J* = 6.5 Hz), 15.61 (d, *J* = 6.6 Hz), 14.14 (s), 10.99 (s) ppm.

Elution mixture: Ethyl Acetate/Acetone 1/1

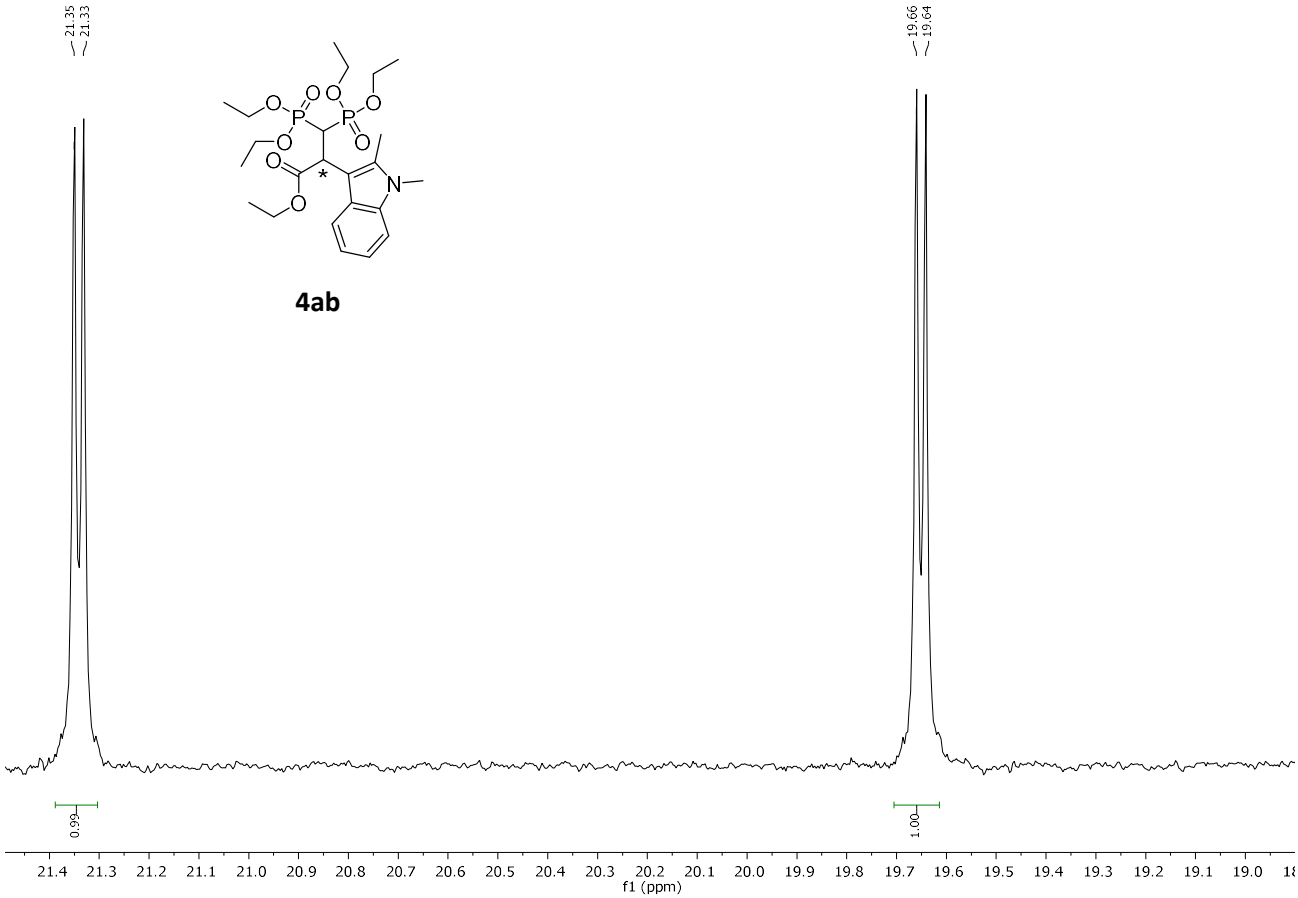


Figure S37. ^{31}P $\{^{1}H\}$-NMR (122 MHz, $CDCl_3$) spectrum of **4ab** at 298K.

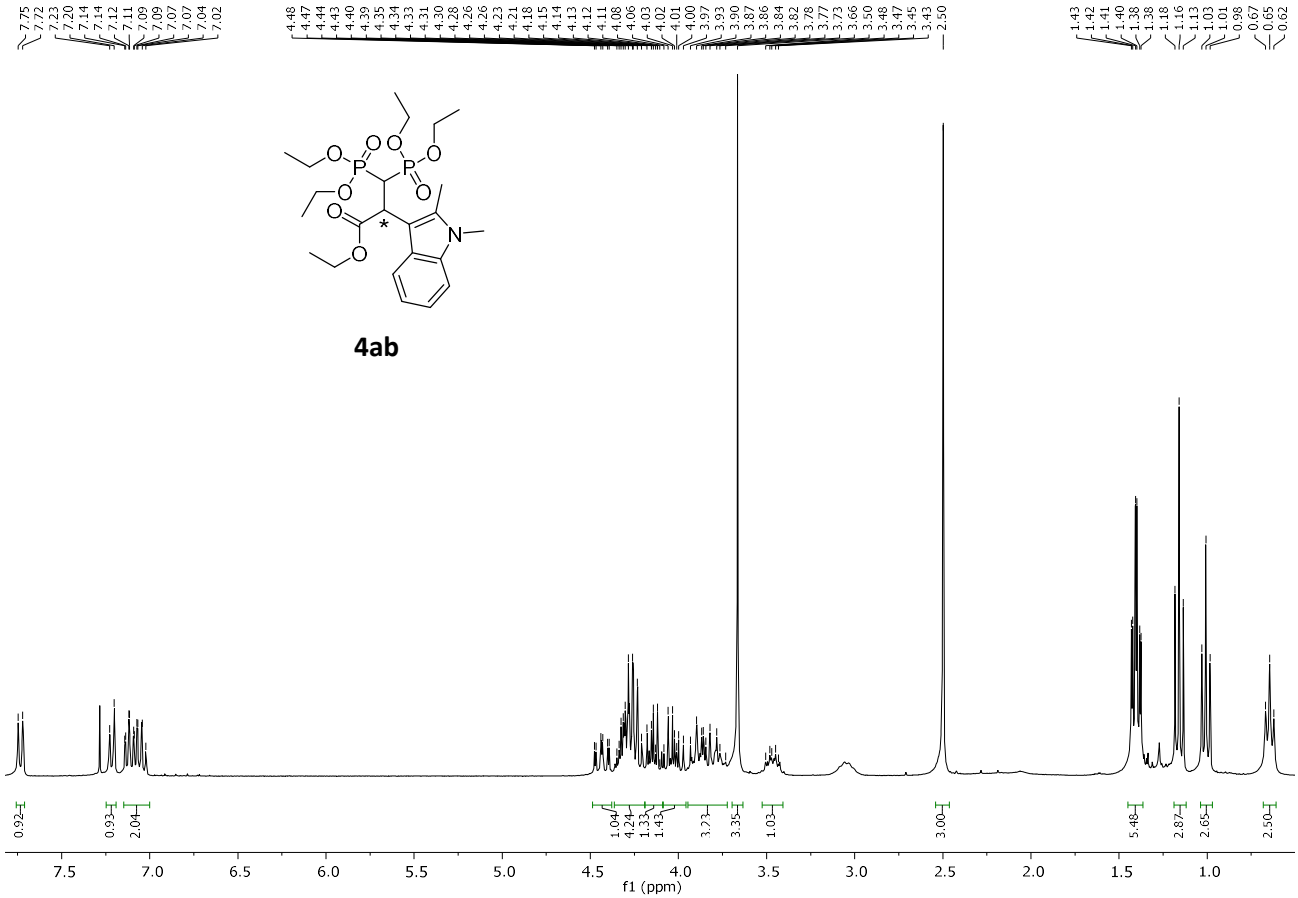


Figure S38. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4ab** at 298K.

EI-MS, (70 eV) m/z: 517 [M^+], 472 [M^+-OEt], 444 [M^+-COOEt], 380 [M^+-$PO(OEt)_2$].

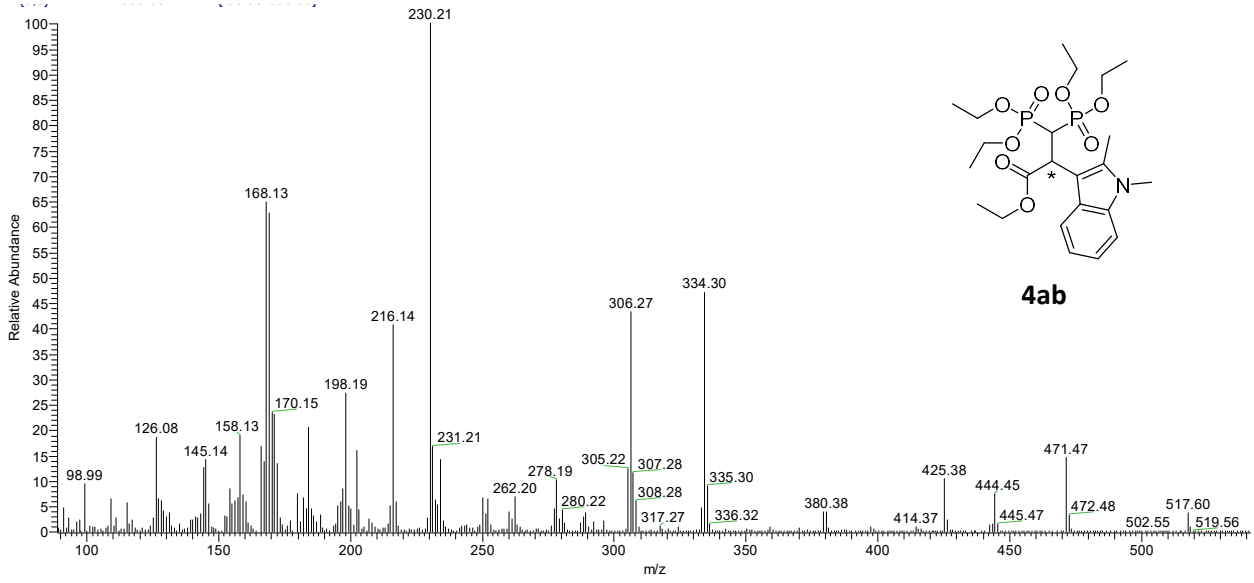
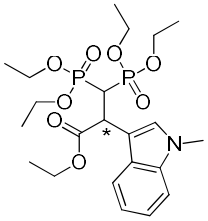


Figure S39. EI-MS spectrum of **4ab**



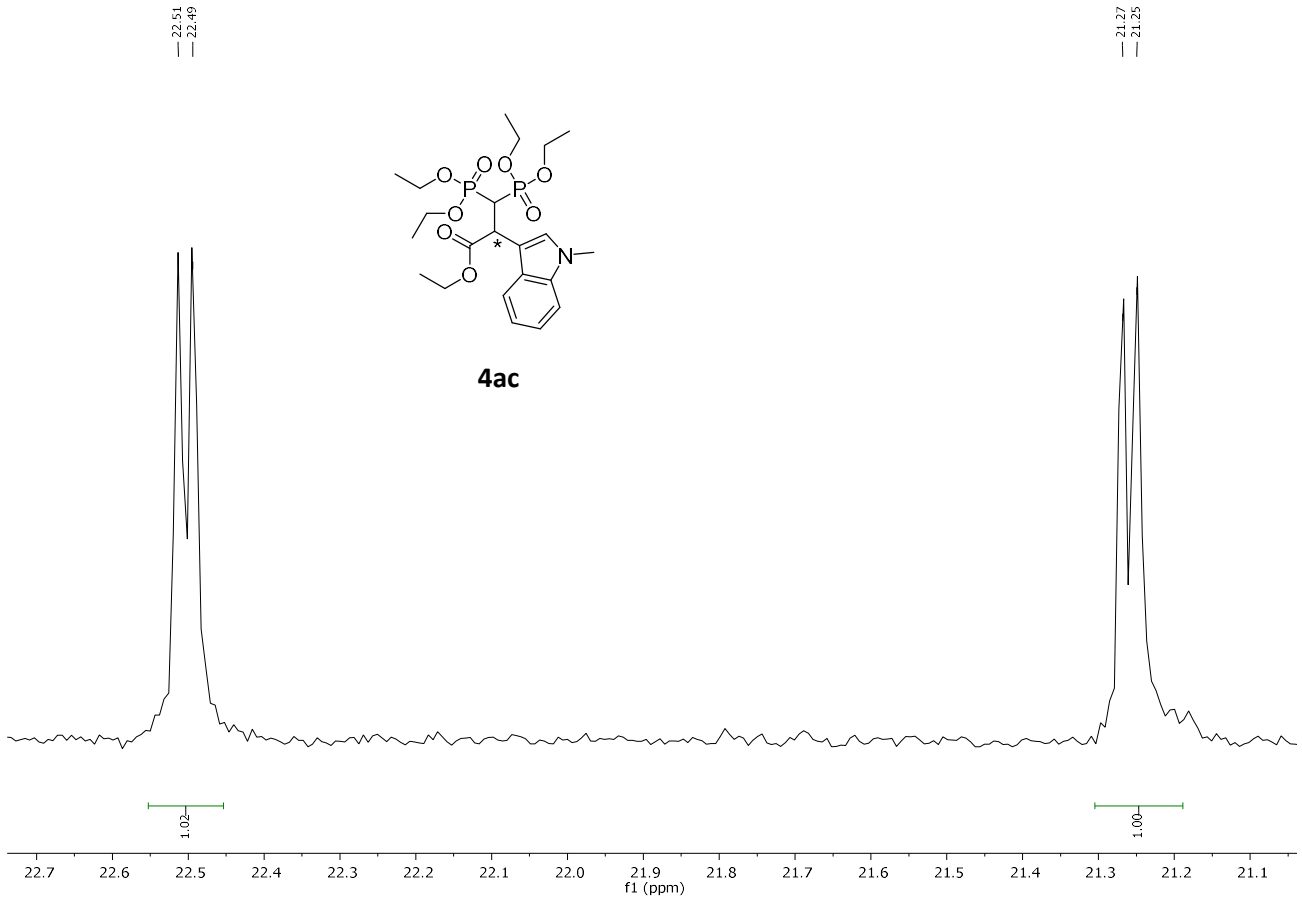
4ac

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J=7.8 Hz, 1H), 7.24 (s, 1H), 7.21-7.14 (m, 2H), 7.13-7.06 (m, 1H), 4.48 (ddd, J=11.5, 10.0, 7.8 Hz, 1H), 4.25-4.04 (m, 6H), 3.93-3.78 (m, 2H), 3.75 (s, 3H), 3.66 (ddd, J=18.6, 11.4, 6.6 Hz, 2H), 3.50-3.39 (m, 1H), 1.31 (td, J=7.1 Hz, 6H), 1.18 (t, J=7.1 Hz, 3H), 1.03 (t, J=7.1 Hz, 3H), 0.86 (t, J=7.1 Hz, 3H) ppm

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 22.50 (d, J=2.3 Hz, 1P), 21.26 (d, J=2.3 Hz, 1P) ppm

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$): δ 172.68 (dd, J=16.5, 3.8 Hz), 137.14 (s), 130.28 (s), 128.01 (s), 121.82 (s), 120.62 (s), 119.56 (s), 109.42 (s), 108.71 (dd, J=14.1, 4.7 Hz), 63.41 (d, J=6.5 Hz), 62.98 (d, J=6.6 Hz), 62.68 (d, J=6.7 Hz), 62.23 (d, J=6.6 Hz), 61.74 (s), 41.39 (s), 3.22 (s), 48.83 (dd, J=136.8, 127.7 Hz), 30.13 (s), 16.72 (t, J=5.5 Hz), 16.38 (d, J=6.6 Hz), 16.17 (d, J=6.6 Hz), 14.42 (s) ppm.

Elution mixture: Ethyl Acetate/Acetone 1/1



4ac

Figure S40. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **4ac** at 298K.

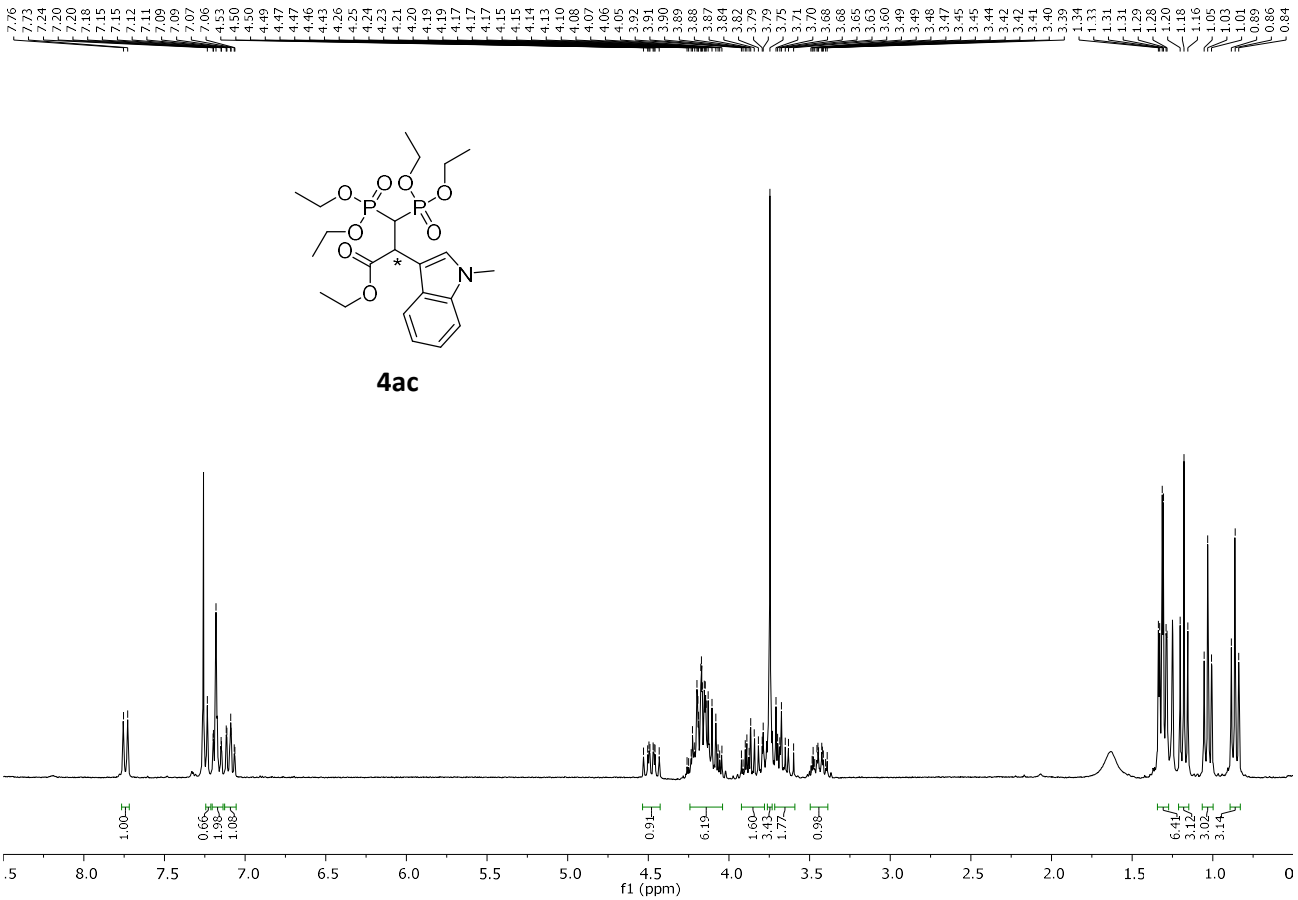


Figure S41. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4ac** at 298K.

EI-MS, (70 eV) m/z: 503 [M^+], 458 [M^+-OEt-H], 430 [M^+-COOEt], 366 [M^+-$PO(OEt)_2$], 321 [M^+-$PO(OEt)_2$-OEt-H], 293 [M^+-$PO(OEt)_2$-COOEt-H].

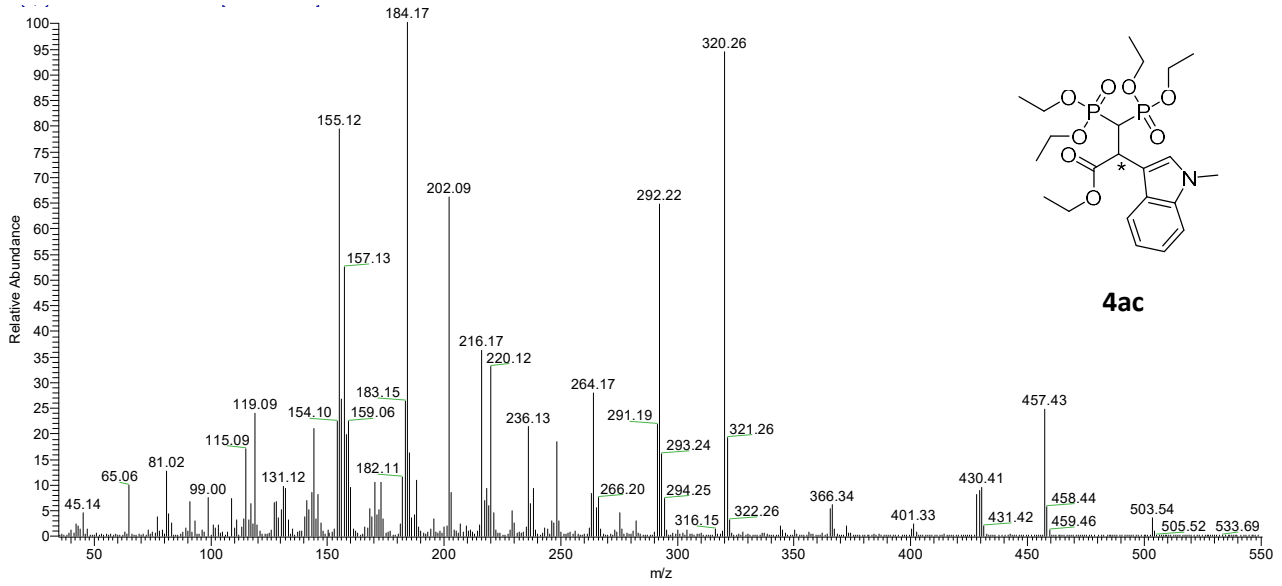
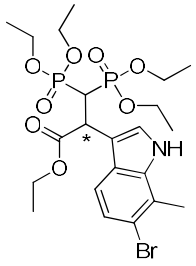


Figure S42. EI-MS spectrum of **4ac**



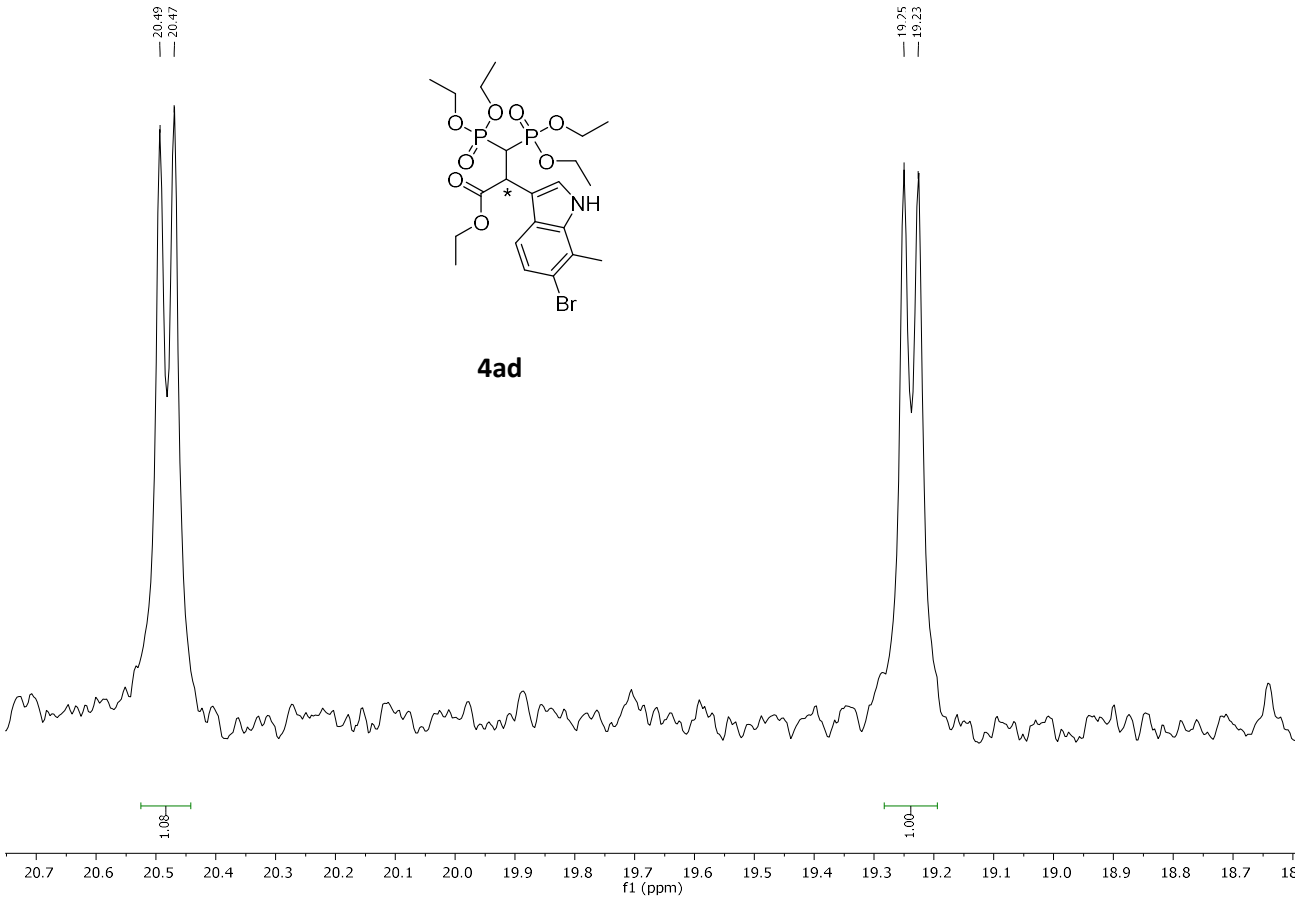
4ad

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.32 – 7.16 (m, 2H), 4.45 (ddd, *J* = 11.7, 9.8, 8.2 Hz, 1H), 4.28 – 4.08 (m, 6H), 3.98 – 3.48 (m, 5H), 2.50 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H) ppm

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 20.48 (d, J=2.9 Hz, 1P), 19.24 (d, J=2.9 Hz, 1P) ppm

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 172.37 (dd, *J* = 17.3, 5.8 Hz), 134.70 (s), 128.55 (s), 127.42 (s), 125.73 (s), 122.50 (s), 119.98 (s), 112.55 (s), 109.98 (dd, *J* = 14.6, 3.5 Hz), 63.44 (d, *J* = 6.6 Hz), 63.12 (d, *J* = 6.6 Hz), 62.89 (d, *J* = 6.9 Hz), 62.48 (d, *J* = 6.7 Hz), 61.90 (s), 41.46 – 41.29 (m), 40.58 (dd, *J* = 136.7, 128.7 Hz), 30.13 (s), 16.73 (t, *J* = 6.6 Hz), 16.41 (d, *J* = 6.6 Hz), 16.19 (d, *J* = 6.7 Hz), 14.41 (s) ppm.

Elution mixture: n-Hexane/Acetone 1/1



4ad

Figure S43. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **4ad** at 298K.

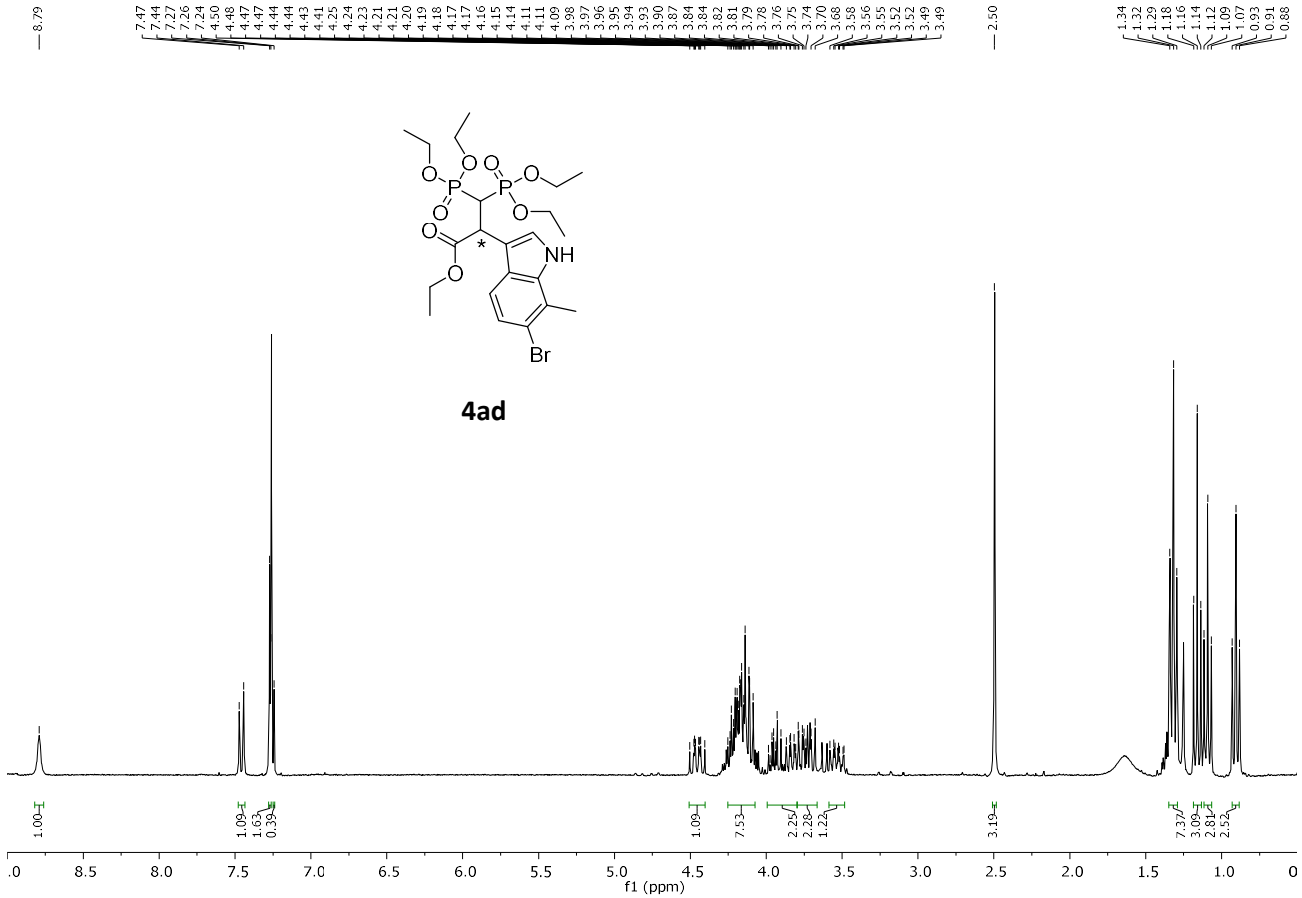


Figure S44. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4ad** at 298K.

EI-MS, (70 eV) m/z: 535 [M^+-OEt-H], 444 [M^+-$PO(OEt)_2$], 400 [M^+-$PO(OEt)_2$-OEt], 372 [M^+-$PO(OEt)_2$-COOEt].

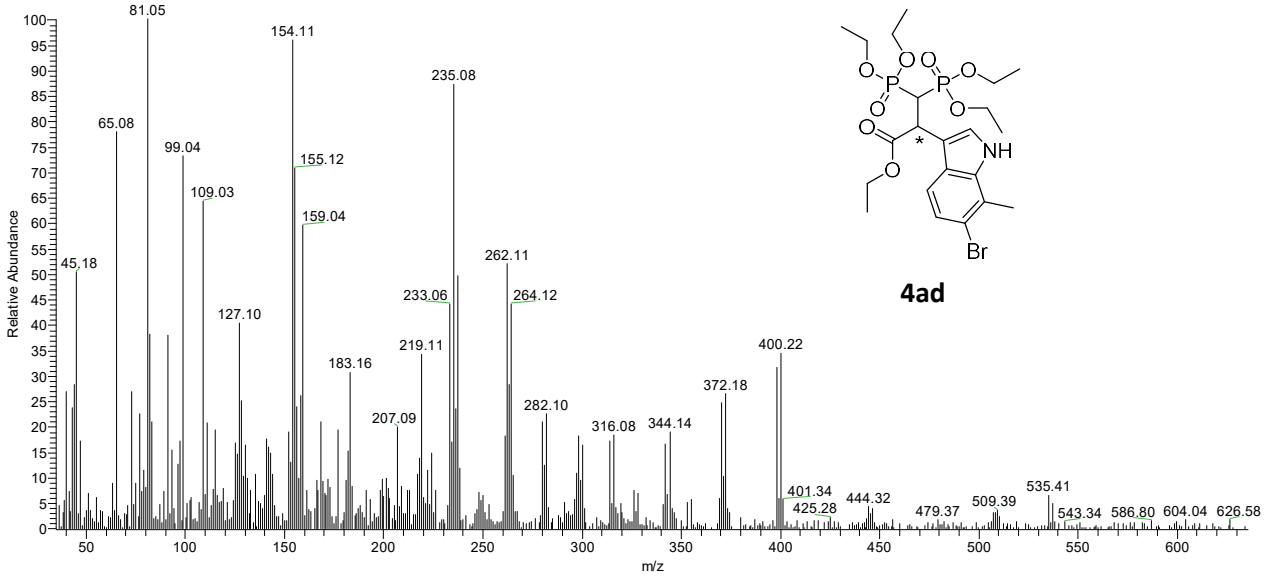
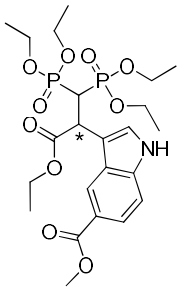


Figure S45. EI-MS spectrum of **4ad**



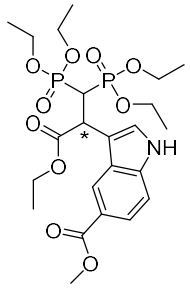
4ae

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.51 (s, 1H), 7.87 (dd, J=8.6, 1.6 Hz, 1H), 7.38-7.35 (m, 2H), 7.33 (s, 1H), 4.53 (dt, J=11.6, 9.5 Hz, 1H), 4.29-4.08 (m, 8H), 3.93 (s, 3H), 3.90-3.73 (m, 2H), 3.71-3.58 (m, 1H), 1.35 (t, J=7.1 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.19 (t, J=7.1 Hz, 3H), 1.05 (t, J=7.1 Hz, 3H), 0.94 (t, J=7.1 Hz, 3H) ppm

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) δ 20.19 (d, *J* = 2.0 Hz, 1P), 19.22 (d, *J* = 2.0 Hz, 1P) ppm.

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 171.00 (dd, *J* = 14.6, 5.1 Hz), 167.31 (s), 137.71 (s), 126.10 (s), 126.05 (s), 122.49 (s), 122.11 (s), 121.01 (s), 110.81 (dd, *J* = 12.7, 4.9 Hz), 110.00 (s), 62.15 (d, *J* = 6.6 Hz), 61.85 (d, *J* = 6.6 Hz), 61.59 (d, *J* = 6.8 Hz), 61.30 (d, *J* = 6.6 Hz), 60.60 (s), 50.87 (s), 40.09 (t, *J* = 3.3 Hz), 39.85 (dd, *J* = 136.2, 129.6 Hz), 28.85 (s), 15.48 (d, *J* = 6.2 Hz), 15.35 (d, *J* = 6.1 Hz), 15.06 (dd, *J* = 8.4, 6.5 Hz), 13.10 (s) ppm.

Elution mixture: Ethyl Acetate/Acetone 1/1



4ae

Figure S46. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **4ae** at 298K.

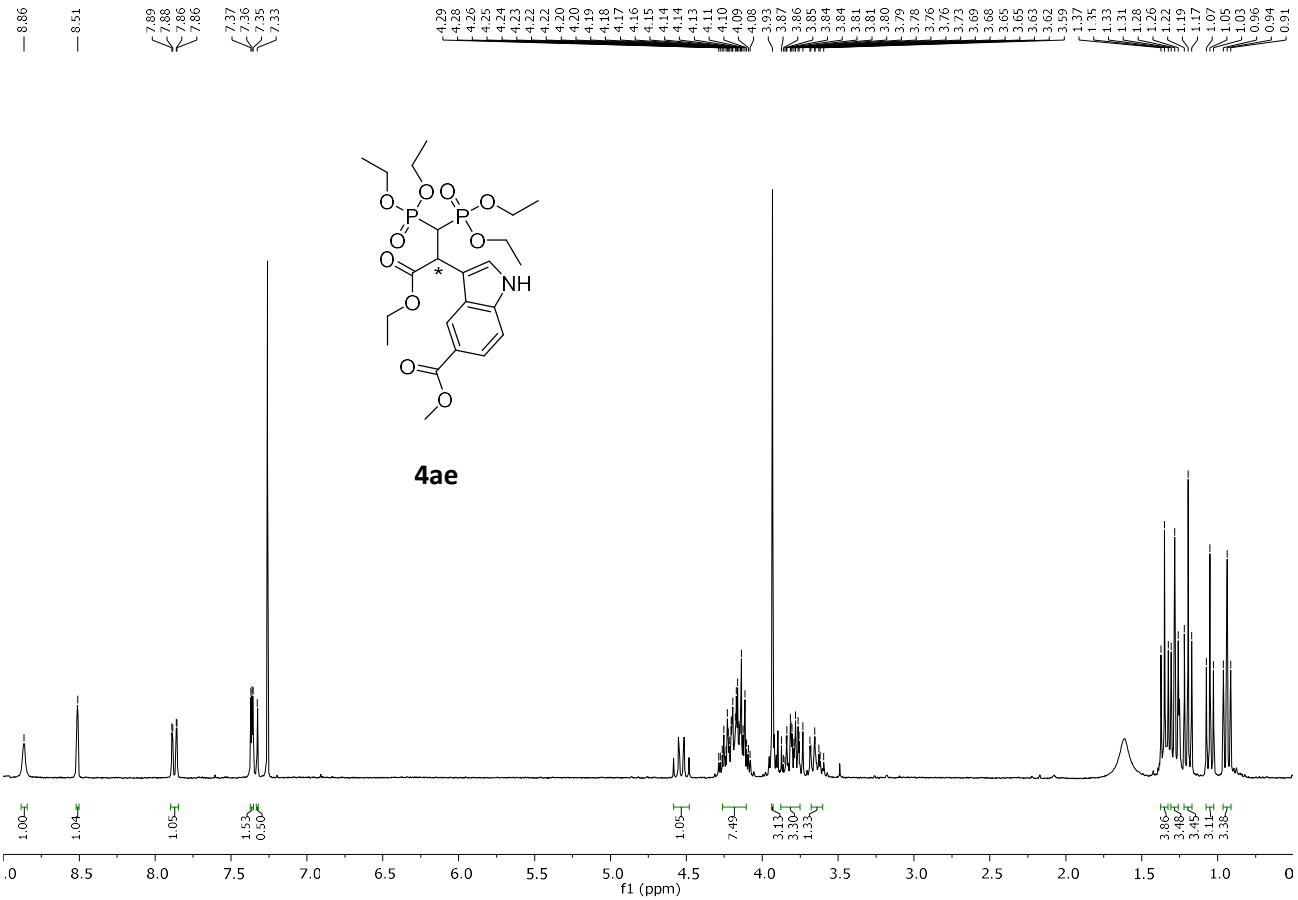


Figure S47. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4ae** at 298K.

EI-MS, (70 eV) m/z: 547 [M^+], 473 [M^+-COOEt-H], 410 [M^+-$PO(OEt)_2$].

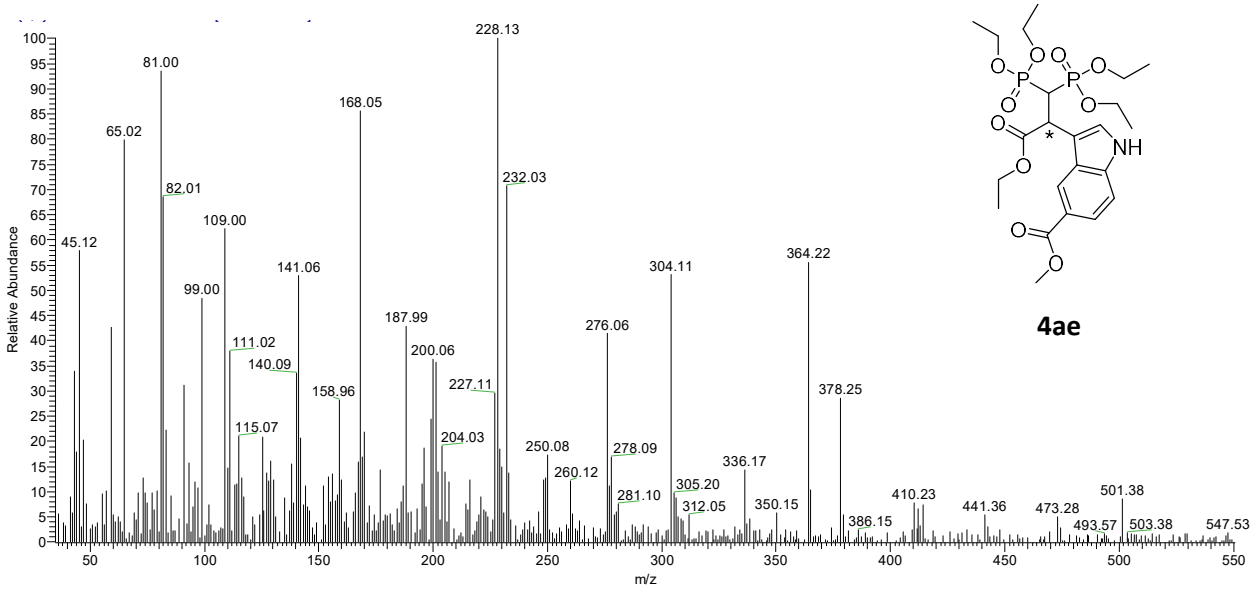
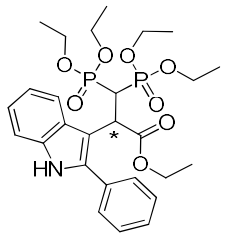


Figure S48. EI-MS spectrum of **4ae**



4af

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.96 – 7.77 (m, 3H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.45 – 7.28 (m, 2H), 7.21 – 7.04 (m, 2H), 4.62 (ddd, *J* = 12.4, 10.0, 2.7 Hz, 1H), 4.26 – 4.06 (m, 6H), 3.95 (td, *J* = 22.5, 12.0 Hz, 1H), 3.79 – 3.64 (m, 1H), 3.63 – 3.45 (m, 2H), 3.16 – 3.02 (m, 1H), 1.32 (dt, *J* = 20.5, 7.1 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.0 Hz, 3H), 0.60 (t, *J* = 7.1 Hz, 3H) ppm

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) δ 21.13 (d, *J* = 2.8 Hz), 19.38 (d, *J* = 2.8 Hz) ppm

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 171.70 (d, *J* = 18.0 Hz), 137.86 (s), 135.93 (s), 132.83 (s), 129.29 (s), 128.99 (s), 128.32 (s), 122.13 (d, *J* = 9.0 Hz), 122.02 (s), 120.04 (s), 110.75 (s), 62.58 (dd, *J* = 77.9, 37.9 Hz), 61.33 (s), 41.19 (s), 29.83 (s), 16.48 (s), 15.72 (s), 14.10 (s) ppm.

Elution mixture: Ethyl Acetate/Acetone 1/1

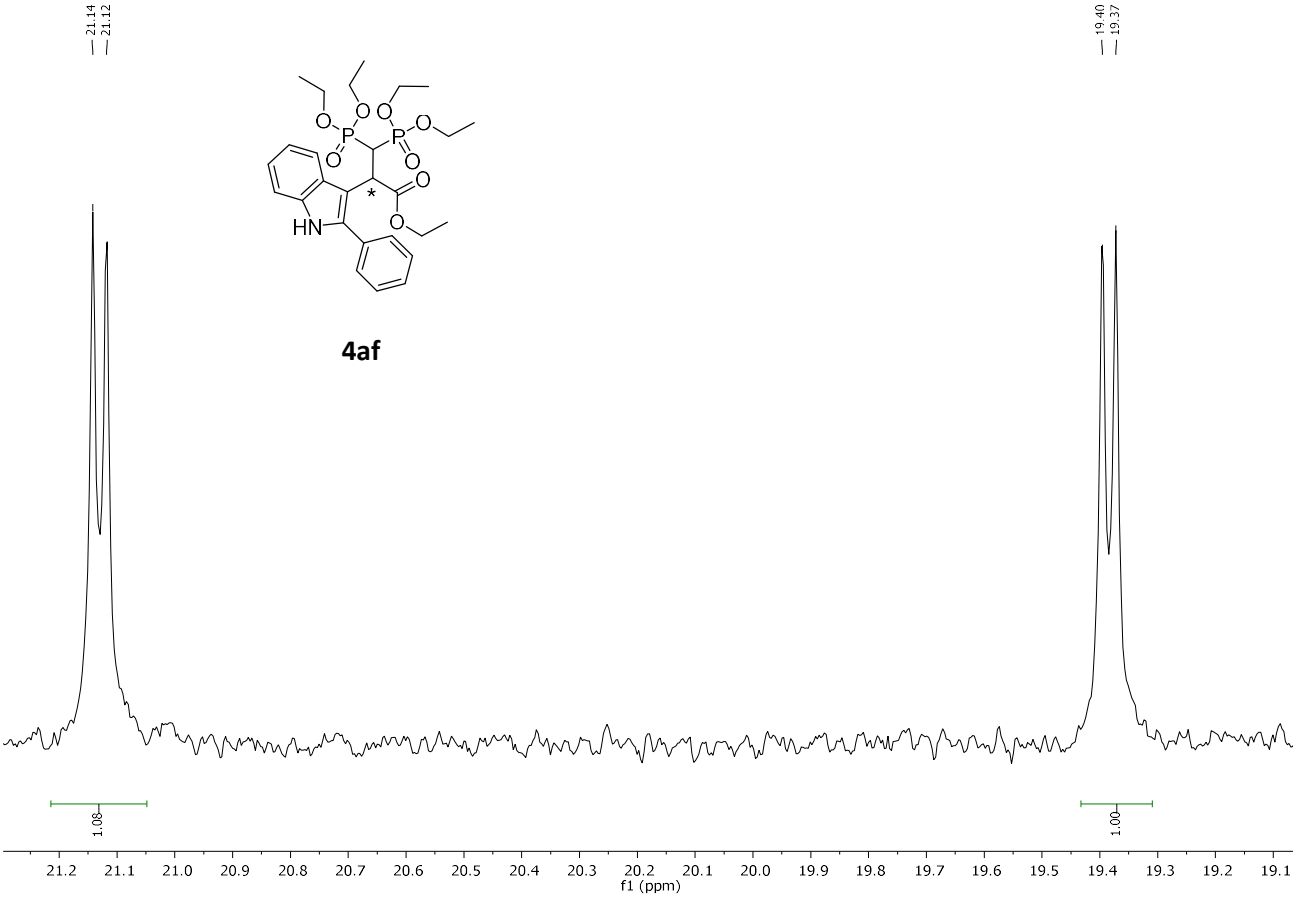


Figure S49. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **4af** at 298K.

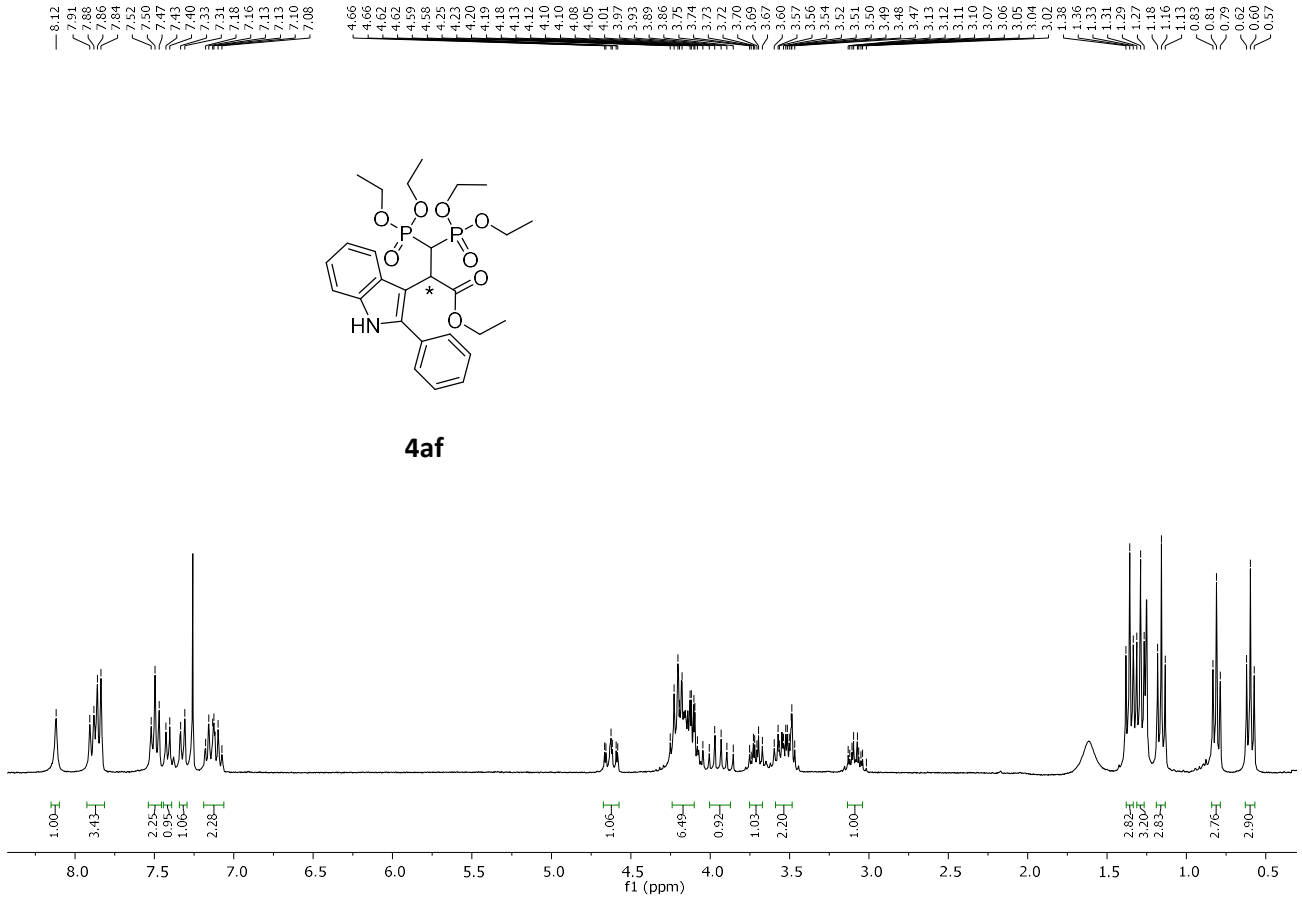


Figure S50. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4af** at 298K.

EI-MS, (70 eV) m/z: 519 [M^+-OEt-H], 474 [M^+-$(OEt)_2$], 428 [M^+-$PO(OEt)_2$].

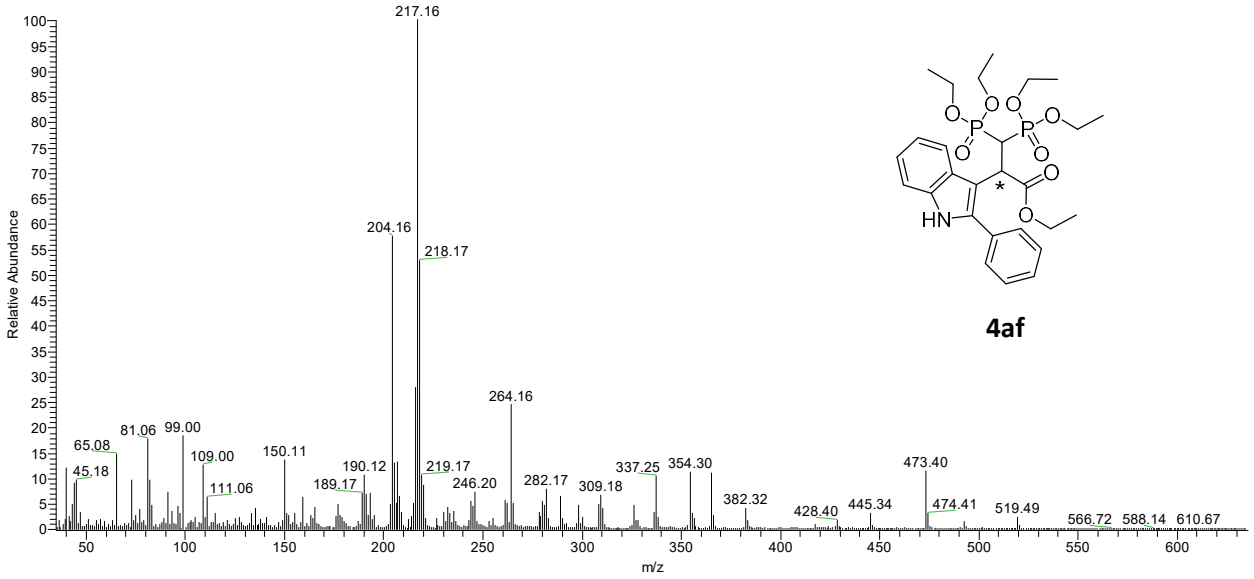
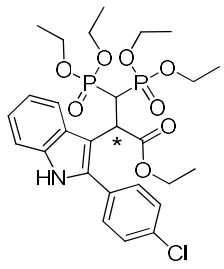


Figure S51. EI-MS spectrum of **4af**



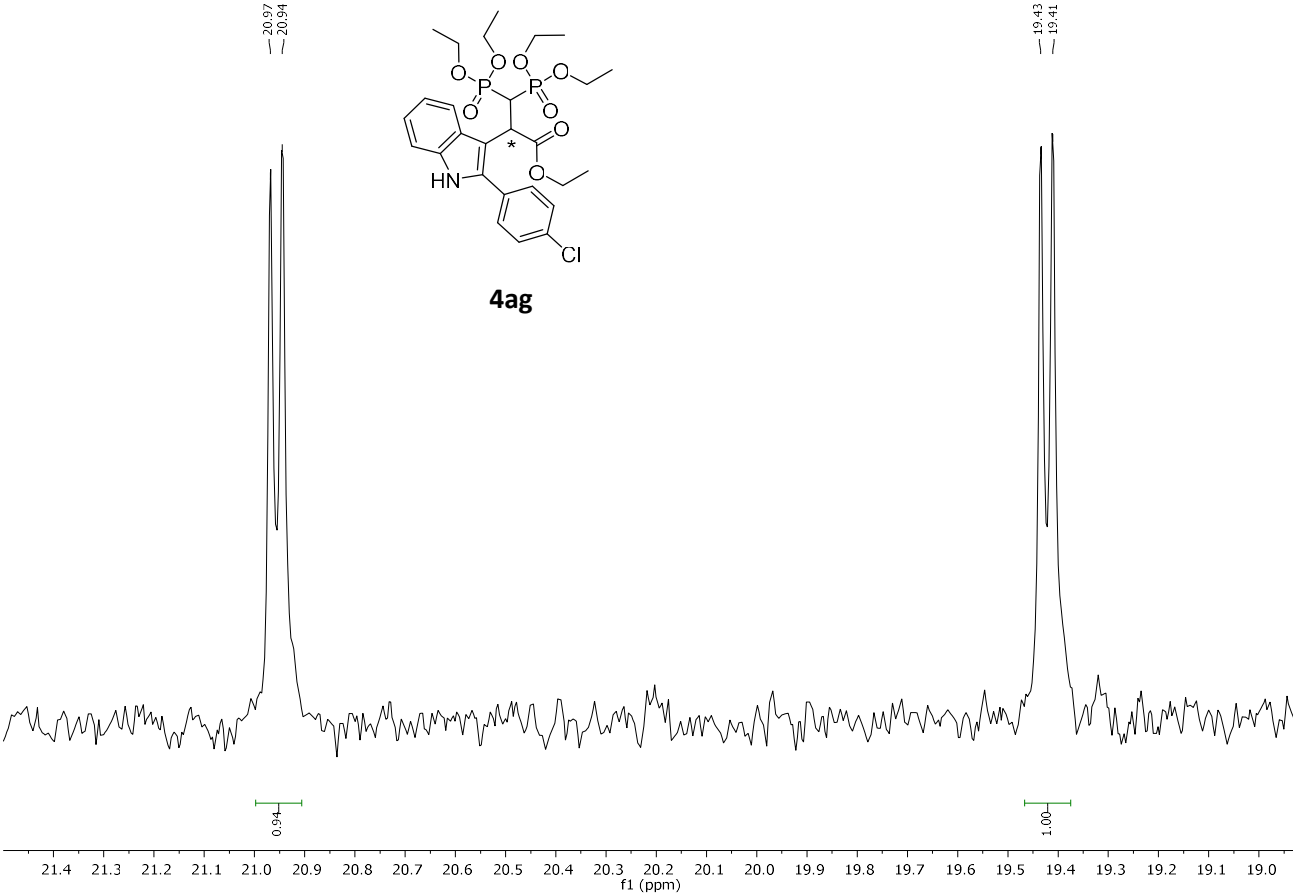
4ag

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.14 (dt, *J* = 15.1, 7.0 Hz, 2H), 4.58 – 4.48 (m, 1H), 4.25 – 4.05 (m, 4H), 3.95 (dd, *J* = 22.5, 10.5 Hz, 2H), 3.87 – 3.74 (m, 1H), 3.72 – 3.57 (m, 2H), 3.53 – 3.43 (m, 1H), 3.07 – 2.96 (m, 1H), 1.34 (dt, *J* = 16.9, 7.1 Hz, 6H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.59 (t, *J* = 7.1 Hz, 3H) ppm.

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 20.96 (d, J=2.9 Hz, 1P), 19.42 (d, J=2.9 Hz, 1P) ppm

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 136.89 (s), 136.25 (s), 134.76 (s), 131.52 (s), 130.91 (s), 129.48 (s), 128.47 (s), 122.77 (s), 122.38 (s), 120.50 (s), 111.07 (s), 63.70 (d, *J* = 6.4 Hz), 63.05 (d, *J* = 6.7 Hz), 62.70 (d, *J* = 7.1 Hz), 62.03 (d, *J* = 6.9 Hz), 61.68 (s), 41.49 (s), 32.36 (s), 30.12 (s), 29.79 (s), 23.12 (s), 16.77 (t, *J* = 5.7 Hz), 16.20 (d, *J* = 6.7 Hz), 15.88 (d, *J* = 6.2 Hz), 14.37 (s) ppm.

Elution mixture: n-Hexane/Acetone 1/1



4ag

Figure S52. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **4ag** at 298K.

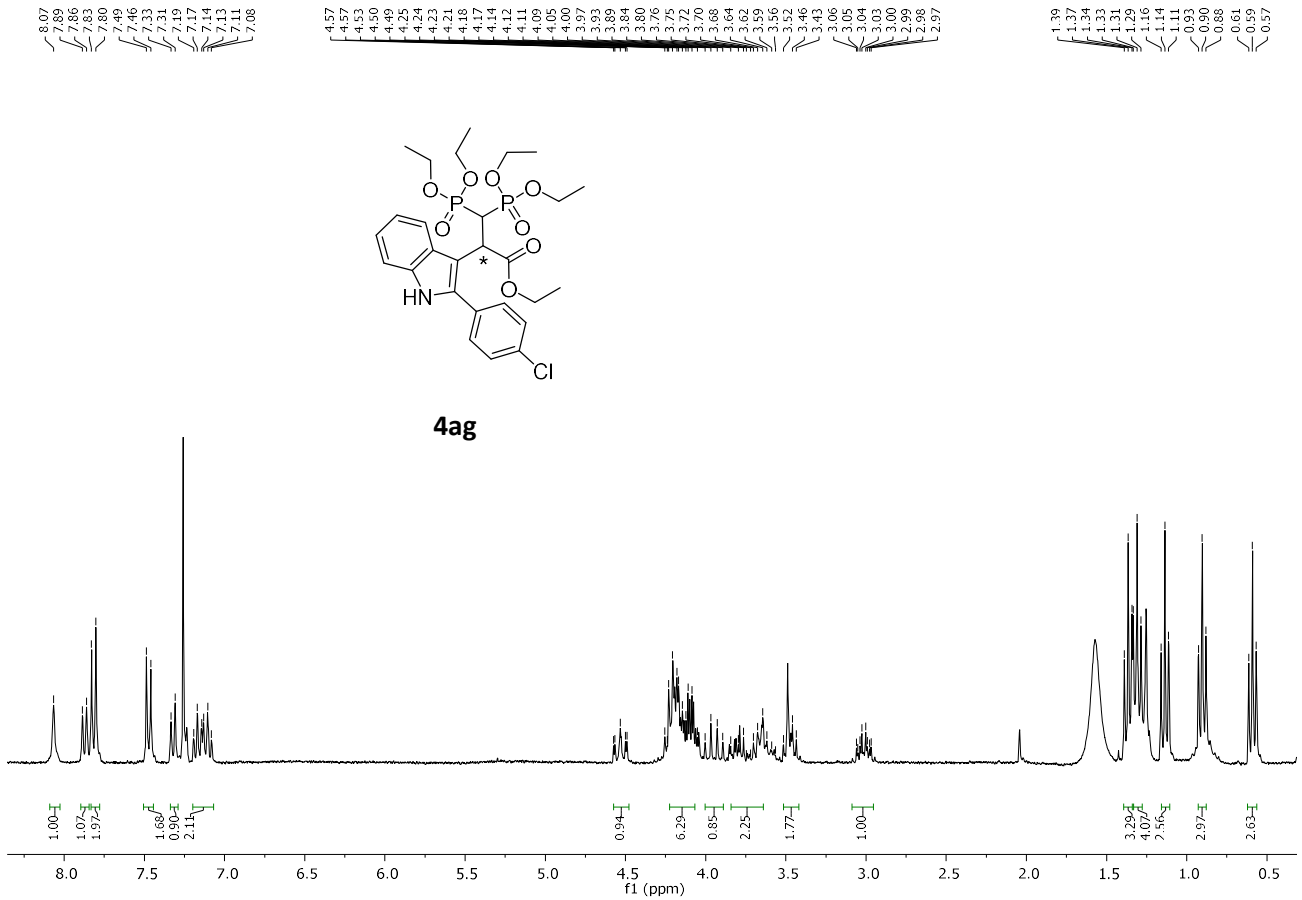


Figure S53. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4ag** at 298K.

EI-MS, (70 eV) m/z: 526 [M^+-COOEt], 462 [M^+-$PO(OEt)_2$], 418 [M^+-$PO(OEt)_2$-OEt].

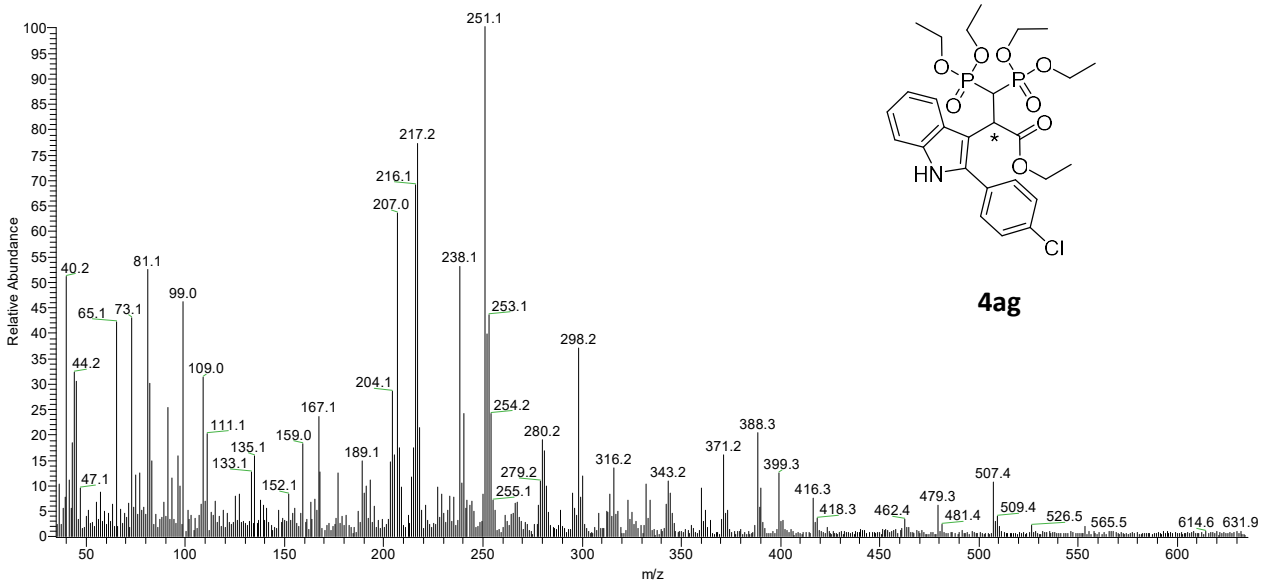
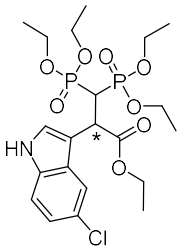


Figure S54. EI-MS spectrum of **4ag**



4ah

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.73 (d, J=1.9 Hz, 1H), 7.32 (d, J=2.5 Hz, 1H), 7.23 (s, 1H), 7.10 (dd, J=8.6, 2.0 Hz, 1H), 4.49-4.39 (m, 1H), 4.29-4.07 (m, 6H), 3.96-3.67 (m, 4H), 3.60 (ddd, J=11.7, 8.6, 5.7 Hz, 1H), 1.32 (q, J=7.0, 6H), 1.19 (t, J=7.1 Hz, 3H), 1.07 (t, J=7.1 Hz, 3H), 0.94 (t, J=7.1 Hz, 3H) ppm

^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$): δ 20.39 (d, J=2.5 Hz), 19.20 (d, J=2.5 Hz) ppm

^{13}C {^{1}H}-NMR (75 MHz, $CDCl_3$) δ 172.09 (dd, J = 17.3, 5.8 Hz), 134.43 (s), 128.28 (s), 127.14 (s), 125.45 (s), 122.23 (s), 119.71 (s), 112.28 (s), 63.17 (d, J = 6.6 Hz), 62.84 (d, J = 6.6 Hz), 62.61 (d, J = 6.9 Hz), 62.21 (d, J = 6.7 Hz), 61.62 (s), 41.23 – 40.96 (m), 40.30 (dd, J = 136.7, 128.7 Hz), 29.85 (s), 16.45 (t, J = 6.6 Hz), 16.13 (d, J = 6.6 Hz), 15.92 (d, J = 6.7 Hz), 14.13 (s) ppm

Elution mixture: Ethyl Acetate/Acetone 1/1

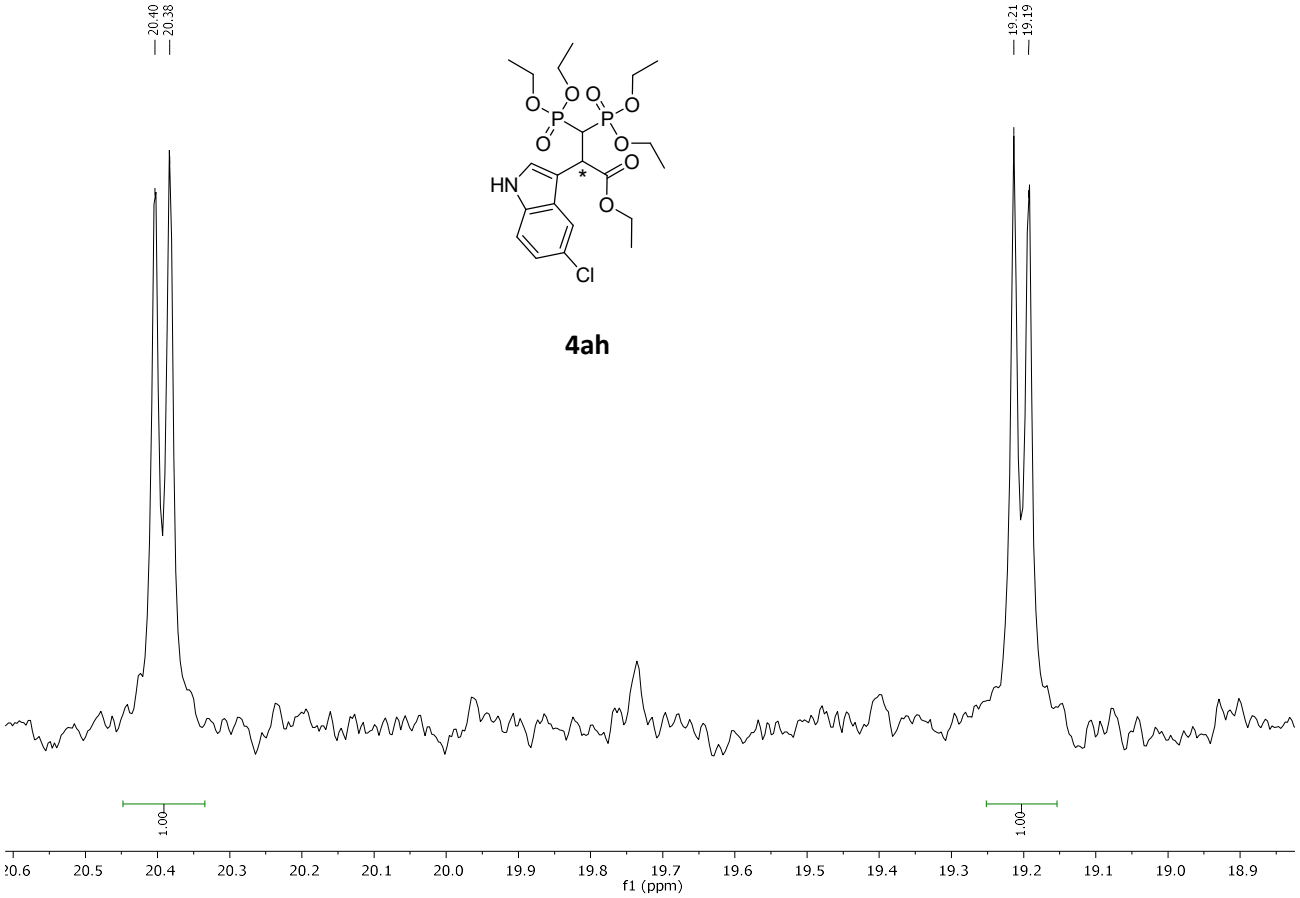


Figure S55. ^{31}P {^{1}H}-NMR (122 MHz, $CDCl_3$) spectrum of **4ah** at 298K.

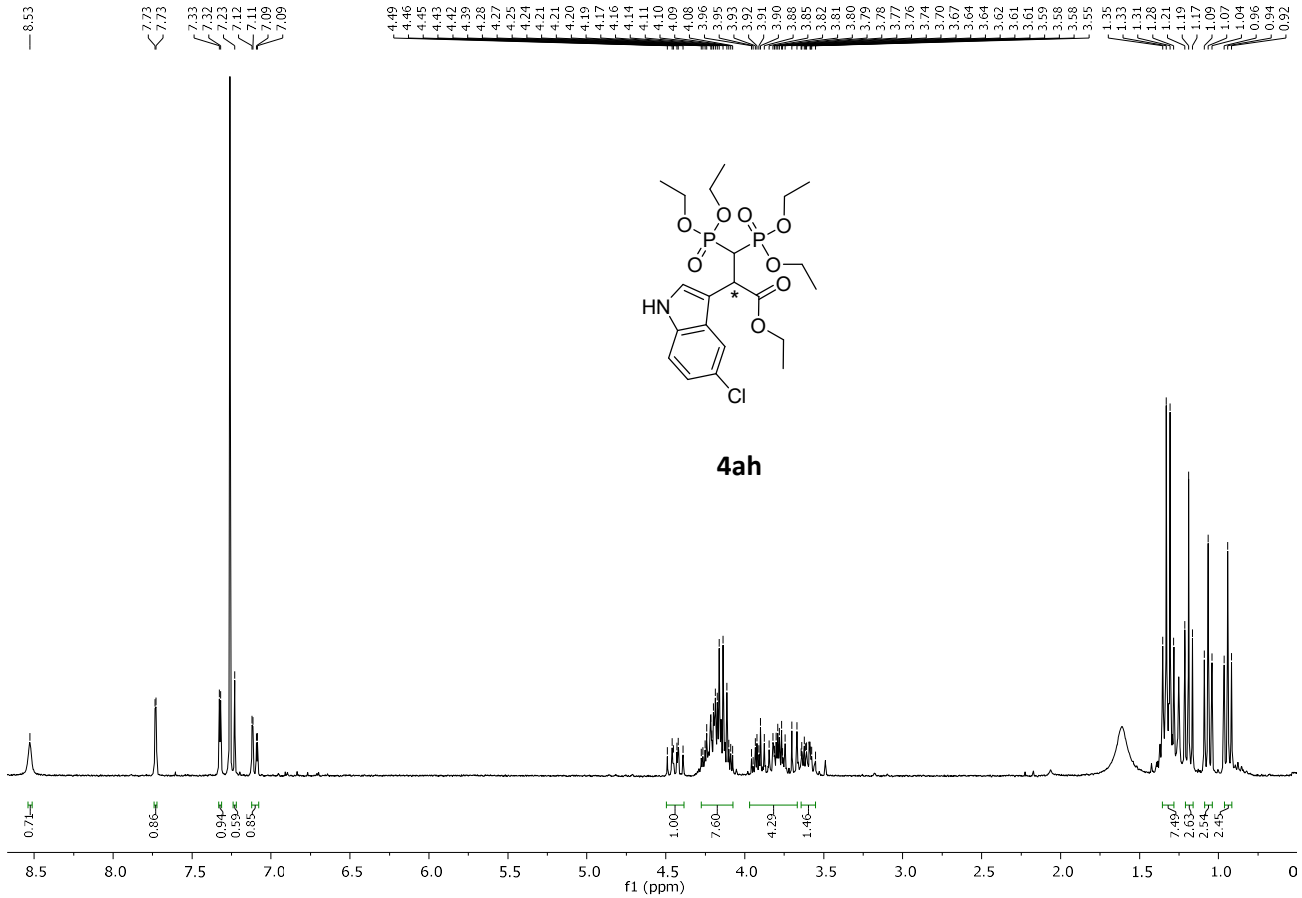


Figure S56. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **4ah** at 298K.

EI-MS, (70 eV) m/z: 523 [M^+], 477 [M^+-OEt-H], 449 [M^+-COOEt-H], 386 [M^+-$PO(OEt)_2$], 342 [M^+-$PO(OEt)_2$-OEt], 314 [M^+-$PO(OEt)_2$-COOEt)].

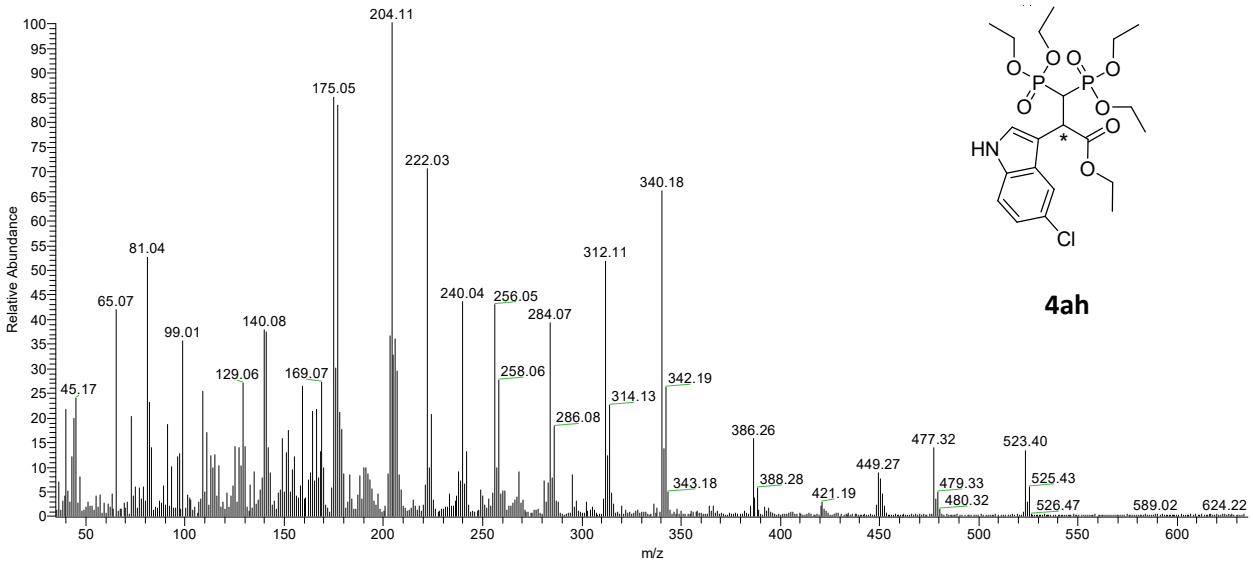
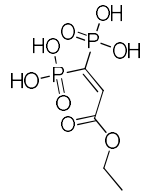


Figure S57. EI-MS spectrum of **4ah**

General procedure for the phosphonic ester deprotection

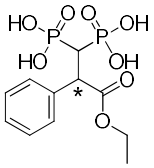
In a round bottom flask equipped with magnetic stirring bar, 50 mg of substrate and 2.5 mL of 1-2 dichloroethane were introduced under anhydrous condition. To the solution, 12 equivalents with respect to the substrate of $(CH_3)_3SiBr$ was added and the solution was left under stirring at 70°C under inert atmosphere for 1.5 hours after which the solvent was removed under vacuum. To the crude mixture, 5 ml of non-anhydrous MeOH were added, further stirring for 2 h at room temperature. The solution was evaporated to dryness obtaining the free bisphosphonic acid that was further characterized by ^{1}H and ^{31}P NMR.



5a

^{1}H-NMR (300 MHz, D_2O): δ 7.07 (dd, *J* = 42.6, 26.8 Hz, 1H), 4.24 – 4.08 (m, 2H), 1.24 – 1.16 (m, 3H) ppm.

^{31}P {^{1}H}-NMR (121.5 MHz, D_2O): δ 8.29 (d, *J* = 46.8 Hz, 1P), 5.49 (d, *J* = 46.9 Hz, 1P) ppm.

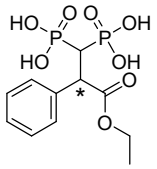


5b

^{1}H-NMR (400 MHz, D_2O): δ 7.35 – 7.29 (m, 2H), 7.26 – 7.19 (m, 3H), 4.05 – 3.87 (m, 3H), 3.20 (broad, 1H), 1.02 (t, *J* = 7.1 Hz, 3H) ppm.

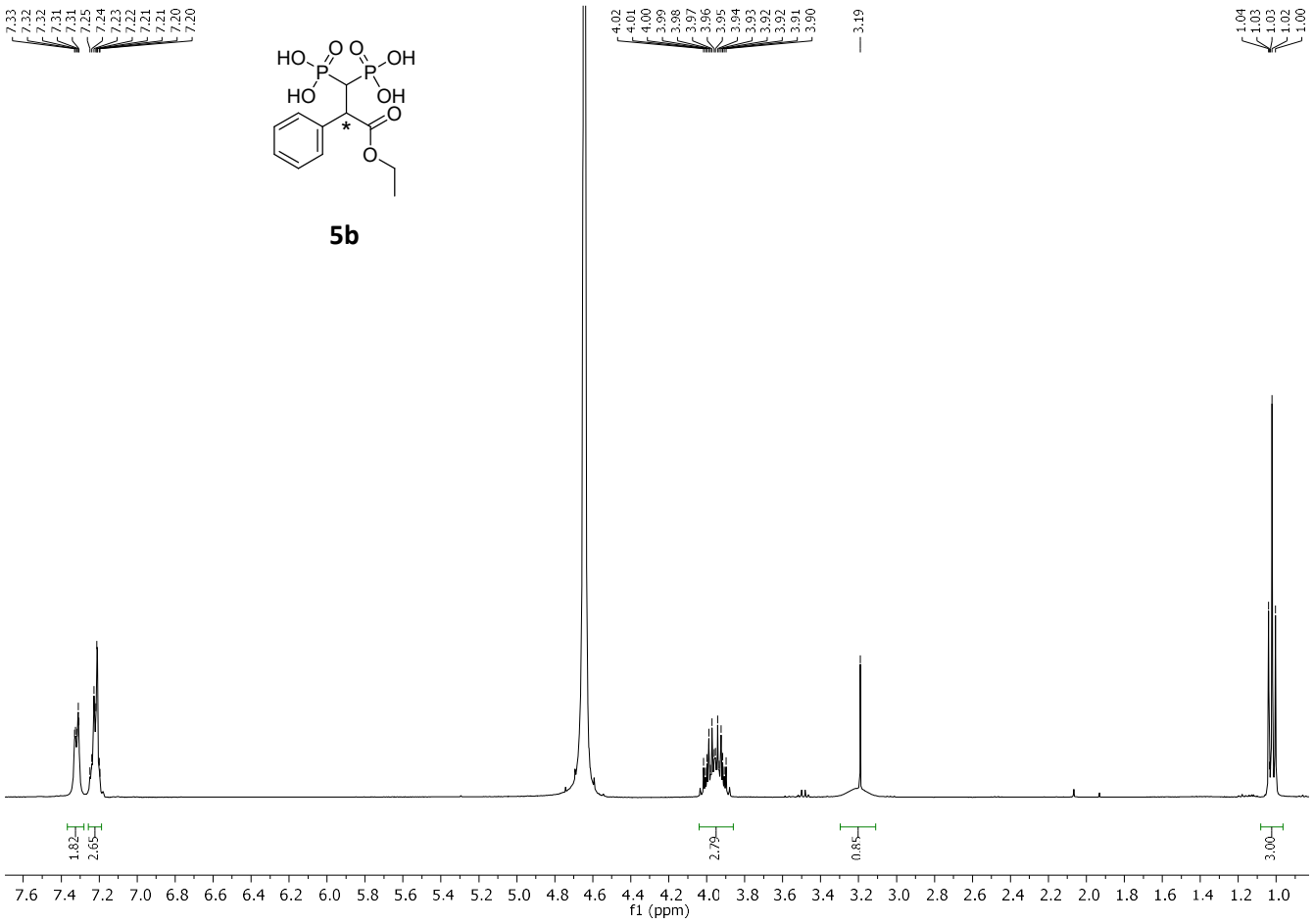
^{31}P {^{1}H}-NMR (162 MHz, D_2O): δ 19.16 (broad signal, 2P) ppm

^{13}C {^{1}H}-NMR (101 MHz, D_2O) δ 174.60 (broad), 135.52 (broad), 129.36 (s), 128.49 (s), 128.24 (s), 62.55 (s), 57.40 (s), 48.83 (s), 12.96 (s), ppm.



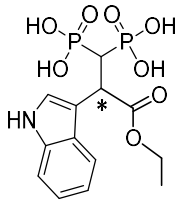
5b

Figure S58. ^{31}P {^{1}H}-NMR (162 MHz, D_2O) spectrum of **5b** at 298K.



5b

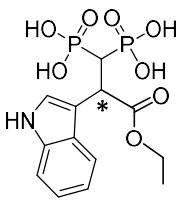
Figure S59. ^{1}H NMR (400 MHz, D_2O) spectrum of **5b** at 298K.



5aa

^{1}H-NMR (300 MHz, D_2O): δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.11 (dt, *J* = 14.8, 7.0 Hz, 2H), 4.37 (broad signal, 1H), 4.11 – 3.92 (m, 2H), 3.46 (td, *J* = 21.2, 10.4 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H).

^{31}P {^{1}H}-NMR (122 MHz, D_2O): δ 17.90 ppm (s. Broad signal, 2P).



5aa

Figure S60. ^{31}P {^{1}H}-NMR (122 MHz, D_2O) spectrum of **5aa** at 298K.

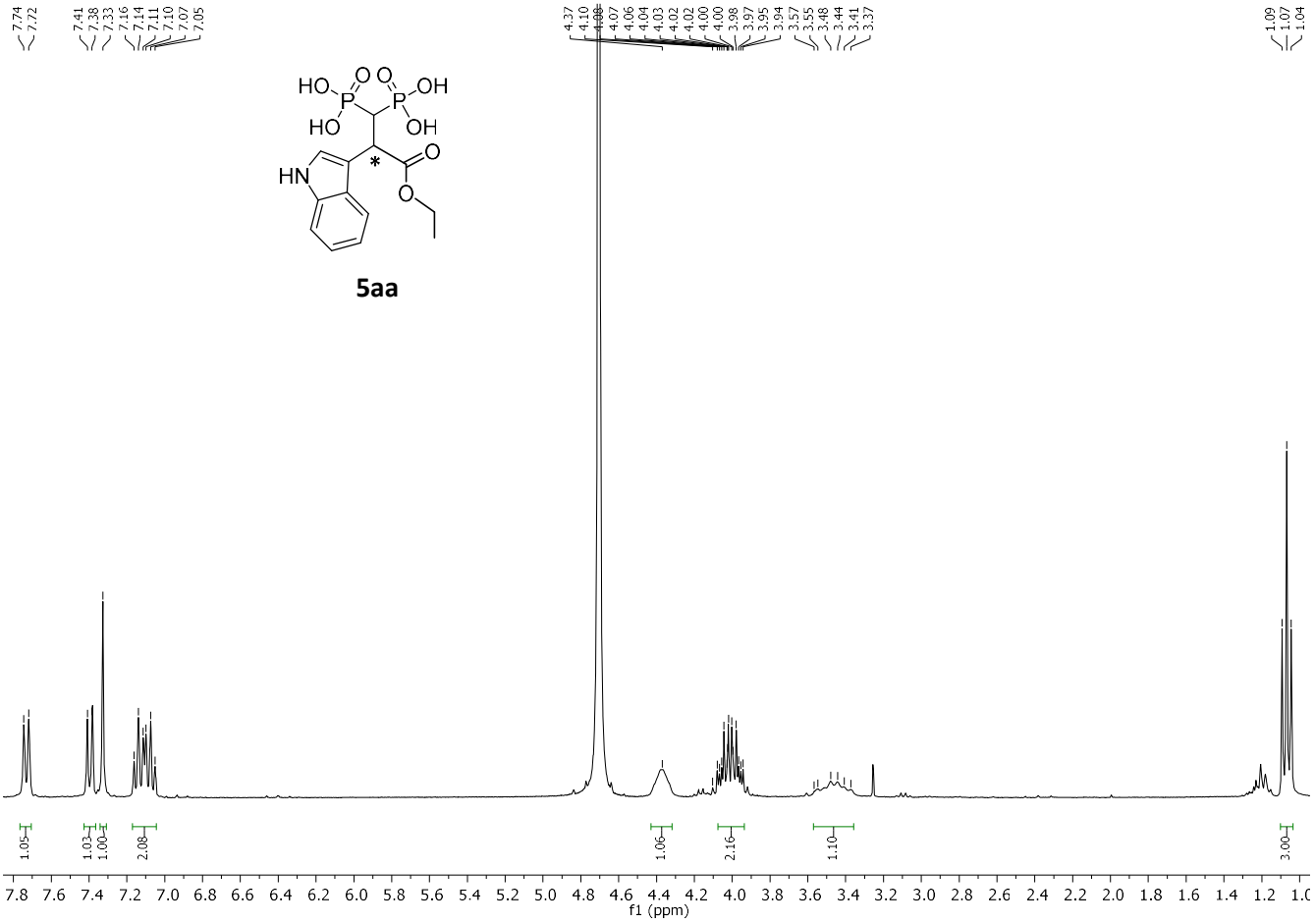


Figure S61. ^{1}H NMR (300 MHz, D_2O) spectrum of **5aa** at 298K.

References

S1 S.M. Nicolle, C.J. Moody, *Chem. Eur. J.*, **2014**, 20, 4420–4425.
S2 X. Creary, *J. Org. Chem.*, **1987**, 52, 5026-5030.