# Organocatalytic Enantioselective Hydrophosphonylation of Aldehydes

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# ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

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**General Experimental Methods**. Purification of reaction products was carried out by flash chromatography using silical-gel (0.063-0.200 mm). Analytical thin layer chromatography was performed on 0.25 mm silical gel 60-F plates. ESI ionization method and mass analyzer type MicroTof-Q were used for the HRMS measurements. $^{1}$H-NMR spectra were recorded at 300 MHz and 400 MHz; $^{13}$C-NMR spectra were recorded at 75 MHz and 100 MHz; $CDCl_3$ as the solvent. Chemical shifts were reported in the $\delta$ scale relative to residual $CHCl_3$ (7.26 ppm) for $^{1}$H-NMR and to the central line of $CDCl_3$ (77 ppm) for $^{13}$C-NMR.

**Materials**. All commercially available solvents and reagents were used as received. The $^{1}$H and $^{13}$C NMR spectra for compounds **4eb**,[1] **4ed**[2] **4ef**,[2] are consistent with values previously reported in the literature.

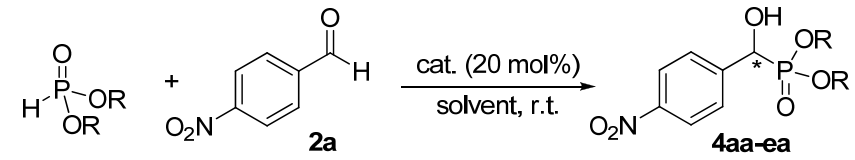
**Representative procedure for squaramide-organocatalyzed hydrophosphonylation reaction of aldehydes**

To a mixture of catalyst **3c** (0.02 mmol), and aldehyde **2a-k** (0.1 mmol) in $CH_3CN$ (0.5 mL), phosphite **1e** (0.2 mmol) was further added in a test tube at –38 ºC. After the reaction time (see Table 3), adducts **4** were isolated by flash chromatography or medium pressure liquid chromatography ($SiO_2$, hexane/EtOAc 7:3). Yields and enantioselectivities are reported in Table 3.

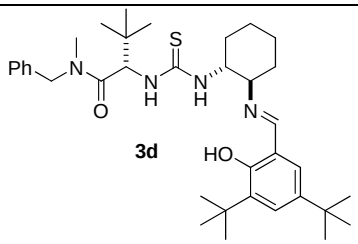
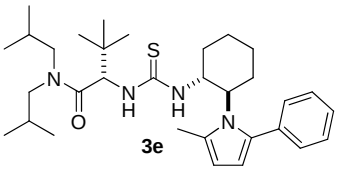
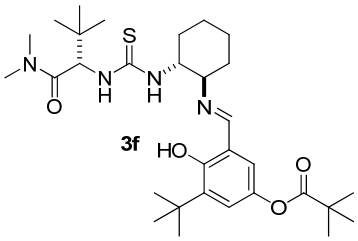
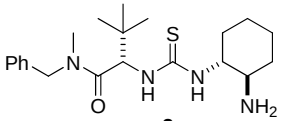
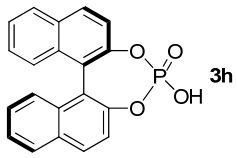
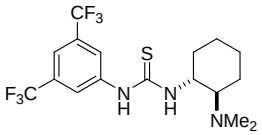
[1] A. R. Katritzky, B. V. Rogovoy, A. Y. Mitrokhin, *Arkivoc* **2002**, (*xiii*), 17.
[2] X. Zhu, S. Wang, S. Zhou, Y. Wei, L. Zhang, F. Wang, Z. Feng, L. Guo, X. Mu, *Inorg. Chem.* **2012**, *51*, 7134.

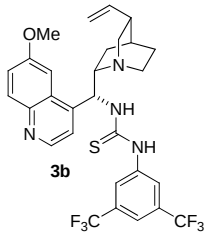
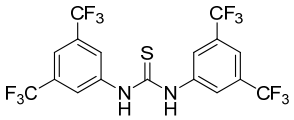
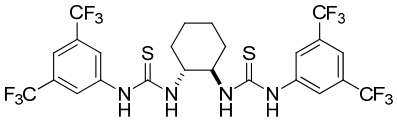
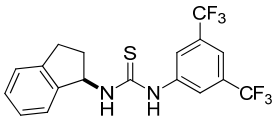
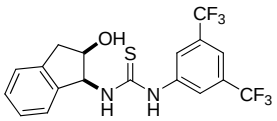
## Screening of Catalysts and Study of the Reaction Conditions

Table S1. Catalytic enantioselective hydrophosphonylation using aldehydes.[a]




R = Bn (**1a**), Me (**1b**), Et (**1c**), *i*Pr (**1d**), Ph (**1e**)

| Entry | Catalyst | Solvent | Phosphite | Time (days) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 |  **3d** | Toluene (0.5) | **1a** | 2 | n.r.[d] | n.d.[e] |
| 2 |  **3e** | Toluene (0.5) | **1a** | 2 | n.r.[d] | n.d.[e] |
| 3 |  **3f** | Toluene (0.5) | **1a** | 2 | n.r.[d] | n.d.[e] |
| 4 |  **3g** | Toluene (0.5) | **1a** | 2 | n.r.[d] | n.d.[e] |
| 5 |  **3h** | Toluene (0.5) | **1a** | 2 | n.d.[e] | Racemic |
| 6 |  **3a** | $CH_3CN$ (0.5) | **1e** | 3 | 52 | 37 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 |  **3b** | $CH_3CN$ (0.5) | **1e** | 2 | 57 | 25 |
| 8 | Quinine, **3i** | Toluene (0.5) | **1a** | 1 | >95[f] | 15 |
| 9 | Quinine, **3i** | Toluene (0.5) | **1c** | 1 | >95[f] | Racemic |
| 10 | Quinine, **3i** | Toluene (0.5) | **1e** | 1 | >95[f] | 6 |
| 11 | Cinchonidine, **3j** | Toluene (0.5) | **1a** | 1 | >95[f] | Racemic |
| 12 | Cinchonidine, **3j** | Toluene (0.5) | **1c** | 1 | >95[f] | Racemic |
| 13 | Cinchonidine, **3j** | Toluene (0.5) | **1e** | 1 | >95[f] | Racemic |
| 14 |  **3k** | Toluene (0.5) | **1c** | 1 | n.r.[d] | n.d.[e] |
| 15 |  **3l** | Toluene (0.5) | **1a** | 1 | n.r.[d] | n.d.[e] |
| 16 |  **3m** | Toluene (0.5) | **1a** | 1 | n.r.[d] | n.d.[e] |
| 17 |  **3n** | Toluene (0.5) | **1a** | 1 | n.r.[d] | n.d.[e] |

[a] Experimental conditions: To a mixture of catalyst **3a-n** (0.02 mmol), and aldehyde **2a** (0.1 mmol) in the corresponding solvent, phosphite **1a-e** (0.2 mmol) was further added in a test tube at room temperature. After the reaction time, adducts **4** were isolated by flash chromatography. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Not reaction observed. [e] Not determined. [f] Conversion by $^1$H-NMR.

**Figure S1.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4ea**

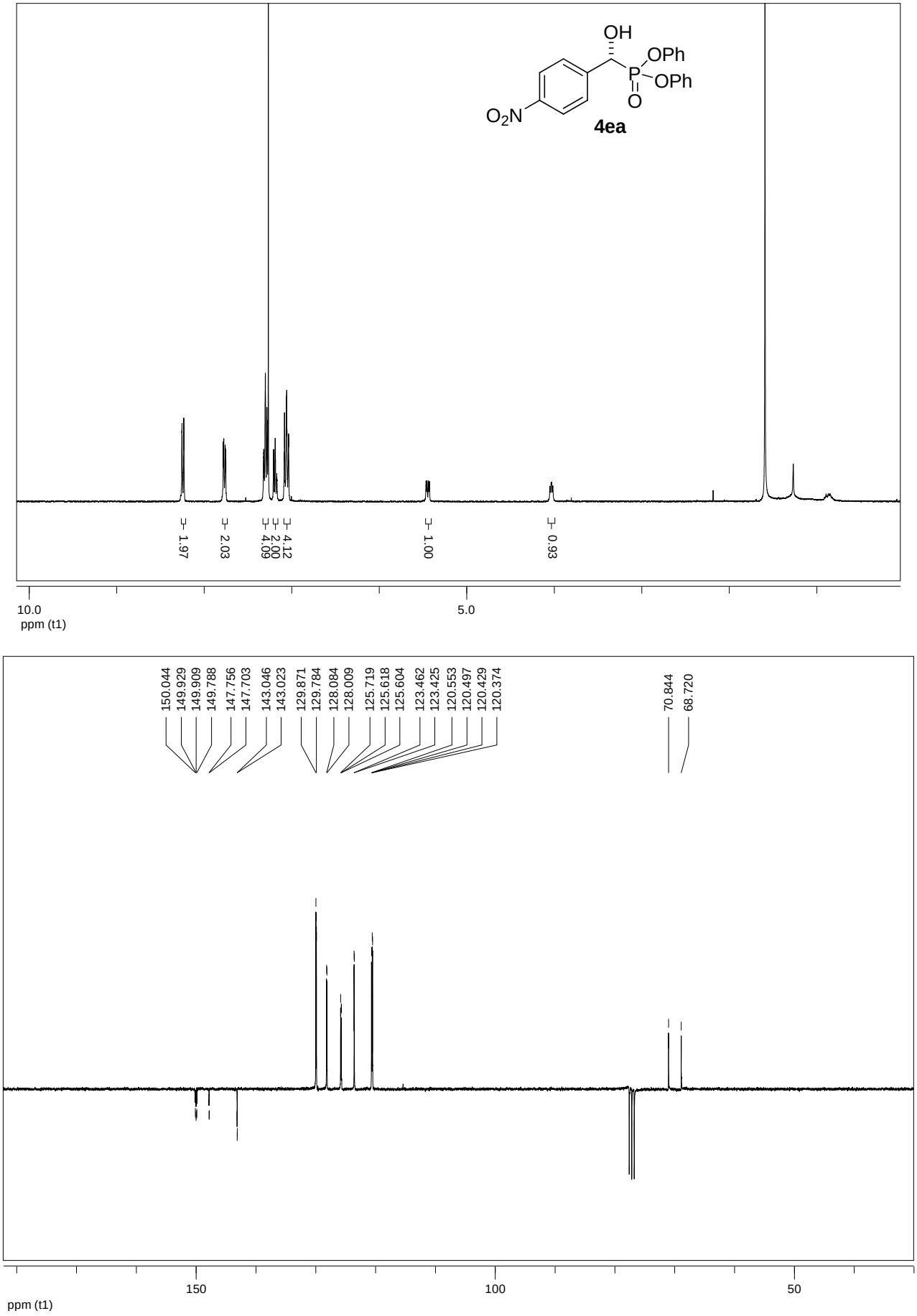
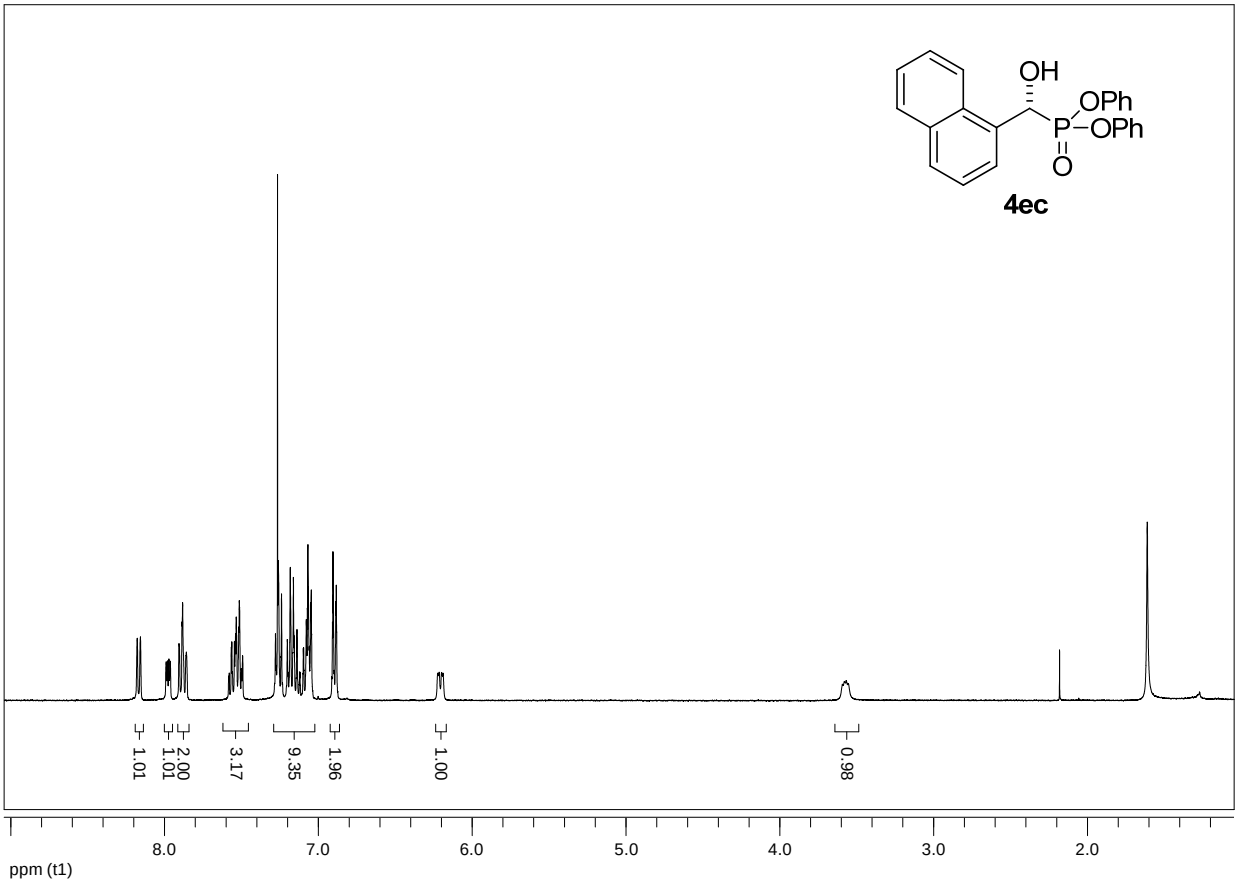


**Figure S2.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4ec**



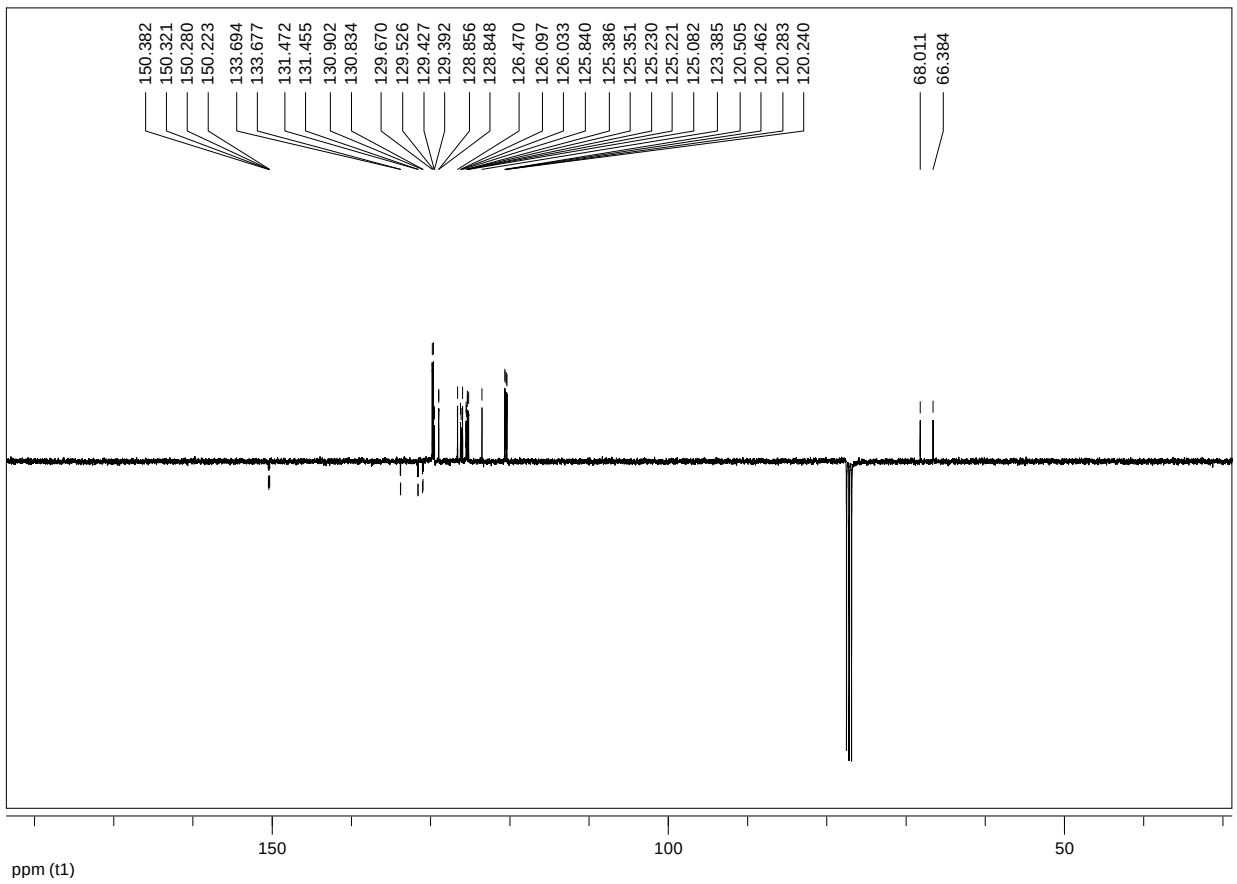
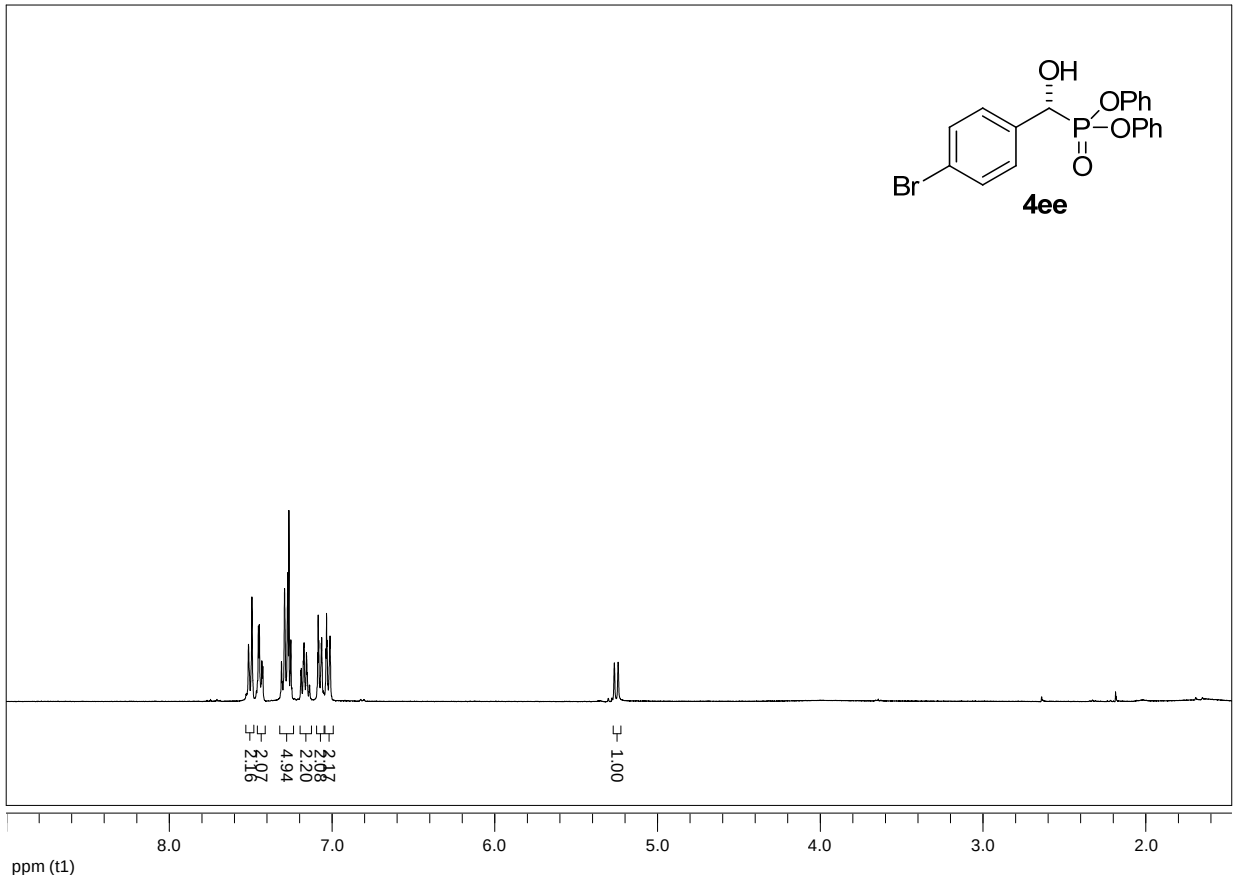



**Figure S3.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4ee**



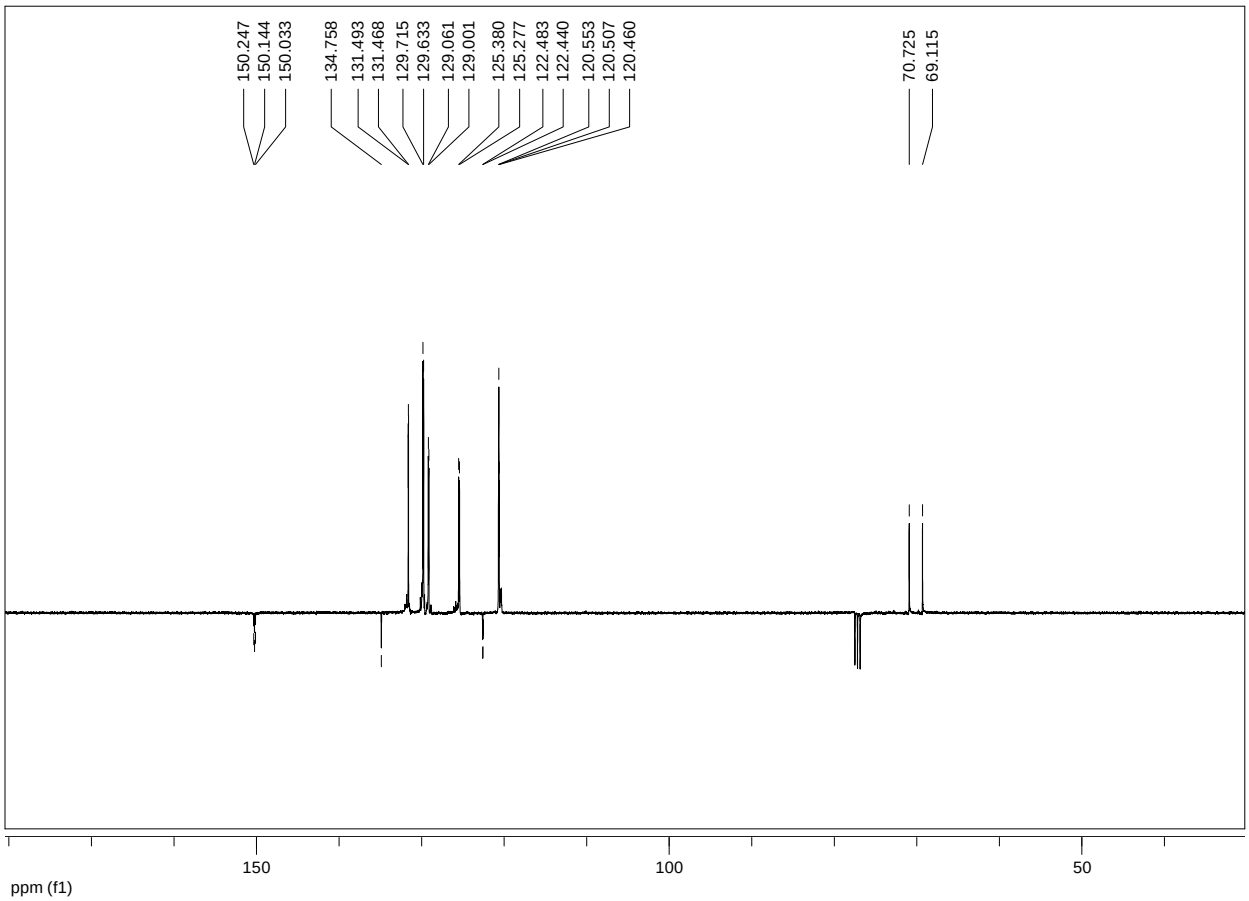
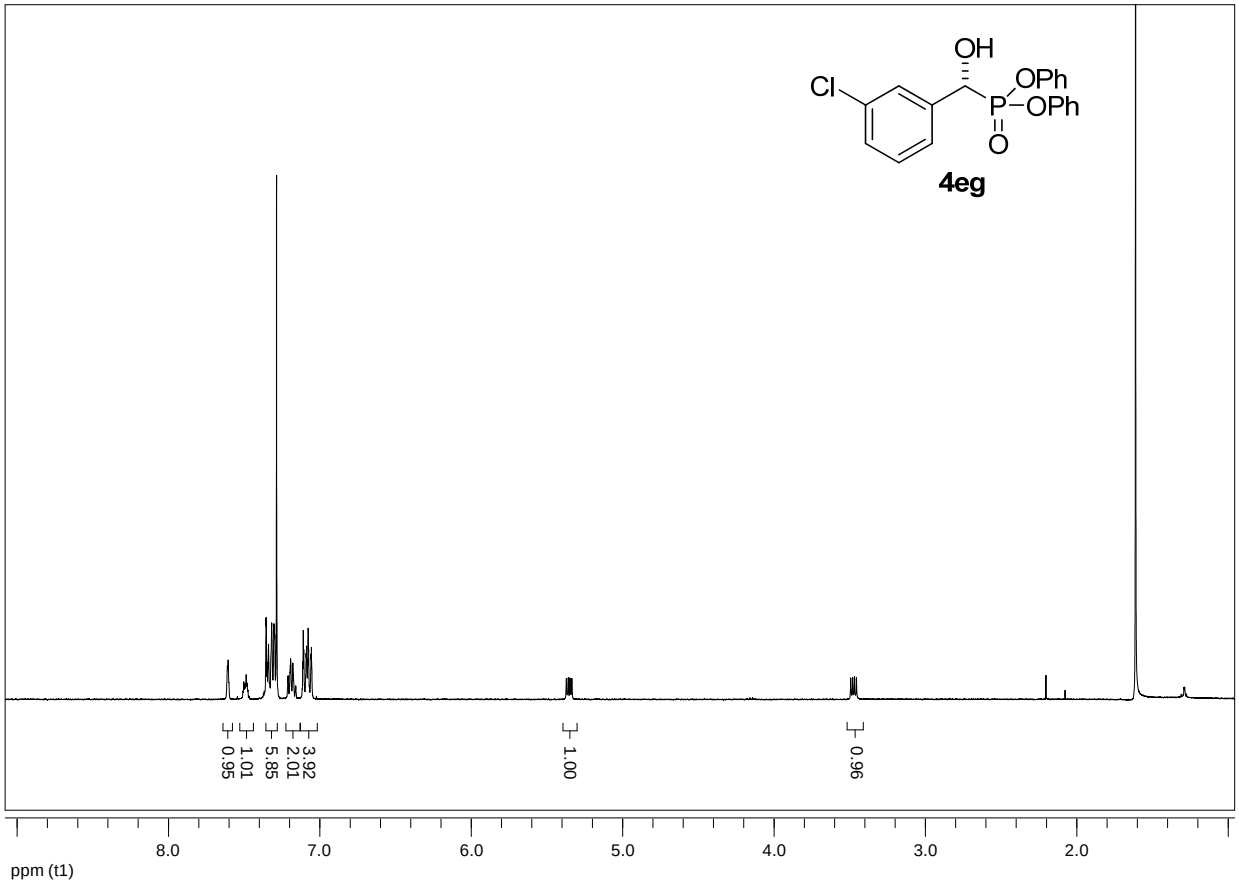



**Figure S4.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4eg**



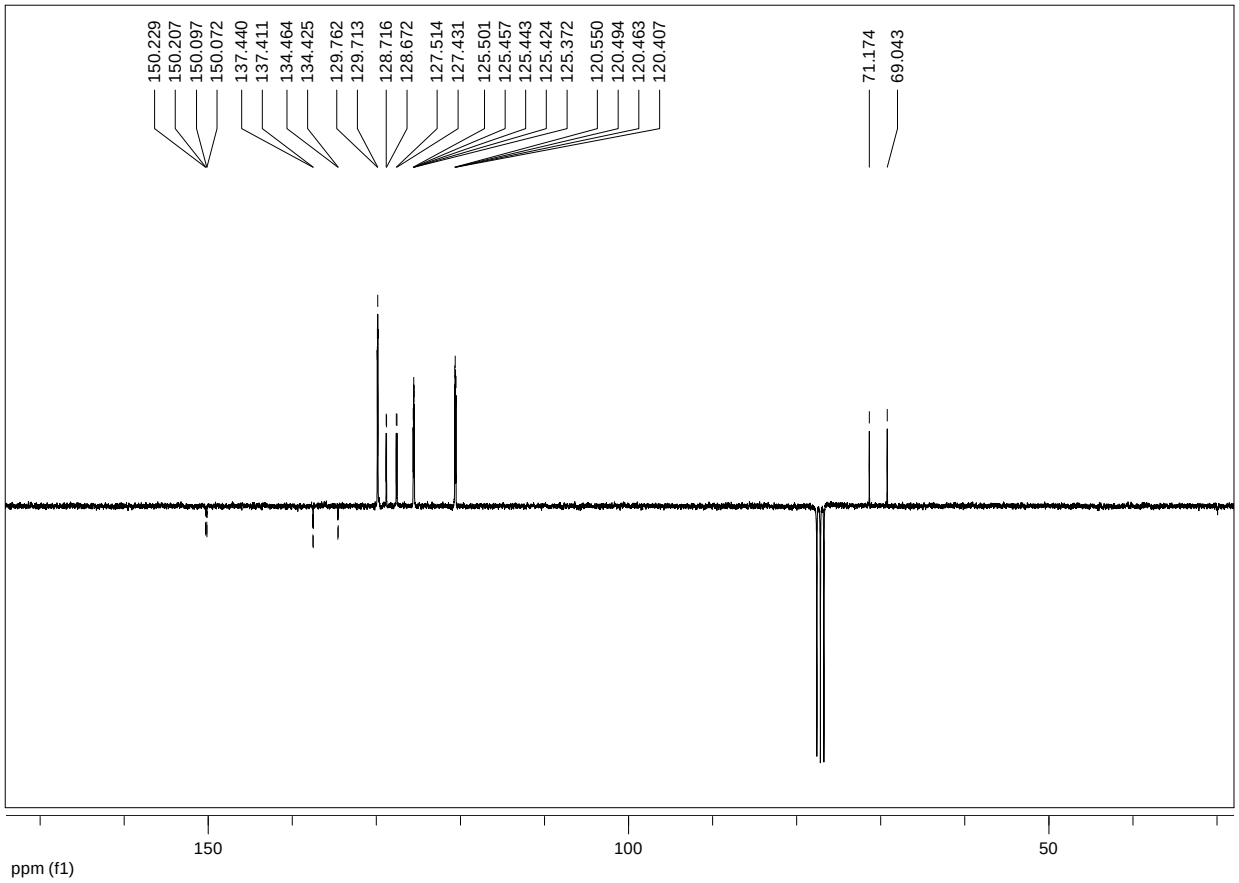
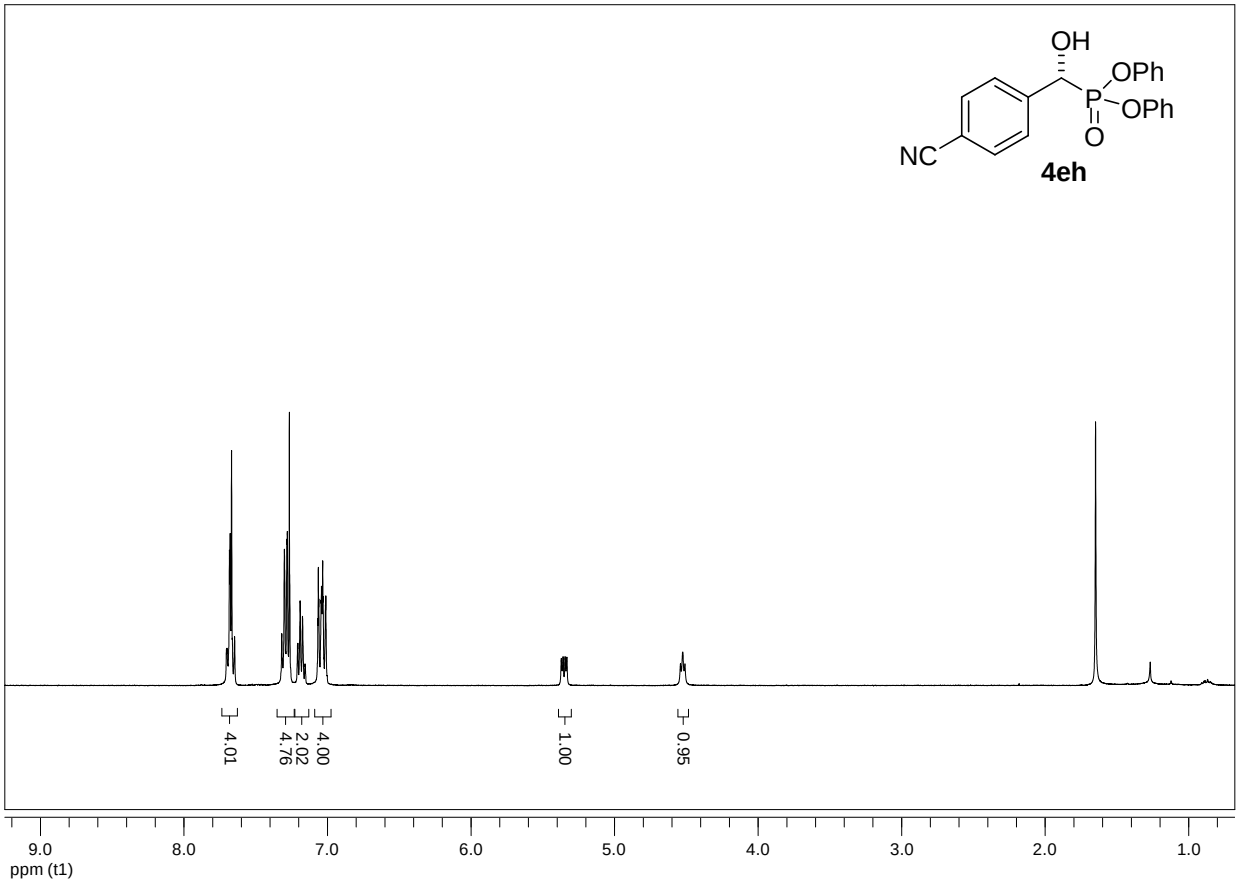



**Figure S5.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4eh**



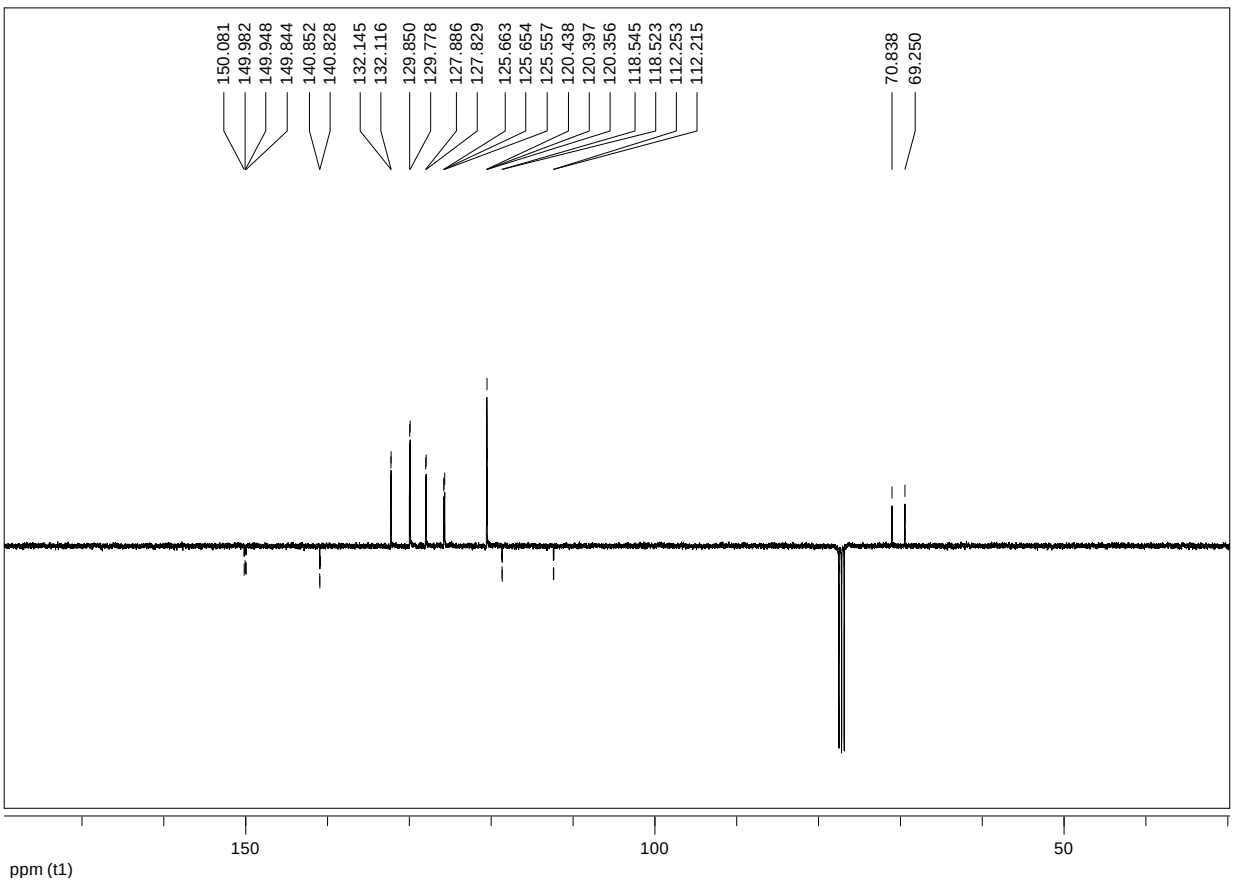
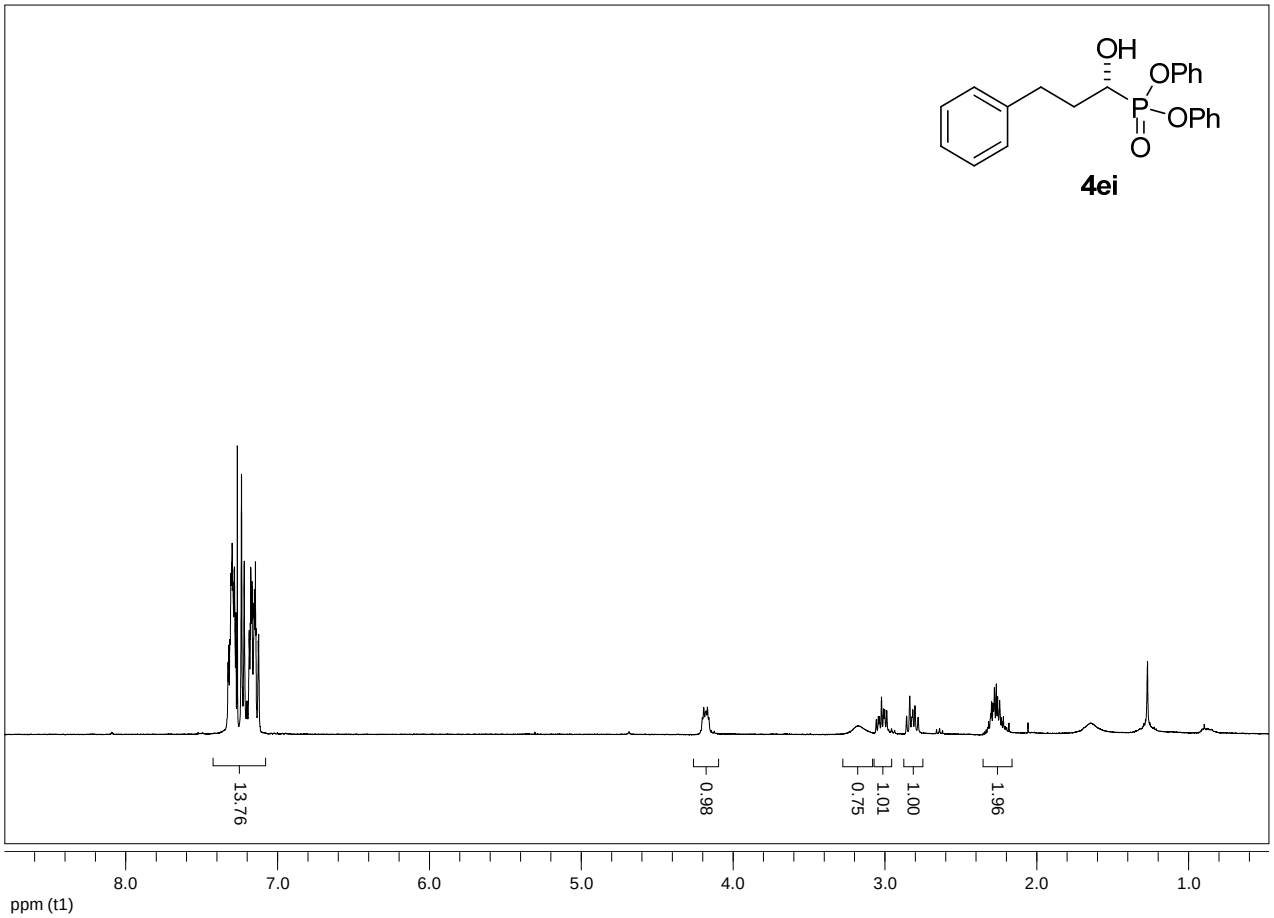



**Figure S6.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4ei**



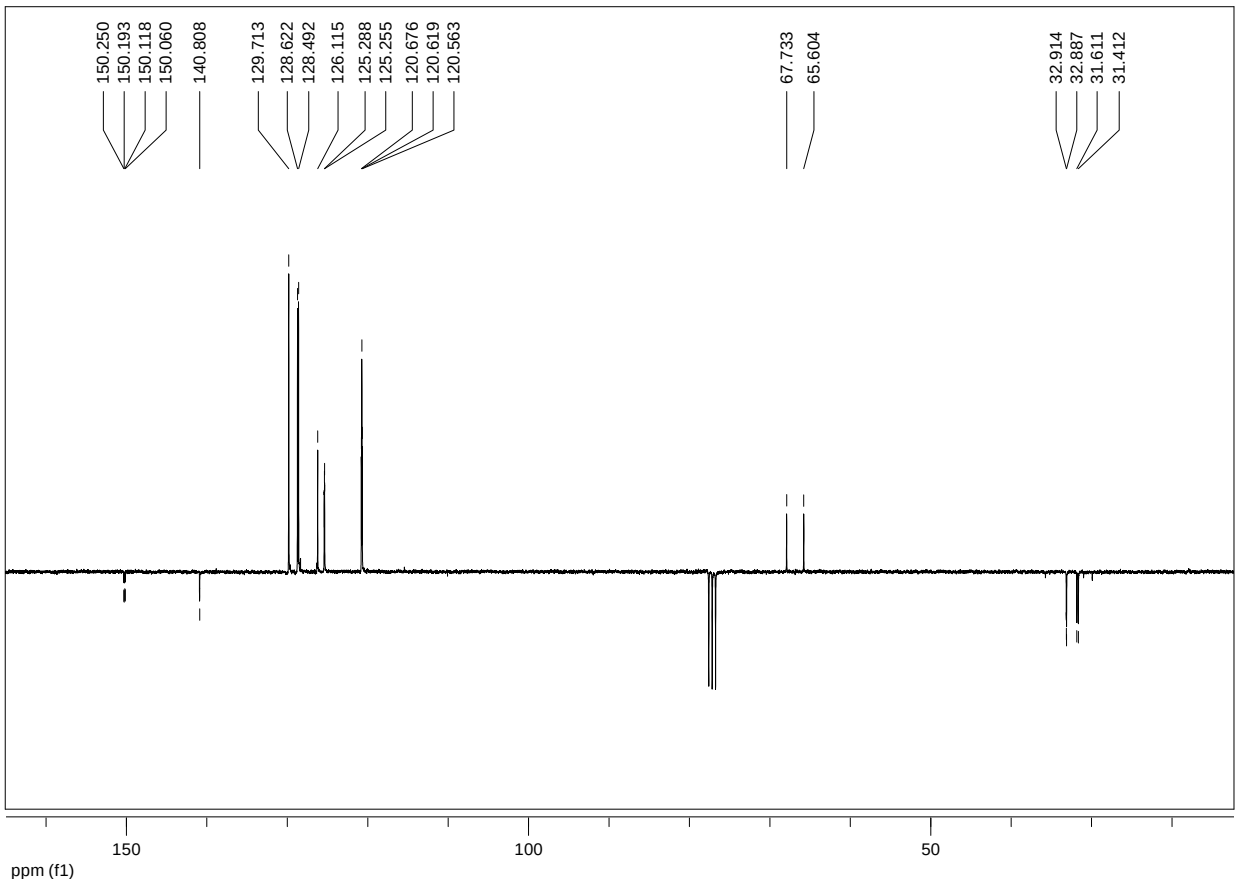
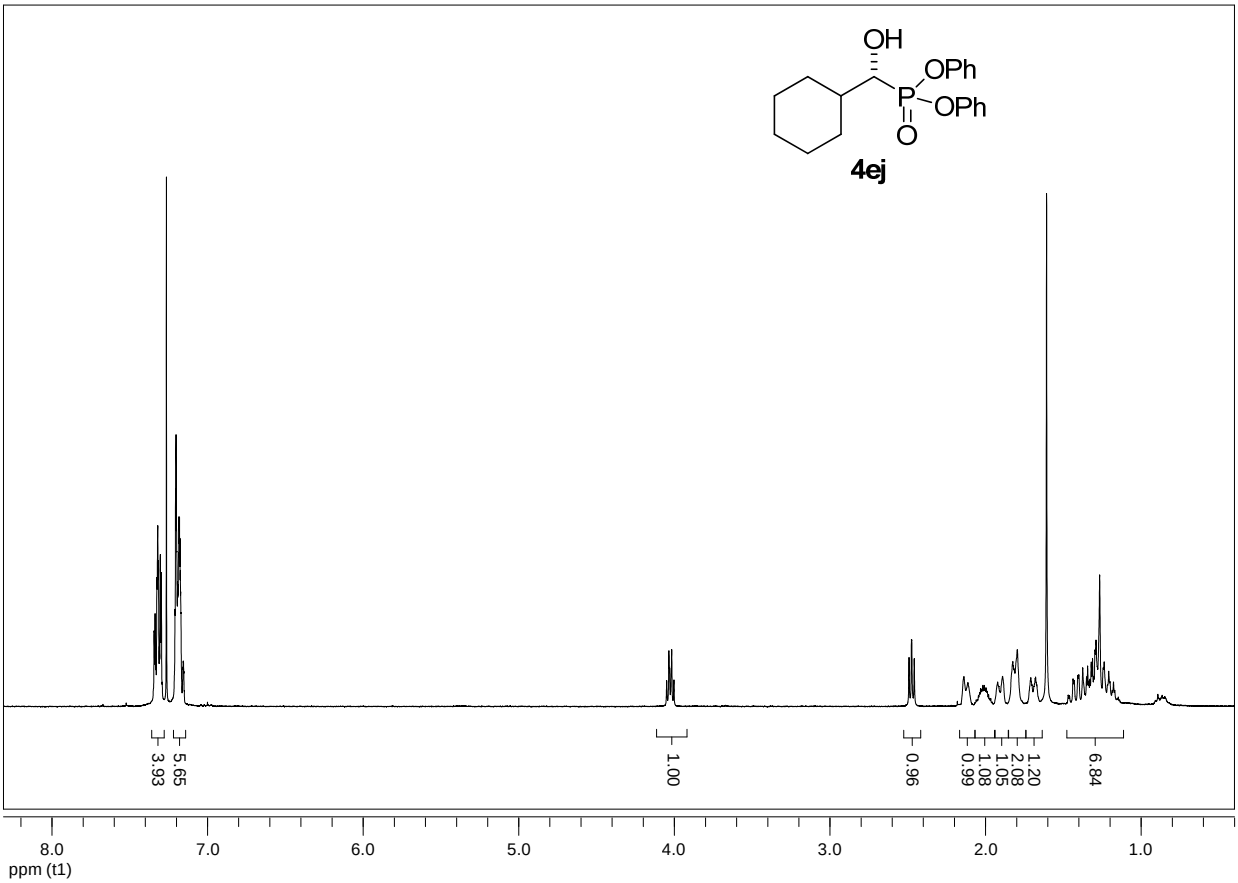



**Figure S7.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4ej**



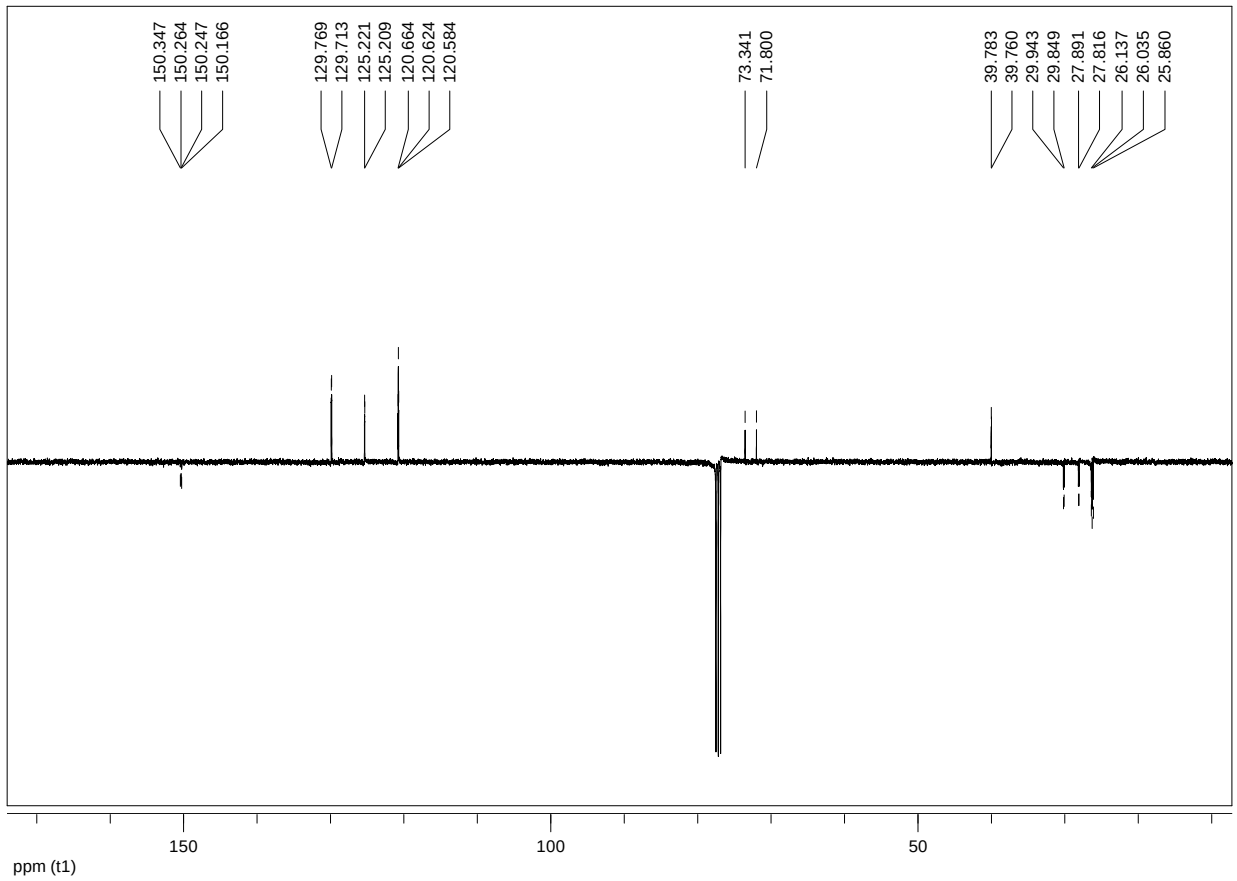
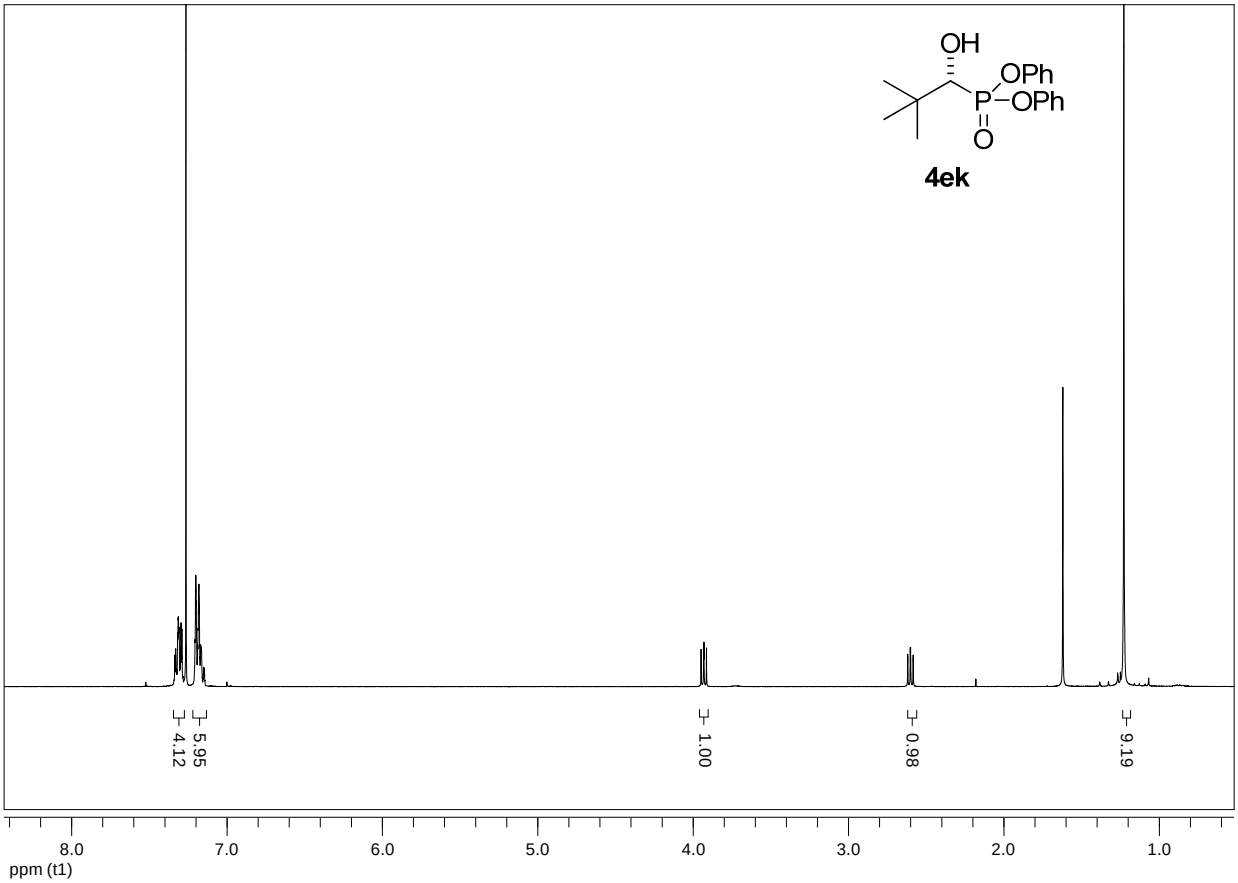
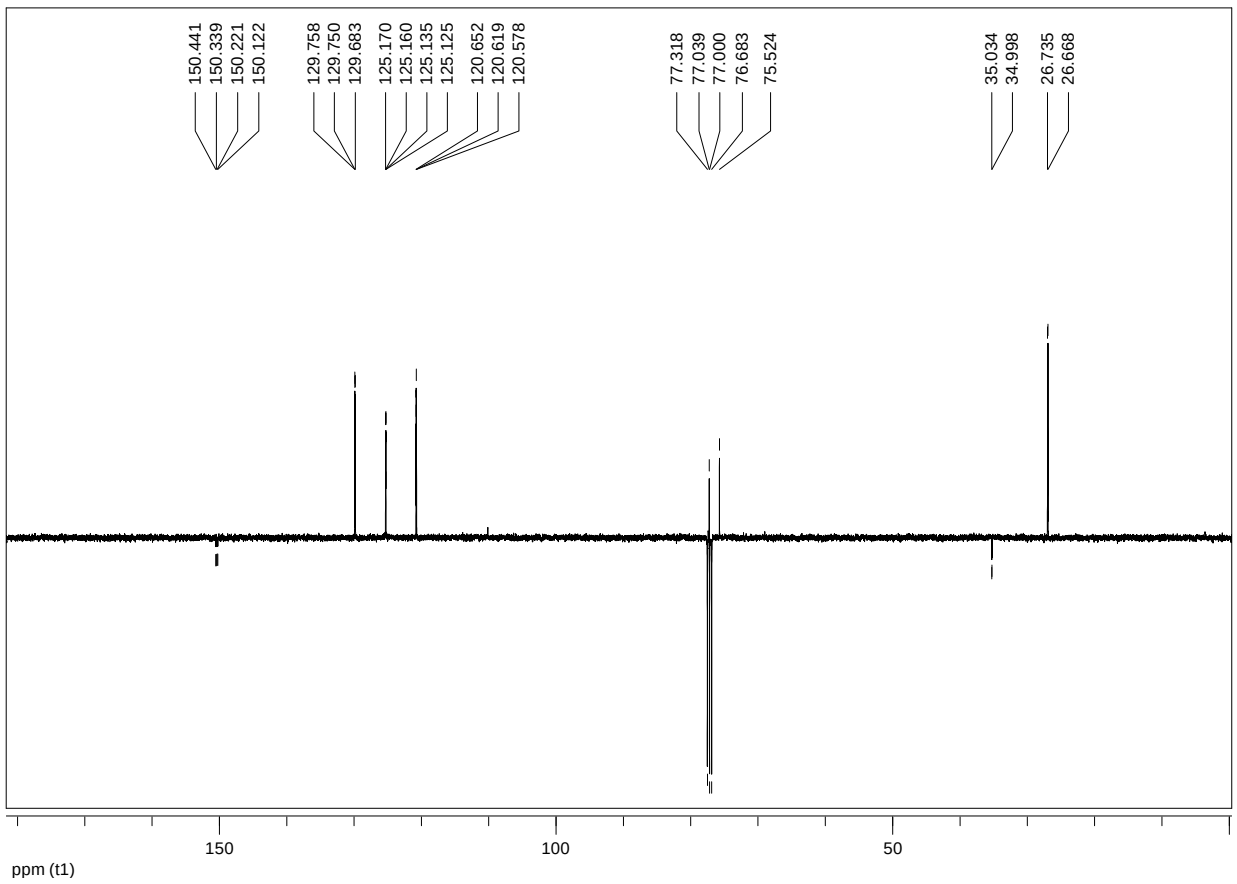
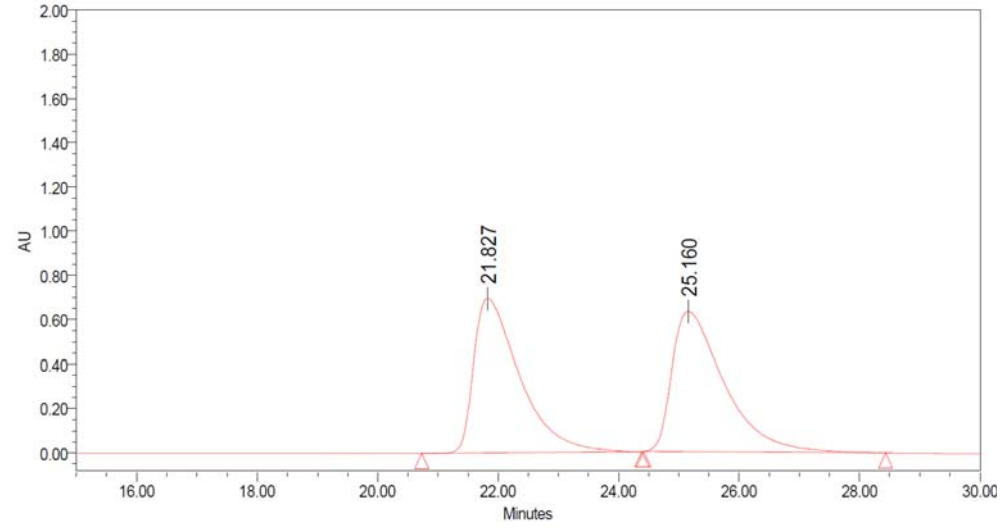



**Figure S8.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4ek**



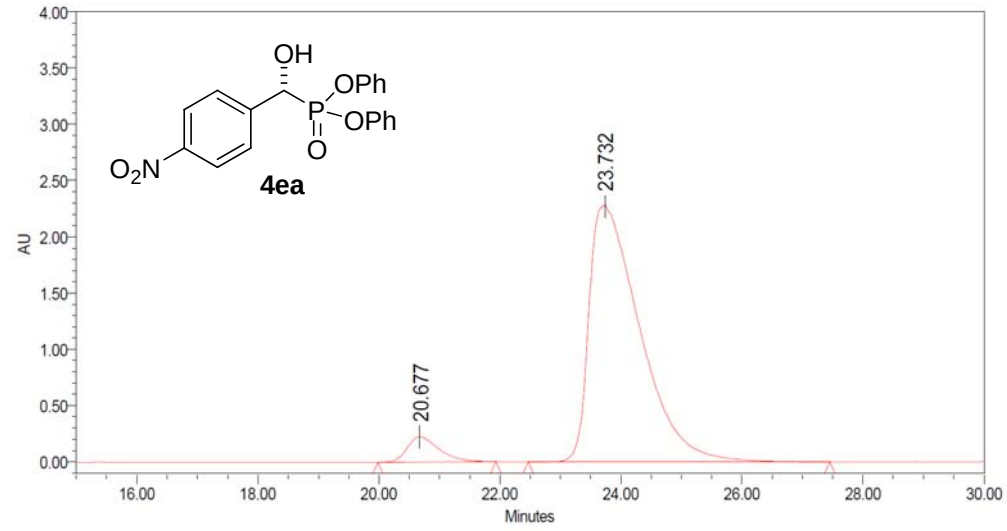
## HPLC CROMATOGRAMS OF COMPOUNDS 4




**Processed Channel: PDA 268.3 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 268.3 nm | 21.827 | 36965003 | 49.20 | 695744 |
| 2 | PDA 268.3 nm | 25.160 | 38163293 | 50.80 | 632692 |

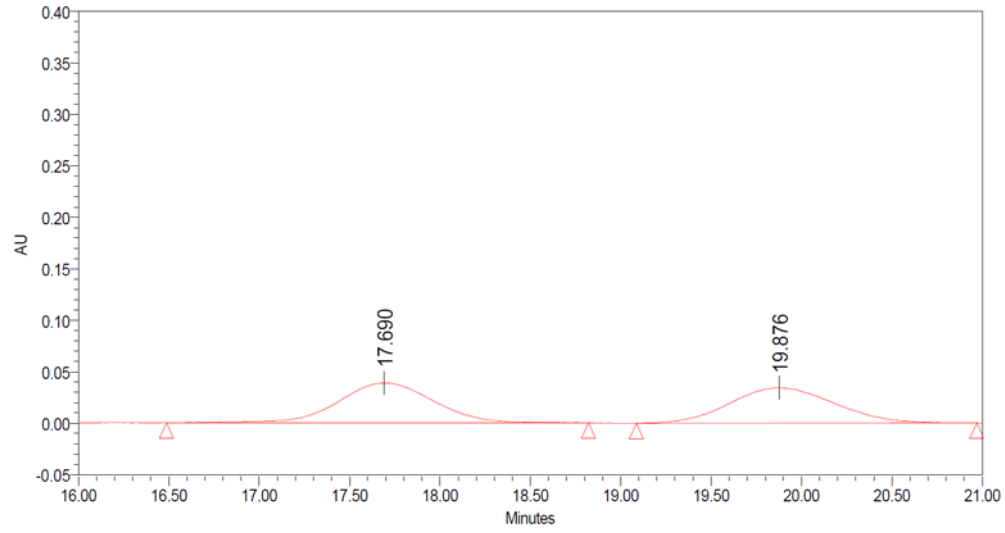
**Figure S9.** Racemic mixture of **4ea**. Daicel Chiralpak IA column (*n*-hexane/AcOEt = 70:30, flow rate 1 mL/min).




**Processed Channel: PDA 268.3 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 268.3 nm | 20.677 | 8332458 | 5.88 | 225378 |
| 2 | PDA 268.3 nm | 23.732 | 133424521 | 94.12 | 2280242 |

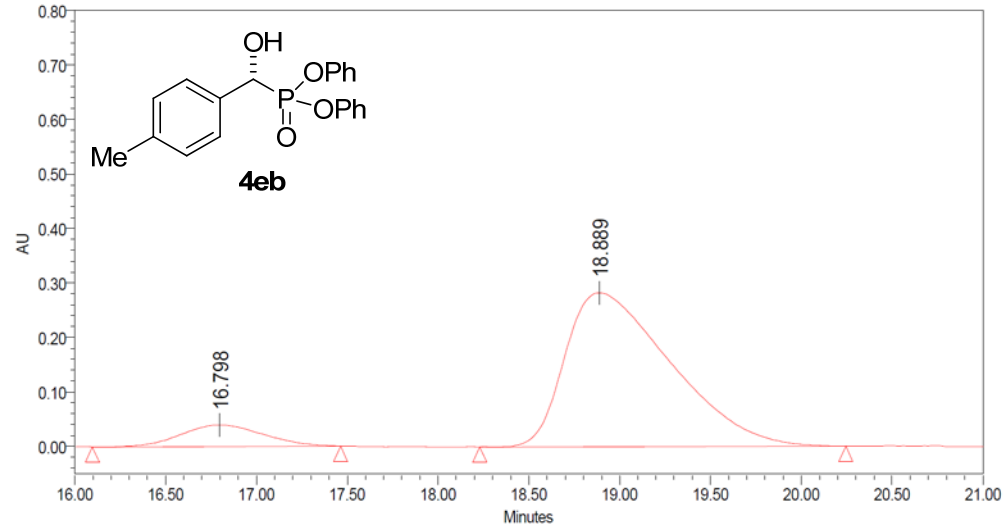
**Figure S10.** Chiral sample of **(*R*)-diphenyl hydroxy(4-nitrophenyl)methylphosphonate (4ea)**




**Processed Channel: PDA 262.0 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 262.0 nm | 17.690 | 1424339 | 50.89 | 38732 |
| 2 | PDA 262.0 nm | 19.876 | 1374490 | 49.11 | 34164 |

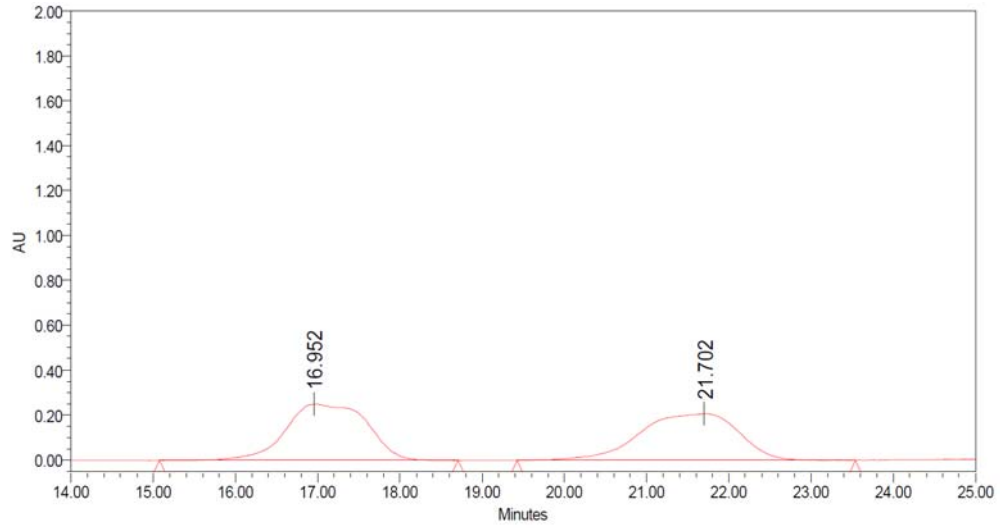
**Figure S11.** Racemic mixture of **4eb**. Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).




**Processed Channel: PDA 262.0 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 262.0 nm | 16.798 | 1239109 | 9.80 | 39547 |
| 2 | PDA 262.0 nm | 18.889 | 11407210 | 90.20 | 282613 |

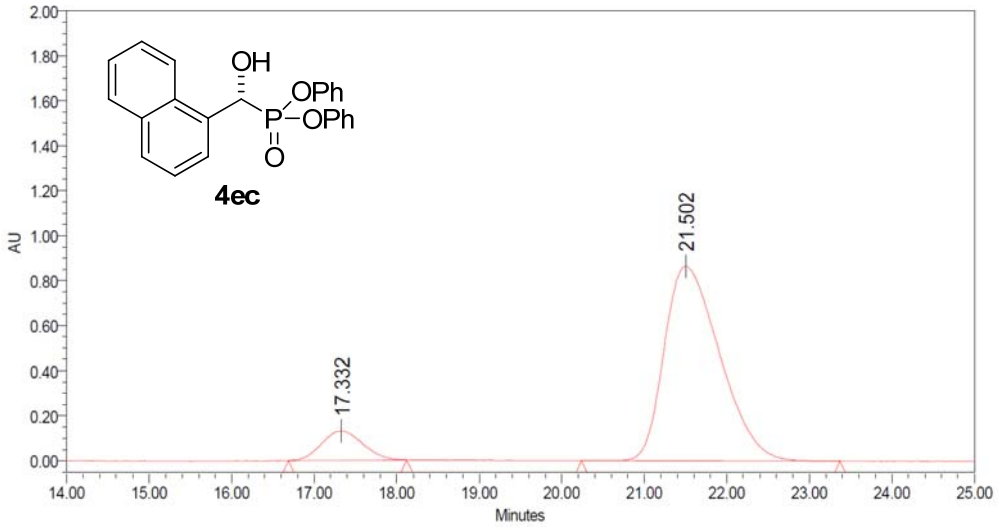
**Figure S12.** Chiral sample of **(*R*)-diphenyl hydroxy(*p*-tolyl)methylphosphonate (4eb)**




**Processed Channel: PDA 283.7 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 283.7 nm | 16.952 | 17342908 | 50.22 | 250704 |
| 2 | PDA 283.7 nm | 21.702 | 17191915 | 49.78 | 207027 |

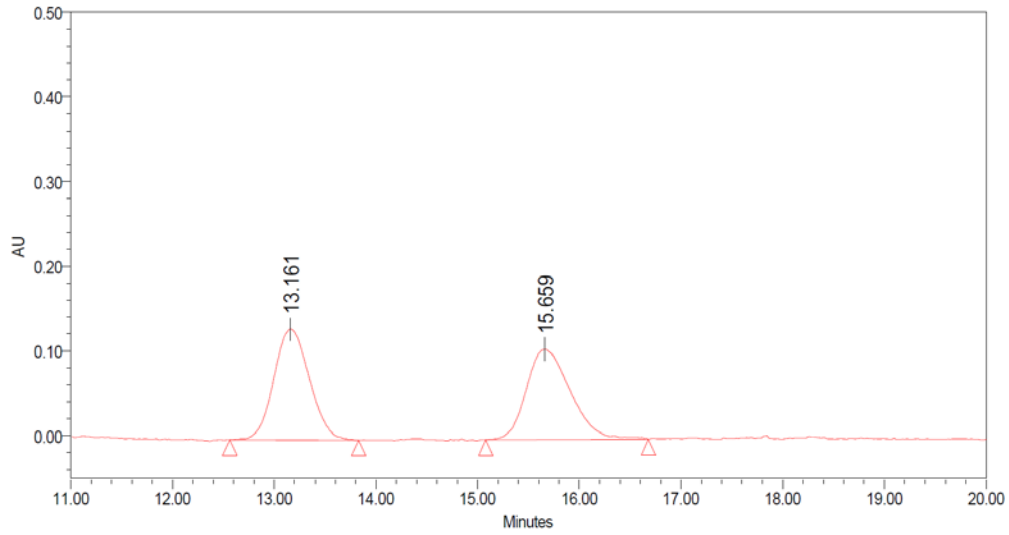
**Figure S13.** Racemic mixture of **4ec**. Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).




**Processed Channel: PDA 283.7 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 283.7 nm | 17.332 | 4496539 | 10.03 | 130154 |
| 2 | PDA 283.7 nm | 21.502 | 40354869 | 89.97 | 863902 |

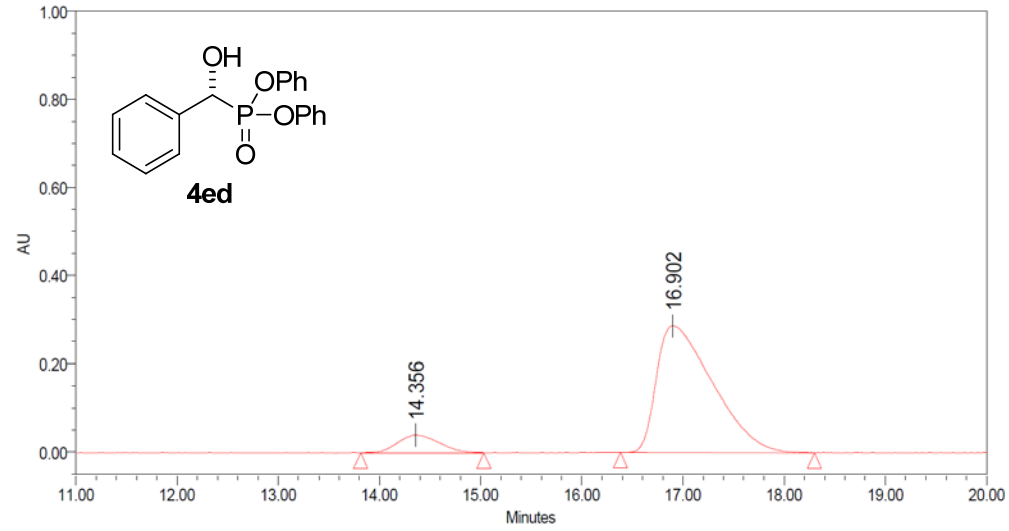
**Figure S14.** Chiral sample of **(*R*)-diphenyl hydroxy(naphthalen-1-yl)methylphosphonate (4ec)**




**Processed Channel: PDA 261.2 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 261.2 nm | 13.161 | 3181004 | 49.68 | 131025 |
| 2 | PDA 261.2 nm | 15.659 | 3222248 | 50.32 | 106750 |

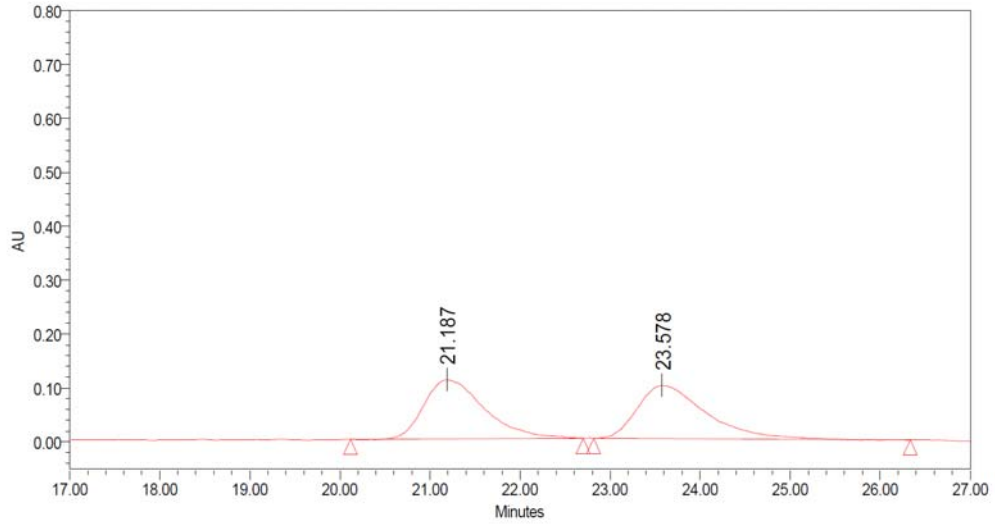
**Figure S15.** Racemic mixture of **4ed**. Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).




**Processed Channel: PDA 261.2 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 261.2 nm | 14.356 | 1133451 | 9.26 | 39930 |
| 2 | PDA 261.2 nm | 16.902 | 11101272 | 90.74 | 286940 |

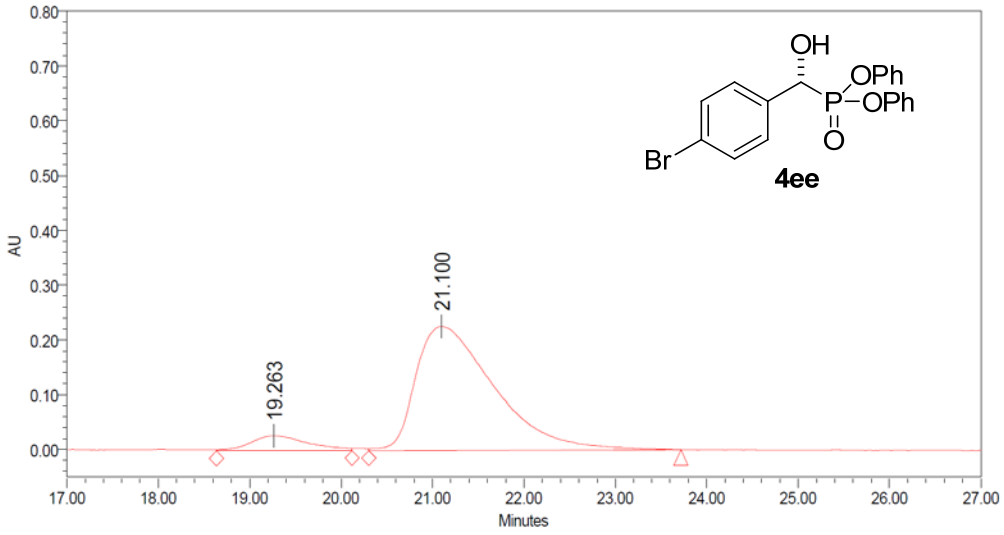
**Figure S16.** Chiral sample of **(*R*)-diphenyl hydroxy(phenyl)methylphosphonate (4ed)**.




**Processed Channel: PDA 260.7 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 260.7 nm | 21.187 | 5103358 | 49.40 | 109767 |
| 2 | PDA 260.7 nm | 23.578 | 5228185 | 50.60 | 98645 |

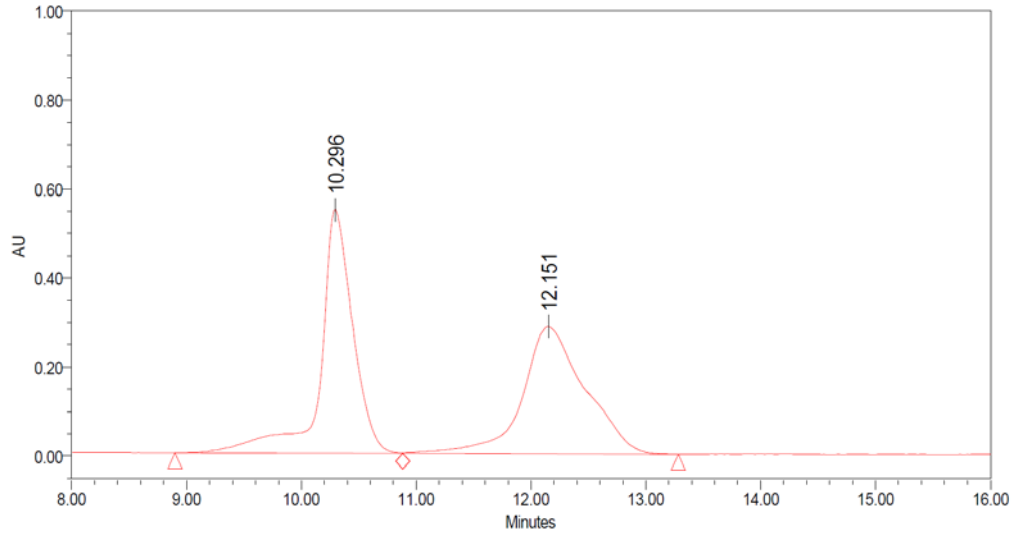
**Figure S17.** Racemic mixture of **4ee**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).




**Processed Channel: PDA 260.7 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 260.7 nm | 19.263 | 1194941 | 8.15 | 27377 |
| 2 | PDA 260.7 nm | 21.100 | 13473294 | 91.85 | 226689 |

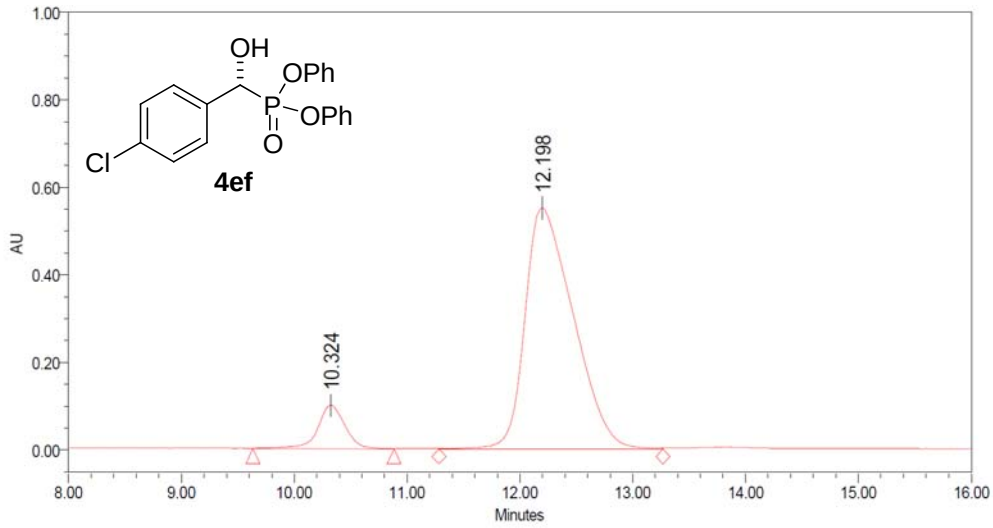
**Figure S18.** Chiral sample of **(*R*)-diphenyl (4-bromophenyl)(hydroxy)methylphosphonate (4ee).**




**Processed Channel: PDA 261.3 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 261.3 nm | 10.296 | 10904399 | 50.07 | 548564 |
| 2 | PDA 261.3 nm | 12.151 | 10874242 | 49.93 | 286768 |

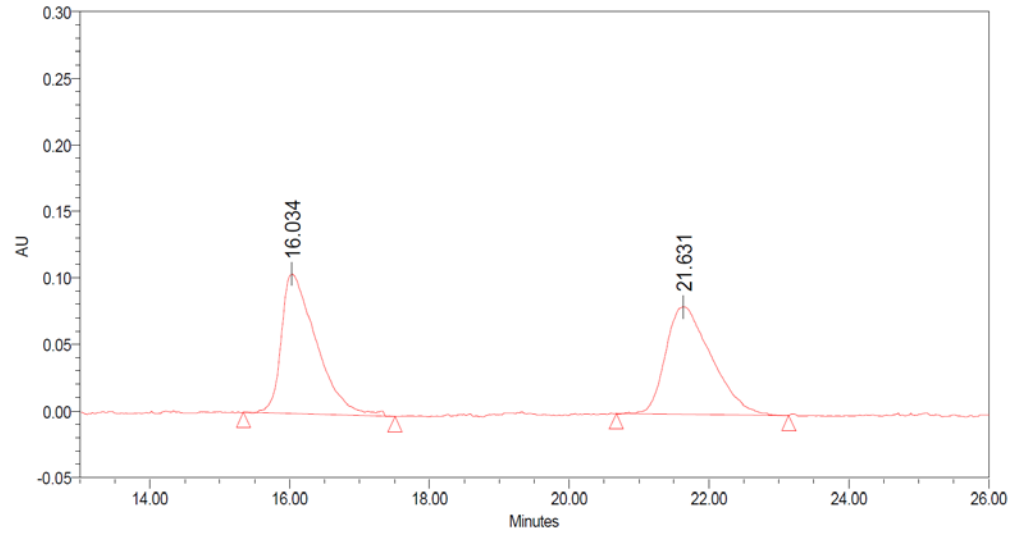
**Figure S19.** Racemic mixture of **4ef**. Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 98:2, flow rate 1 mL/min).




**Processed Channel: PDA 261.3 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 261.3 nm | 10.324 | 1640691 | 9.13 | 99015 |
| 2 | PDA 261.3 nm | 12.198 | 16333188 | 90.87 | 550764 |

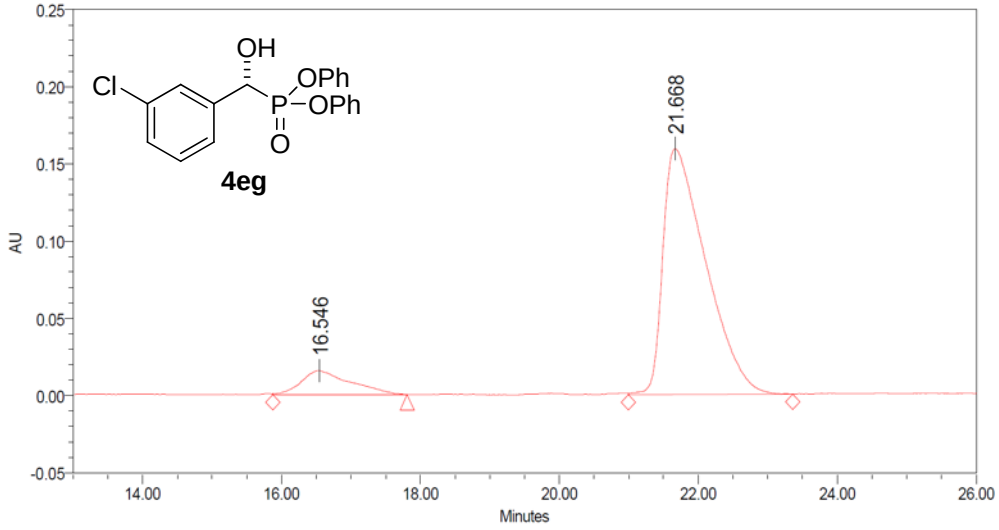
**Figure S20.** Chiral sample of **(*R*)-diphenyl (4-chlorophenyl)(hydroxy)methylphosphonate (4ef).**




**Processed Channel: PDA 272.6 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 272.6 nm | 16.034 | 3639007 | 49.75 | 104602 |
| 2 | PDA 272.6 nm | 21.631 | 3675027 | 50.25 | 80550 |

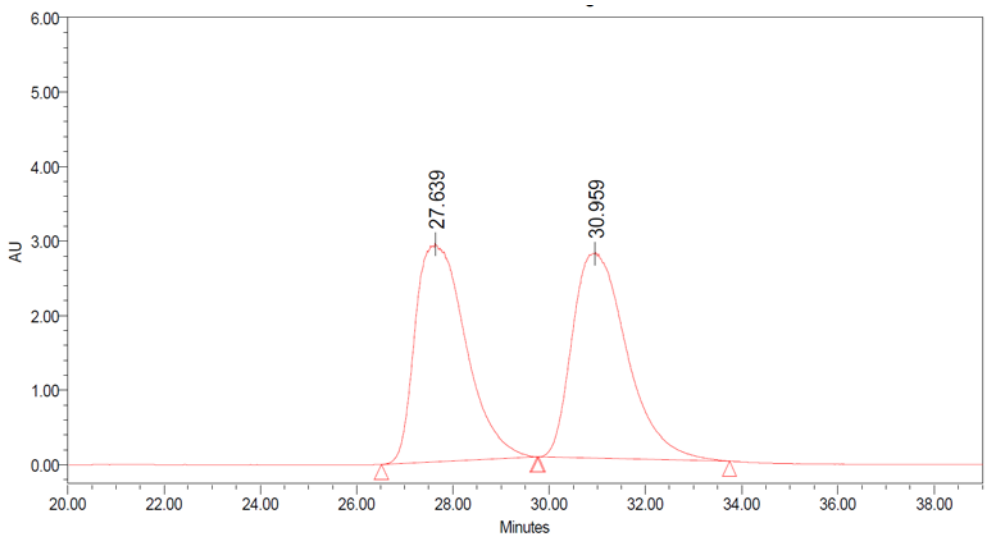
**Figure S21.** Racemic mixture of **4eg**. Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1 mL/min).




**Processed Channel: PDA 272.6 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 272.6 nm | 16.546 | 757006 | 9.96 | 15531 |
| 2 | PDA 272.6 nm | 21.668 | 6843497 | 90.04 | 159285 |

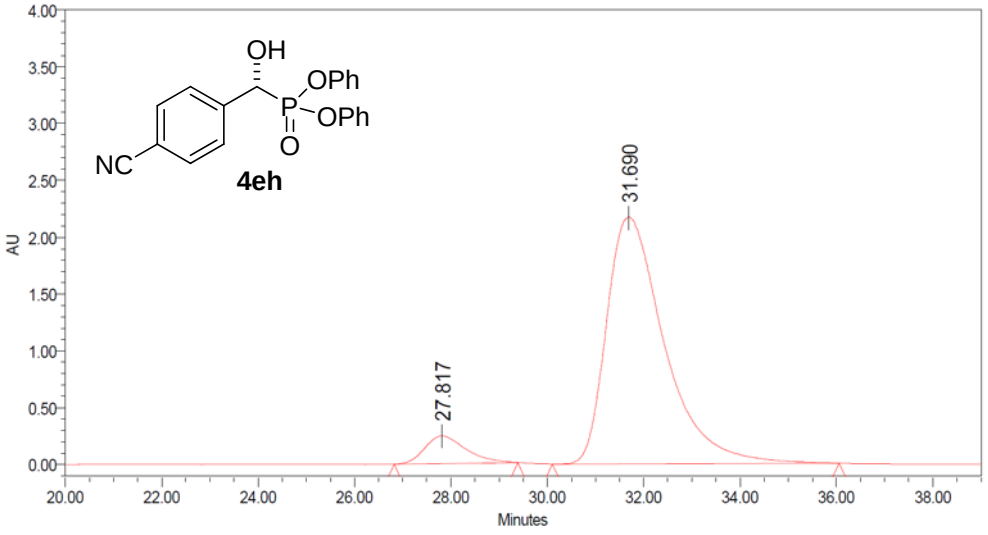
**Figure S22.** Chiral sample of **(*R*)-diphenyl (3-chlorophenyl)(hydroxy)methylphosphonate (4eg)**.




**Processed Channel: PDA 236.4 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 236.4 nm | 27.639 | 213162102 | 49.55 | 2910449 |
| 2 | PDA 236.4 nm | 30.959 | 216998274 | 50.45 | 2746862 |

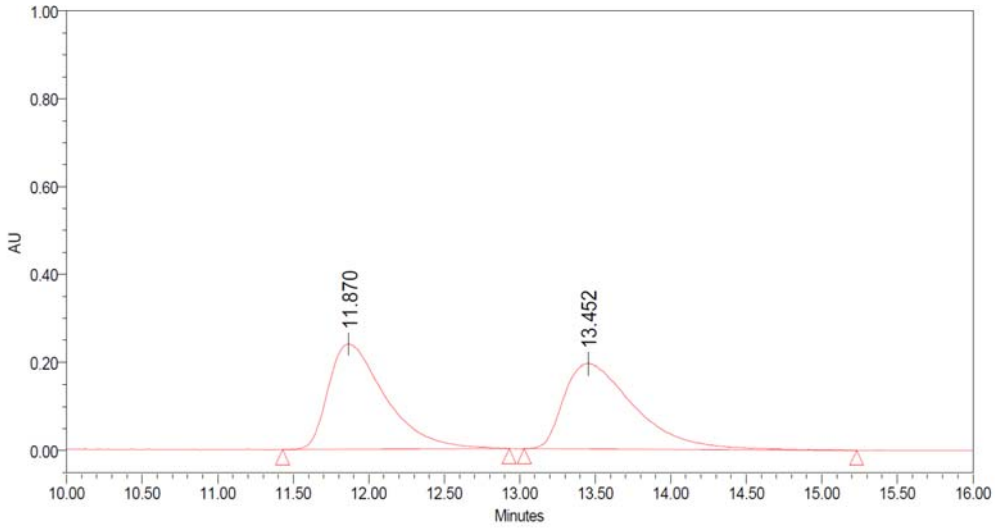
**Figure S23.** Racemic mixture of **4eh**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).




**Processed Channel: PDA 236.4 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 236.4 nm | 27.817 | 14410196 | 7.39 | 243508 |
| 2 | PDA 236.4 nm | 31.690 | 180593876 | 92.61 | 2166462 |

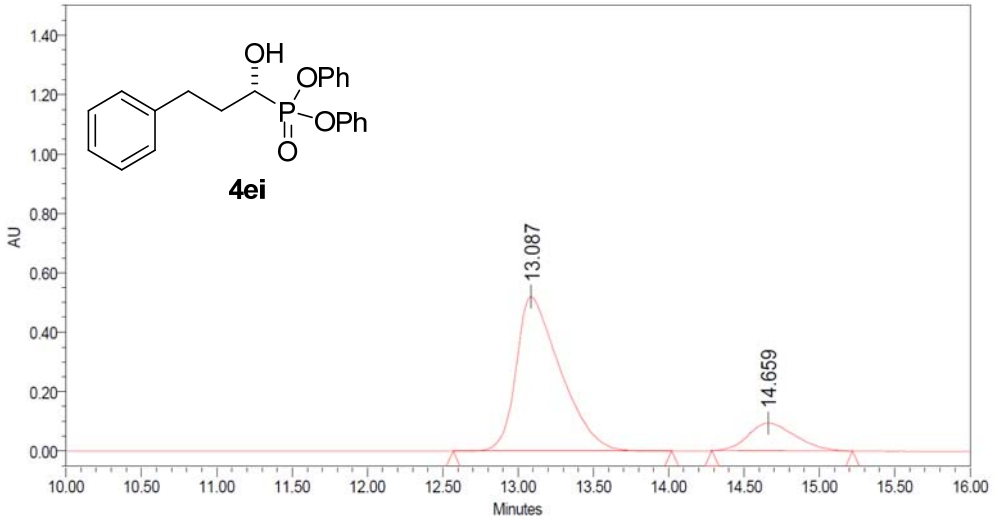
**Figure S24.** Chiral sample of **(*R*)-diphenyl (4-cyanophenyl)(hydroxy)methylphosphonate (4eh)**




**Processed Channel: PDA 261.2 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 261.2 nm | 11.870 | 6263217 | 49.95 | 238301 |
| 2 | PDA 261.2 nm | 13.452 | 6276308 | 50.05 | 193063 |

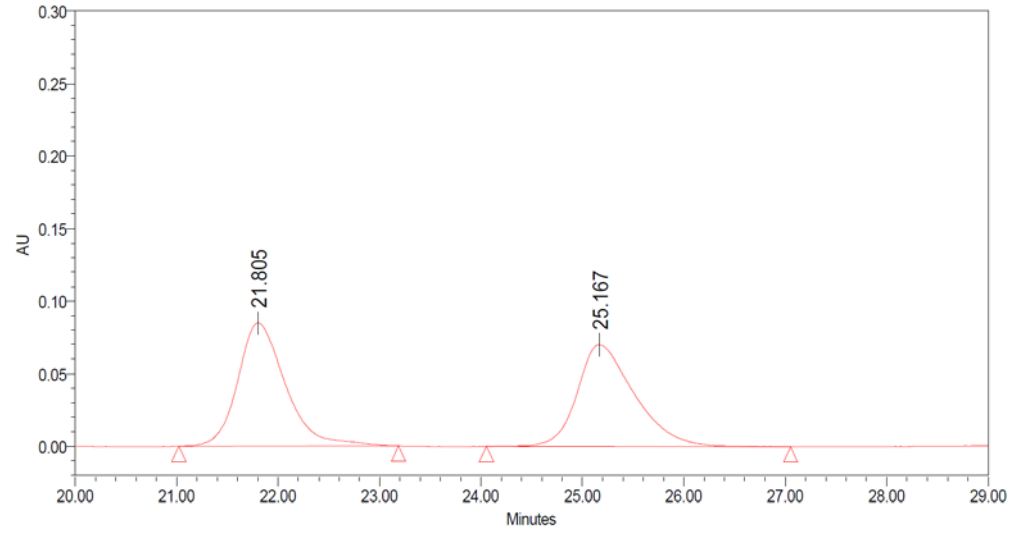
**Figure S25.** Racemic mixture of **4ei**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).




**Processed Channel: PDA 261.2 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 261.2 nm | 13.087 | 10629917 | 84.00 | 521070 |
| 2 | PDA 261.2 nm | 14.659 | 2024931 | 16.00 | 93341 |

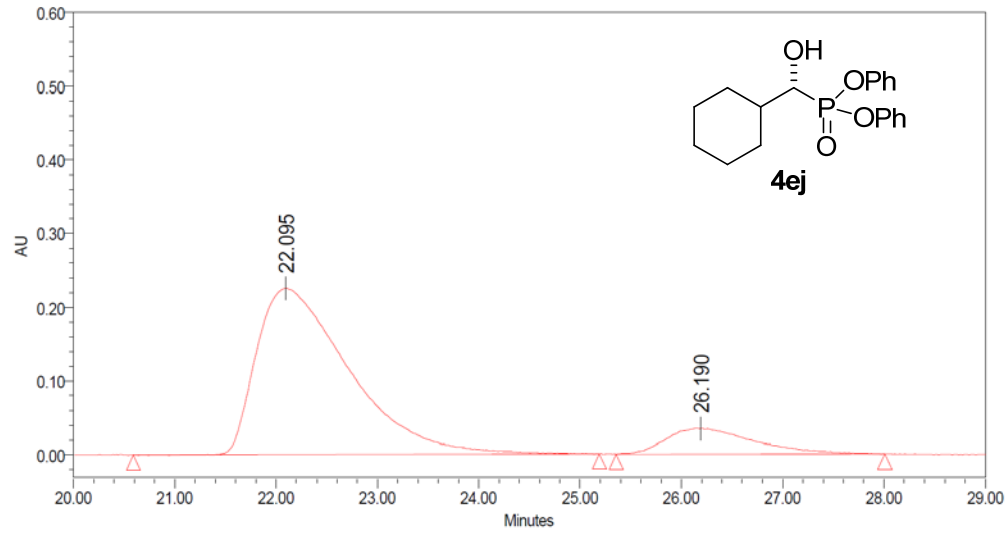
**Figure S26.** Chiral sample of **(*R*)-diphenyl 1-hydroxy-3-phenylpropylphosphonate (4ei)**




**Processed Channel: PDA 262.4 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 262.4 nm | 21.805 | 2784600 | 50.16 | 84848 |
| 2 | PDA 262.4 nm | 25.167 | 2766741 | 49.84 | 70156 |

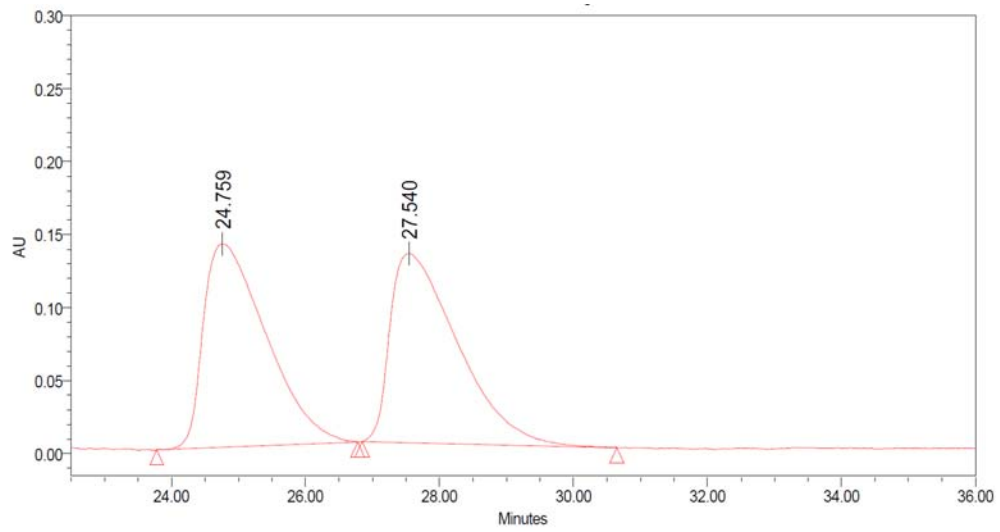
**Figure S27.** Racemic mixture of **4ej**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1 mL/min).




**Processed Channel: PDA 262.4 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 262.4 nm | 22.095 | 14249877 | 87.35 | 225719 |
| 2 | PDA 262.4 nm | 26.190 | 2062997 | 12.65 | 34386 |

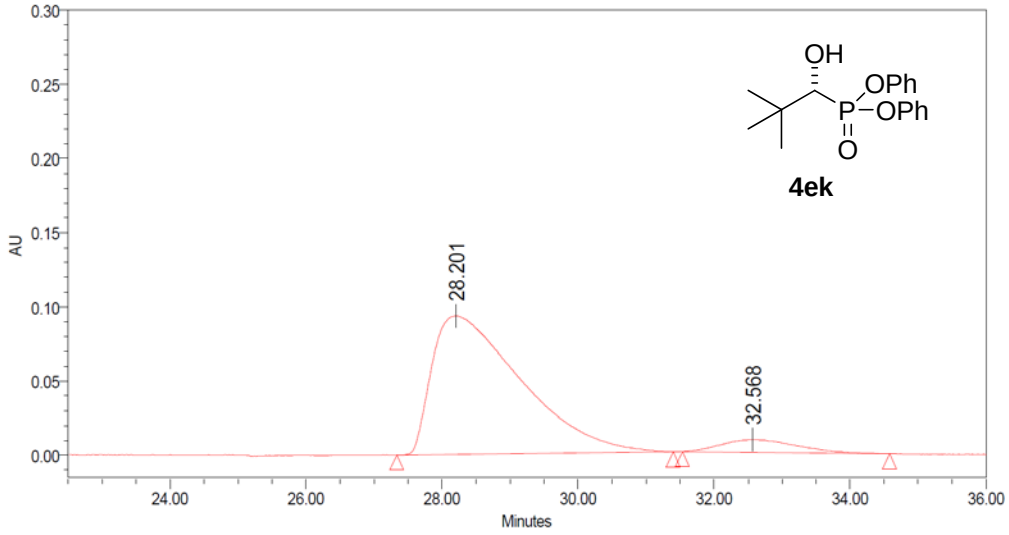
**Figure S28.** Chiral sample of **(*R*)-diphenyl cyclohexyl(hydroxy)methylphosphonate (4ej)**




**Processed Channel: PDA 262.4 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 262.4 nm | 24.759 | 9060405 | 49.86 | 139257 |
| 2 | PDA 262.4 nm | 27.540 | 9110016 | 50.14 | 129584 |

**Figure S29.** Racemic mixture of **4ek**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 98:2, flow rate 1 mL/min).



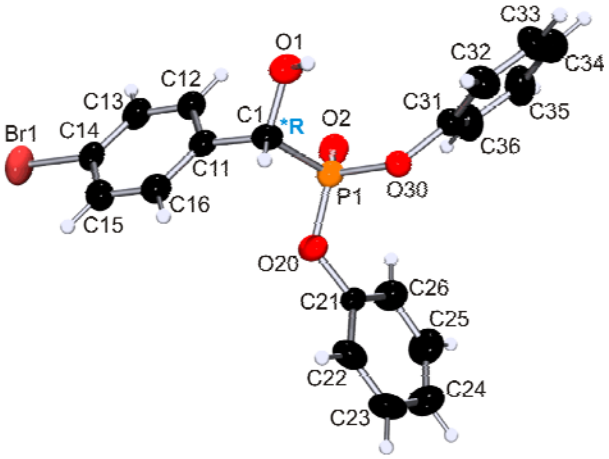

**Processed Channel: PDA 262.4 nm**

| | Processed Channel | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | PDA 262.4 nm | 28.201 | 8470790 | 92.72 | 93208 |
| 2 | PDA 262.4 nm | 32.568 | 665509 | 7.28 | 8616 |

**Figure S30.** Chiral sample of **(*R*)-diphenyl-1-hydroxy-2,2-dimethylpropylphosphonate (4ek)**

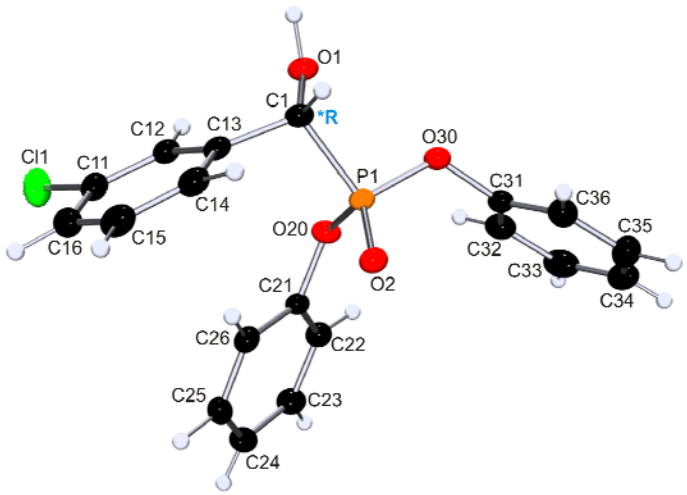
## X-RAY CRYSTALLOGRAPHY

Crystal data, data collection and refinement parameters for complexes **1** and **2** were recorded with a Bruker Kappa APEX2 diffractometer equipped with an area detector and graphite monochromated Mo Kα radiation (0.71073 Å). Data reduction was done with the APEX2 software.[3] The structure was solved by direct methods and refined by full-matrix least-squares methods based on $F^2$ using SHELXL-97 and WinGX programs.[4] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were positioned geometrically and refined with isotropic displacement parameters according to the riding model. Distance and angle calculations were performed using the SHELXL-97 and WinGX programs.[4]




Crystal data of **(*R*)-4ee**: $[C_{19}H_{16}BrO_4P]$, orthorhombic, *P21212*, $a$ = 9.2741(10) Å, $b$ = 38.324(4) Å, $c$ = 5.0810(5) Å, $Z$ = 4, $M_r$ = 419.20 g mol$^{-1}$, $V$ = 1805.9(3) Å$^3$, $D_{calcd}$ = 1.542 g cm$^{-3}$, $\lambda$(Mo Kα) = 0.71073 Å, T = 100 K, $\mu$ = 2.385 mm$^{-1}$, 28933 reflections collected, 4788 unique ($R_{int}$ = 0.0931), $R1(F_o)$ = 0.0599 [$I > 2\sigma(I)$], $wR2$ ($F_o^2$) = 0.1583 (all data), GOF = 1.038. CCDC 953498.

[3] APEX2 Bruker AXS Inc., Madison, Wisconsin, USA, **2011**.
[4] (a) G. M. Sheldrick, SHELXS-97 and SHELXL-97; University of Göttingen, Germany, **1997**; (b) Farrugia, L. J. *WinGX*; University of Glasgow, Great Britain, **1998**.




Crystal data of **(*R*)-4eg**: $[C_{19}H_{16}ClO_4P]$, orthorhombic, *P212121*, $a$ = 6.2873(11) Å, $b$ = 12.402(2) Å, $c$ = 22.054(4) Å, $Z$ = 4, $M_r$ = 374.74 g mol$^{-1}$, $V$ = 1719.7(5) Å$^3$, $D_{calcd}$ = 1.447 g cm$^{-3}$, $\lambda$(Mo Kα) = 0.71073 Å, T = 100 K, $\mu$ = 0.336 mm$^{-1}$, 19889 reflections collected, 4095 unique ($R_{int}$ = 0.0352), $R1(F_o)$ = 0.0315 [$I > 2\sigma(I)$], $wR2$ ($F_o^2$) = 0.0883 (all data), GOF = 1.047. CCDC 953499.