(2*S*,5*S*)-5-(METHYLAMINO)-4,4-DIPHENYL-1,3,2-DIOXAPHOSPHORINANE-2-OXIDE AS A PRELIGAND IN PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION

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GENERAL

NMR spectra were recorded with Bruker Avance DRX 400 (162.0, 400.1, 100.6 MHz for $^{31}P\{^{1}H\}$, ^{1}H, $^{13}C\{^{1}H\}$, respectively) and Bruker Avance 600 (242.9, 600.1, 150.9 MHz for $^{31}P\{^{1}H\}$, ^{1}H, $^{13}C\{^{1}H\}$, respectively) instruments. The chemical shifts are referenced to residual solvent peaks (^{1}H), $CDCl_3$ or CD_2Cl_2 ($^{13}C\{^{1}H\}$) and H_3PO_4 85% in D_2O as external standard ($^{31}P\{^{1}H\}$ NMR). The assignment of ^{1}H and $^{13}C\{^{1}H\}$ signals and the establishment of the structure of $\mathbf{2_{min}}$ и $\mathbf{2_{maj}}$ were carried out using DEPT, $^{1}H,^{1}H$–COSY, $^{1}H,^{13}C$–HSQC и $^{1}H,^{1}H$–NOESY. FTIR spectra were recorded on Thermo Scientific Nicolet iS5 Spectrometer. Elemental analysis was carried out on a Carlo Erba EA1108 CHNS-O CHN analyzer. Enantiomeric analysis of the products of catalytic reactions was performed with a Staier HPLC system. High-resolution mass spectra were recorded on a LCMS-9030 device (Shimadzu, Japan) by electrospray ionization mass spectrometry (ESI-MS). Measurements were carried out in positive ion mode; samples were dissolved in CH_2Cl_2 and injected into the mass-spectrometer chamber from an HPLC system LC-40 Nexera (Shimadzu, Japan). The following parameters were used: capillary voltage 4.0 kV; mass scanning range: m/z 100–1000; external calibration with solution NaI in MeOH/H_2O; drying and heating gases (nitrogen) (each 10 L/min); nebulizing gas (nitrogen) (3 L/min); interface temperature: 250C; flow rate 100% MeOH 0.4 mL/min. Molecular ions in the spectra were analyzed and matched with the appropriately calculated *m*/*z* and isotopic profiles in the LabSolutions v.5.114 program.

The full geometry optimization procedure for all model structures was performed in Cartesian coordinates using the Gaussian-09 program package [1] within the framework of density functional theory (DFT). The three-parameter hybrid exchange Becke's functional [2] was used in combination with the correlation functional of Lee, Yang, and Parr (B3LYP).[3] Symmetry restrictions were not applied during the geometry optimization procedure. The standard valence-split 6-31+G* basis sets, including diffuse and polarization d-functions on atoms of the second and third periods, were used. This level of quantum chemical calculation is acceptable for investigating isomerism in similar chemical systems.[4] Hessian matrices were calculated analytically in all cases, and all model structures correspond to minima on the potential energy surface (no imaginary frequencies). Thermodynamic functions were determined under

GENERAL

standard conditions (pressure 1 atm and temperature 298.15 K). Solvation effects ($CDCl_3$) were accounted for within the SMD [5] continuum model.

All reactions were carried out in anhydrous solvents under dry argon. Pd-precursors $[Pd(allyl)Cl]_2$,[6] $[Pd_2(dba)_3](CHCl_3)$,[7] $[Pd(COD)Cl_2]$ [8] and $[Pd(COD)(diphenylallyl)]BF_4$, [9] as well as catalytic substrates (*E*)-1,3-diphenylallyl acetate (**4a**) [6] (*E*)-1,3-diphenylallyl ethyl carbonate (**4b**) [10] were synthesized according to literature procedures. For the preparation of analytically pure samples, the obtained compounds were additionally dried in high vacuum (10^{-3} Torr) for 16 h.

$Pd(OAc)_2$, dimethyl malonate, di-*tert*-butyl malonate, dibenzyl malonate and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) were purchased from «Merck».

EXPERIMENTAL SECTION

(2*S*,5*S*)-5-(methylamino)-4,4-diphenyl-1,3,2-dioxaphosphinane 2-oxide (2).

A solution of deoxygenated water (0.024 mL, 1.31 mmol) in THF (3 mL) was added to a vigorously stirred solution of bicyclophosphoramidite **1** (0.37 g, 1.31 mmol) in THF (3 mL) at −78 °C. The reaction solution was slowly heated to 20 °C, stirred for 16 h, concentrated under reduced pressure (40 Torr), and the resulting solid residue was dried in vacuo (10^{-3} Torr). Product **2** was suspended in pentane (10 mL), the precipitate was washed with pentane (2 x 10 mL) and dried in vacuo (10^{-3} Torr).

Yield 0.354 g (90%), white powder, m. p. 76–78 °C. Found (%): C, 63.58; H, 6.04; N, 4.51. $C_{34}H_{29}NO_2P_2$. Calcld. (%): C, 63.36; H, 5.98; N, 4.62. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 °C, δ, ppm, *J*/Hz): 2.40 (s, 3H; CH_3), 3.64-3.66 (br.m, 1H; H^b), 4.14 (dd, ^2J(H,H) = 11.3, ^3J(H,P) = 4.2, 1H; CH_2), 4.35-4.41 (m, 1H; CH_2), 7.54 (d, ^1J(H,P) = 759.4, 1H; H^a) (**2**$_{maj}$, 76%), 2.26 (s, 3H; CH_3), 2.94 (br.t, ^3J(H,H) ≈ 6.1, 1H; H^b), 3.57 (ddd, ^2J(H,H) = 11.7, ^3J(H,P) = 8.8, ^3J(H,H) = 7.3, 1H; CH_2), 3.69-3.75 (m, 1H; CH_2), 6.56 (d, ^1J(H,P) = 644.2, 1H; H^a) (**2**$_{min}$, 24%), 7.10-7.56(m, 10H; CH(Ph)) (**2**$_{maj}$ **+ 2**$_{min}$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25 °C, δ, ppm, *J*/Hz): 33.53 (s; CH_3), 60.19 (d, ^3J(C,P) = 8.9; CH^b), 66.41 (d, ^2J(C,P) = 8.2; CH_2), 91.59 (d, ^2J(C,P) = 8.6; CPh_2), 124.83 (s; *o*-CH(Ph)), 125.17 (s; *o*-CH(Ph)), 128.13 (s; *p*-CH(Ph)), 128.31 (s; *p*-CH(Ph)), 128.99 (s; *m*-CH(Ph)), 129.18 (s; *m*-CH(Ph)), 140.98 (d, ^3J(C,P) = 5.1; C(Ph)), 141.52 (s; C(Ph)) (**2**$_{maj}$, 76%), 39.96 (s; CH_3), 49.95 (d, ^3J(C,P) = 7.7; CH^b), 62.76 (d, ^2J(C,P) = 4.2; CH_2), 127.59 (s; CH(Ph)), 128.36 (s; CH(Ph)), 128.41 (s; CH(Ph)), 128.53 (s; CH(Ph)), 128.73 (s; CH(Ph)), 130.45 (s; CH(Ph)) (**2**$_{min}$, 24%). ^{31}P{^{1}H} NMR (162.0 MHz, $CDCl_3$, 25 °C, δ, ppm): -4.65 (**2**$_{maj}$, 76%), 4.90 (**2**$_{min}$, 24%). FTIR (KBr, CH_2Cl_2), ν/cm^{-1}: 3310 (N—H); 2373 (P—H), 1195 (P=O); (solid), ν/cm^{-1}: 2359 (P—H), 1205 (P=O). M/z = 304.1098 (calcld. 304.1102 for [**2** + H]$^+$), 100%; 326.0920 (calcld. 326.0922 for [**2** + Na]$^+$), 70%; 629.1939 (calcld. 629.1946 for [(**2**)$_2$ + Na]$^+$), 20%.

(2*S*,5*S*)-*N*-methyl-4,4-diphenyl-2-((trimethylsilyl)oxy)-1,3,2-dioxaphosphinan-5-amine (3).

BSA (0.55 mL, 2.25 mmol) was added to a $CDCl_3$ solution of **2** (45 mg, 0.15 mmol) in a NMR-tube. The reaction mixture was shaken and left overnight, after which NMR spectra were recorded.

^{1}H NMR (600.1 MHz, $CDCl_3$, 25 °C, δ, ppm, *J*/Hz): 2.16 (s, 3H; NCH_3), 2.42 (t, ^3J(H,H) = 6.1, 1H; CH), 3.29 (dt, ^2J(H,H) = 11.0, ^3J(H,H) = ^3J(H,P) = 6.6, 1H; CH_2), 3.60 (ddd, ^2J(H,H) = 11.0, ^3J(H,P) =

7.8, ^{3}J(H,H) = 5.8, 1H; CH_2) (**3**$_{maj}$, 72%), 2.30-2.31 (m, 3H; NCH_3) 3.70-3.73 (m, 1H; CH), 3.81-3.85 (m, 1H; CH_2), 4.47-4.50 (m, 1H; CH_2) (**3**$_{min}$, 28%), 7.07-7.44 (m, 10H; CH(Ph)) (**3**$_{maj}$ **+ 3**$_{min}$) -0.16-0.18 (m; 689H; $SiCH_3$), 1.87 (s; 97H; $SiCH_3$), 1.94 (s; 19H; $SiCH_3$), 5.25 (br.s, 3H; NH) (**3**$_{maj}$ **+ 3**$_{min}$, BSA and TMS acetamide). $^{13}C\{^{1}H\}$ NMR (150.9 MHz, $CDCl_3$, 25 °C, δ, ppm, *J*/Hz): 41.27 (s; NCH_3), 50.19 (d, ^{3}J(C,P) = 5.6; CH), 59.16 (d, ^{2}J(C,P) = 3.3; CH_2), 126.63 (s; CH(Ph)), 127.54 (s; CH(Ph)), 127.89 (s; CH(Ph)), 128.22 (s; CH(Ph)), 128.85 (s; CH(Ph)), 131.08 (s; CH(Ph)), 138.71 (s; C(Ph)), 141.53 (s; C(Ph)) (**3**$_{maj}$, 72%), 59.15-59,31 (m; NCH_3, CH), 57.46 (d, ^{2}J(C,P) = 2.8; CH_2), 125.94 (s; CH(Ph)), 125.96 (s; CH(Ph)), 126.65 (s; CH(Ph)), 126.81 (s; CH(Ph)), 126.95 (s; CH(Ph)), 144.29 (s; C(Ph)), 146.13 (s; C(Ph)) (**3**$_{min}$, 28%) 0.77-2.52 (m), 23.27 (s), 24.94 (s), 24.99 (s), 160.22 (s), 175.84 (s) (**3**$_{maj}$ **+ 3**$_{min}$, BSA and TMS acetamide). $^{31}P\{^{1}H\}$ NMR (242.9 MHz, $CDCl_3$, 25 °C, δ, ppm): 114.48 (**3**$_{min}$, 28%), 117.95 (**3**$_{maj}$, 72%). M/z = 304.101 (calcld. 304.1102 for $[\mathbf{2} + H]^{+}$), 100%; 326.0923 (calcld. 326.0922 for $[\mathbf{2} + Na]^{+}$), 65%; 629.1948 (calcld. 629.1946 for $[(\mathbf{2})_2 + Na]^{+}$), 38%.

Reaction of oxygen-substituted phosphine oxide 2 with [Pd(allyl)Cl]$_2$.

A solution of **2** (45 mg, 0.15 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a vigorously stirred solution of $[Pd(allyl)Cl]_2$ (27.4 mg, 0.075 mmol (the molar ratio **2** : Pd = 1) or 13.7 mg, 0.0375 mmol (the molar ratio **2** : Pd = 2)) in CH_2Cl_2 (2.5 мл). The solution was left to stir overnight at r. t., then concentrated under reduced pressure (40 Torr) and the resulting solid residue was dried in vacuo (10^{-3} Torr). The product was dissolved in CH_2Cl_2 (≈0.5 mL) and added dropwise to pentane (10 mL) with vigorous stirring. The precipitate was centrifuged and dried in a vacuum (10^{-3} Torr).

In situ **reaction of oxygen-substituted phosphine oxide 2 with an excess of BSA and [Pd(allyl)Cl]$_2$.**

BSA (0.55 mL, 2.25 mmol) was added to a solution of 2 (45 mg, 0.15 mmol) in $CDCl_3$ (0.5 mL). The mixture was left overnight and then added to a sample of $[Pd(allyl)Cl]_2$ (27.4 mg, 0.075 mmol or 11.0 mg, 0.03 mmol) in an NMR-tube. The reaction mixture was shaken, then the $^{31}P\{^{1}H\}$ NMR spectrum was recorded. The solution was concentrated under reduced pressure (40 Torr), and the resulting solid residue was dried in vacuo (10^{-3} Torr).

EXPERIMENTAL SECTION

Pd(allyl)(3)Cl ⇄ [Pd(allyl)(3)]Cl. $^{31}P\{^{1}H\}$ NMR (242.9 MHz, $CDCl_3$, 25 °C, δ, ppm): 90.60 (7%), 101.36 (8%), 104.66 (64%), 110.23 (15%), 113.04 (3%), 113.31 (3%). M/z = 492.0906 (calcld. 492.0920 for [**2** + H + $2C_3H_5$ + Pd]$^+$), 62%; 522.0836 (calcld. 522.0846 for [Pd(allyl)(**3**)]$^+$), 16%; 733.0810 (calcld. 733.0825 for [(**2** - $H)_2$ + Na + Pd]$^+$), 51%.

Asymmetric alkylation of (*E*)-1,3-diphenylallyl acetate (4a) and (*E*)-1,3-diphenylallyl ethyl carbonate (4b) with dialkylmalonates.

A solution of the Pd-precursor (0.0025 mmol of $[Pd(allyl)Cl]_2$, $[Pd_2(dba)_3](CHCl_3)$ or 0.005 mmol of $[Pd(COD)Cl_2]$, [Pd(COD)(diphenylallyl)]BF_4), $Pd(OAc)_2$) and the appropriate compound **1** or **2** (0.005 mmol or 0.01 mmol) in the appropriate solvent (1.5 mL) was stirred for 40 min. The appropriate substrate (0.25 mmol) was added and the solution was stirred for 15 min, then the appropriate dialkyl malonate (0.44 mmol) and a base (BSA (0.11 mL, 0.44 mmol)/potassium acetate (0.002 g) composition or caesium carbonate (0.163 g, 0.5 ммоль)) was added. The reaction mixture was stirred for 24 h, diluted with toluene, THF or CH_2Cl_2 (2 mL) and filtered through a thin pad of SiO_2. The solution was concentrated under reduced pressure (40 Torr), and the resulting solid residue containing (*E*)-dimethyl-2-(1,3-diphenylallyl)malonate (**5a**),[11,12] (*E*)-di-*tert*-butyl-2-(1,3-diphenylallyl)malonate (**5b**) [13] or (*E*)-dibenzyl-2-(1,3-diphenylallyl)malonate (**5c**) [14] was dried in vacuo (10^{-3} Torr). To determine the conversion of substrates **4a,b** and enantiomeric excesses of products **5a-c**, the resulting residue was dissolved in the appropriate eluent (8 mL) and a sample was taken for HPLC analysis on a chiral stationary phase.

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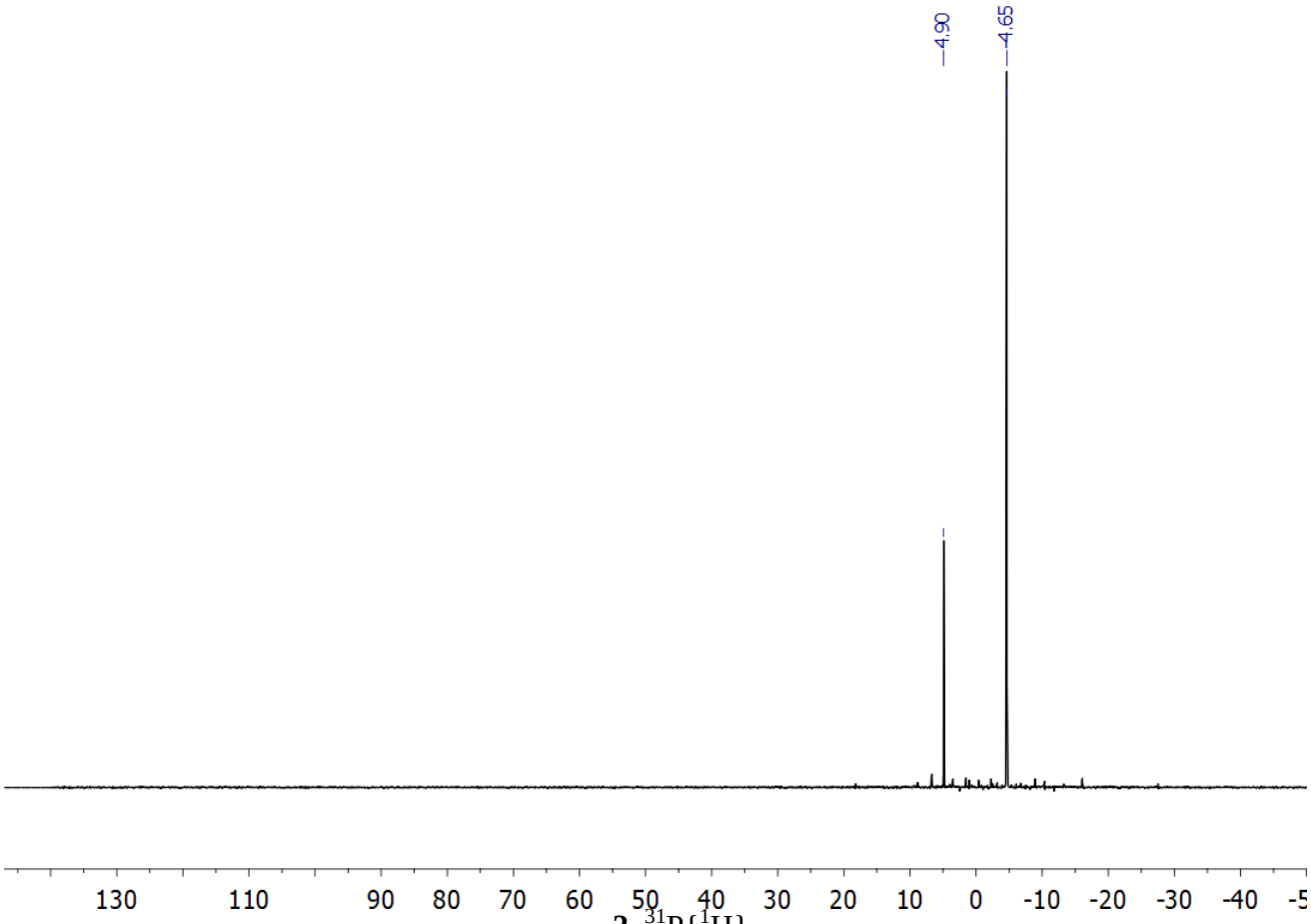
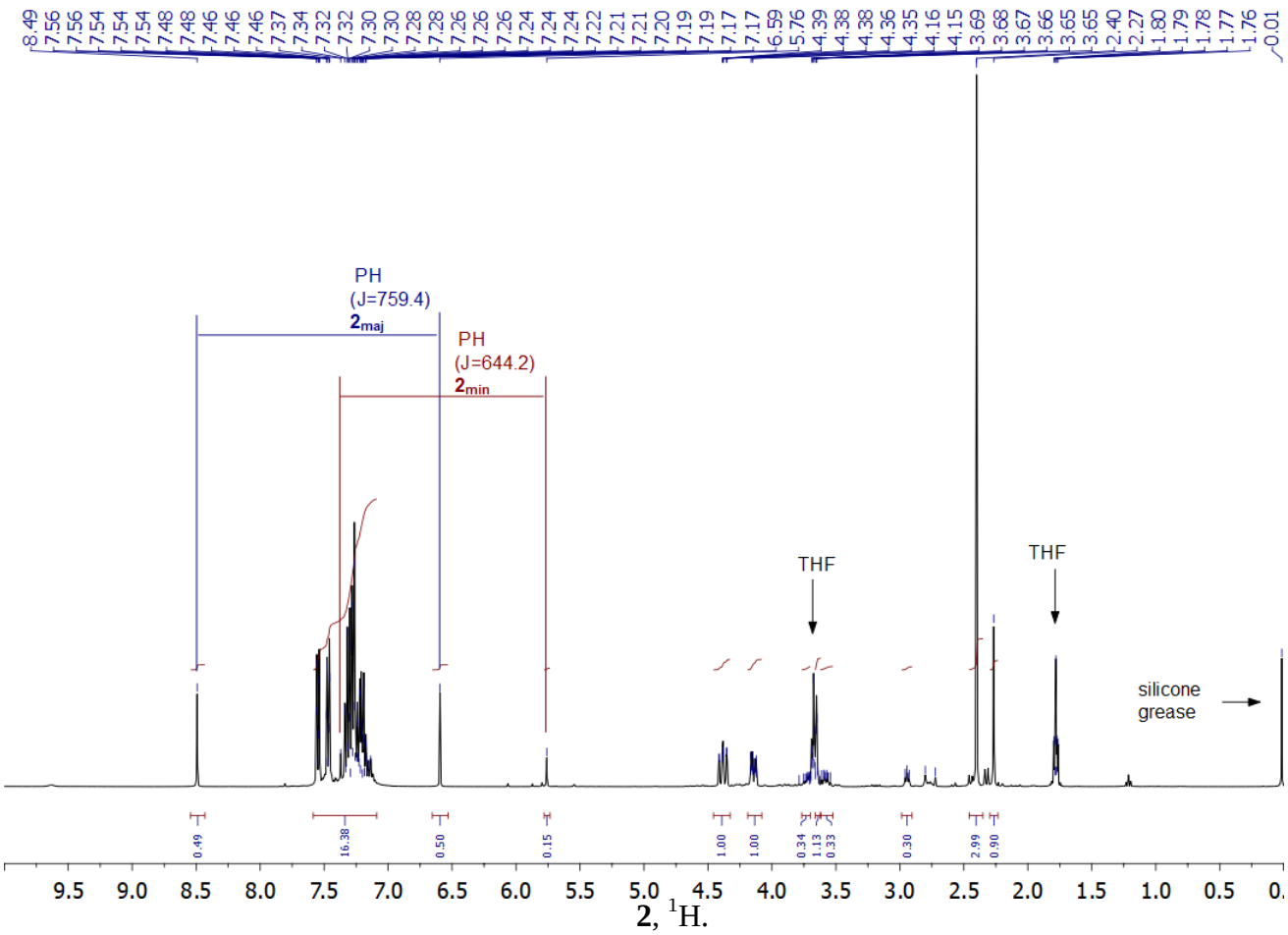
SPECTRA OF NEW COMPOUNDS

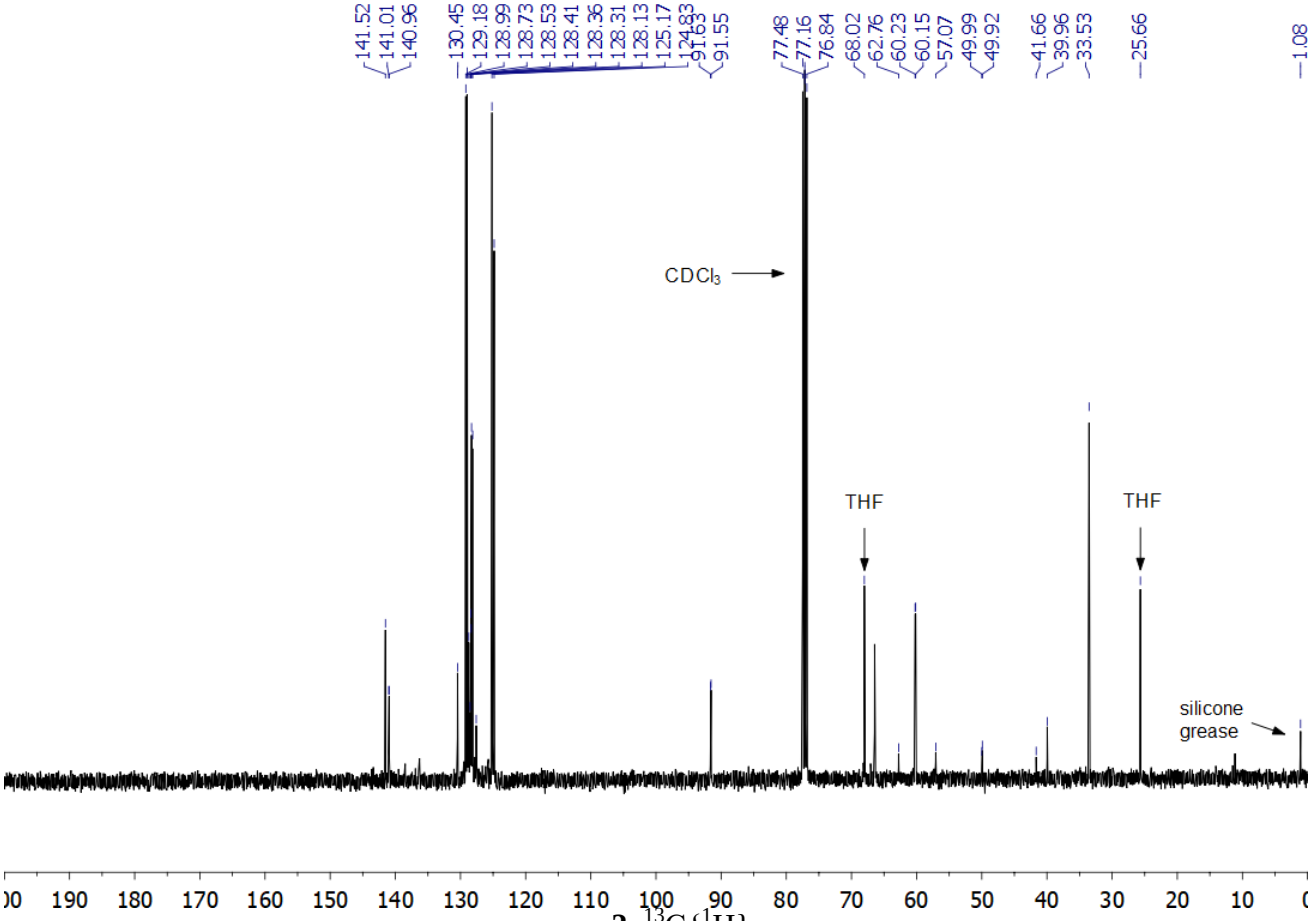


2, $^{31}P\{^{1}H\}$.



2, ^{1}H.

SPECTRA OF NEW COMPOUNDS



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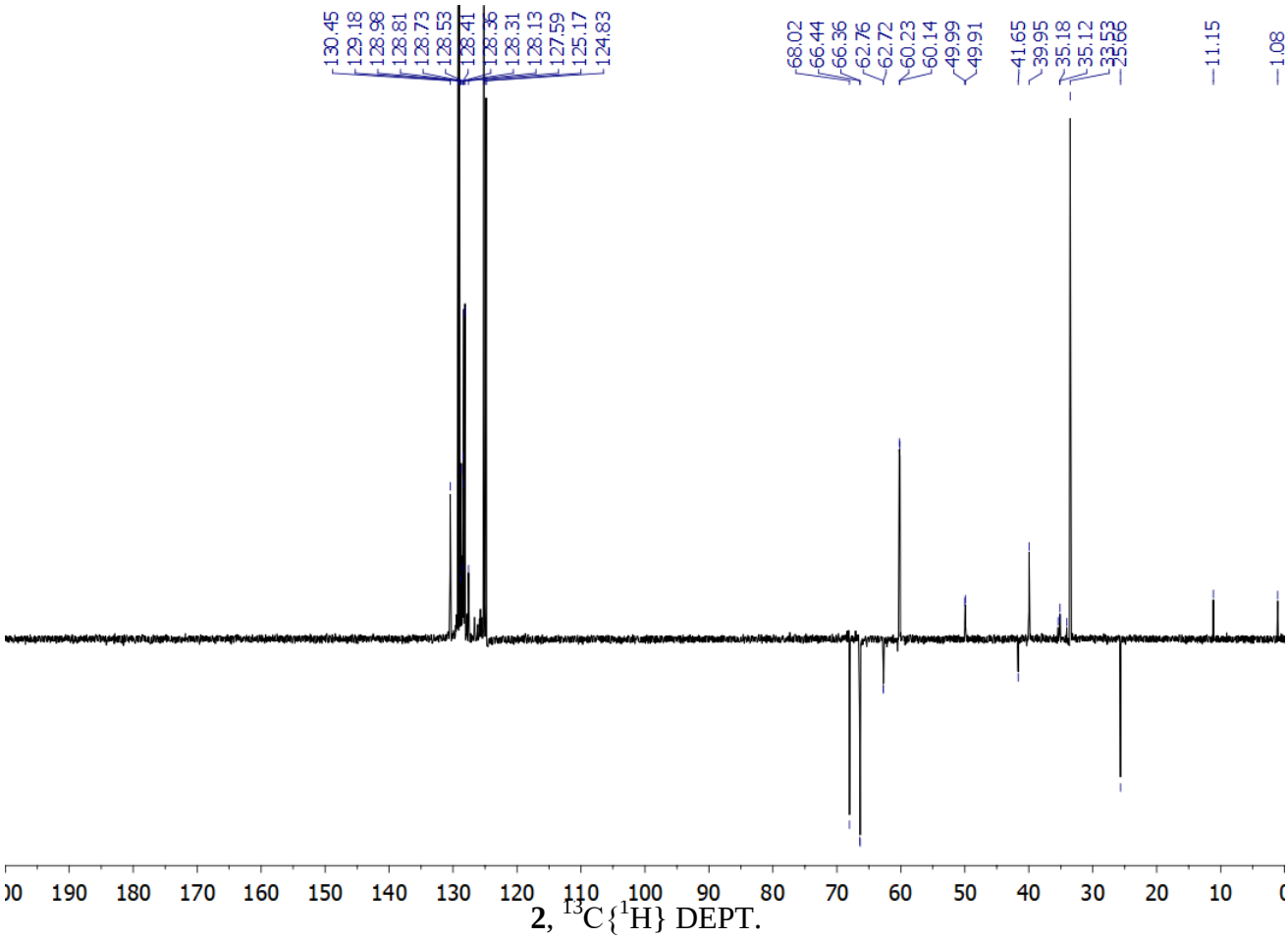

2, $^{13}C\{^{1}H\}$ DEPT.

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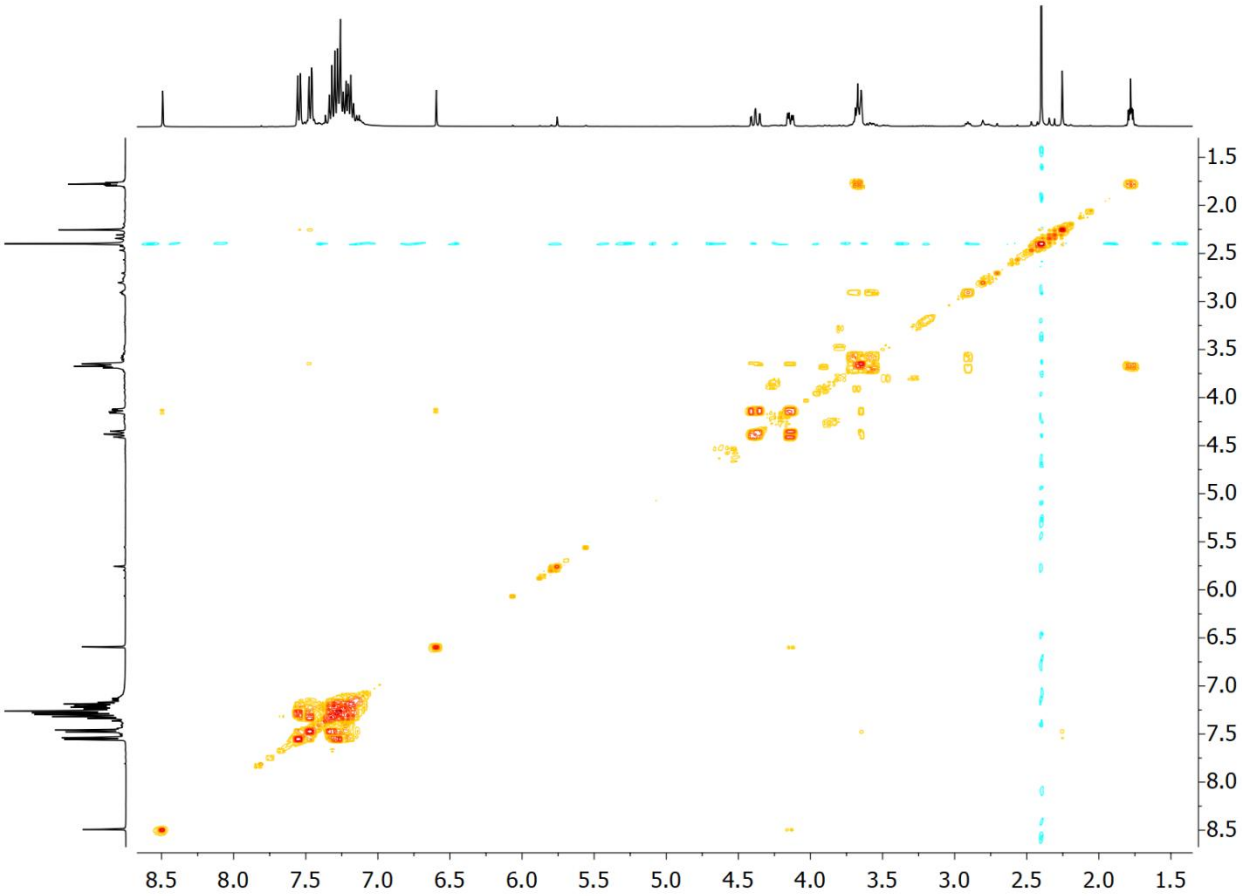

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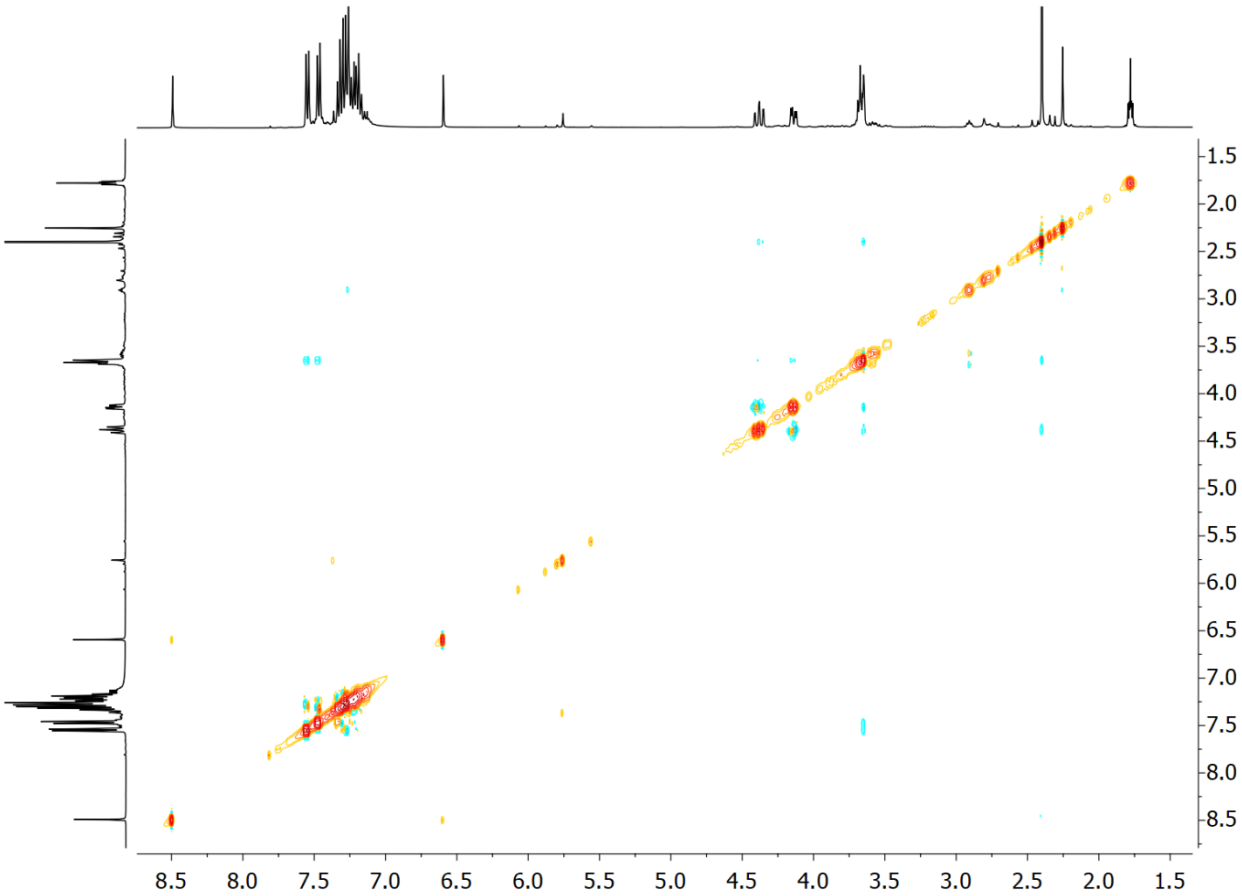

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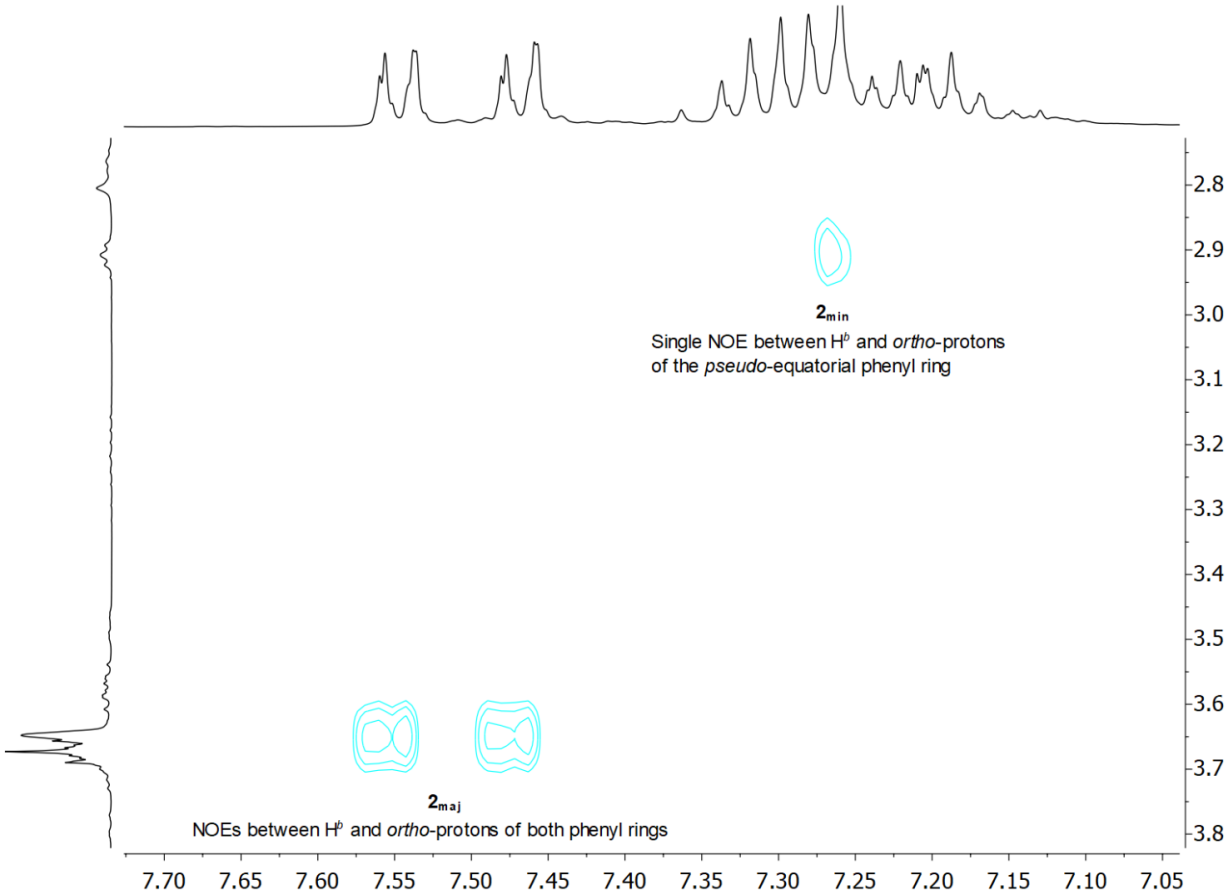
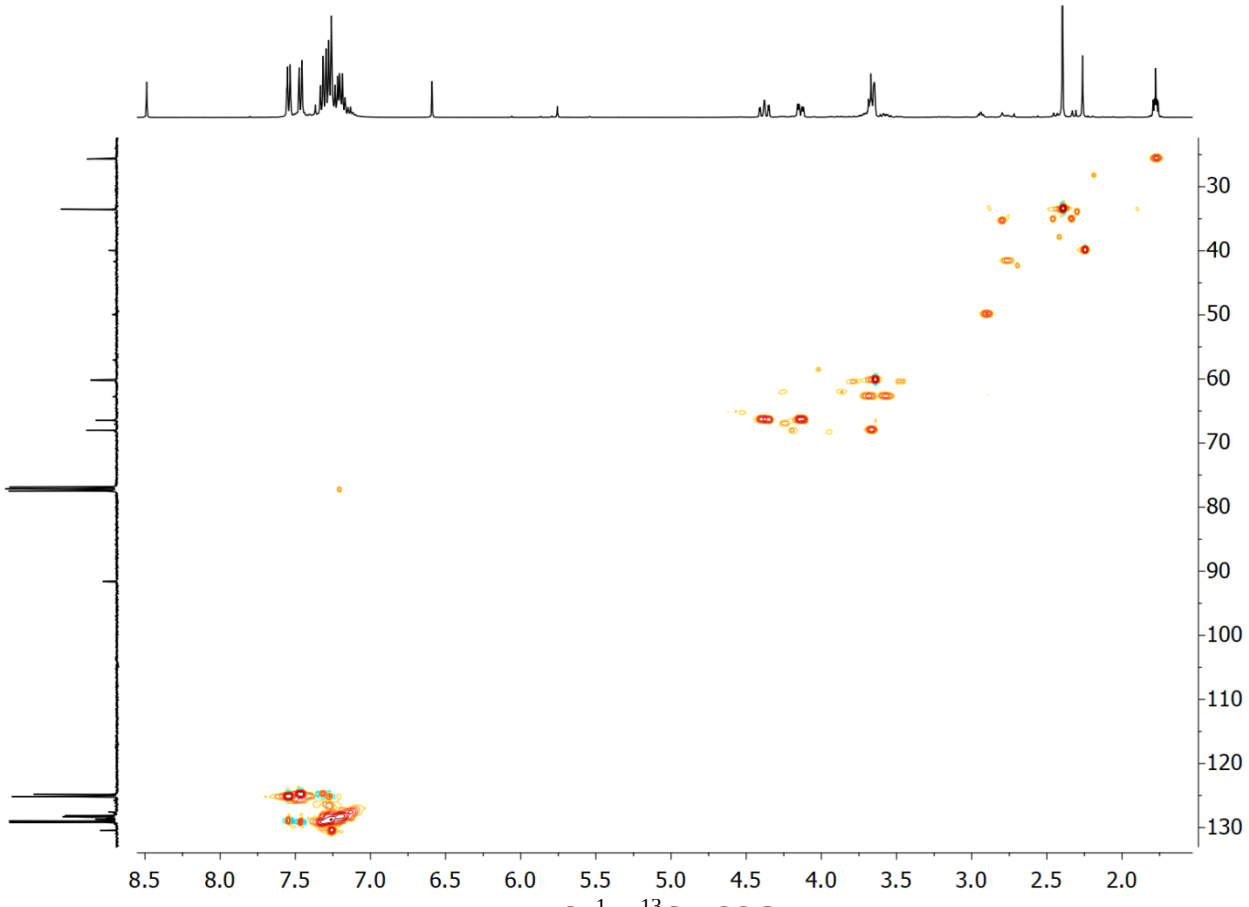


2, ^{1}H-^{1}H NOESY, region showing the key cross-peaks.



2, ^{1}H-^{13}C HSQC.

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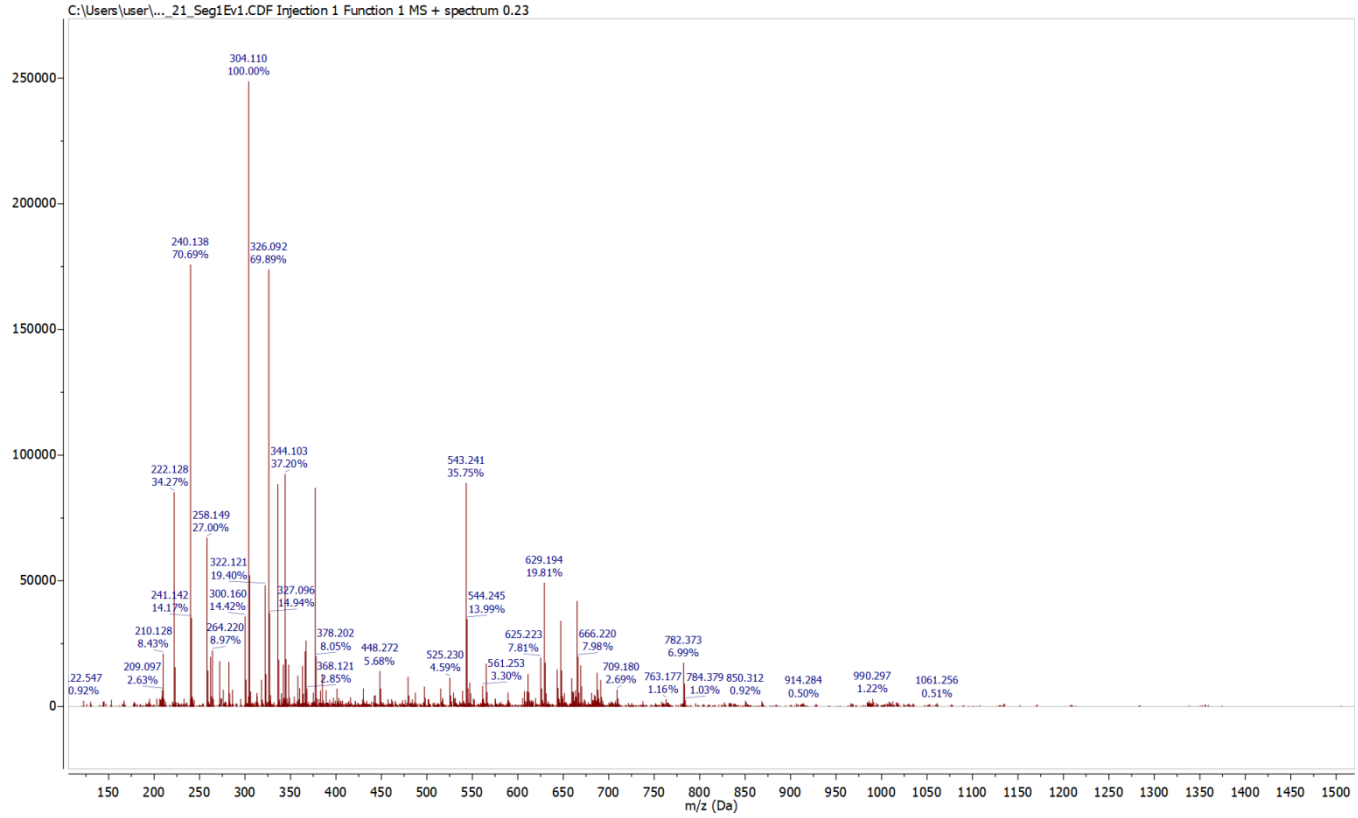

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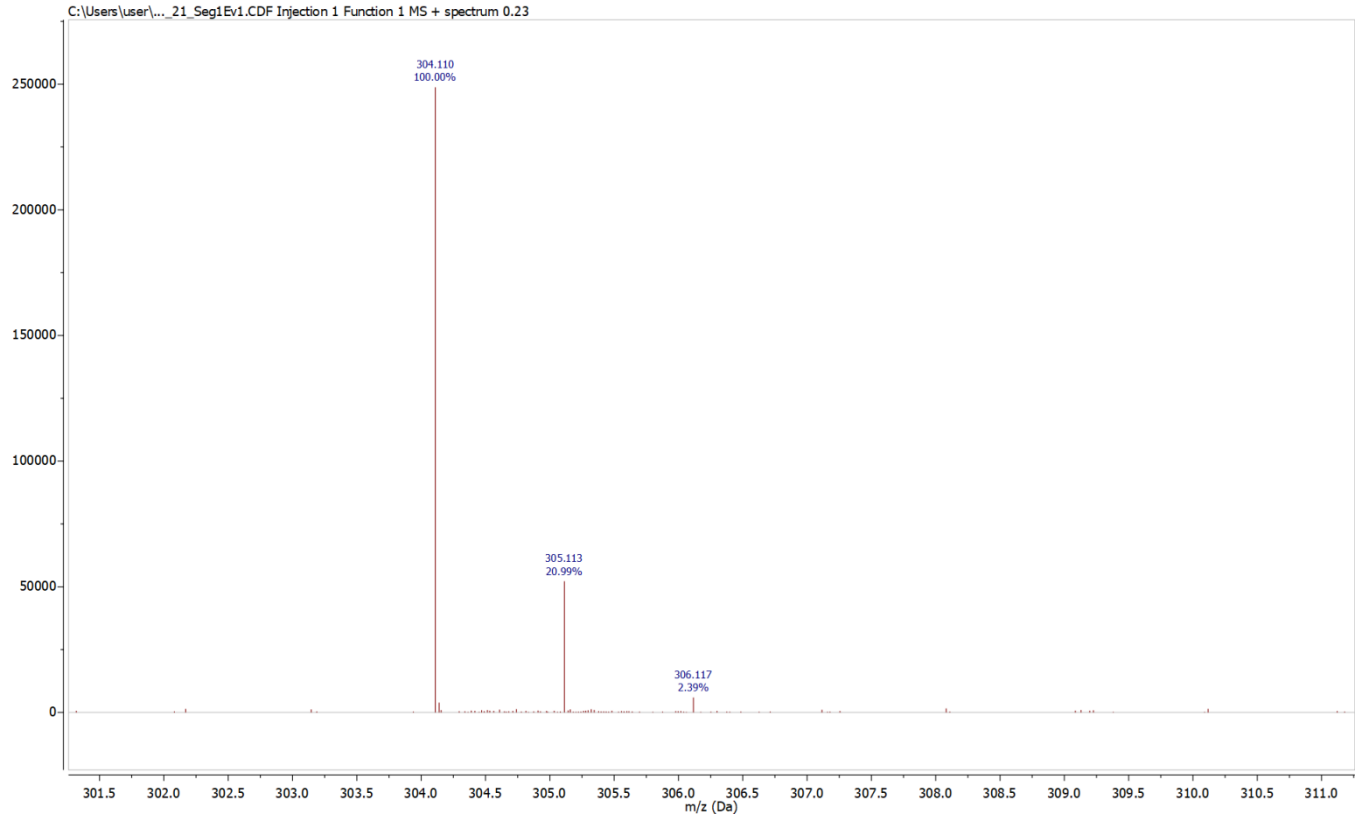
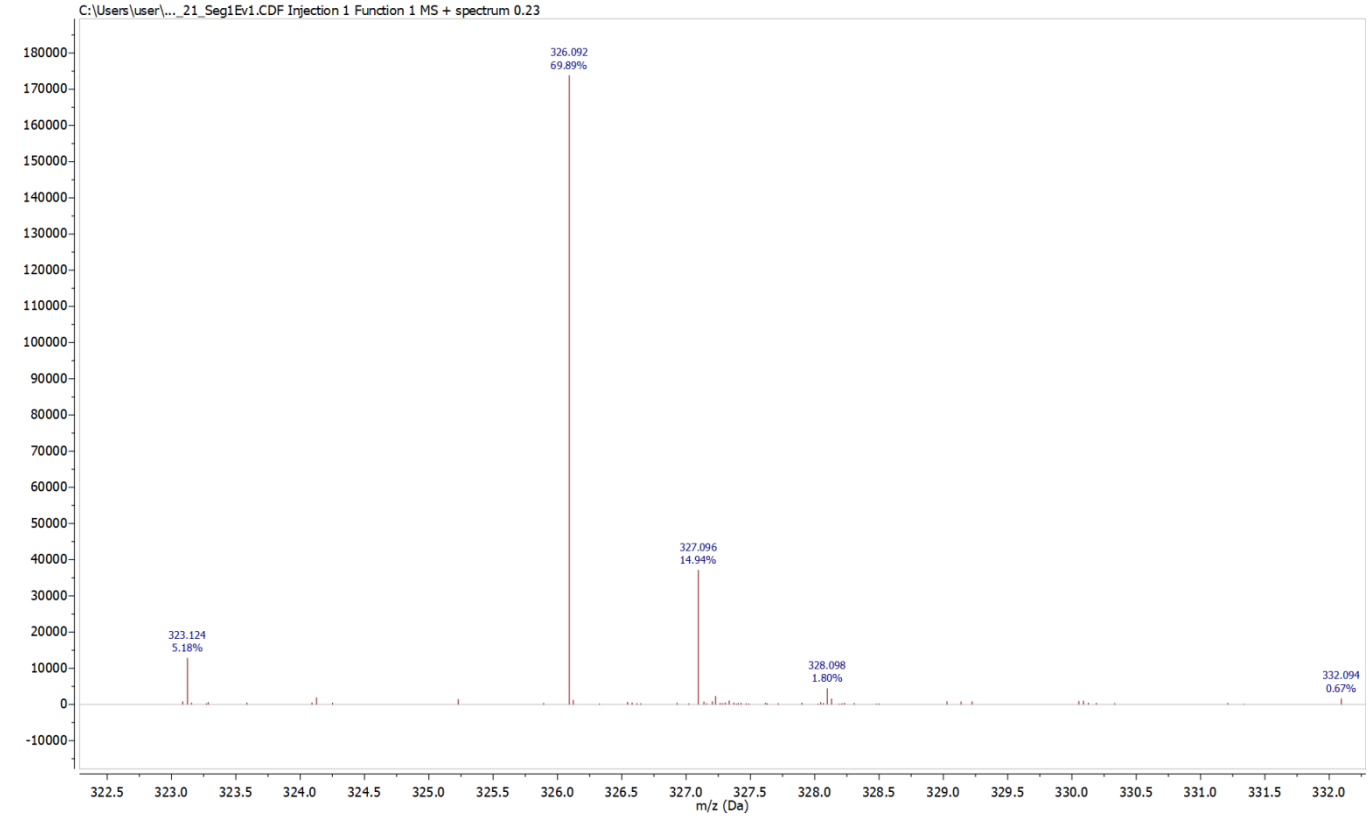


2, HRMS, **2 + H** region.

SPECTRA OF NEW COMPOUNDS



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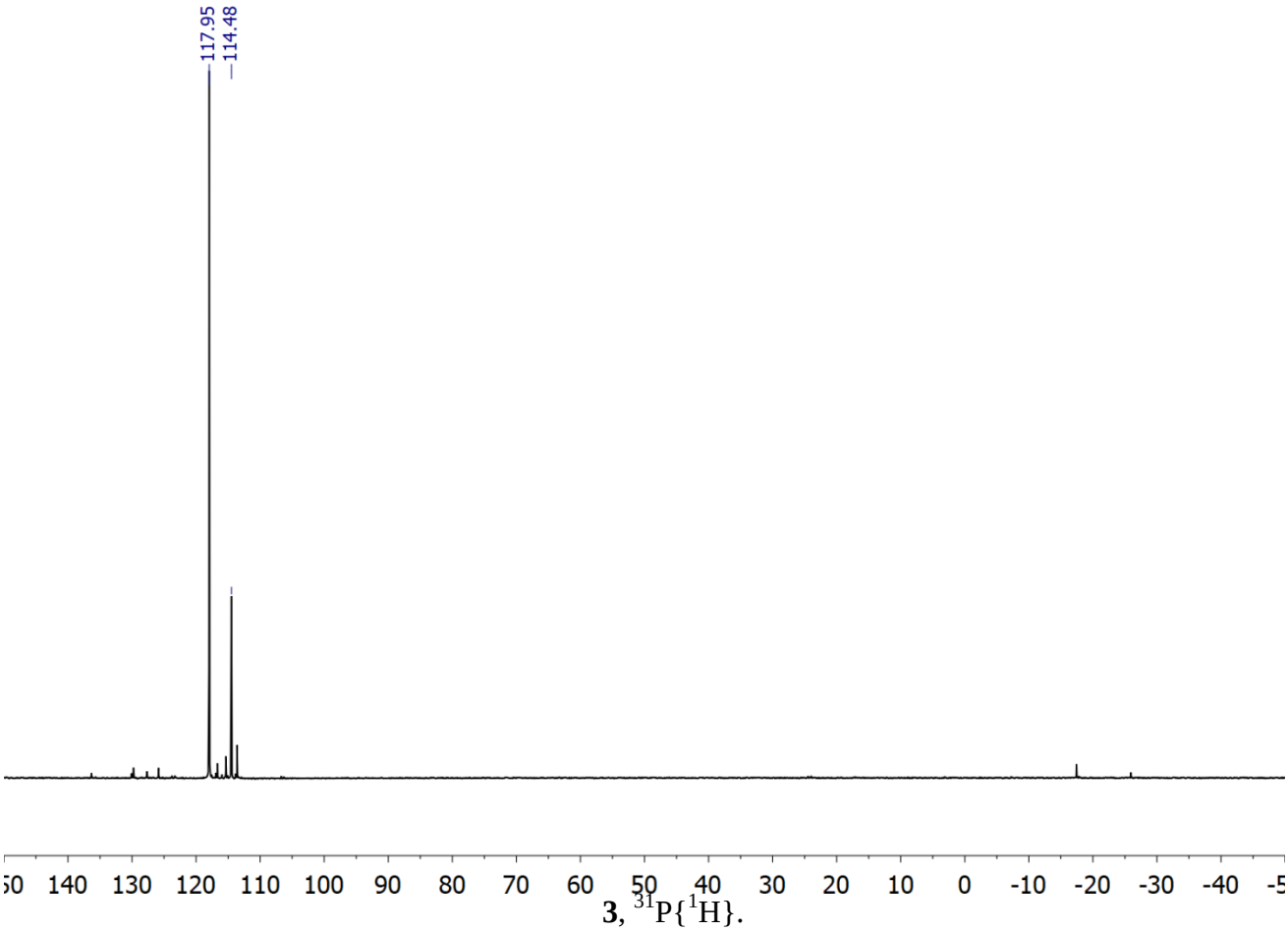
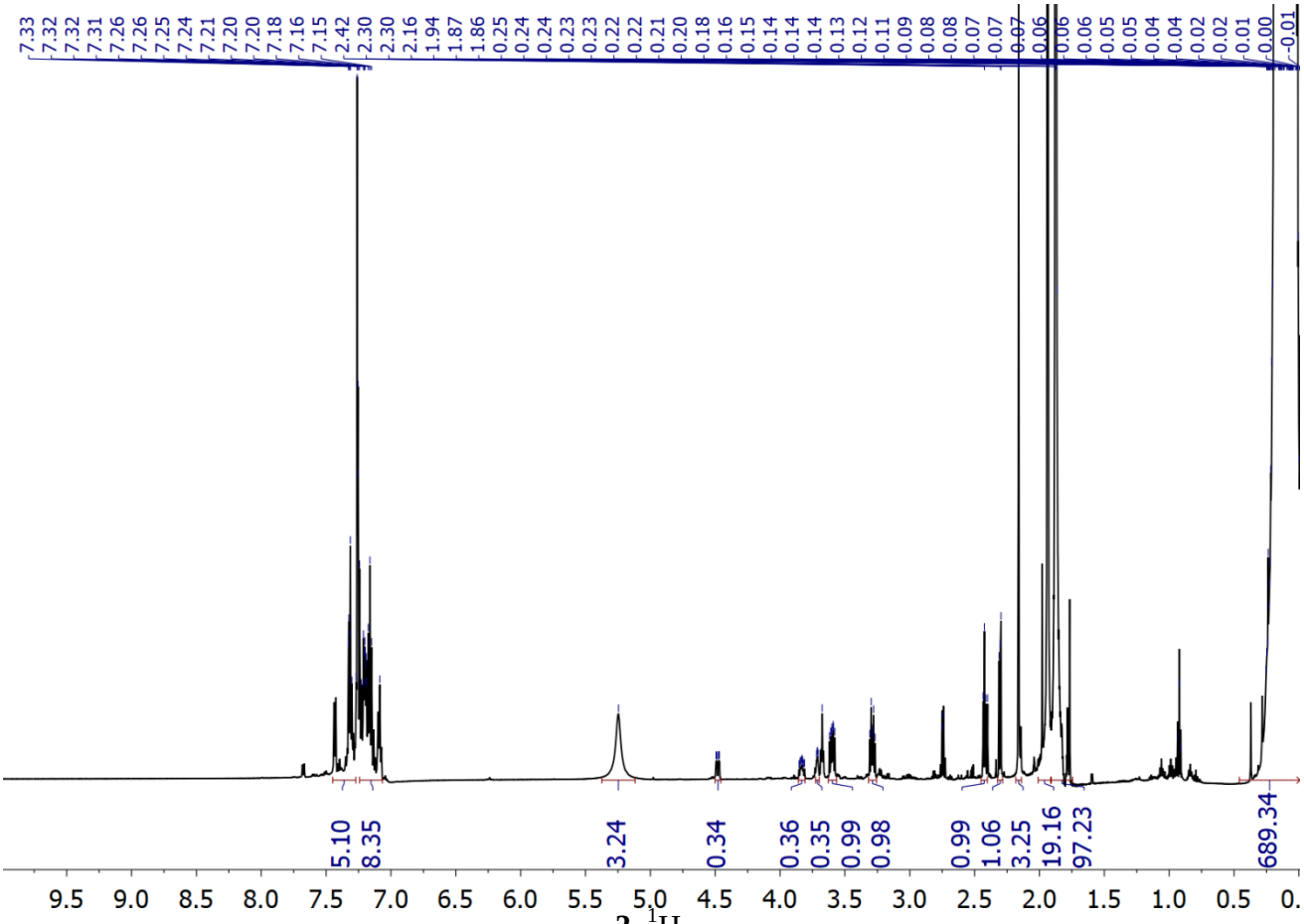
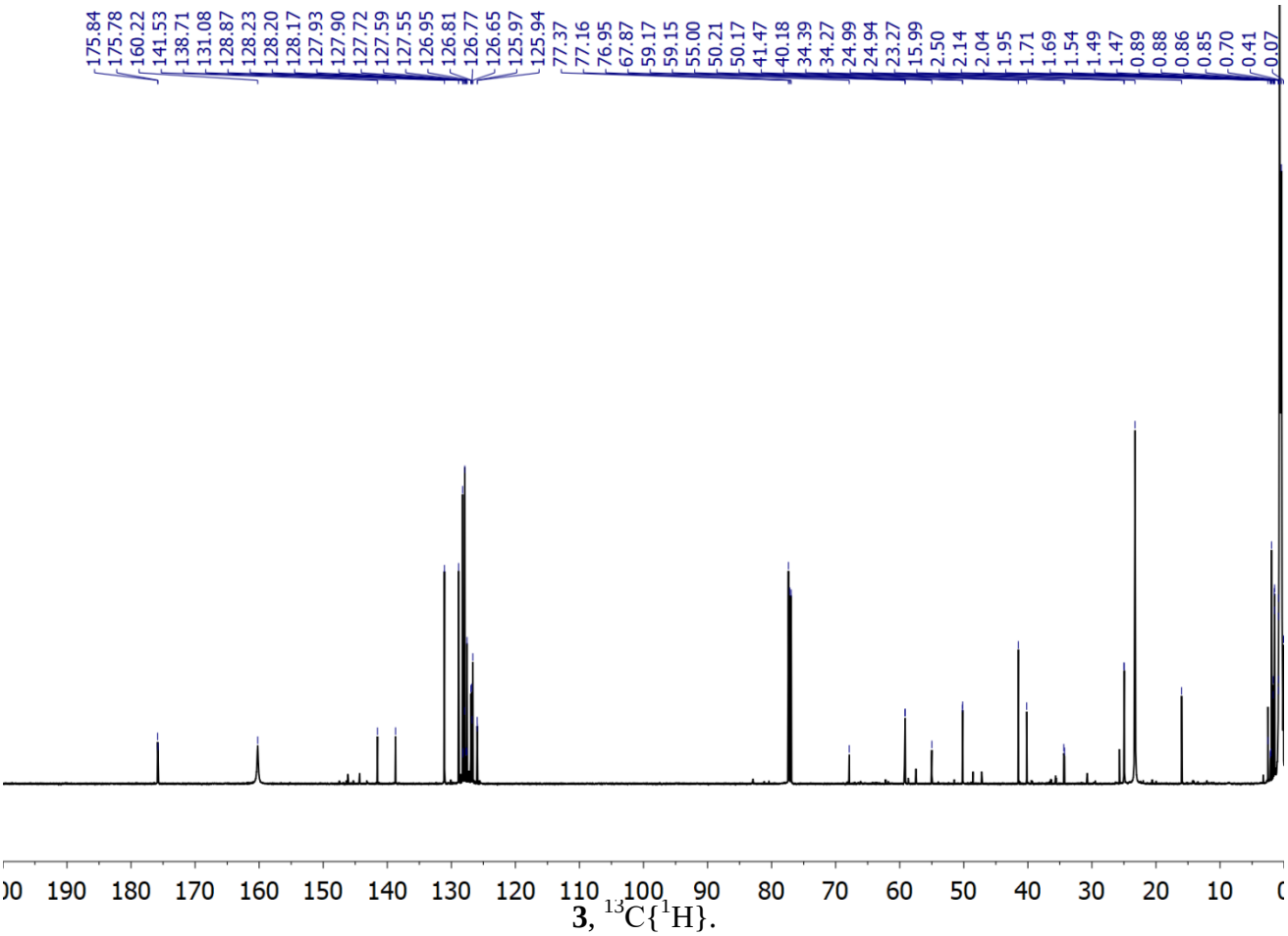


3, $^{31}P\{^{1}H\}$.

SPECTRA OF NEW COMPOUNDS

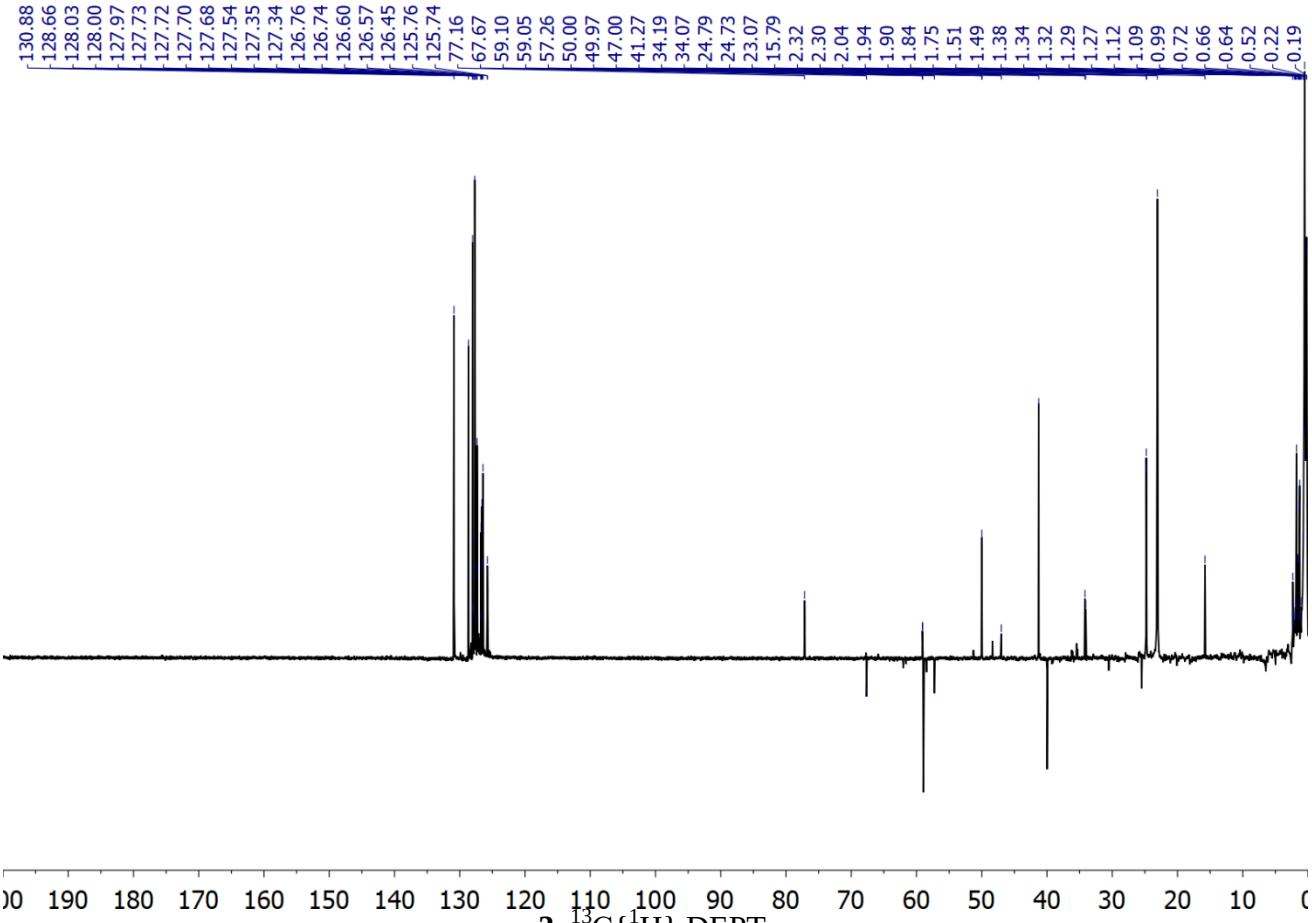


3, ^{1}H.



3, ^{13}C{^{1}H}.

SPECTRA OF NEW COMPOUNDS



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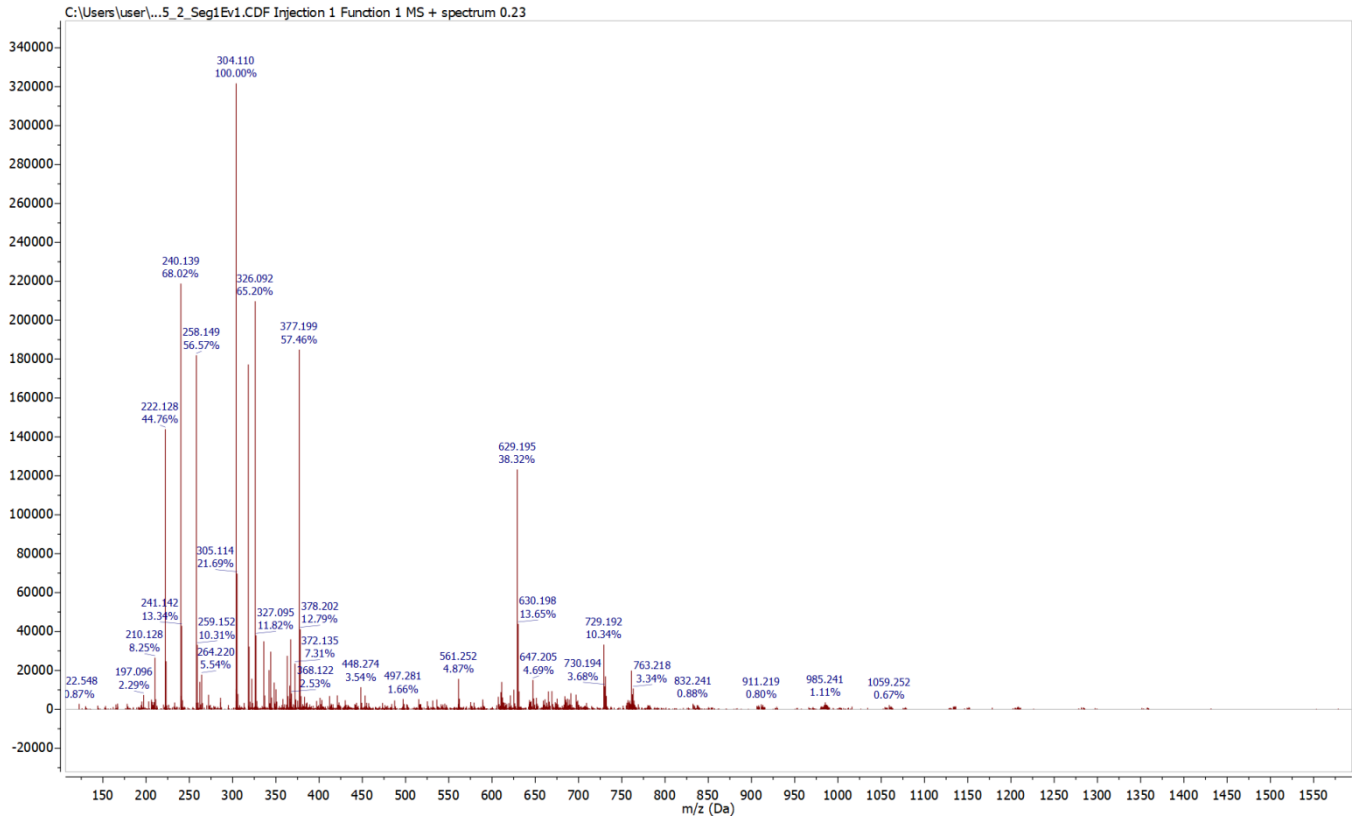
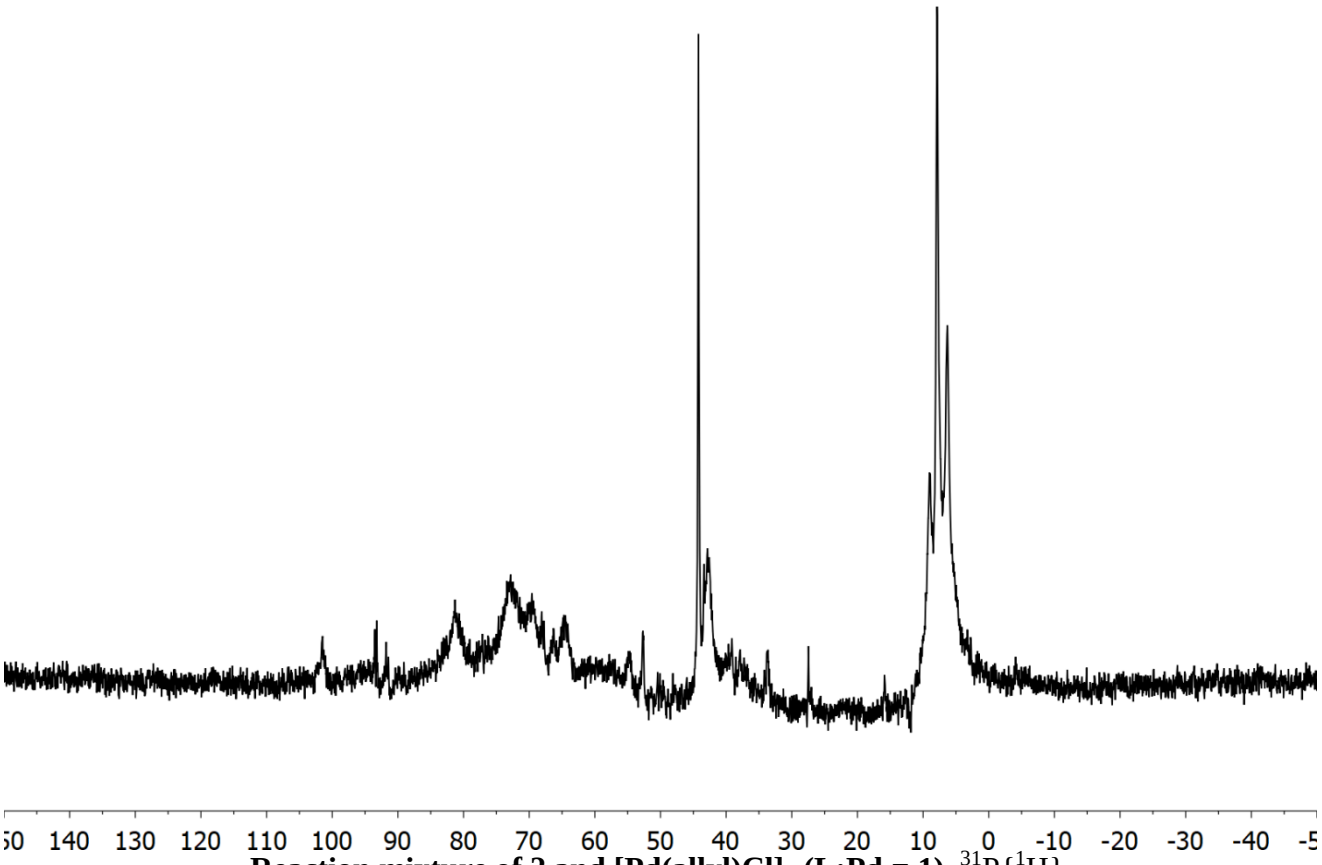
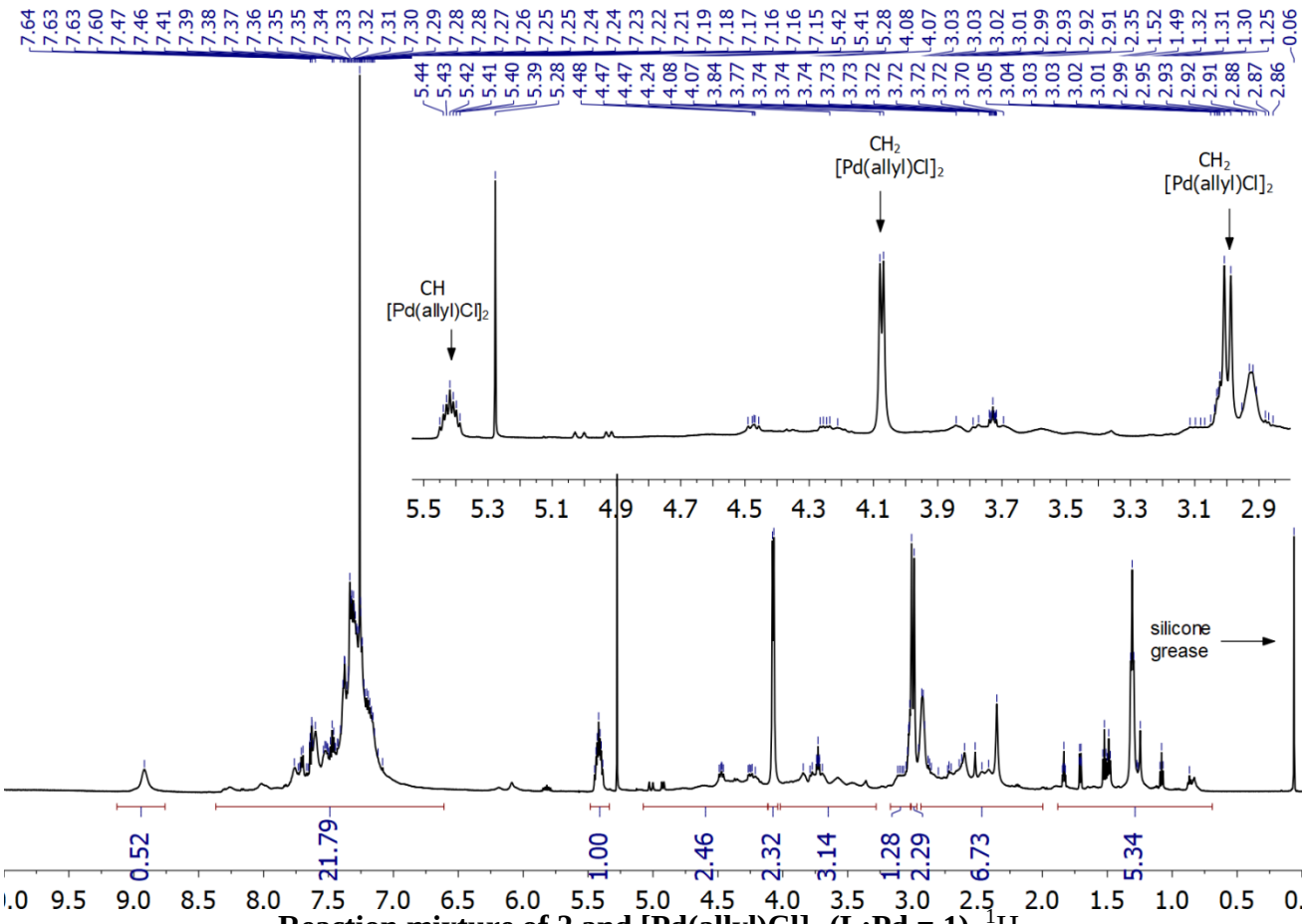


3, HRMS, full spectrum.

SPECTRA OF NEW COMPOUNDS

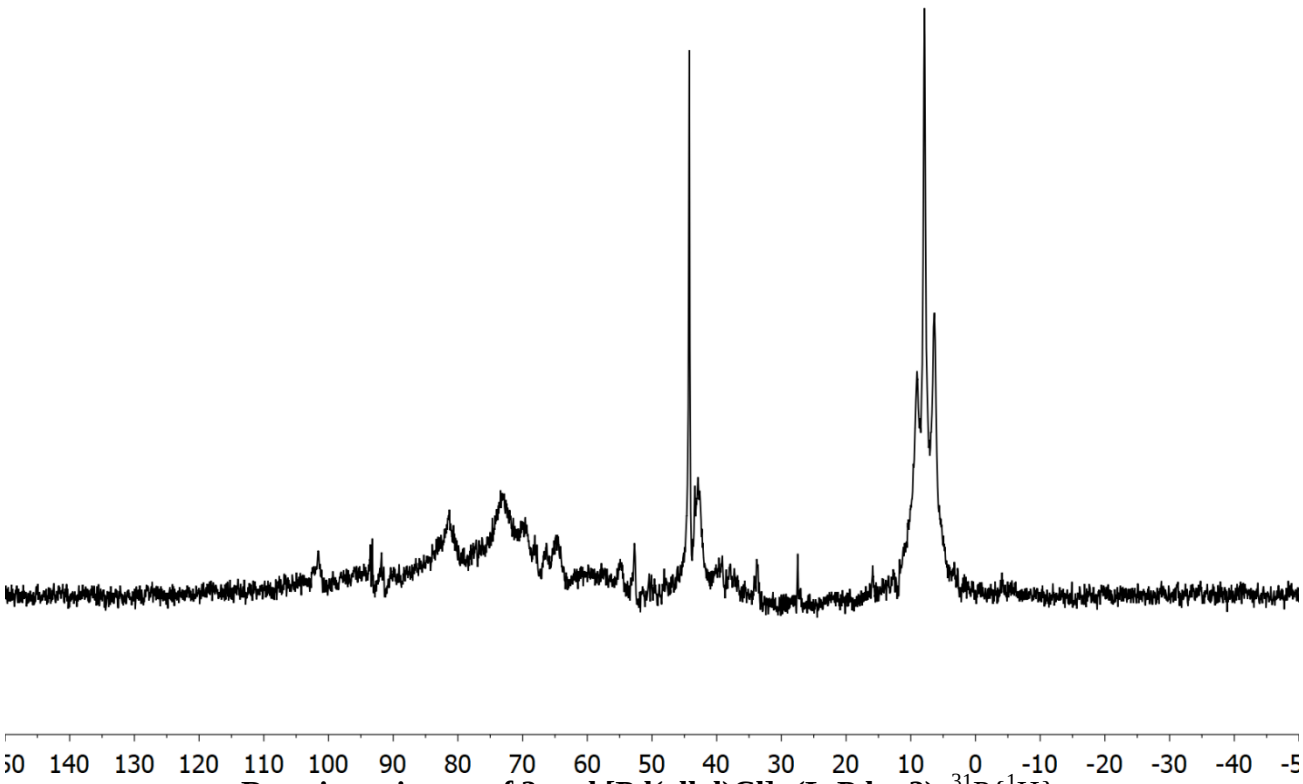


Reaction mixture of 2 and [Pd(allyl)Cl]$_2$ (L:Pd = 1), $^{31}P\{^1H\}$.

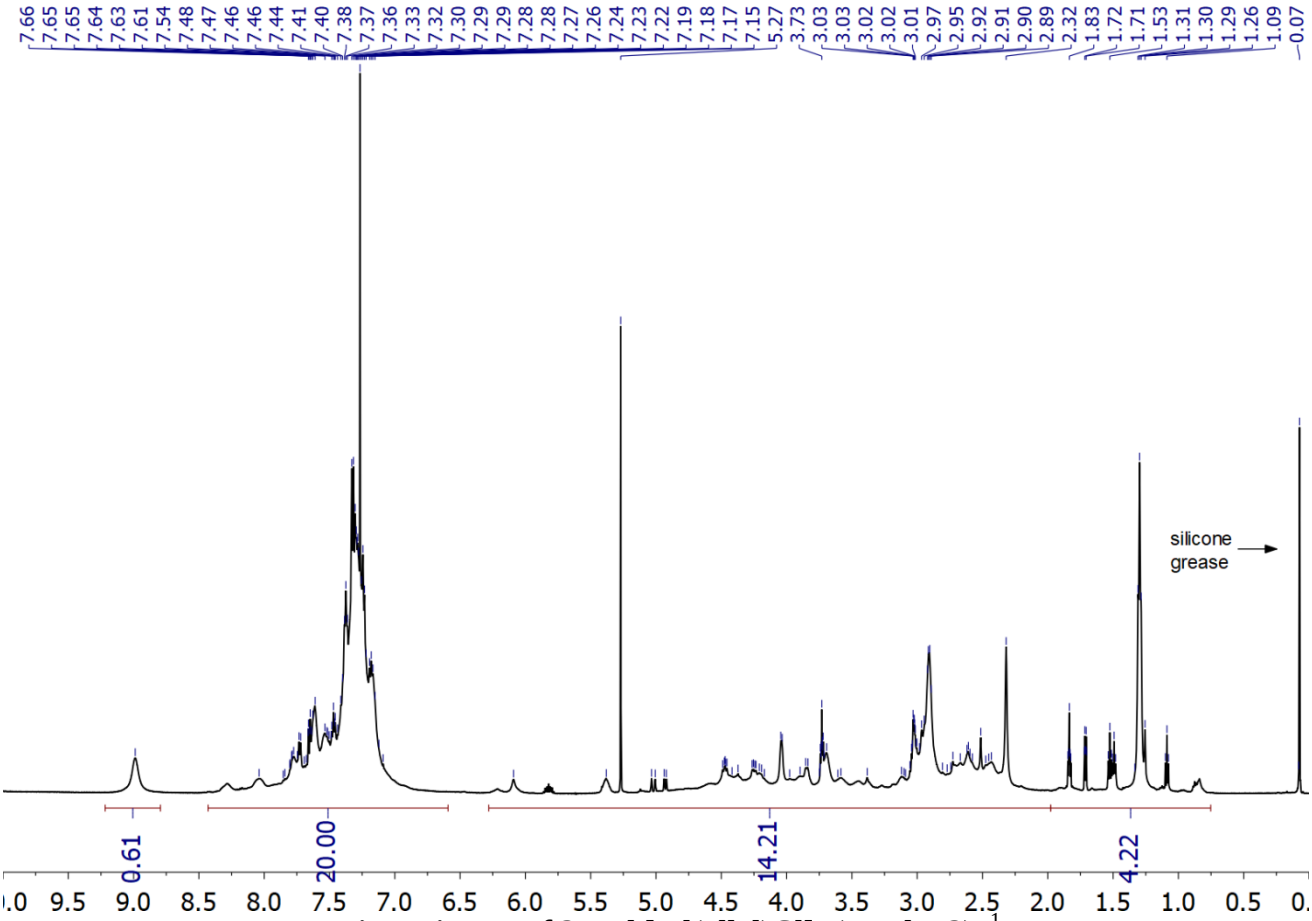


Reaction mixture of 2 and [Pd(allyl)Cl]$_2$ (L:Pd = 1), ^1H.

SPECTRA OF NEW COMPOUNDS

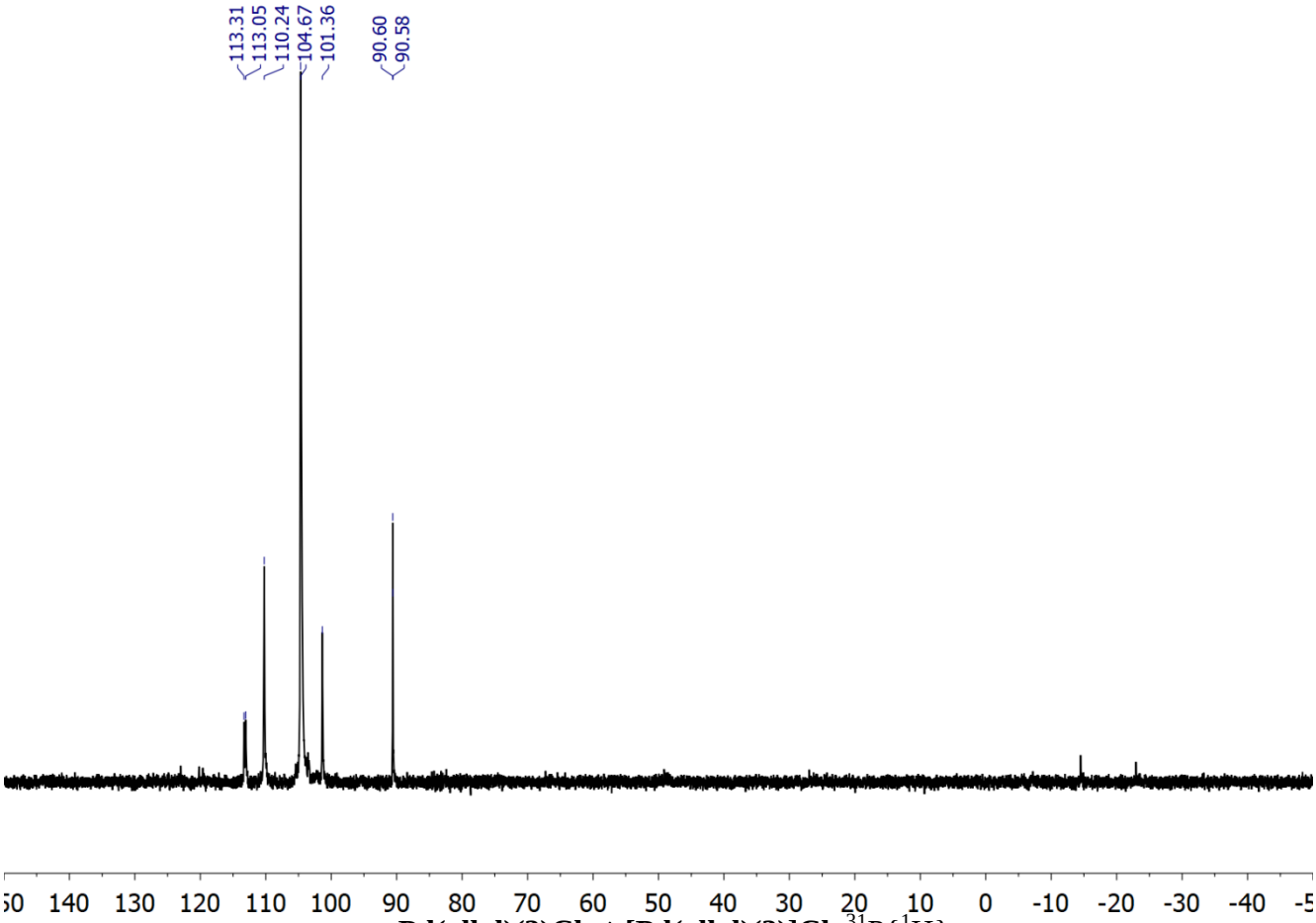


Reaction mixture of 2 and [Pd(allyl)Cl]$_2$ (L:Pd = 2), $^{31}P\{^1H\}$.

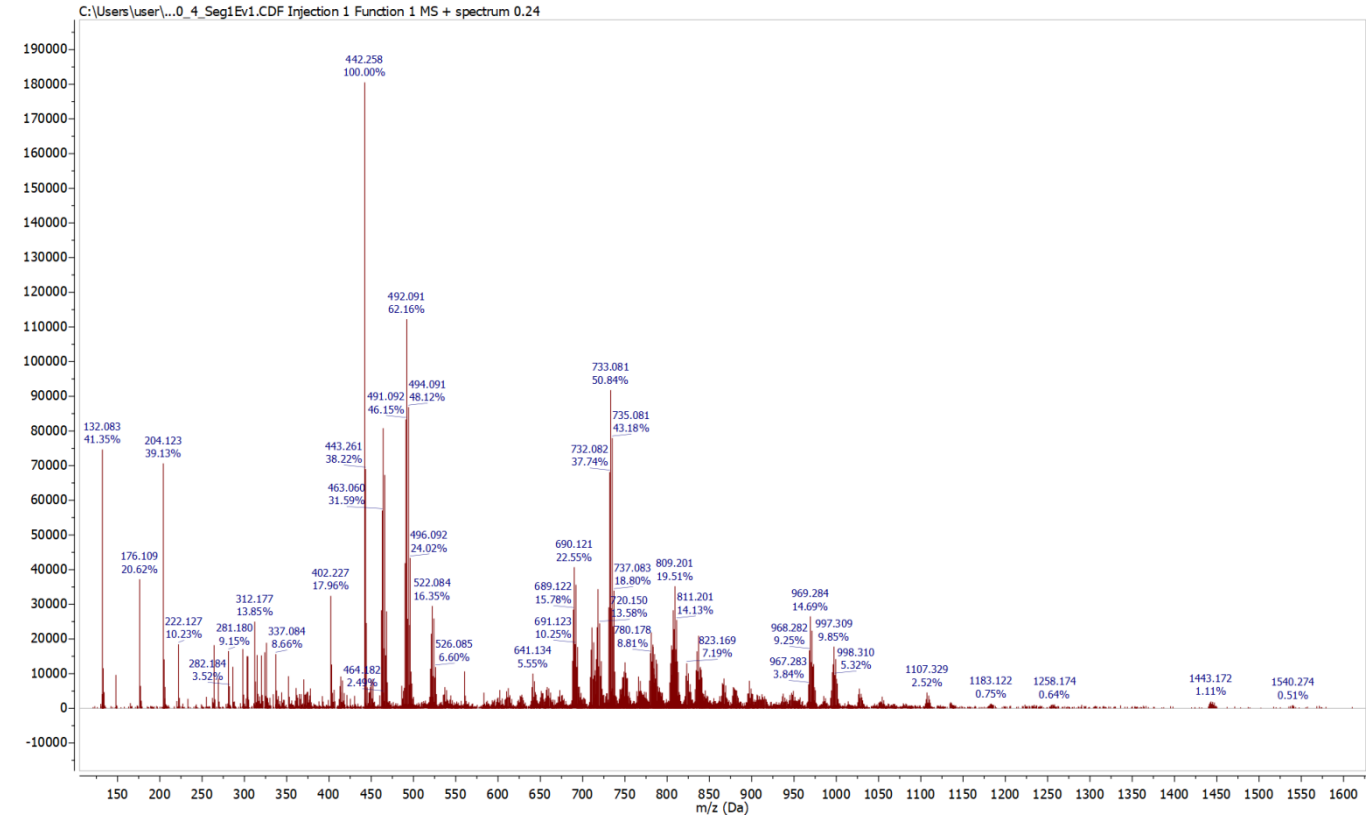


Reaction mixture of 2 and [Pd(allyl)Cl]$_2$ (L:Pd = 2), ^1H.

SPECTRA OF NEW COMPOUNDS

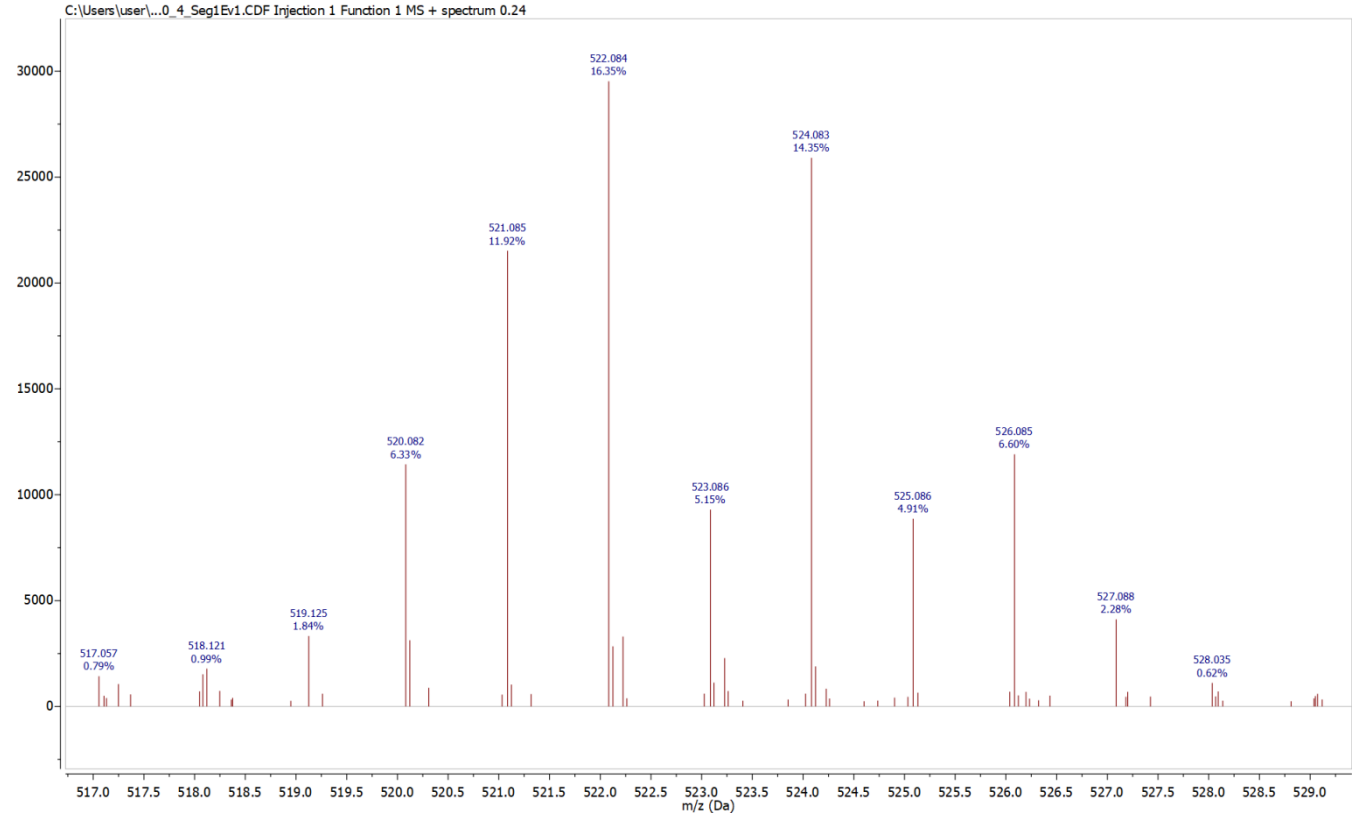


Pd(allyl)(3)Cl ⇄ [Pd(allyl)(3)]Cl, $^{31}P\{^{1}H\}$.

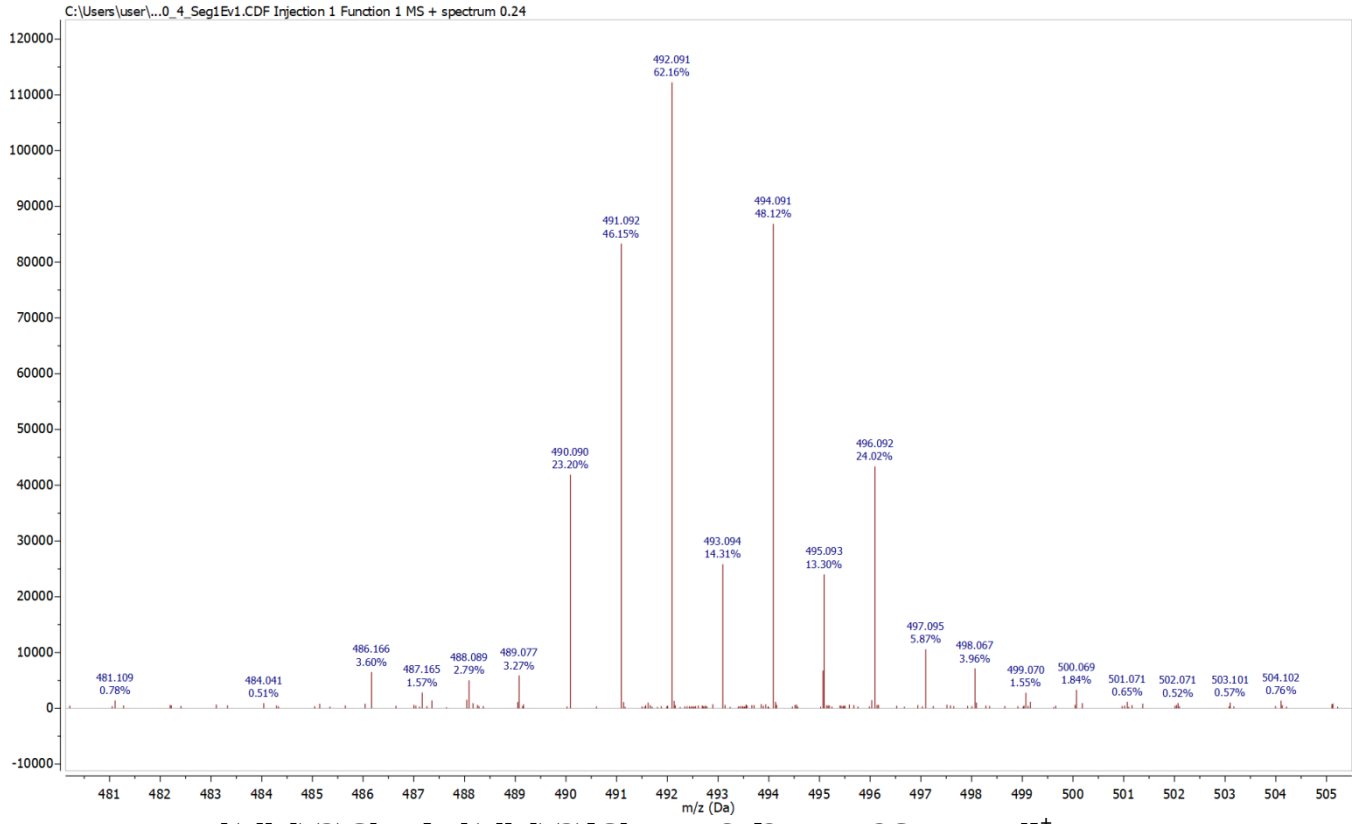


Pd(allyl)(3)Cl ⇄ [Pd(allyl)(3)]Cl, HRMS full spectrum.

SPECTRA OF NEW COMPOUNDS

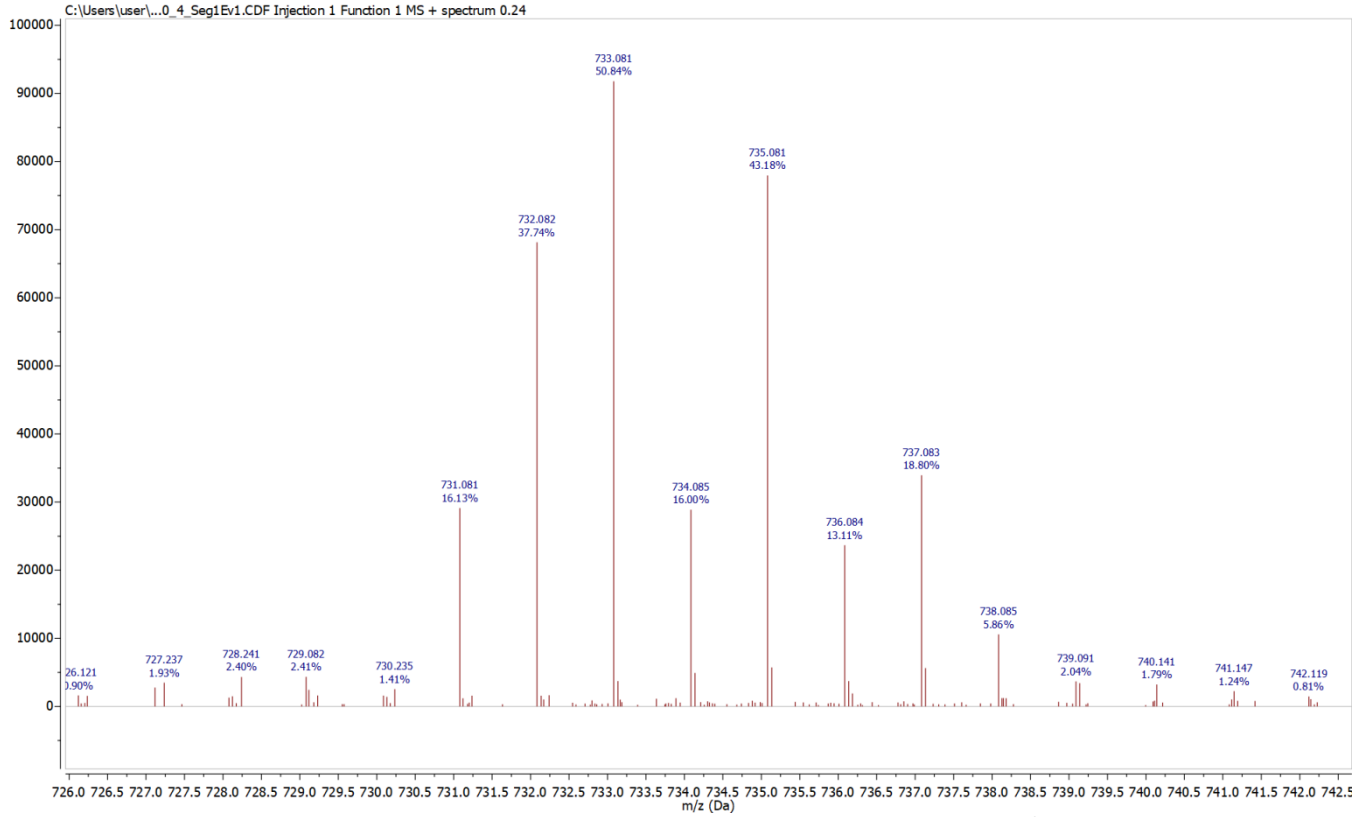


Pd(allyl)(3)Cl ⇄ [Pd(allyl)(3)]Cl, HRMS, **[Pd(allyl)(3)]** region.

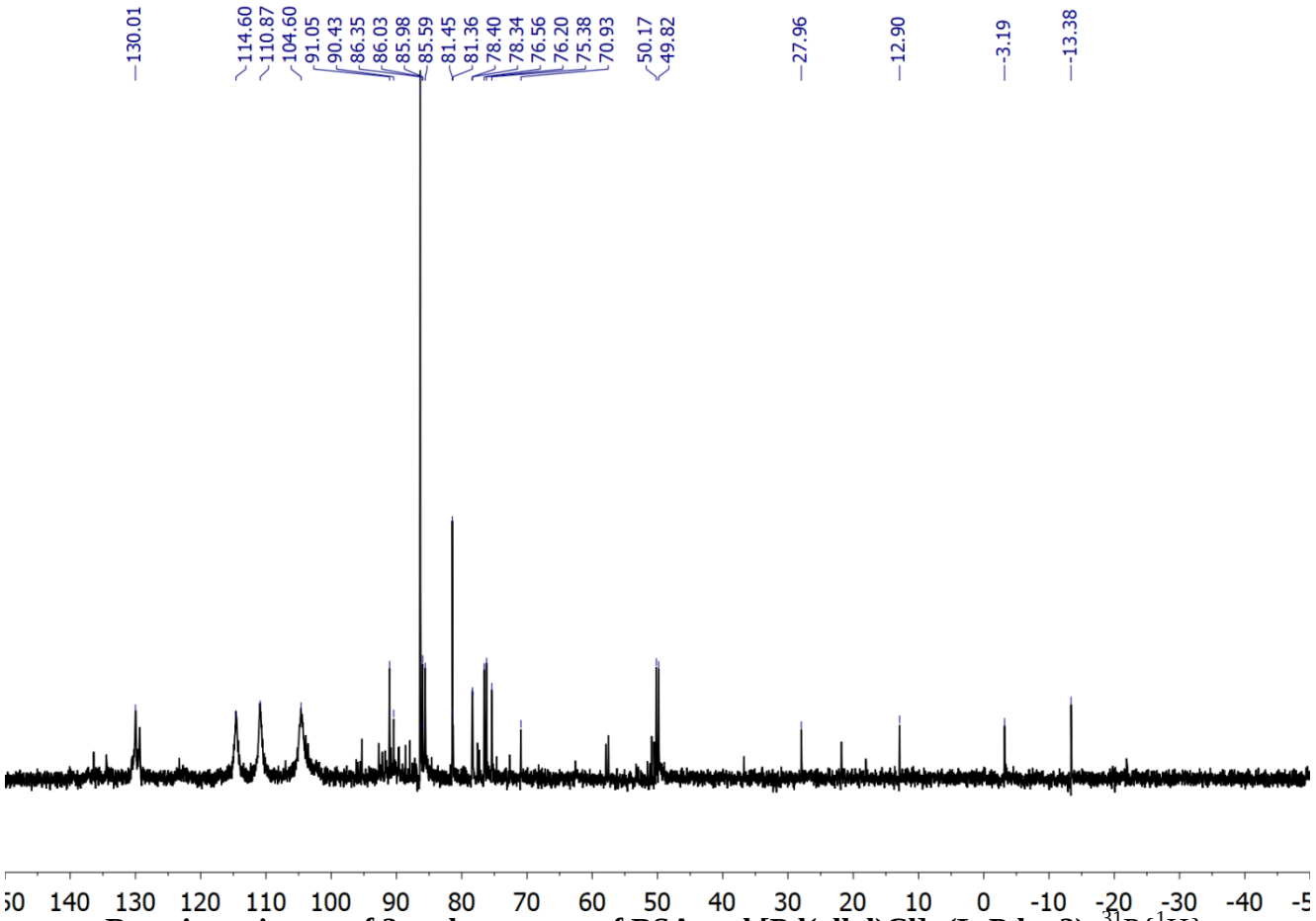


Pd(allyl)(3)Cl ⇄ [Pd(allyl)(3)]Cl, HRMS, **[2 + H + 2C_3H_5 + Pd]$^+$** region.

SPECTRA OF NEW COMPOUNDS

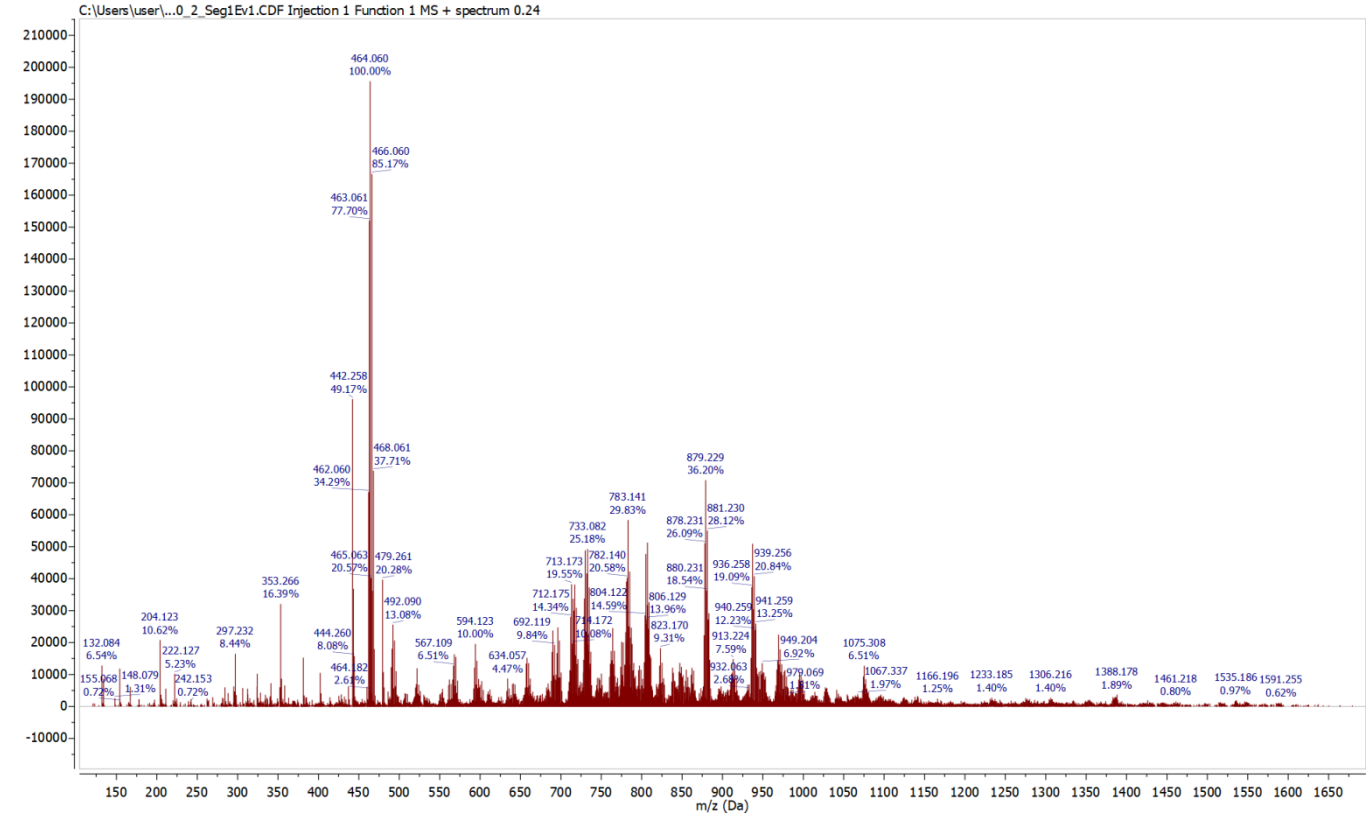


Pd(allyl)(3)Cl ⇄ [Pd(allyl)(3)]Cl, HRMS, **$[(2 - H)_2 + Na + Pd]^+$** region.



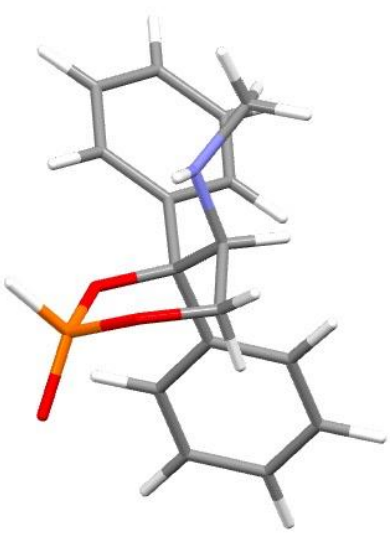
Reaction mixture of 2 and an excess of BSA and $[Pd(allyl)Cl]_2$ (L:Pd = 2), $^{31}P\{^1H\}$.

SPECTRA OF NEW COMPOUNDS

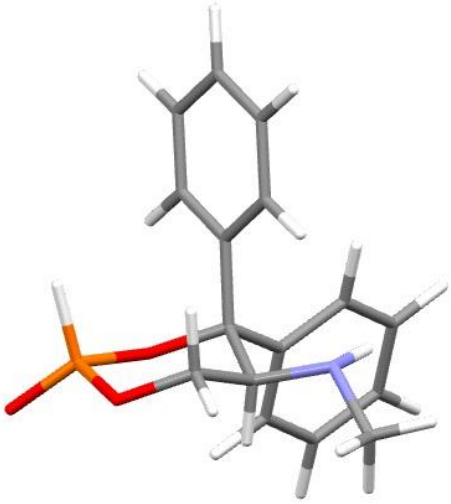


Reaction mixture of 2 and an excess of BSA and [Pd(allyl)Cl]$_2$ (L:Pd = 2), HRMS.

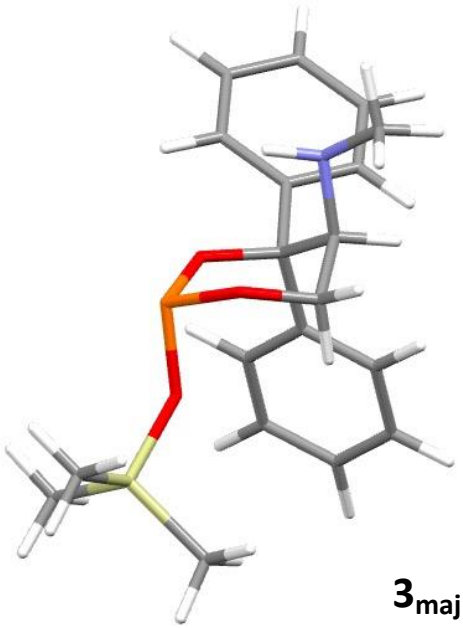
CALCULATED STRUCTURES



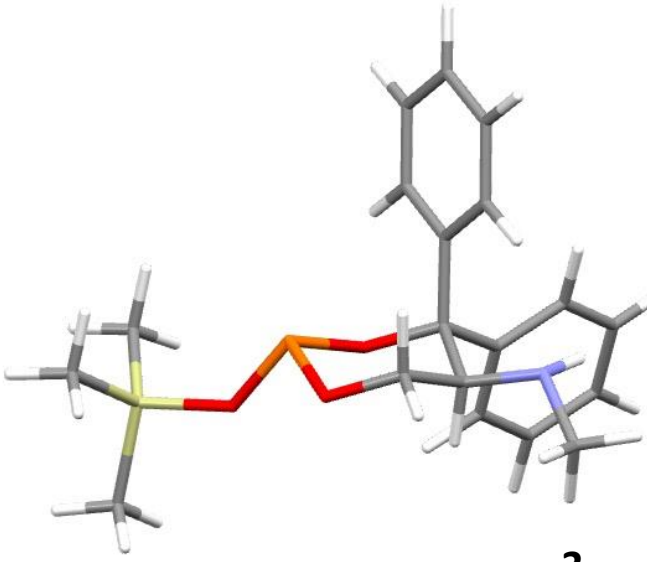
2maj



2min



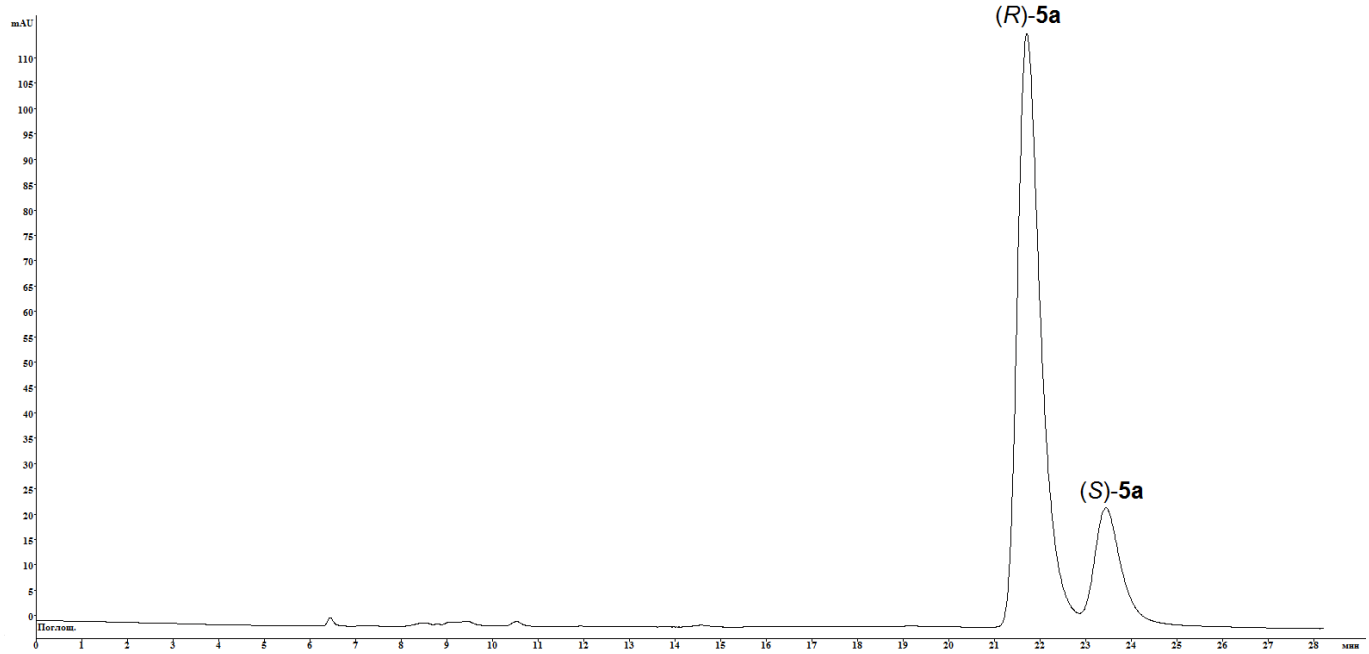
3maj



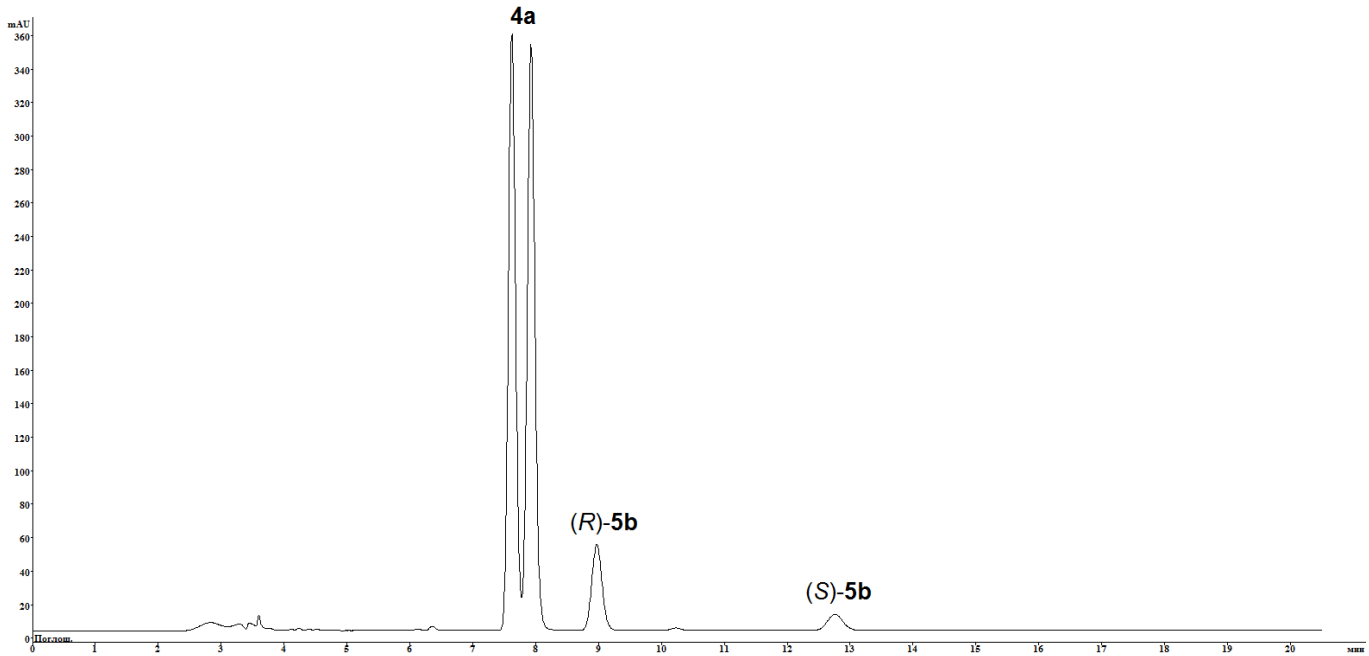
3min

DFT-calculated conformers of **2** and **3**.

HPLC TRACES

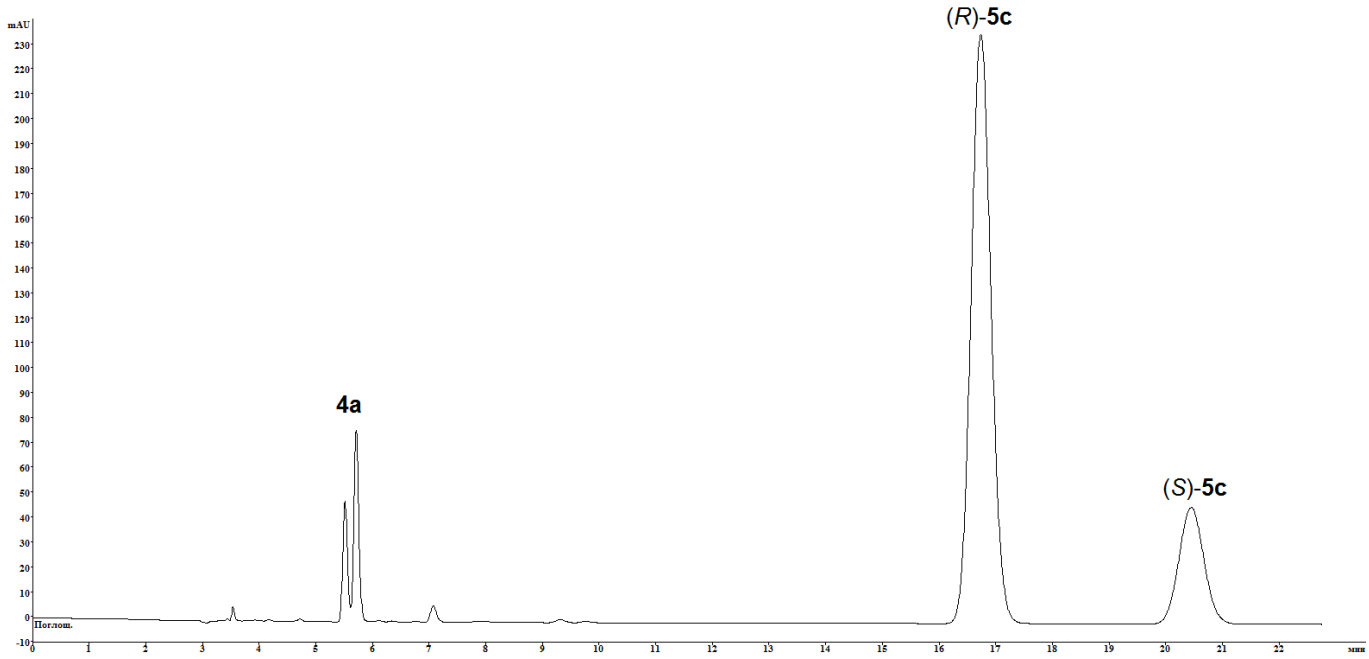


Chiral HPLC trace for the Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate (**4a**) with dimethyl malonate (entry 13 in Table 1).



Chiral HPLC trace for the Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate (**4a**) with di-*tert*-butyl malonate (entry 9 in Table 1).

HPLC TRACES



Chiral HPLC trace for the Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate (**4a**) with dibenzyl malonate (entry 10 in Table 1).