Synthesis and [*C]CO-labelling of (C,N) *gem*-dimethylbenzylamine-palladium complexes for potential applications in Positron Emission Tomography

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Electronic Supplementary Information

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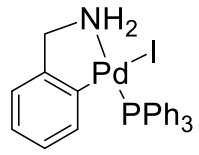
1) Precursors syntheses and ^{13}C-carbonylations

a. General information

All commercial materials were used without further purification, unless indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER AVANCE I 300 Mhz (^{1}H: 300MHz, ^{13}C: 75.3MHz, ^{31}P: 121.5 MHz) or BRUKER AVANCE III 600 Mhz (^{1}H: 600MHz, ^{13}C: 150.6 MHz) spectrometers. The chemical shifts for the NMR spectra are reported in ppm relative to the solvent residual peak. Coupling constants J are reported in hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; td, triplet of doublet. Yields refer to isolated material determined to be pure by NMR spectroscopy and thin-layer chromatography (TLC), unless specified in the text. Analytical TLCs were performed on Fluka Silica Gel 60 F254. High resolution mass spectra were performed by the CESAMO (Talence, France) and were recorded on Qq-TOF tandem mass spectrometer (API Q-STAR Pulsari, Applied Biosystems).

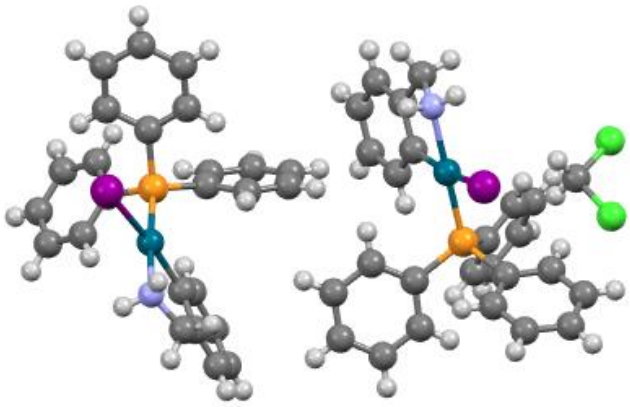
b. Experimental procedures

[2-(Aminomethyl)phenyl-κ^2-C,N]iodotriphenylphosphinepalladium 2



2

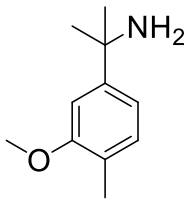
In a tube, *o*-iodobenzylamine (100 mg, 0.43 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (496 mg, 0.43 mmol, 1.0 eq.) were added. The tube was sealed and purged with nitrogen three times. Toluene (3 mL) was added and the resulting solution was briefly sonicated, then stirred at room temperature for 16 h. The solid was filtered and washed with cold Et_2O to give complex **2** (215 mg, 0.36 mmol, 84 %) as a pale yellow solid. ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.78-7.70 (m, 6H), 7.46-7.32 (m, 9H), 7.10-7.07 (m, 1H), 6.88-6.82 (m, 1H), 6.44-6.33 (m, 2H), 4.41-4.36 (m, 2H), 3.92-3.86 (m, 2H). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 43.0. These signals were in accordance to the literature.[1] Monocrystals of compound **2** were obtained by slow diffusion of Et_2O in CH_2Cl_2. Crystallographic data were acquired at CESAMO (UMR 5255) on a Bruker APEX 2 DUO. A single crystal was mounted and immersed in a stream of nitrogen gas [T = 150(2) K]. Data were collected, using a microfocus sealed tube of Mo K_α radiation (k = 0.71073 Å) on a KappaCCD diffractometer. Data collection and cell refinement were performed using APEX2 2013.10-0 (Bruker AXS Inc.), and SAINT v8.34A (Bruker AXS Inc.). Data reduction was performed using SAINT v8.34A (Bruker AXS Inc.). Correction for absorption was performed using multi-scan integration as included in SADABS V2012/1 (Bruker AXS). Structure solutions were found by charge flipping methods (SUPERFLIP (Palatinus & Chapuis, 2007) EDMA (Palatinus et al., 2012)) and refined with (SHELXL).[2]



*Mercury drawing of the crystalline structure of **2** obtained by X-Ray diffraction analysis (CCDC 2070121)*

[1] K. Karami, M. Bahrami Sheni, N. Rahimi, *Appl. Organometal. Chem.*, 2013, **27**, 437-443.
[2] G. M. Sheldrick, *Acta Crystallographica Section A.*, 2008, **64**, 112-122.

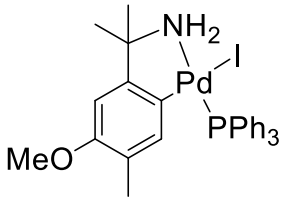
2-(3-Methoxy-4-methylphenyl)propan-2-amine 6



6

To a stirred solution of **5** (1 g, 5.5 mmol, 1.0 eq.) in dry Et_2O (0.1 M) at 0 °C under N_2 was added MeMgBr in Et_2O (4.6 mL, 12.7 mmol, 2.8 M, 2.3 eq.). The mixture was stirred at room temperature for 4 h. Then, a saturated solution of ammonium chloride was added (20 mL) and the aqueous layer was extracted three times with Et_2O (3 x 20 mL). The combined organic layers were washed with water (20 mL), dried on Na_2SO_4 and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/Et_2O, 8:2) affording 2-(3-methoxy-4-methylphenyl)propan-2-ol (740 mg, 4.1 mmol, 81 % yield) as a white solid engaged directly in the next step. ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.12-7.03 (m, 2H), 6.92 (dd, J = 7.7 Hz, J = 1.7 Hz, 1H), 3.86 (s, 3H), 2.20 (s, 3H), 1.59 (s, 6H). To a solution of 2-(3-methoxy-4-methylphenyl)propan-2-ol (740 mg, 4.45 mmol, 1.0 eq.) and sodium azide (636 mg, 9.79 mmol, 2.2 eq.) in 50 mL of $CHCl_3$, was added TFA (1.3 mL, 17.8 mmol, 4.0 eq.) at 0 °C. The solution was stirred for 16 h 0°C and the mixture was quenched with a saturated solution of $NaHCO_3$, extracted with dichloromethane and dried over Na_2SO_4. After filtration, the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/Et2O, 9:1) affording the 1-(1-azidoisopropyl)-3-methoxy-4-methylbenzene (722 mg, 3.79 mmol, 85 %) as a colorless oil engaged directly in the final step. ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.11 (d, J = 7.6 Hz, 1H), 6.93-6.88 (m, 2H), 3.86 (s, 3H), 2.21 (s, 3H), 1.63 (s, 6H). To a stirred solution of 1-(1-azidoisopropyl)-3-methoxy-4-methylbenzene (722 mg, 3.78 mmol, 1.0 eq.) in dry Et_2O (0.1M) at 0 °C under N_2 was added lithium aluminium hydride (280 mg, 7.5 mmol, 2.0 eq.) portion wise. The heterogeneous mixture was stirred at room temperature for 16 h. Then, 0.5 mL of water was slowly added to the mixture followed by 0.5 mL of NaOH (10%) and 1.5 mL of water. Then Na_2SO_4 was added to dry the solution and then the mixture was filtered under a short pad of celite. The volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (DCM/MeOH/Et_3N, 90:9:1) affording compound **6** (468 mg, 2.61 mmol, 75 %) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.07 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 6.94 (dd, J = 7.8 Hz, J = 1.8 Hz, 1H), 3.82 (s, 3H), 2.42 (s, 2H), 2.18 (s, 3H), 1.50 (s, 6H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 157.6, 148.6, 130.3, 124.7, 116.4, 106.9, 55.4, 52.9, 32.5, 15.8. HRMS (ESI) $C_{11}H_{17}ON^{23}Na$ $[M+Na]^+$ calculated 202.12024, found 202.12007; $[M-NH_2]^+$ calculated 163.1100, found 163.1115.

[2-(1-Aminoisopropyl)-3-methoxy-4-methylphenyl-κ^2-C,N]iodotriphenylphosphinepalladium 7

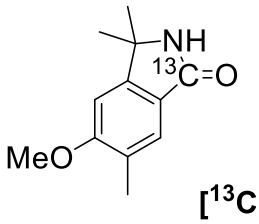


7

To a stirred solution of **6** (18 mg, 0.1 mmol, 1.0 eq.) in 1 mL of benzene/MeOH (1:1) at room temperature under N_2 was added $Pd(OAc)_2$ (22 mg, 0.1 mmol, 1.0 eq.). The mixture was stirred at room temperature for 1h. After confirmation of the complete conversion of the starting material ^{1}H NMR analyses of an aliquot, the volatiles were removed under reduced pressure to give a yellow solid which was dissolved in acetone (1 mL), and KI (16.7 mg, 0.1 mmol, 1.0 eq.) was added. The mixture was stirred 1h at room temperature and then PPh_3 (27 mg, 0.1 mmol, 1.0 eq.) was added before stirring for one extra hour. The volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (dichloromethane/MeOH 95:5 then 90:10) affording complex **7** (34 mg, 50 μmol, 50%) as an amorphous pale yellow solid. ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.77-7.66 (m, 6H), 7.45-7.32 (m, 9H), 6.36 (s, 1H), 6.07 (dd, J = 6.3 Hz, J = 0.7 Hz, 1H), 3.85 (br s, 2H), 3.76 (s, 3H), 1.78 (s, 6H), 1.28 (s, 3H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 155.3, 155.0, 139.4, 135.6, 135.4, 135.3, 135.0, 134.1, 132.9, 132.2, 130.6, 128.2, 128.1, 127.8, 105.0, 66.2, 55.4, 32.8, 15.7. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 41.8. HRMS (ESI) $C_{29}H_{32}ON^{127}IP^{102}Pd$ $[M+H]^+$ calculated 670.0317, found 670.0316.

5-Methoxy-3,3,6-trimethylisoindolin-1-one-1-^{13}C [^{13}C]8

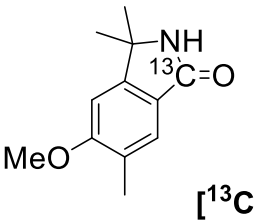
From complex 7



[^{13}C]8

In the chamber 1 of the two-chamber system was added of $Ph_2MeSi^{13}COOH$ (14 mg, 0.05 mmol, 1.0 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system were added successively complex **7** (34 mg, 0.05 mmol, 1.0 eq.), and Na_2CO_3 (11 mg, 0.1 mmol, 2.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with N_2. Then, 1 ml of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µl of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 50°C for 23 hours. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (dichloromethane/MeOH: 95/5) affording the lactam **[^{13}C]8** (3.0 mg, 0.024 mmol, 29 %) as a white amorphous solid. ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.55 (d, J = 2.3 Hz, 1H), 6.75 (s, 1H), 6.34 (br s, 1H), 3.91 (s, 3H), 2.25 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 169.8 (^{13}C-enriched), 161.6, 153.3, 147.4, 127.5, 125.6, 101.7, 58.7, 55.7, 28.1, 16.5. HRMS (ESI) $C_{11}{}^{13}CH_{16}NO_2$ $[M+H]^+$ calculated 207.1209, found 207.1207.

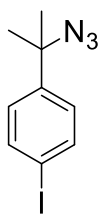
From supported complex 7-PS



[^{13}C]8

To a stirred solution of compound **6** (11 mg, 0.06 mmol, 1.0 eq.) in 1 mL of benzene/MeOH (1:1) at room temperature under N_2 was added $Pd(OAc)_2$ (13 mg, 0.06 mmol, 1.0 eq.). The mixture was stirred at room temperature for 1 h and the volatiles were removed under reduced pressure to give a yellow solid which was dissolved in acetone (1 mL), and KI (16.0 mg, 0.09 mmol 1.5 eq) was added. The mixture was stirred 1 h at room temperature and then triphenylphosphine polymer-bound (100-200 mesh, extent of labeling: ~3 mmol/g) (41 mg, 0.09 mmol, 1.5 eq.) was added before stirring for one extra hour. Then, the solid was filtered under vacuum and washed with CH_2Cl_2 and Et_2O, affording the supported complex **7-PS** as a yellow/orange powder, which was directly used for the next step. In the chamber 1 of the two-chamber system were added of Ph_2MeSi-COOH (13 mg, 0.05 mmol, 0.83 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system were added successively the supported complex **7-PS** (0.06 mmol, 1.0 eq.), and Na_2CO_3 (12.3 mg, 0.1 mmol, 2.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with N_2. Then, 1 ml of dry THF were added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 5 µl of a solution of TBAF (1M in THF, 5 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]8** as a white powder (5.2 mg, 0.025 mmol, 51%). ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.55 (d, J = 2.3 Hz, 1H), 6.75 (s, 1H), 3.92 (s, 3H), 2.26 (s, 3H), 1.52 (s, 6H). δ (ppm): 169.6 (^{13}C-enriched). HRMS (ESI) $C_{11}{}^{13}CH_{16}NO_2$ $[M+H]^+$ calculated 207.1209, found 207.1207.

1-(2-Azidopropan-2-yl)-4-iodobenzene 10

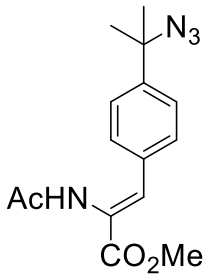


10

To a solution of methyl magnesium bromide (3.0 M, 3.5 mL, 10.5 mmol, 2.7 eq.) in 5 mL of THF was added methyl-4-iodobenzoate **9** (1.02 g, 3.88 mmol, 1.0 eq.) in 5 mL of THF dropwise at -78°C. The reaction mixture was stirred at the -78°C for 30 min, and added a second portion of methyl magnesium bromide (3.0 M, 3.5 mL, 10.5 mmol, 2.7 eq.) was added dropwise at -78 °C. The resulting mixture was stirred for 2h at room temperature, quenched with 10 mL of saturated ammonium chloride solution and extracted three times with EtOAc. The combined organic layers were washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to afford the 2-(4-iodophenyl)propan-2-ol (875 mg, 3.33 mmol, 86%) as a pale yellow oil, which was engaged

in the next step without further purification. To a solution of 2-(4-iodophenyl)propan-2-ol (578 mg, 2.2 mmol, 1.0 eq.) and sodium azide (313 mg, 4.8 mmol, 2.2 eq.) in 2.2 mL of $CHCl_3$ at - 10 °C was slowly added a solution of TFA (0.9 mL, 11.7 mmol, 5.2 eq.) in 2.2 mL of $CHCl_3$. The mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with an aqueous solution of ammonia (30% w/w), the layers were separated and the aqueous layer was extracted three times with $CHCl_3$. The combined organic phases were washed with brine, dried with $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel flash chromatography (cyclohexane) affording compound **10** (377.8 mg, 1.32 mmol, 60%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.72-7.67 (m, 2H), 7.21-7.17 (m, 2H), 1.61 (s, 6H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 144.6, 137.7 (2C), 127.4 (2C), 93.1, 63.6, 28.4 (2C). HRMS (FI) $C_9H_{10}{}^{127}IN_3$ $[M]^+$ calculated 286.9919, found 286.9918.

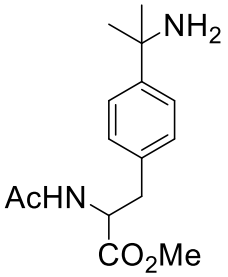
Methyl-2-acetamido-3-(4-(2-azidopropan-2-yl)phenyl)acrylate 12



12

Under inert atmosphere, 196 (143.5 mg, 0.5 mmol, 1.0 eq.), acrylate **11** (107 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.), Bu_4NCl (152 mg, 0.55 mmol, 1.1 eq.), $NaHCO_3$ (113 mg, 1.35 mmol, 2.7 eq.) were dissolved in 7 mL of DMF. The reaction was stirred 16h at 85°C. The mixture was diluted with brine and extracted three times with dichloromethane. The combined organic layer was washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (50/50: cyclohexane/ethyl acetate) affording compound **12** (115.8 mg, 0.38 mmol, 77%) as an off-white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.50-7.45 (m, 4H), 7.36-7.33 (m, 1H), 7.04 (br s, 1H), 3.85 (s, 3H), 2.15 (s, 3H), 1.63 (s, 6H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 168.8, 165.8, 146.0, 132.8, 131.7, 130.0, 125.5, 124.3, 63.6, 52.8, 28.3, 23.5. HRMS (ESI/TOF$^+$) $C_{15}H_{18}N_4O_5$ $[M+Na]^+$ calculated 325.1923, found 325.1915.

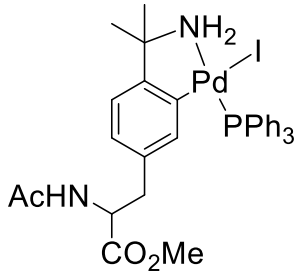
Methyl 2-acetamido-3-(4-(2-aminopropan-2-yl)phenyl)propanoate 13



13

Compound **12** (134.5 mg, 0.44 mmol, 1.0 eq.) was dissolved in 9 mL of MeOH and Pd/C (10% w/w, 137 mg, 0.13 mmol, 0.3 eq.) was added to the mixture. The reaction was stirred 4 days under a hydrogen atmosphere (1 atm), filtered over Celite before removing the solvent of the filtrate *in vacuo*. The residue was purified by silica gel flash chromatography (90/19/1 : dichloromethane/methanol/triethylamine) to afford compound **13** (113 mg, 0.41 mmol, 85%) as a colorless oil. ^{1}H NMR (300 MHz, MeOD) δ (ppm): 7.47-7.42 (m, 2H), 7.28-7.24 (m, 2H), 4.65 (dd, J = 9.0 Hz, J = 5.6 Hz, 1H), 3.71 (s, 3H), 3.16 (dd, J = 13.9 Hz, J = 5.6 Hz, 1H), 2.94 (dd, J = 13.9 Hz, J = 9.0 Hz, 1H), 1.92 (s, 3H), 1.64 (s, 6H). ^{13}C NMR (75.3 MHz, MeOD) δ (ppm): 172.0, 171.7, 143.5, 136.3, 129.1, 124.5, 54.0, 53.7, 51.4, 36.5, 28.4, 20.9. HRMS (ESI/TOF$^+$) $C_{15}H_{22}N_2O_3$ $[M+Na]^+$ calculated 301.1522, found 301.1522.

[Methyl 2-acetamido-3-(4-(2-aminopropan-2-yl)phenyl)propanoate-κ^2-C,N]iodotriphenyl-phosphinepalladium 14

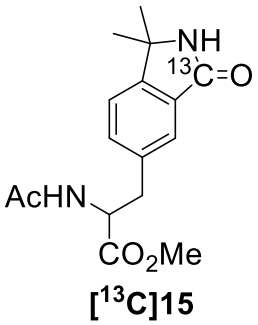


14

To a stirred solution of **13** (10.1 mg, 36 μmol, 1.0 eq.) in 1 mL of benzene/MeOH (1:1) at room temperature under N_2 was added $Pd(OAc)_2$ (8.0 mg, 36 μmol, 1.0 eq.). The mixture was stirred at room temperature for 1h at room temperature. Then, the volatiles were removed under reduced pressure to give a yellow solid which was dissolved in 1 mL of acetone and KI (6.0 mg, 36 μmol, 1.0 eq.) was added. The mixture was stirred 1h at room temperature and then PPh_3 (9.4 mg, 36 μmol, 1.0 eq.) was added and the mixture stirred for one hour. The volatiles were removed under reduced pressure. The residue was purified by preparative TLC on silica (95/5: dichloromethane/methanol) affording complex **14** (11.7 mg, 15 μmol, 42%) as an amorphous yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.74-7.64 (m, 6H), 7.47-7.33 (m, 9H), 6.69 (d, J = 7.6 Hz, 1H), 6.57 (dd, J = 7.6 Hz, J = 1.7 Hz, 1H), 6.05 (d, J = 5.4 Hz, 1H), 5.31 (d, J = 6.65 Hz, 1H), 4.31 (q, J = 6.4 Hz, 1H), 3.82-3.77 (m, 2H), 3.54 (s, 3H),

2.31-2.29 (m, 2H), 1.78 (d, J = 4.8 Hz, 6H), 1.69 (s, 3H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 172.1, 169.4, 156.0, 154.4, 138.2, 138.1, 135.5, 135.3, 133.2, 133.1, 132.7, 132.1, 131.9, 130.8, 128.3, 128.1, 125.0, 122.5, 66.1, 52.8, 52.1, 37.4, 32.7, 32.6, 23.1. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 41.4.

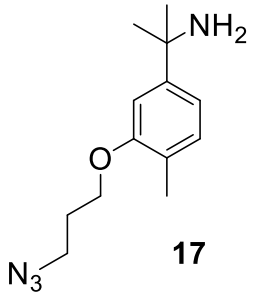
Methyl 2-acetamido-3-(1,1-dimethyl-3-oxoisoindolin-5-yl-3-13C)propanoate [^{13}C]15



[^{13}C]15

In the chamber 1 of the two-chamber system were added of Ph_2MeSi-COOH (3.3 mg, 14 μmol, 0.9 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system were added successively complex **14** (11.7 mg, 15 μmol, 1.0 eq.), and Na_2CO_3 (3.2 mg, 30 μmol, 2.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with N_2. Then, 1 ml of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 3 µl of a solution of TBAF (1M in THF, 3 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 16 hours. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH: 95/5) affording lactam **[^{13}C]15** (1.8 mg, 6 μmol, 43 %) as an amorphous white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.51-7.49 (m, 1H), 7.30 (d, *J* = 0.9 Hz, 2H), 6.00-5.91 (m, 2H), 4.90 (dt, *J* = 7.8 Hz, *J* = 5.6 Hz, 1H), 3.74 (s, 3H), 3.24 (dd, J = 13.9 Hz, J = 5.5 Hz, 1H), 3.15 (dd, J = 13.9 Hz, J = 5.5 Hz, 1H), 2.00 (s, 3H), 1.51 (s, 6H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 169.0 (^{13}C-enriched). HRMS (ESI/TOF$^+$) $C_{15}{}^{13}CH_{20}N_2O_4$ $[M+Na]^+$ calculated 328.1376, found 328.1365.

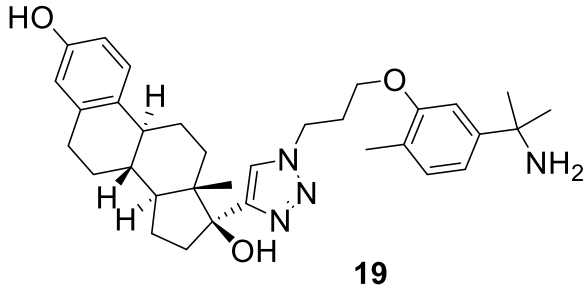
2-(3-(3-Azidopropoxy)-4-methylphenyl)propan-2-amine 17



17

To a stirred solution of **6** (301 mg, 1.68 mmol, 1.0 eq.) in 15 mL of dry dichloromethane at 0°C under N_2 was slowly added BBr_3 (2.5 mL, 2.52 mmol, 1 M in CH_2Cl_2, 1.5 eq.). The mixture was stirred at room temperature for 17h. Then, H_2O vas added (146 μL, 8.4 mmol, 5.0 eq.) was added to the mixture to quench the excess of BBr_3. Na_2SO_4 was then added to dry the solution, and the mixture was filtered and washed with EtOAc and MeOH. The volatiles were removed under reduced pressure and the residue was purified by by silica gel flash chromatography (dichloromethane/MeOH 98:2 to 90:10) to 2-(3-hydroxy-4-methylphenyl)propan-2-amine (246 mg, 1.49 mmol, 89%) as an amorphous colorless solid which was engaged directly in the next step. ^{1}H NMR (300MHz, MeOD) δ (ppm): 7.14 (d, *J* = 7.8 Hz, 1H), 6.87 (m, 2H), 2.18 (s, 3H), 1.69 (s, 6H). HRMS (ESI) $C_{10}H_{14}NO$ $[M-H]^+$ calculated 164.10809, found 164.1081; $[M-NH_2]^+$ calculated 149.10, found 149.0960. To a stirred solution of the crude 2-(3-hydroxy-4-methylphenyl)propan-2-amine (242 mg, 1.46 mmol, 1.0 eq.) in 10 mL of dry DMF at r.t. under N_2 was slowly added NaH (90% w/w, 58 mg, 2.19 mmol, 1.5 eq.) portion wise. The mixture was stirred at 0°C for 1 h. Then 3-azidopropyl 4-methylbenzenesulfonate **16** (334 mg, 1.31 mmol, 0.9 eq.) was added to the mixture at room temperature and the solution was stirred for 15h at 70°C. The mixture was then poured into water, the aqueous layer was extracted three times with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/MeOH 95:5 then 90:10), affording compound **17** as a colourless oil (136 mg, 0.94 mmol, 42%). ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 7.28-7.13 (m, 2H), 7.04-6.91(m, 1H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.22 (s, 3H), 2.03-1.94 (m, 2H), 1.71 (s, 6H). ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 157.1, 130.7, 126.6, 116.5, 107.9, 64.8, 56.6, 48.4, 28.8, 15.9. HRMS (ESI) $C_{13}H_{21}N_4O$ $[M+H]^+$ calculated 249.1710, found 249.1708; $[M-NH_2]^+$ calculated 232.1400, found 232.1442.

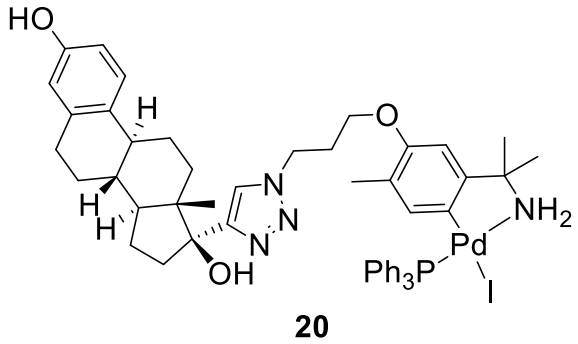
17-(1-(3-(4-Methylphenyl)propan-2-amine)propyl)-1H-1,2,3-triazol-4-yl)-estradiol 19



19

Under inert atmosphere, compound **17** (40 mg, 0.16 mmol, 1.0 eq.) was dissolved in 1.8 mL of THF. Ethynylestradiol (47 mg, 0.16 mmol, 1.0 eq.), copper iodide (1.5 mg, 8 μmol, 0.05 eq.) and tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA, 4 mg, 8 μmol, 0.05 eq.) were then added successively. The mixture was stirred at 50°C for 16 hours. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (dichloromethane/MeOH 90:10 then 80:20) affording compound **19** (73 mg, 0.13 mmol, 84%) as a white amorphous powder. ^{1}H NMR (600 MHz, MeOD) δ (ppm): 7.76 (s, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.90 (d, J = 2.1 Hz, 1H), 6.85 (dd, J = 7.9, 2.0 Hz, 1H), 6.51 (dd, J = 8.5, 2.7 Hz, 1H), 6.47 (d, J = 2.7 Hz, 1H), 4.45 (t, J = 6.9 Hz, 2H), 2.85-2.69 (m, 2H), 2.64 (t, J = 7.8 Hz, 2H), 2.47-2.34 (m, 1H), 2.18 (t, J = 7.6 Hz, 2H), 2.14 (s, 3H), 2.10-2.05 (m, 1H), 2.00-1.90 (m, 2H), 1.84-1.80 (m, 1H), 1.64 (s, 6H), 1.61-1.56 (m, 2H), 1.47-1.28 (m, 5H), 1.03 (s, 3H), 0.61-0.56 (m, 1H). ^{13}C NMR (600 MHz, MeOD) δ (ppm): 157.1, 156.0, 155.6, 138.8, 132.4, 127.1, 126.2, 124.3, 117.7, 116.1, 113.7, 113.4, 83.2, 61.2, 45.0, 41.0, 38.5, 34.4, 30.7 29.2, 28.8, 27.5, 26.7, 24.6, 15.9, 14.8. HRMS (ESI) $C_{33}H_{45}O_3N_4$ $[M+H]^+$ calculated 545.3486, found 545.3483.

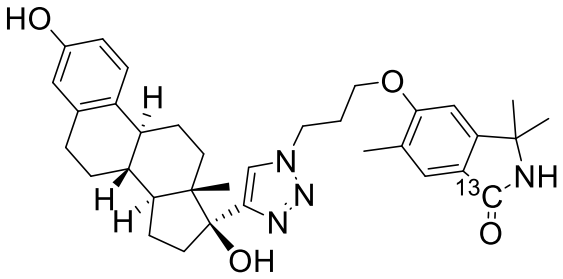
[17-(1-(3-(4-Methylphenyl)propan-2-amine)propyl)-1H-1,2,3-triazol-4-yl)-estradiol-κ^2-C,N]iodotriphenylphosphinepalladium 20



20

To a stirred solution of **19** (60 mg, 0.11 mmol, 1.0 eq.) in 1 mL of benzene/MeOH (1:1) at room temperature under N_2 was added $Pd(OAc)_2$ (25 mg, 0.11 mmol, 1.0 eq.). The mixture was stirred at room temperature for 1h. Then, the volatiles were removed under reduced pressure to give a yellow solid which was dissolved in 1 mL of acetone, and KI (18 mg, 0.11 mmol, 1.0 eq.) was added. The mixture was stirred 1 h at room temperature and then PPh_3 (29mg, 0.11 mmol, 1.0 eq.) was added before stirring for one extra hour. The volatiles were removed under reduced pressure. The residue was purified by preparative TLC (dichloromethane/MeOH 9:1) affording complex **20** (61 mg, 59 μmol, 53%) as an orange amorphous solid. ^{1}H NMR (300MHz, MeOD) δ (ppm): 7.74-7.64 (m, 6H), 7.46-7.32 (m, 9H), 6.96 (d, J = 8.4 Hz, 1H), 6.56 (dd, J = 8.4 Hz, J = 2.6 Hz, 1H), 6.50 (d, J = 2.6 Hz, 1H), 6.31 (s, 1H), 6.07 (d, J = 6.4 Hz, 1H), 4.59-4.54 (m, 2H), 3.87-3.69 (m, 2H), 2.81-2.71 (m, 2H), 2. 39-2.30 (m, 3H), 2.11-1.72 (m, 6H), 1.60 (s, 3H), 1.54 (s, 6H), 1.49-1.24 (m, 7H), 1.00 (s, 3H), 0.61-0.49 (m, 1H). ^{13}C NMR (75.3 MHz, THF-d_8) δ (ppm): 155.4, 153.6, 137.2, 135.4, 135.3, 135.2, 135.2, 135.0, 134.8, 134.3, 133.7, 130.8, 130.1, 129.9, 128.1, 127.8, 127.7, 127.6, 127.4, 127.3, 125.6, 121.6, 114.9, 112.6, 105.4, 81.4, 64.1, 48.0, 47.0, 46.4, 43.6, 39.9, 37.8, 33.1, 31.4, 30.3, 29.7, 29.4, 27.6, 26.5, 14.9, 13.8. ^{31}P NMR (121.5 MHz, acetone-d_6) δ (ppm): 40.1. HRMS (ESI) $C_{51}H_{58}O_3N_4P^{102}Pd$ $[M-I]^+$ calculated 907.3297, found 907.3289.

5-(3-(4-Estradiol-1H-1,2,3-triazol-1-yl)propoxy)-3,3,6-trimethylisoindolin-1-one-1-^{13}C [^{13}C]21



[^{13}C]21

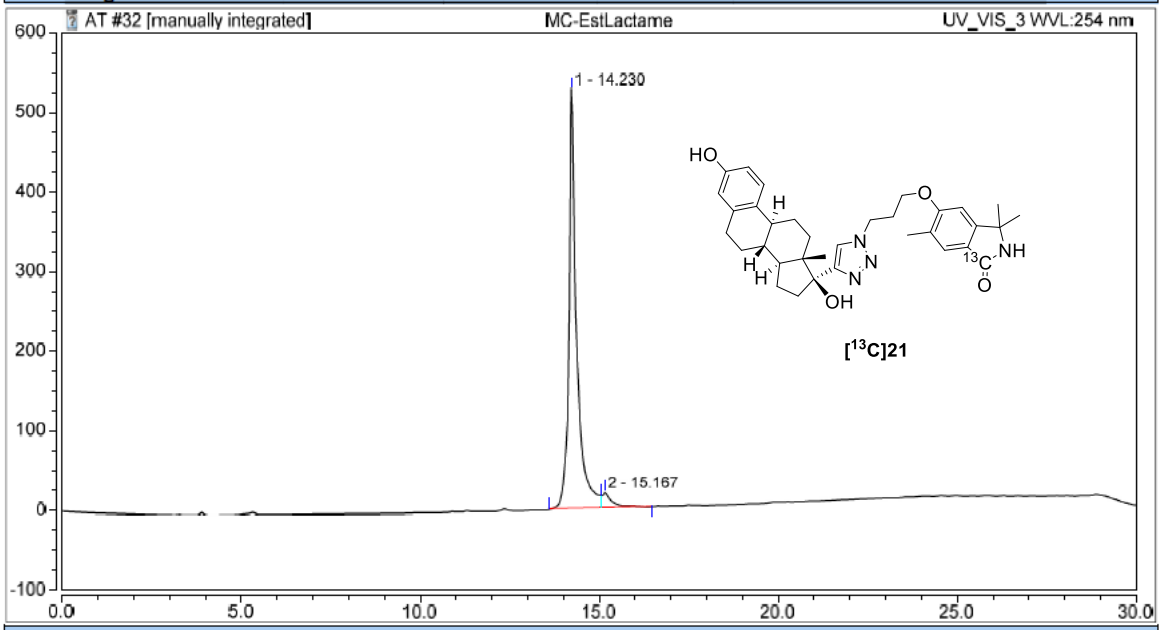
To a stirred solution of complex **20** (51 mg, 0.05 mmol, 1.0 eq.) in 0.5 mL of dry THF at room temperature under N_2 was added the triphenylphosphine polymer-bound (100-200 mesh, extent of labeling: ~3 mmol/g) (204 mg, 0.5 mmol, 10 eq.). The mixture was stirred at room temperature for 16h. Then, the mixture was filtrated and the solid was washed with MeOH, dichloromethane and Et_2O to give the 250 mg of the supported complex **20-PS**, which was then divided in 5 equal batches (50 mg, 0.01 mmol for each batch). In the chamber 1 of the two-chamber system were added of $Ph_2MeSi^{13}COOH$ (3 mg, 0.01 mmol, 1.0 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system were added successively the supported complex **20-PS** (50 mg, 0.01 mmol, 1.0 eq.), and Na_2CO_3 (3 mg, 0.02 mmol, 2.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with N_2. Then, 1 ml of dry THF were added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70°C, then 2 µl of a solution of TBAF (1M in THF, 2 μmol, 15 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was filtered on sintered glass, washed with methanol and concentrated under reduced pressure affording without further purification the desired product **[^{13}C]21** as an amorphous white solid (2.6 mg, 5.0 μmol, 46%). The chemical purity was established by analytical UV-HPLC at 254 nm using a reverse phase column (Luna 5µm C18 100Å, 4.6mm*250mm) eluted with acetonitrile (+0.1%TFA) and water (+0.1%TFA) at a flow rate of 1 mL/min (gradient from 5/95 to 95/5 in 20 min). The retention time of **[^{13}C]21** was 14.2 min. The chemical purity of **[^{13}C]21** was measured to 96% (254 nm). ^{1}H NMR (300MHz, MeOD) δ (ppm): 7.81 (s, 1H), 7.47 (dd, J = 2.8 Hz, J = 0.7 Hz, 1H), 6.97 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.45 (dd, J = 8.2 Hz, J = 2.8 Hz, 1H), 6.40 (d, J = 2.6 Hz, 1H), 4.69 (t, J = 6.7 Hz, 2H), 4.10-3.99 (m, 2H), 2.74-2.67 (m, 2H), 2.52-2.43 (m, 3H), 2.31 (s, 3H), 2.14-1.92 (m, 5H), 1.75-1.65 (m, 1H), 1.60-1.48 (m, 4H), 1.41 (d, J = 5.4 Hz, 6H), 1.23-1.09 (m, 1H), 1.01 (s, 3H), 0.64-0.56 (m, 1H). ^{13}C NMR (75.3 MHz, MeOD) δ (ppm): 170.3 (^{13}C-enriched). HRMS (ESI) $C_{33}{}^{13}CH_{42}N_4O_4{}^{23}Na$ $[M+Na]^+$ calculated 594.3143, found 594.3131.

Chromatogram and Results

Injection Details

Injection Name:	**MC-EstLactame**	*Run Time (min):*	**30.00**
Vial Number:	**GD3**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_3**
Calibration Level:		*Wavelength:*	**200.0**
Instrument Method:	**5 a 95 Acn 20 min**	*Bandwidth:*	**1**
Processing Method:	**New Processing Method(4)**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**05/avr./18 11:37**	*Sample Weight:*	**1.0000**

Chromatogram



[^{13}C]21

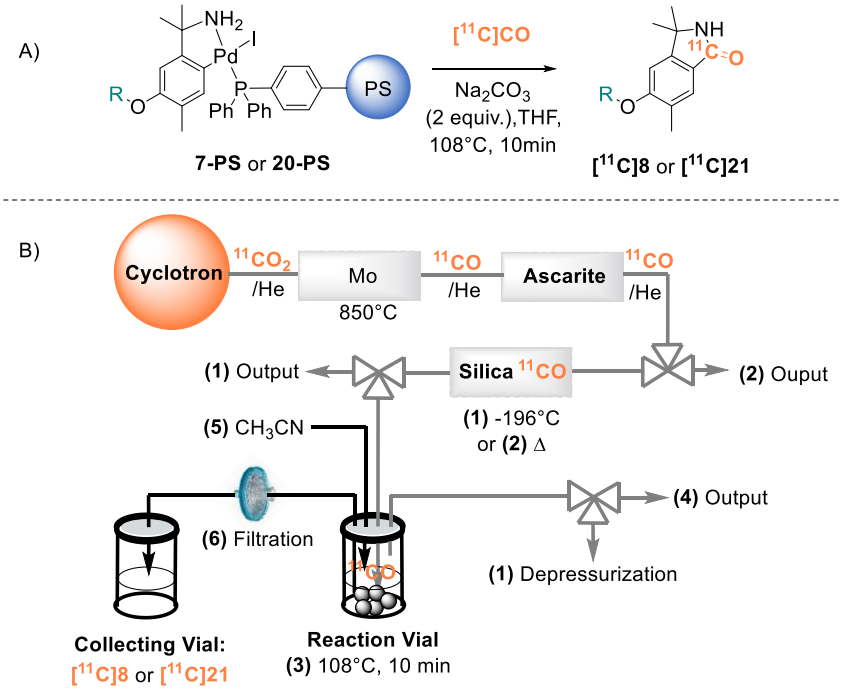
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		14.230	130.596	526.472	95.38	96.45	n.a.
2		15.167	6.326	19.356	4.62	3.55	n.a.
Total:			**136.922**	**545.828**	**100.00**	**100.00**	

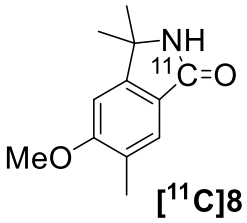
2) ^{11}C-carbonylation reactions

a. General procedure

[^{11}C]Carbon dioxide was produced by the ^{14}N(p,α)^{11}C nuclear reaction using a nitrogen gas target (containing 1% oxygen) pressurised to 150 psi and bombarded with 16 MeV protons using the General Electric Medical Systems PETtrace 200 cyclotron. Typically, the irradiation time was ~40 minutes using a 60 µA beam current. After irradiation, [^{11}C]carbon dioxide was trapped and concentrated on 4Å molecular sieves. The trapped [^{11}C]CO_2 was released from molecular sieves in a stream of Helium (30 mL/min) by heating them to 350°C. [^{11}C]CO_2 was reduced on-line to [^{11}C]carbon monoxide after passing through a quartz tube filled with Molybdenum powder heated to 850°C. The produced [^{11}C]carbon monoxide was transferred in the system set-up with a Helium flow (25 mL/min), where it was condensed on a silica gel trap at -196°C (Step 1 in the following Scheme). After complete entrapment, the trap was heated (Step 2 in the following Scheme) in order to release the [^{11}C]CO into the reaction vial (4 mL) previously loaded with the supported complex (50.0 mg, 10 µmol, 1.0 eq.) and Na_2CO_3 (2.1 mg, 20 µmol, 2.0 eq.) dissolved in THF (0.6 mL), crimped with a microwave cap and depressurised with a syringe (30 mL). The [^{11}C]CO trap was flushed briefly to the reaction vial before disconnection of the Helium low-flow. The vial was stirred for 10 min in an oil bath pre-heated at 108°C (Step 3 in the following Scheme). The radioactivity was measured in the reaction vial. Then, the vial was flushed three times with air (Step 4 in the following Scheme), and the remaining radioactivity in the vial was measured again. Trapping efficiency was calculated from the percentage ratio of radioactivity remaining in the reaction vial over the initial radioactivity before the flush. Acetonitrile (5 mL) was added in the vial (Step 5 in the following Scheme) and the heterogeneous mixture was filtrated through a syringe filter (Acrodisc, 25mm, 1.0 µm glass fiber) in the collecting vial (Step 6 in the following Scheme). The radiochemical purity (RCP) was established by analytical radio-HPLC using a P680 HPLC pump from Dionex equipped with a 20 µL injection loop connected in series, a variable wavelength UV detector from Dionex (UVD 170U), and a sodium iodide radiodetector of in-house design. Radiochemical conversion (RCC) was obtained by multiplying of the trapping efficiency by the RCP. Radiochemical yield was calculated from the percentage ratio of the decay-corrected radioactivity in the collecting vial over the initial radioactivity in the reaction vial at the end of the reaction (before the air flush).



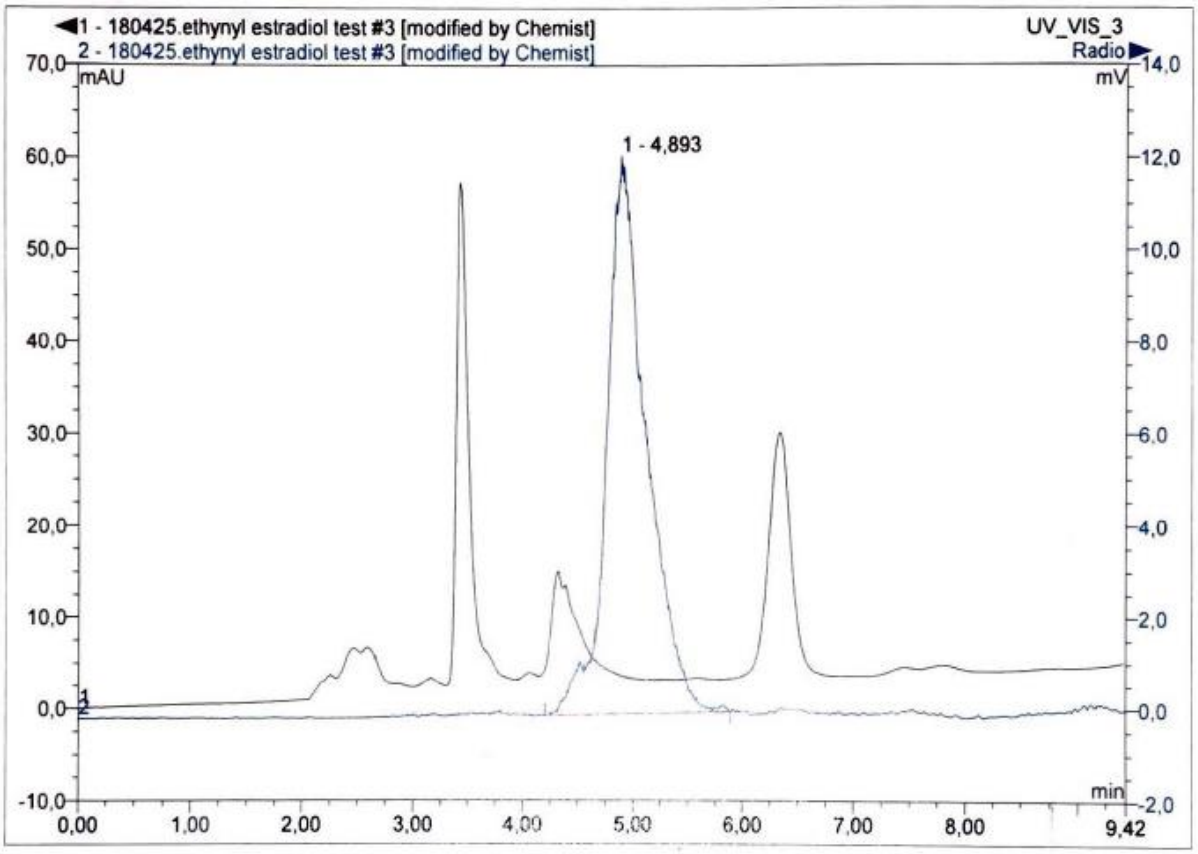
b. *[^{11}C]- 5-Methoxy-3,3,6-trimethylisoindolin-1-one* ***[^{11}C]8***



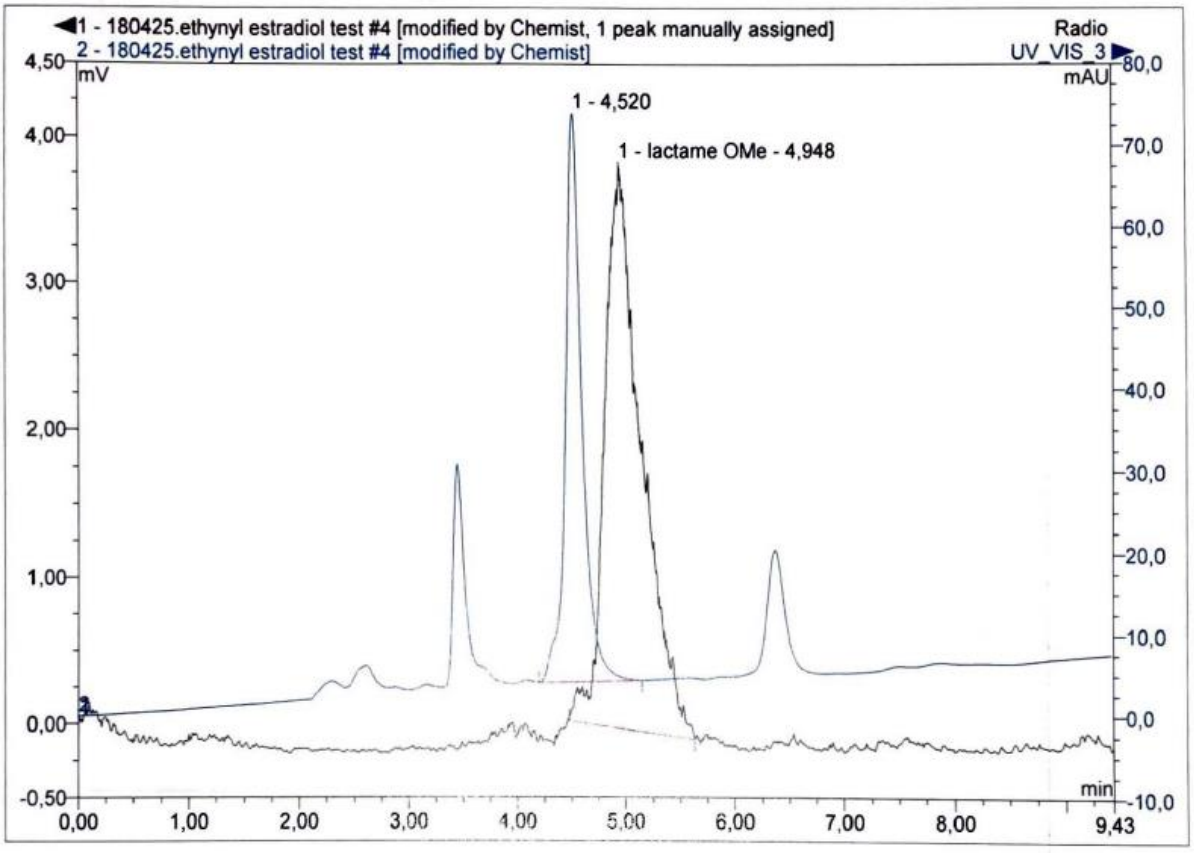
[^{11}C]8

The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 3µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (60/40) at a flow rate of 0.5 mL/min (retention time for radio detection: 4.95 min, retention time for UV detection: 4.52 min). The values for **[^{11}C]8** were RCP > 98%, RCC = 22% and RCY = 11%.

	Exp.	**1**
End of the reaction	**Time (min)**	10
	Activity in the reaction vial (MBq)	911
After flush of CO	**Time (min)**	12
	Activity in the reaction vial (MBq)	186
	Trapping efficiency (%)	22
After filtration	**Time (min)**	15
	Activity in the collecting vial (MBq)	82
	Radiochemical purity RCP (%)	>98
	Radiochemical conversion RCC (%)	22
	Radiochemical yield RCY (%)	11

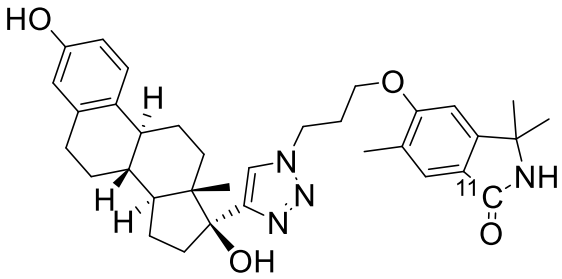


UV and radio-chromatogram of the analytical HPLC of **[^{11}C]8**



UV and radio-chromatogram of the analytical HPLC of **[^{11}C]8** *co-injected with* [^{13}**C]8**

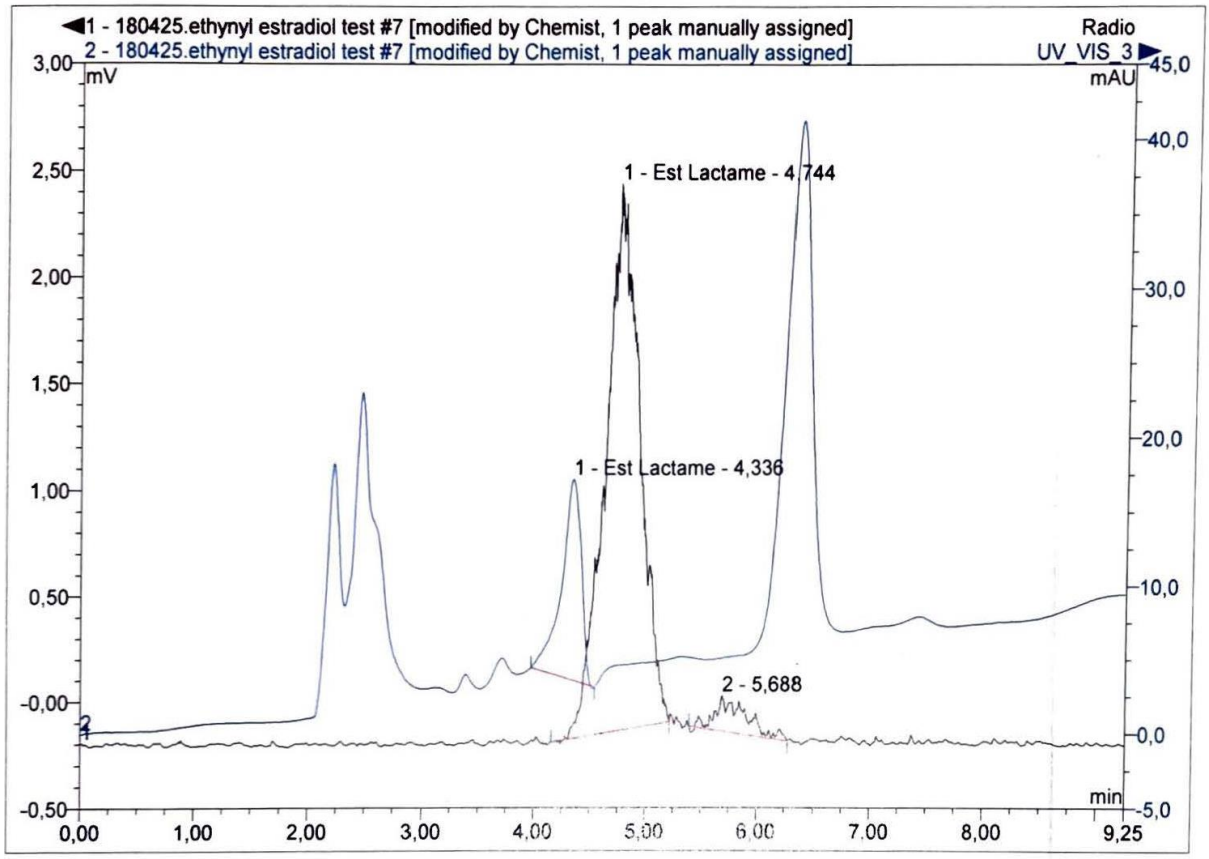
c. *[^{11}C]- 5-(3-(4-Estradiol-1H-1,2,3-triazol-1-yl)propoxy)-3,3,6-trimethylisoindolin-1-one* ***[^{11}C]21***



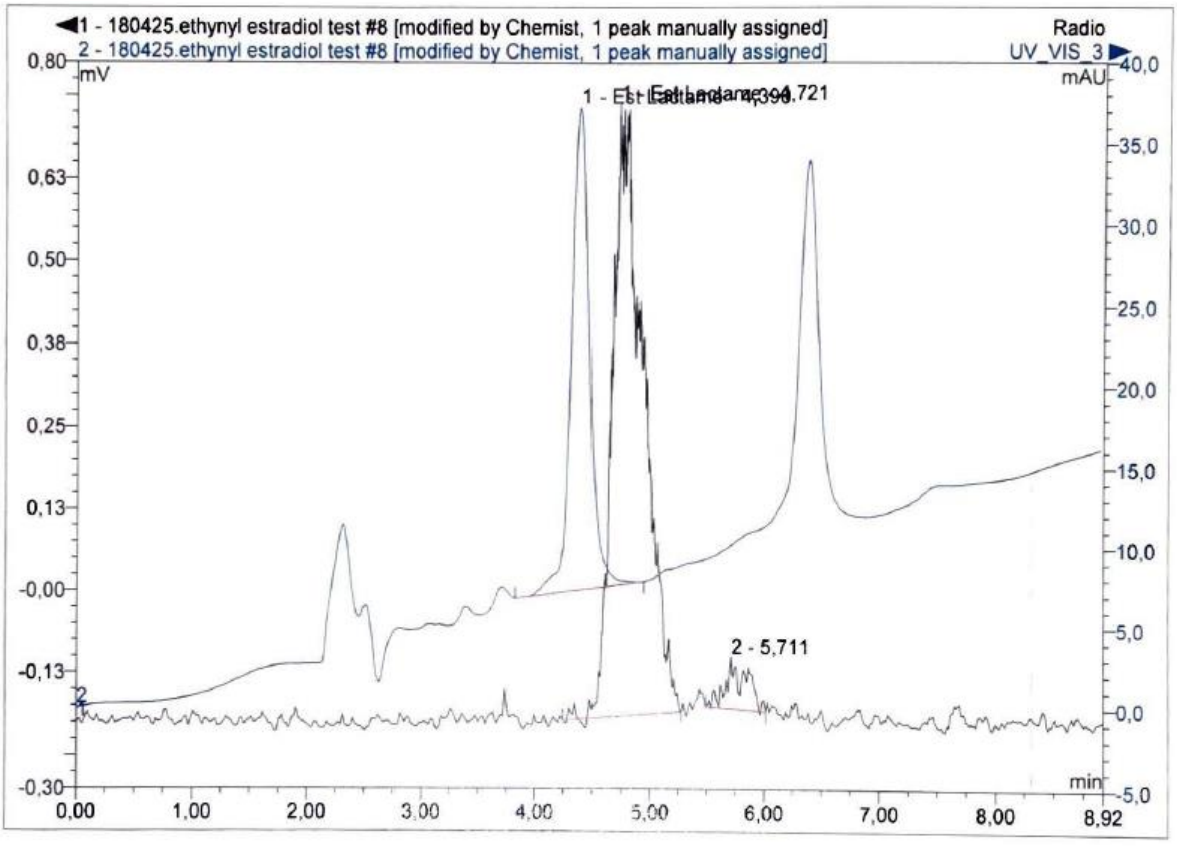
[^{11}C]21

The radiochemical purity (RCP) was established by analytical radio-HPLC using a reverse phase column (Luna 3µ C8 100Å) eluted with acetonitrile and 70mM NaH_2PO_4 (60/40) at a flow rate of 0.5 mL/min (retention time for radio detection: 4.74 min, retention time for UV detection: 4.34 min). The values for **[^{11}C]21** were RCP = 93%, RCC = 6% and RCY = 2%.

	Exp.	**1**
End of the reaction	**Time (min)**	10
	Activity in the reaction vial (MBq)	1080
After flush of CO	**Time (min)**	12
	Activity in the reaction vial (MBq)	62
	Trapping efficiency (%)	6
After filtration	**Time (min)**	15
	Activity in the collecting vial (MBq)	15.3
	Radiochemical purity RCP (%)	93
	Radiochemical conversion RCC (%)	6
	Radiochemical yield RCY (%)	2



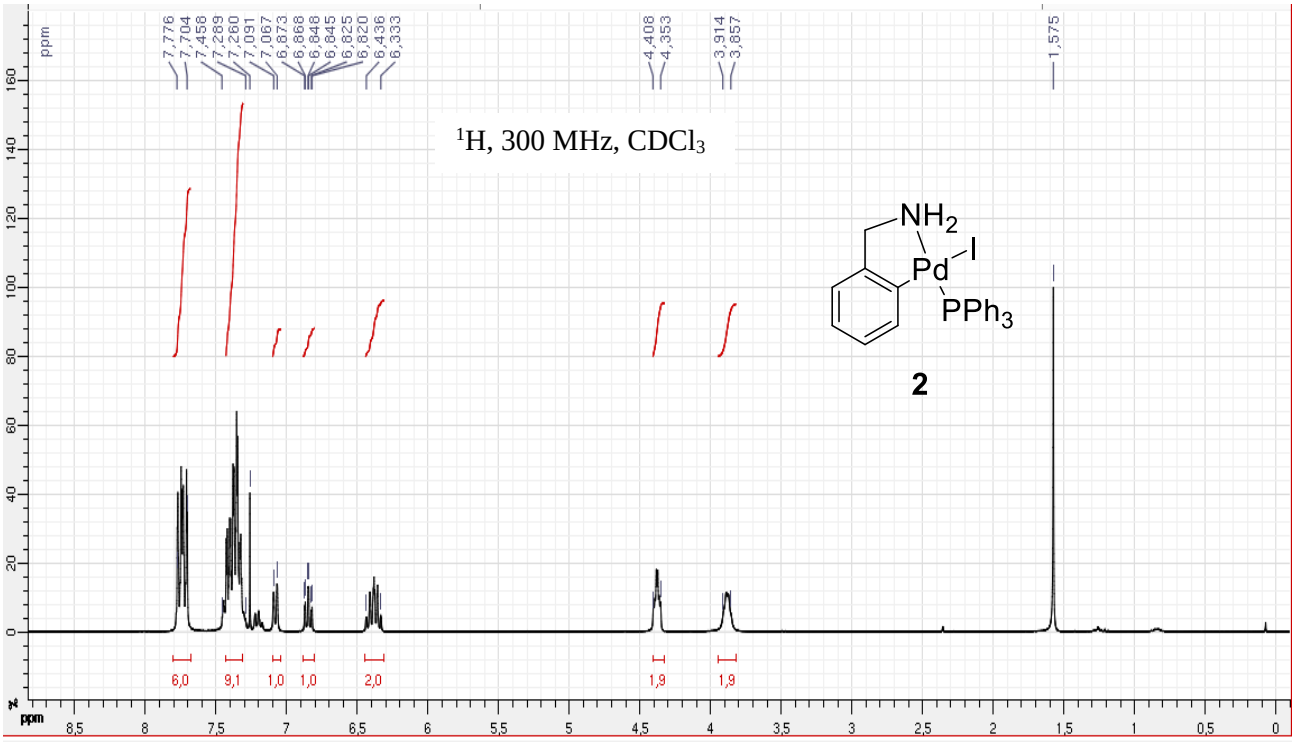
UV and radio-chromatogram of the analytical HPLC of **[^{11}C]21**

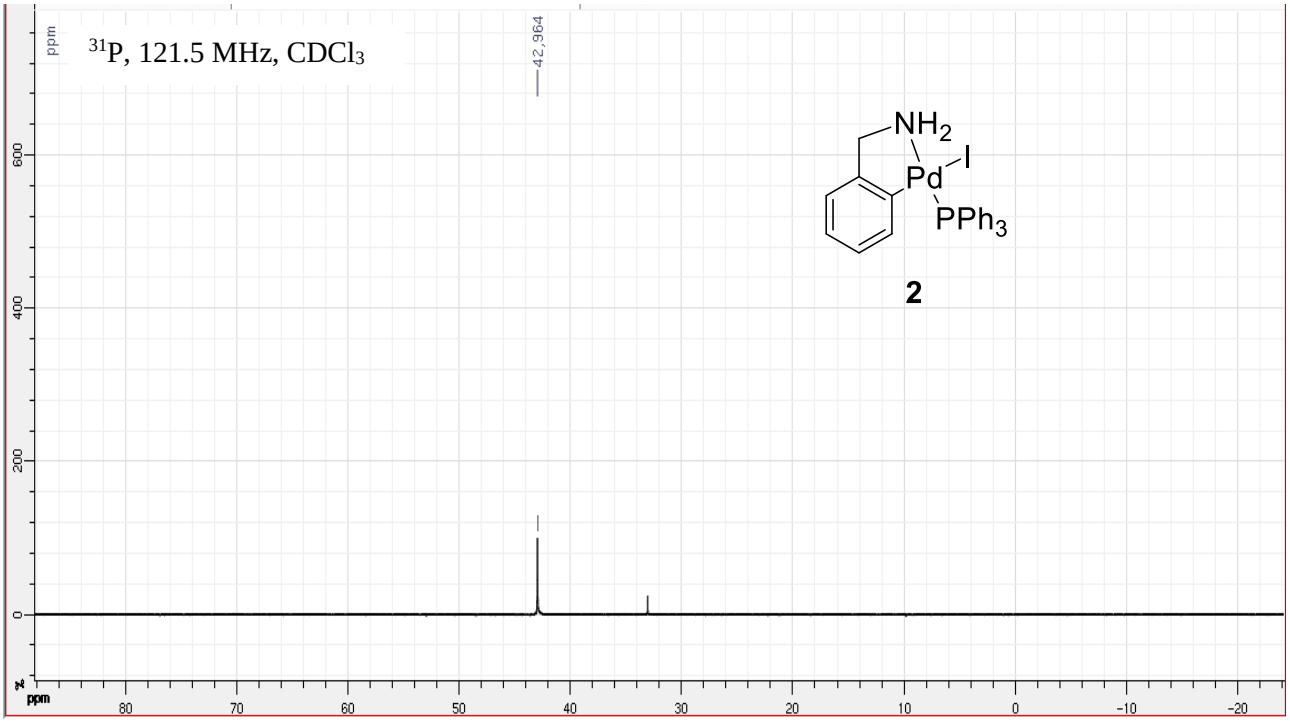


UV and radio-chromatogram of the analytical HPLC of **[^{11}C]21** *co-injected with* [^{13}C]**21**

3) NMR Spectra

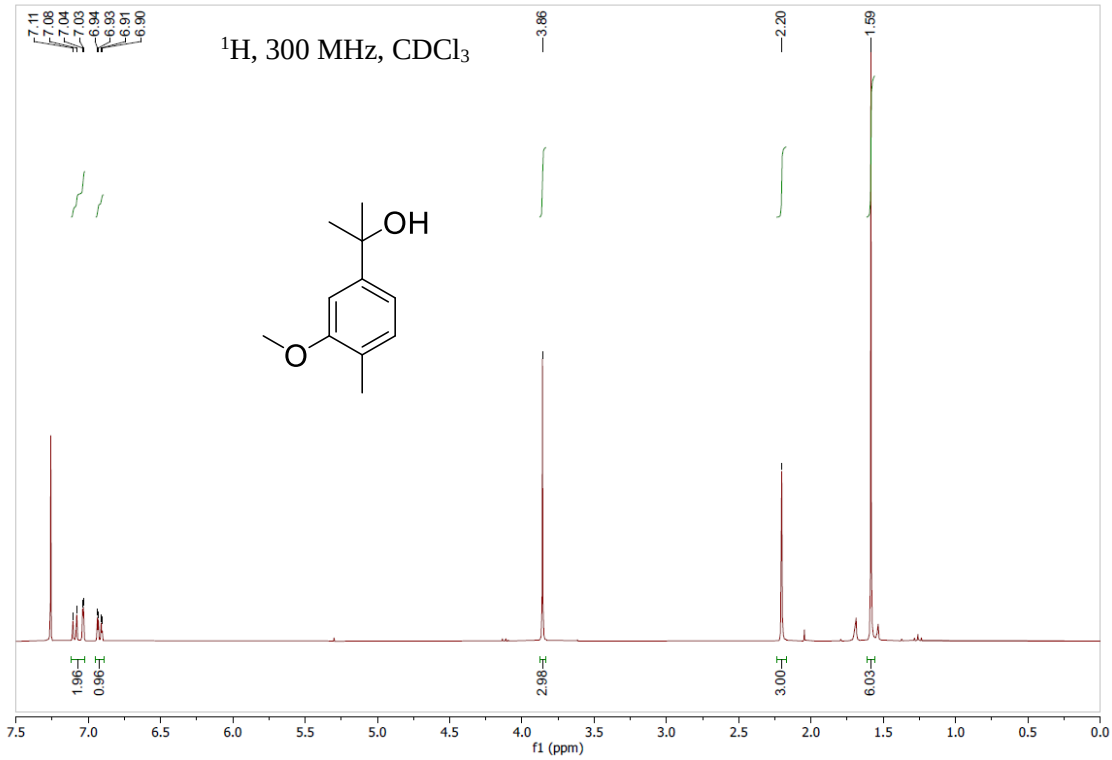
*a. Complex **2***



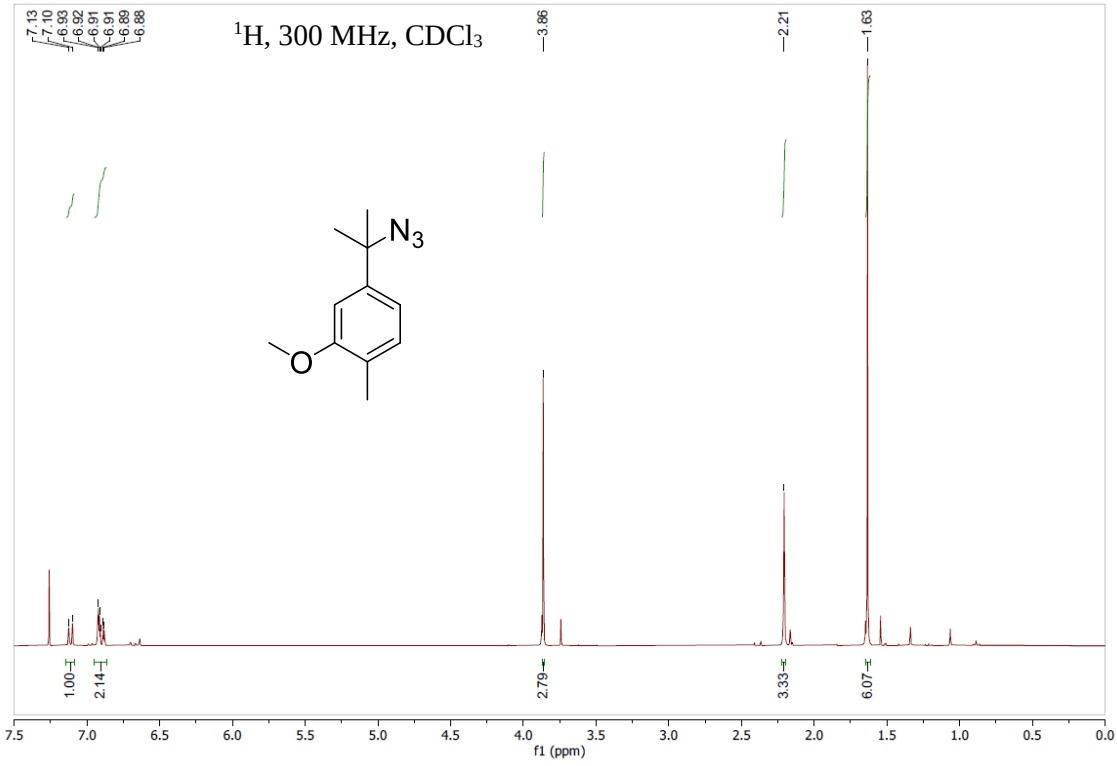


*b. Compound **6***

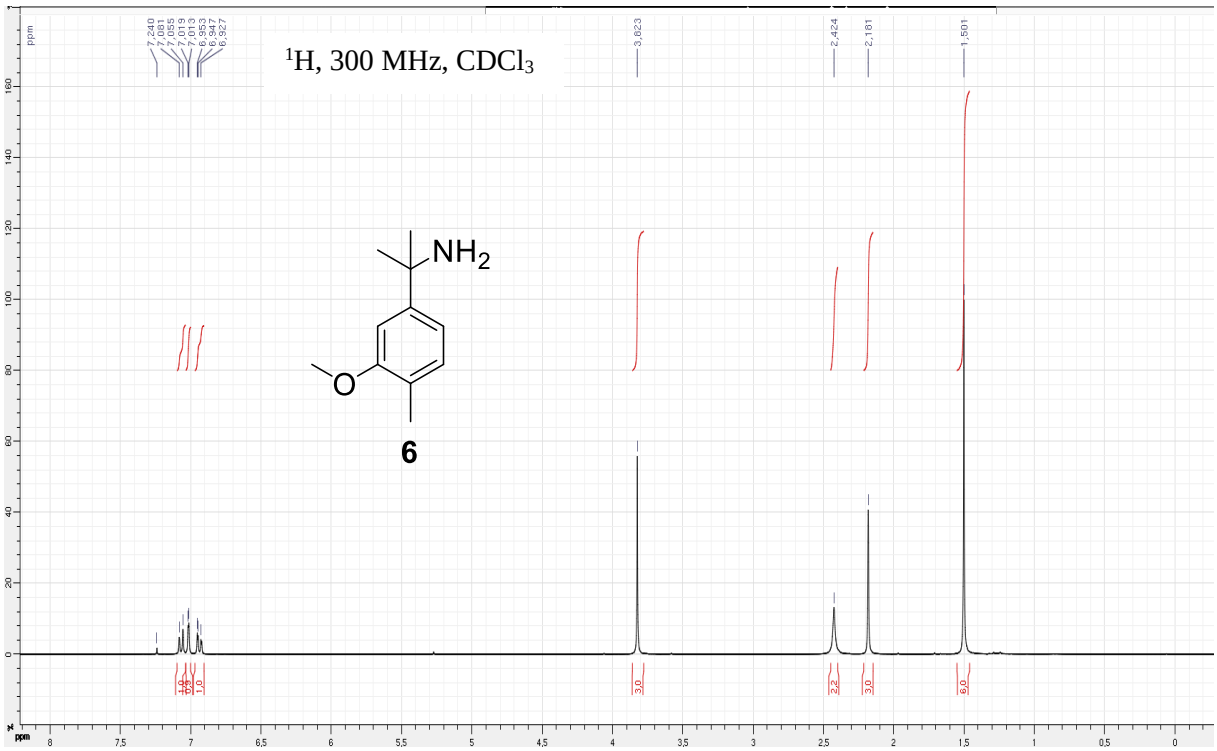
2-(3-Methoxy-4-methylphenyl)propan-2-ol

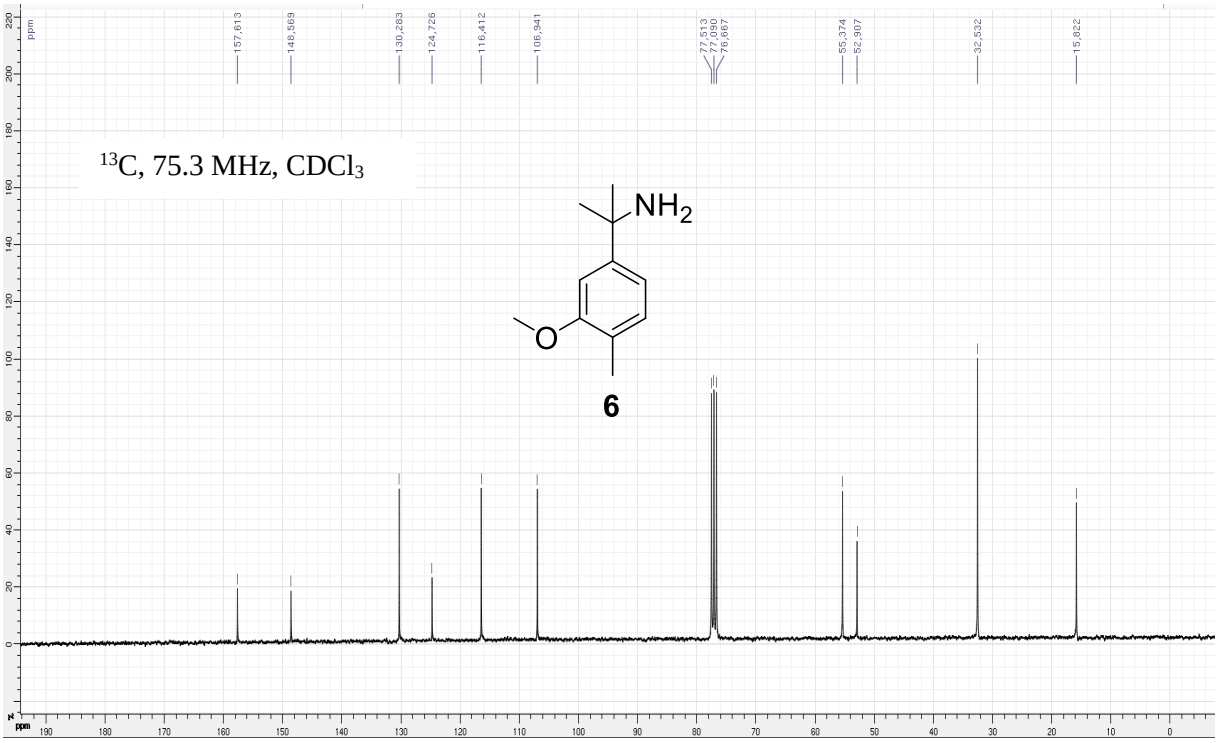


1-(1-Azidoisopropyl)-3-methoxy-4-methylbenzene



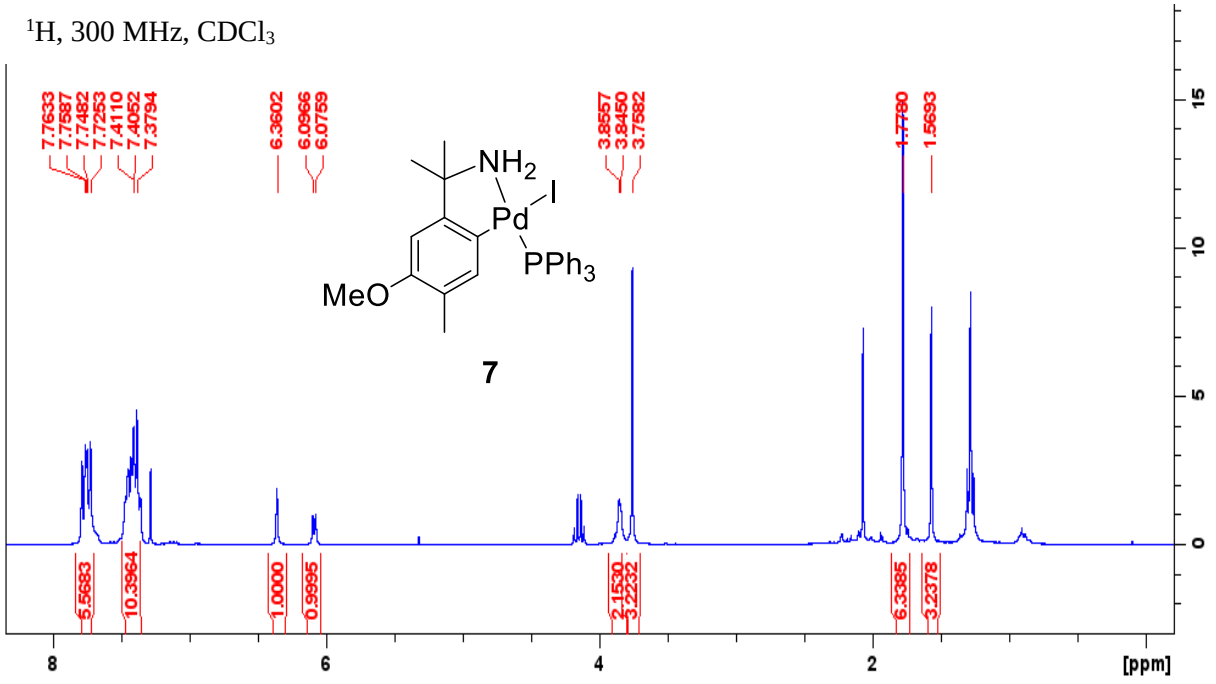
Compound 6



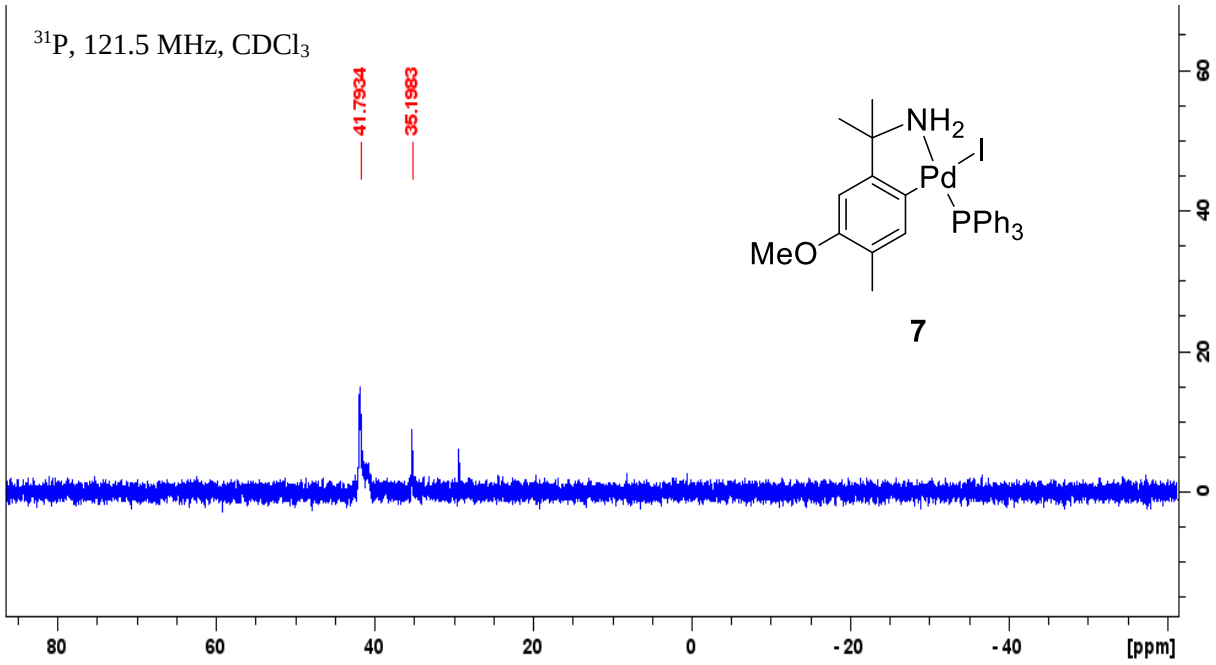


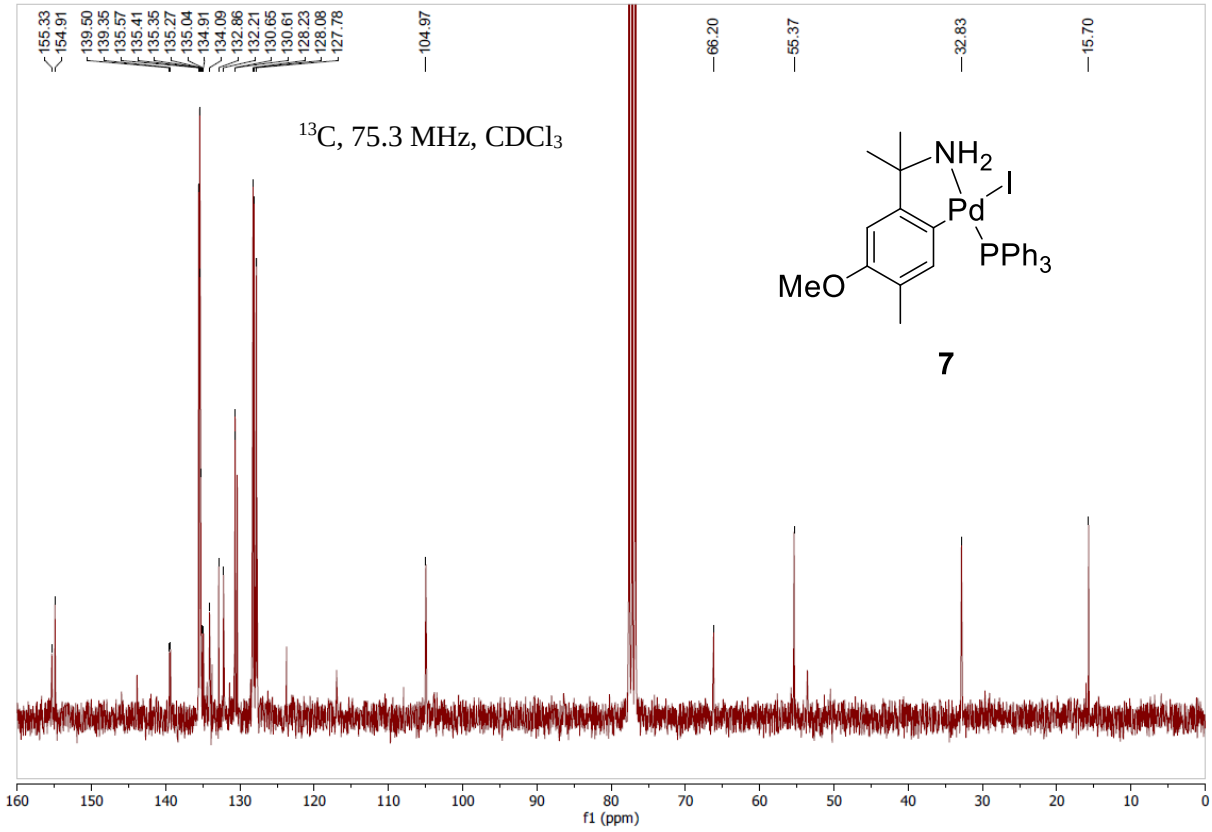
*c. Complex **7***

^{1}H, 300 MHz, $CDCl_3$



^{31}P, 121.5 MHz, $CDCl_3$

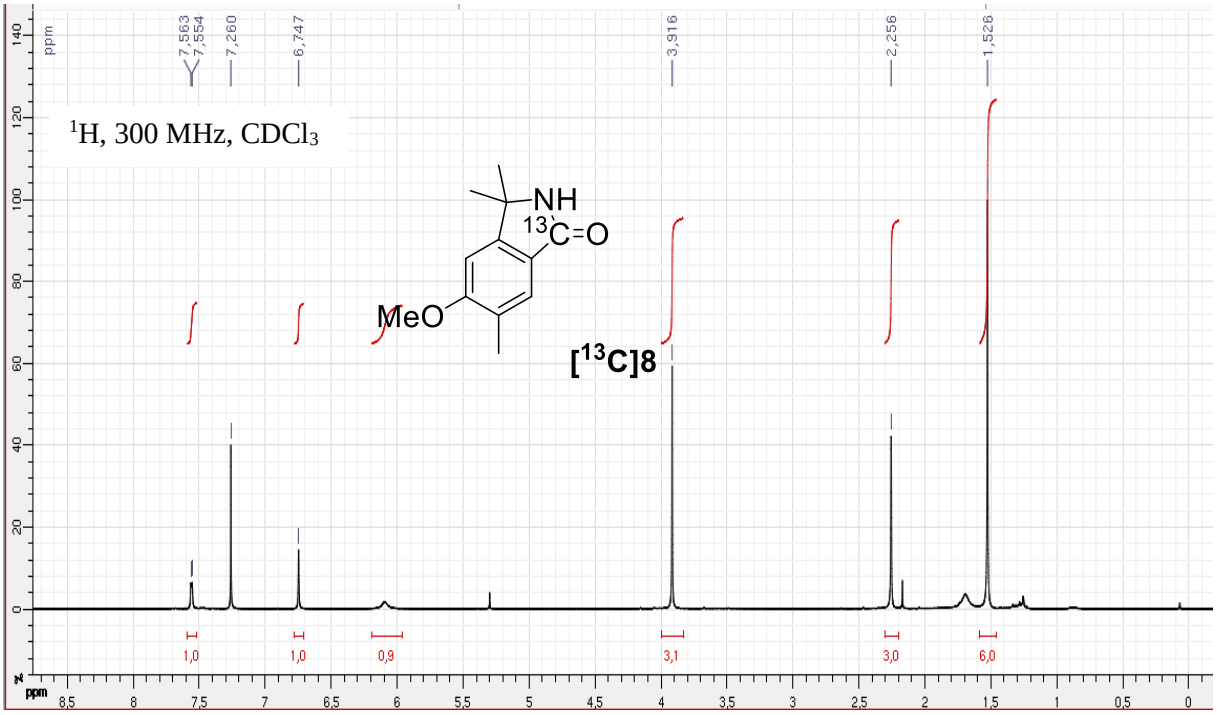


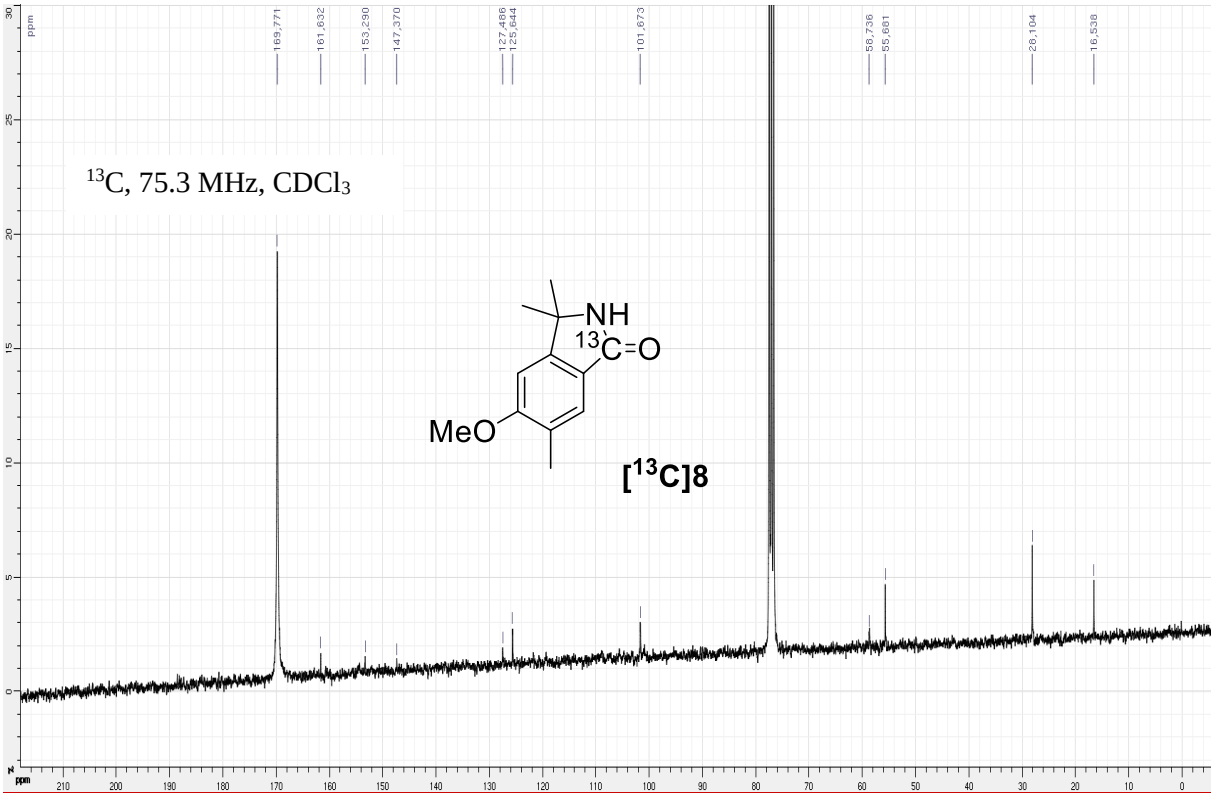

155.33
154.91
139.50
139.35
135.57
135.41
135.35
135.27
135.04
134.91
134.09
132.86
132.21
130.65
130.61
128.23
128.08
127.78
104.97
66.20
55.37
32.83
15.70
^{13}C, 75.3 MHz, $CDCl_3$
NH2
I
Pd
PPh3
MeO
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

7

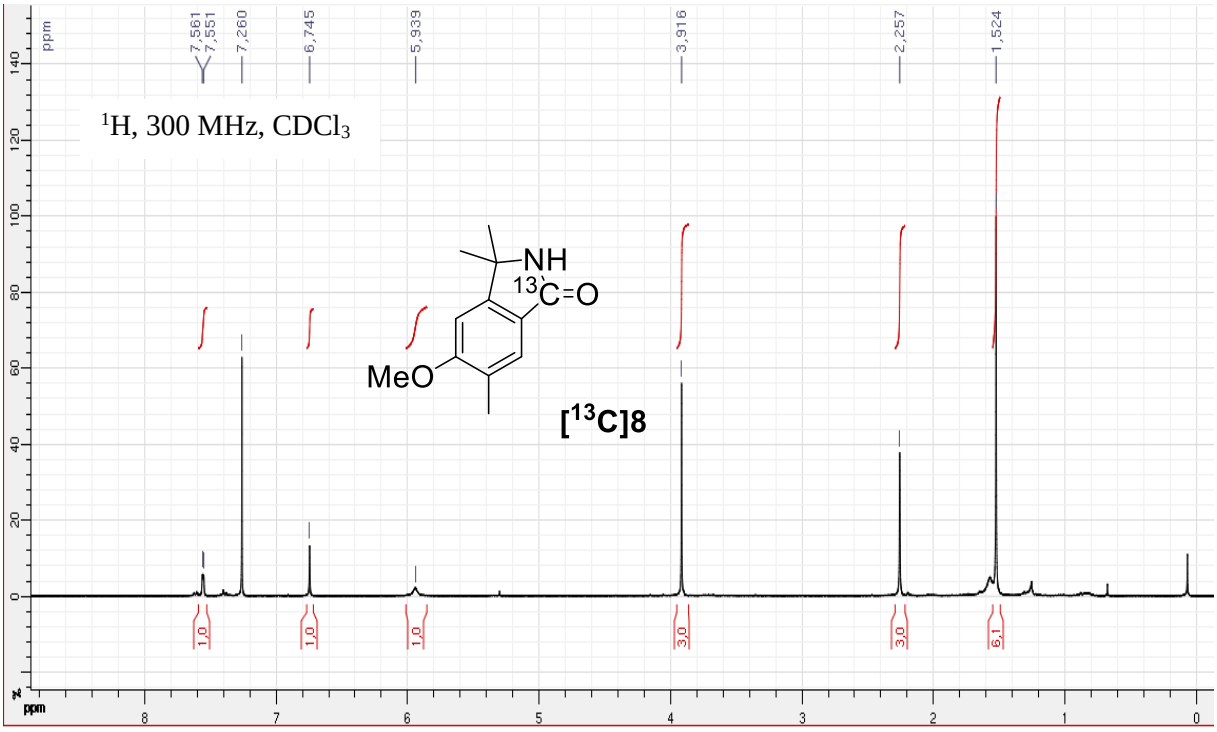
*d. Compound **[^{13}C]8***

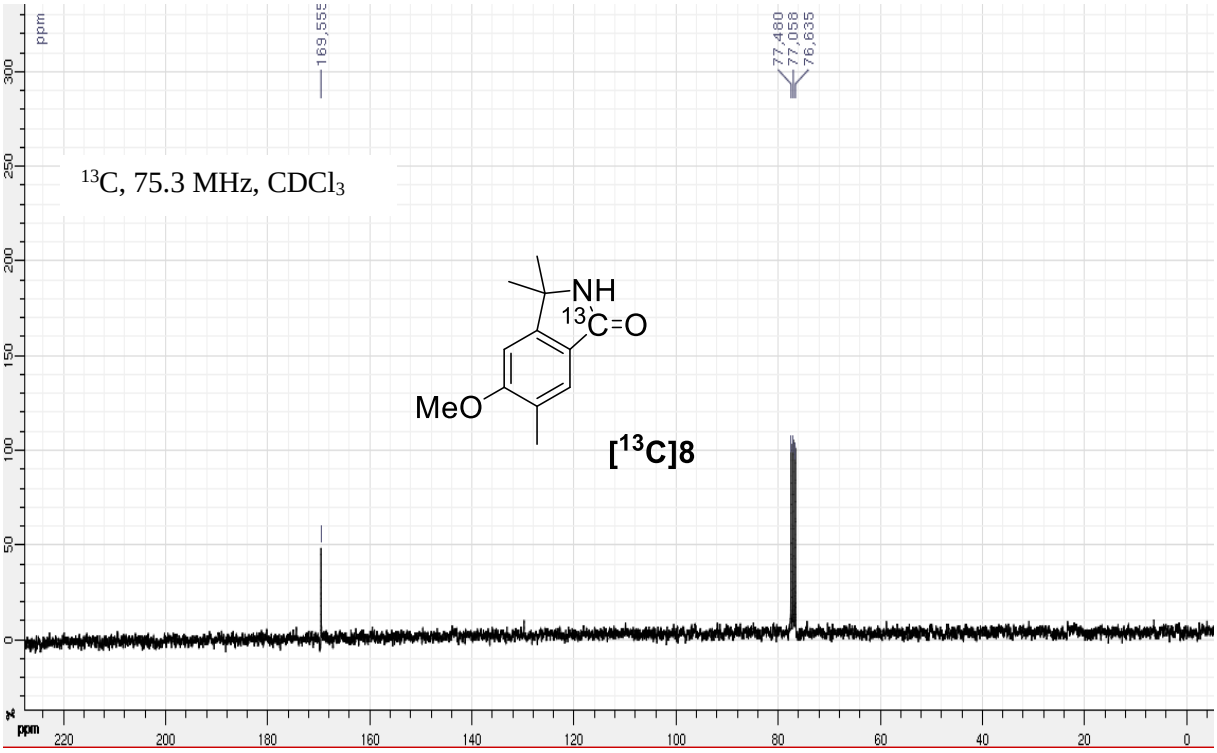
*From complex **7**.*



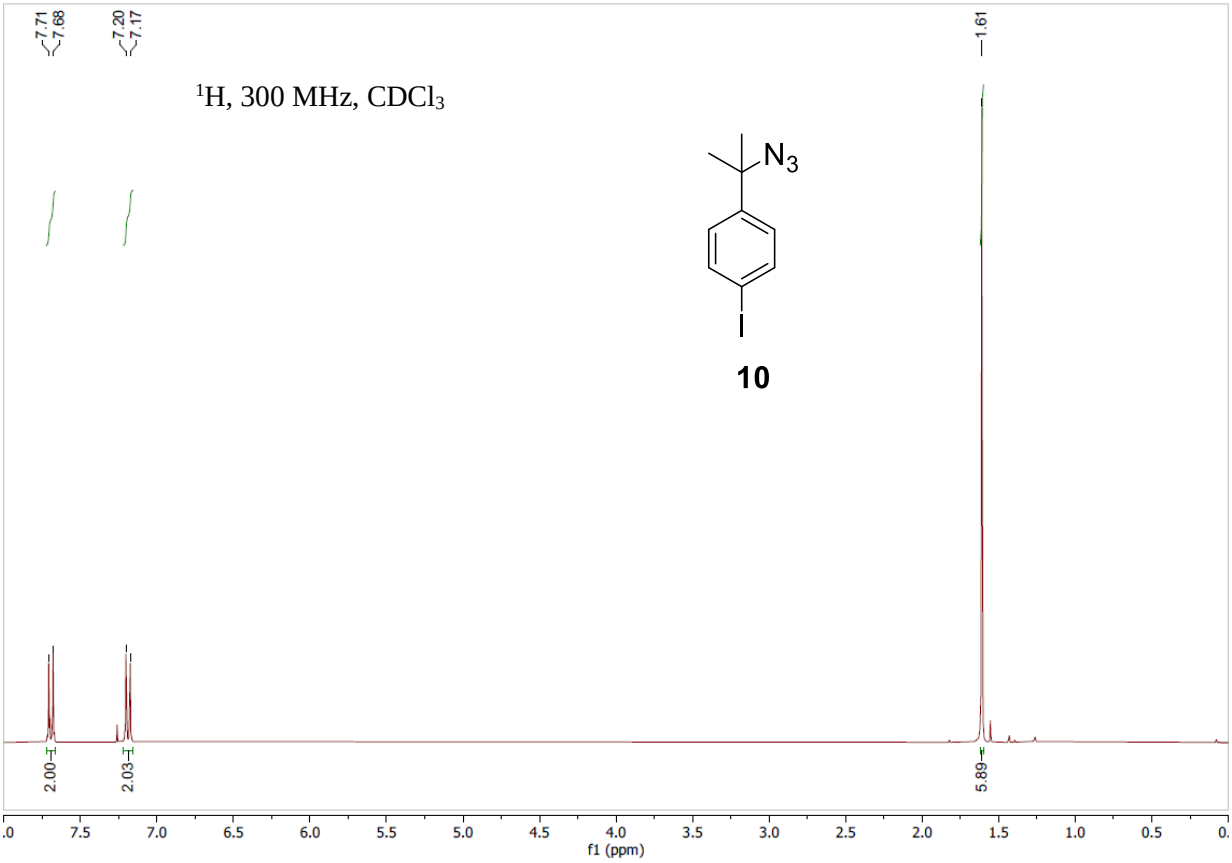


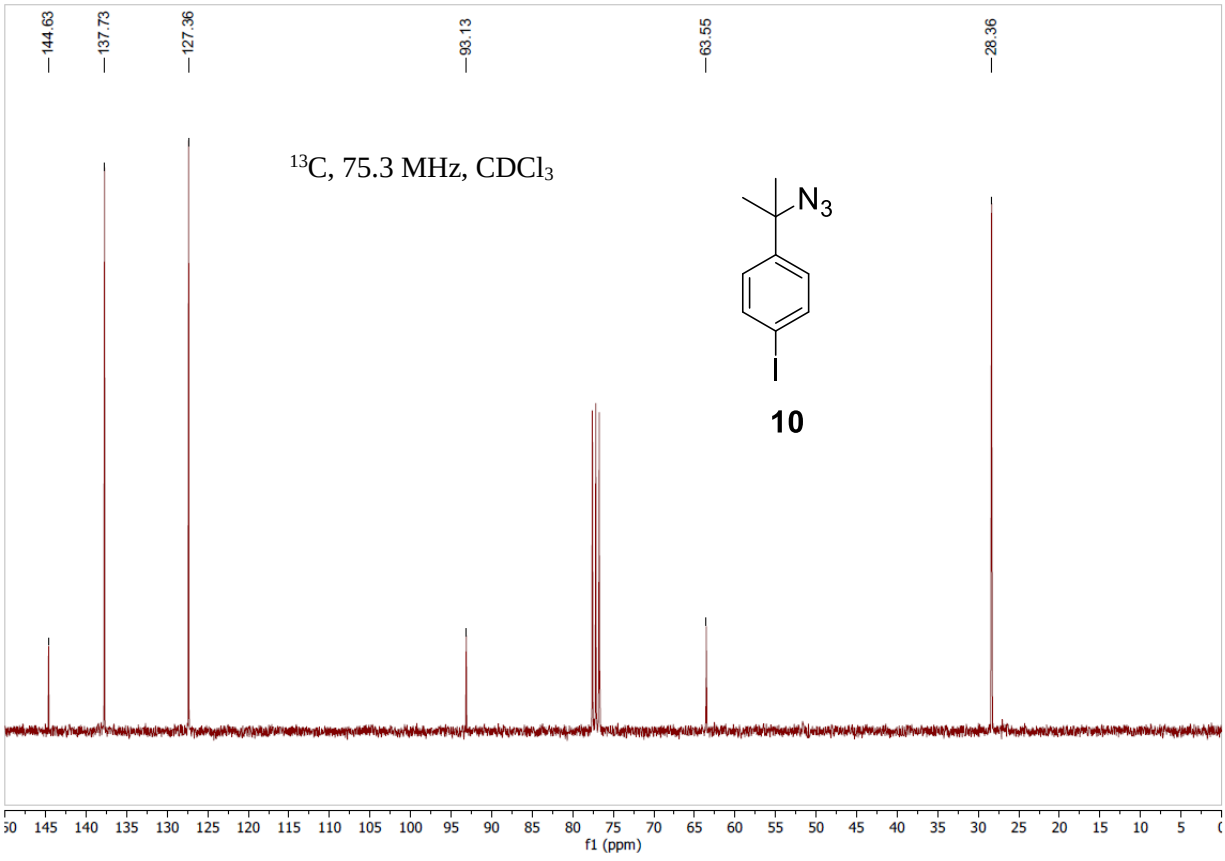
*From supported complex **7-PS** after filtration.*



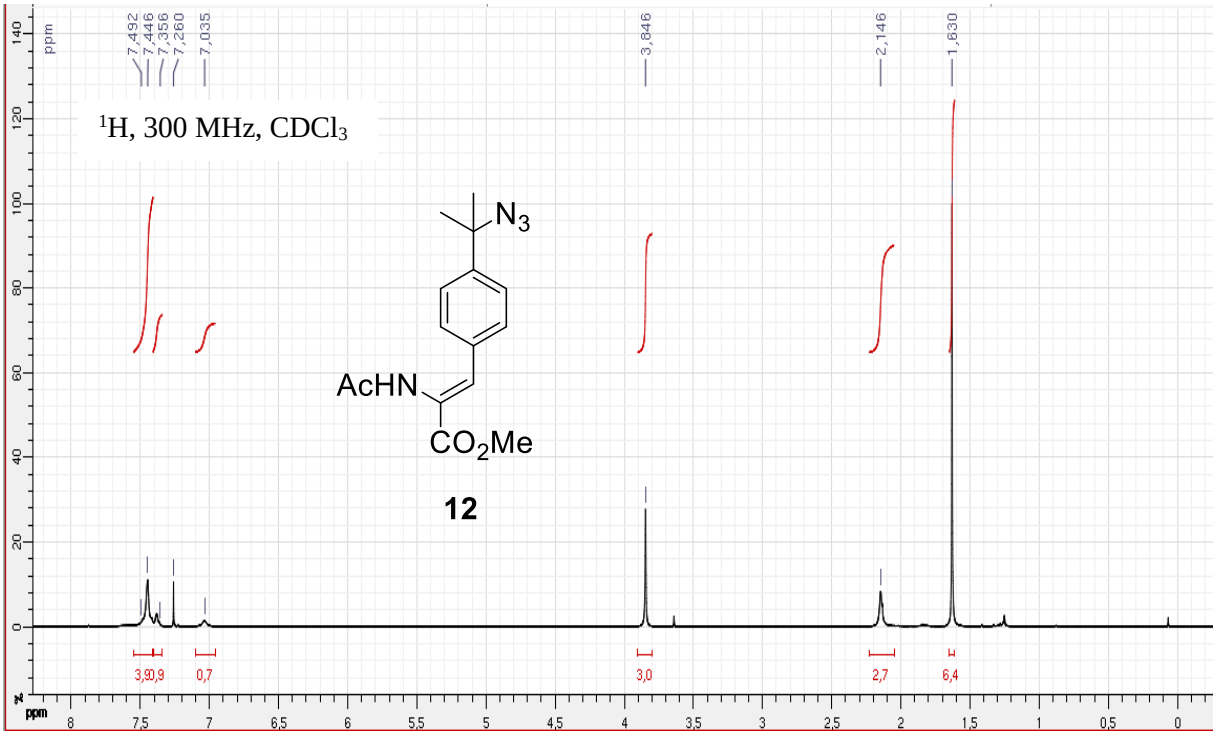


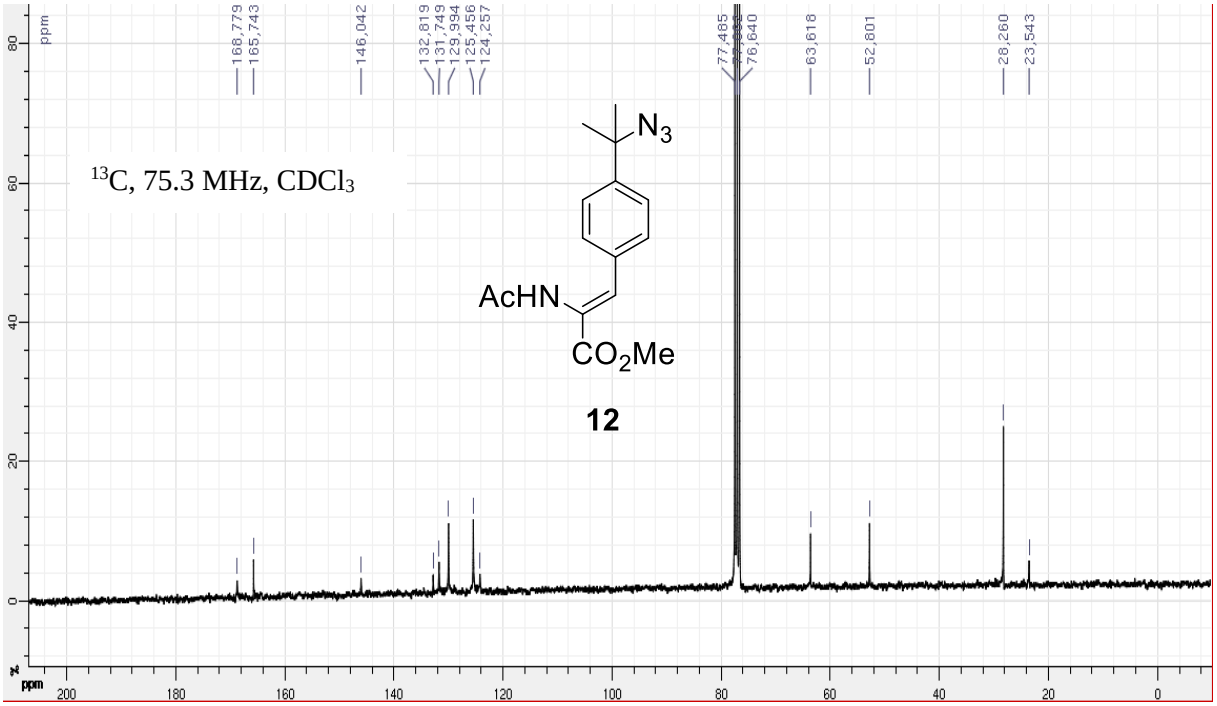
*e. Compound **10***



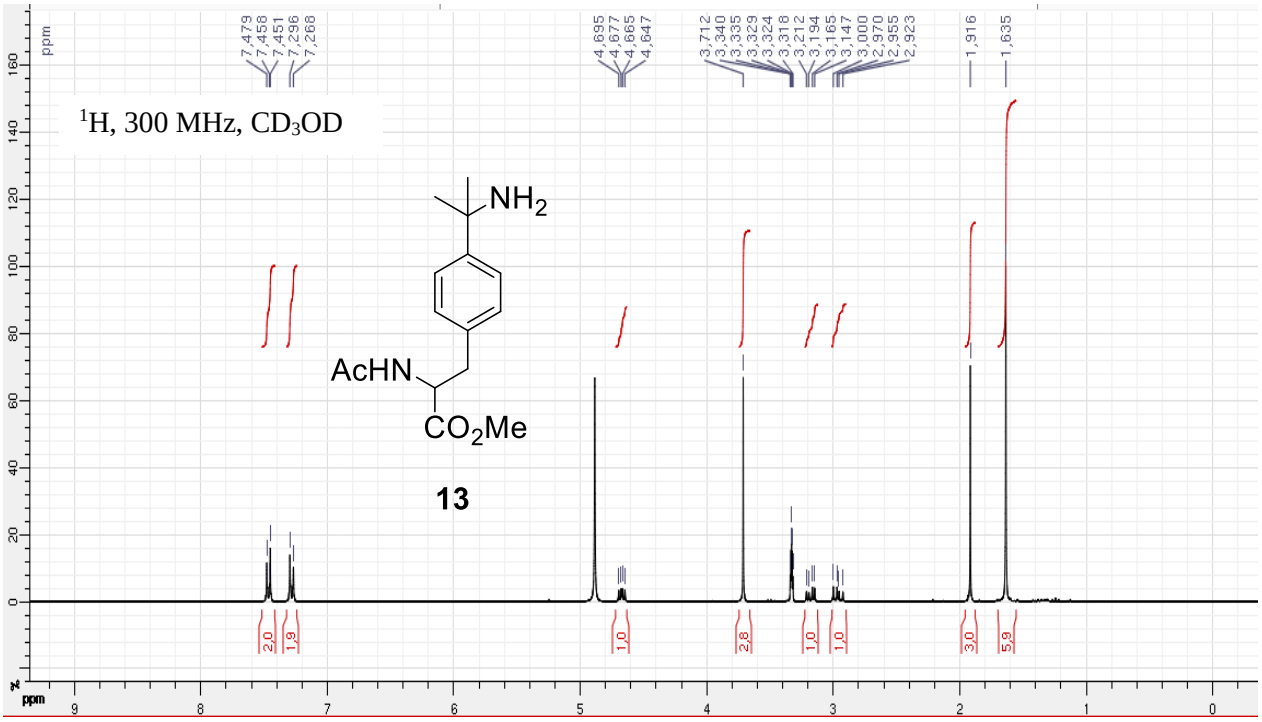


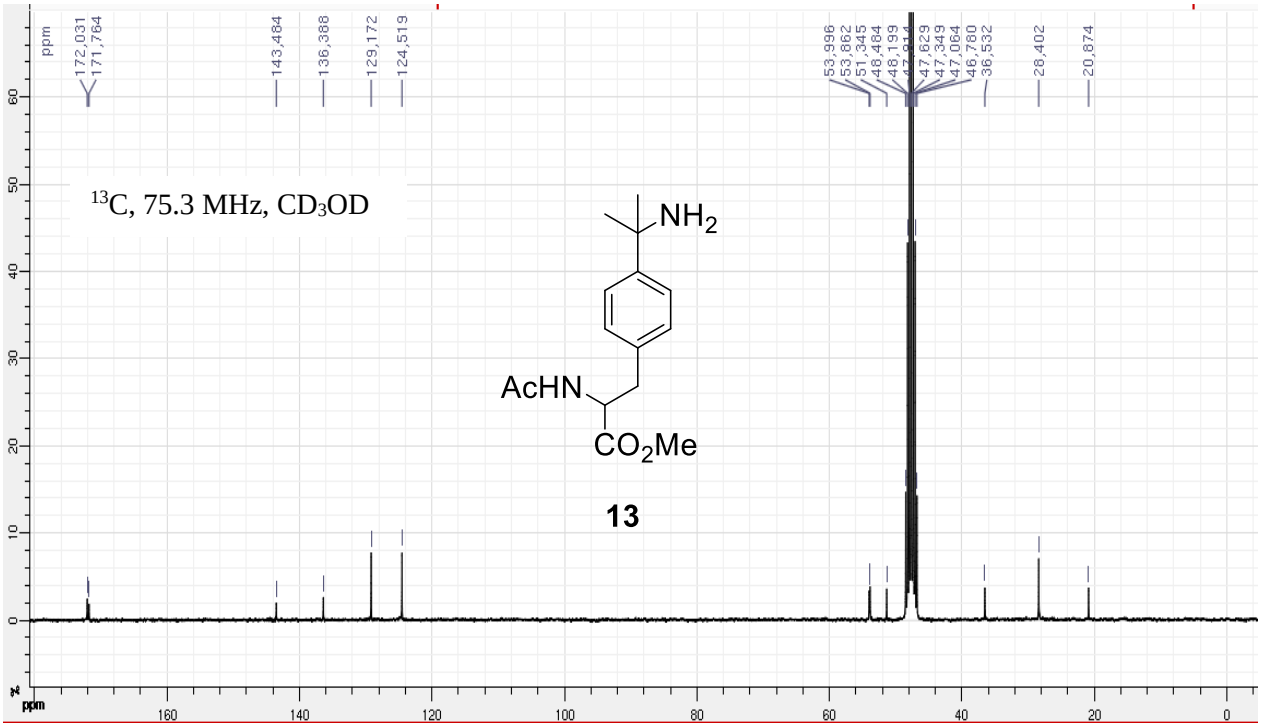
*f. Compound **12***



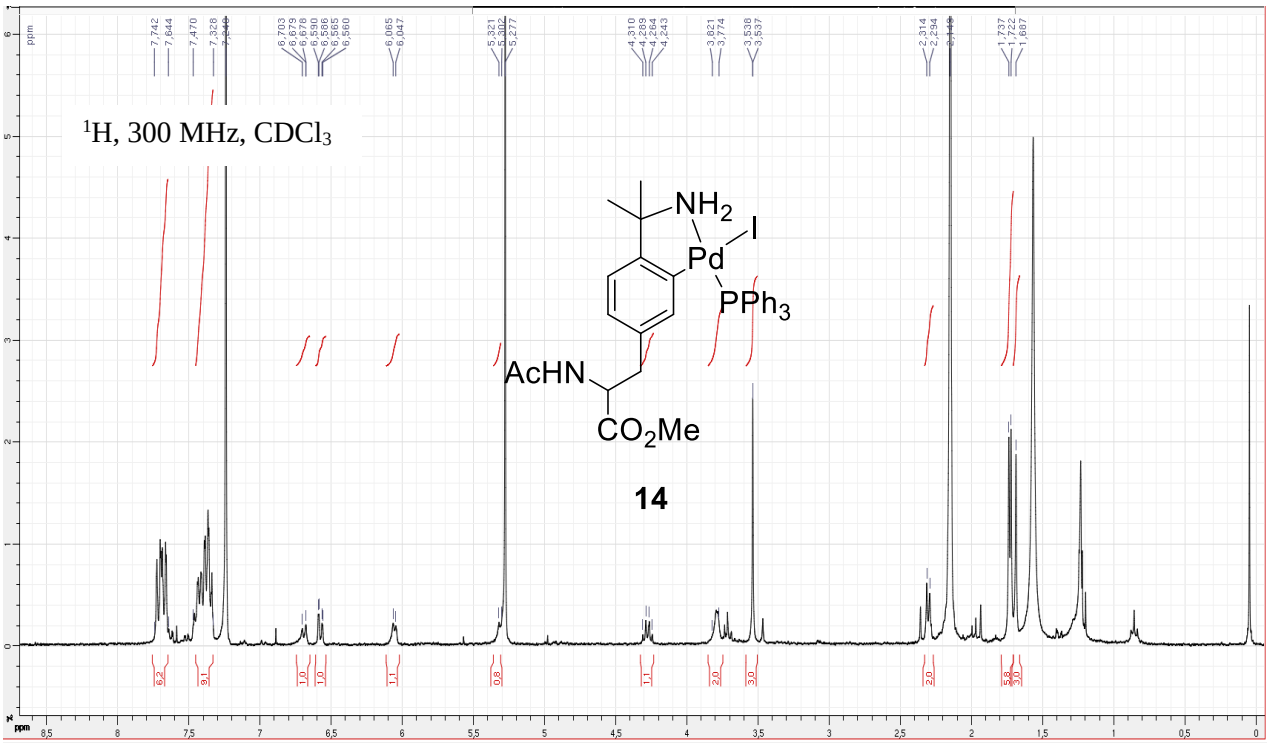


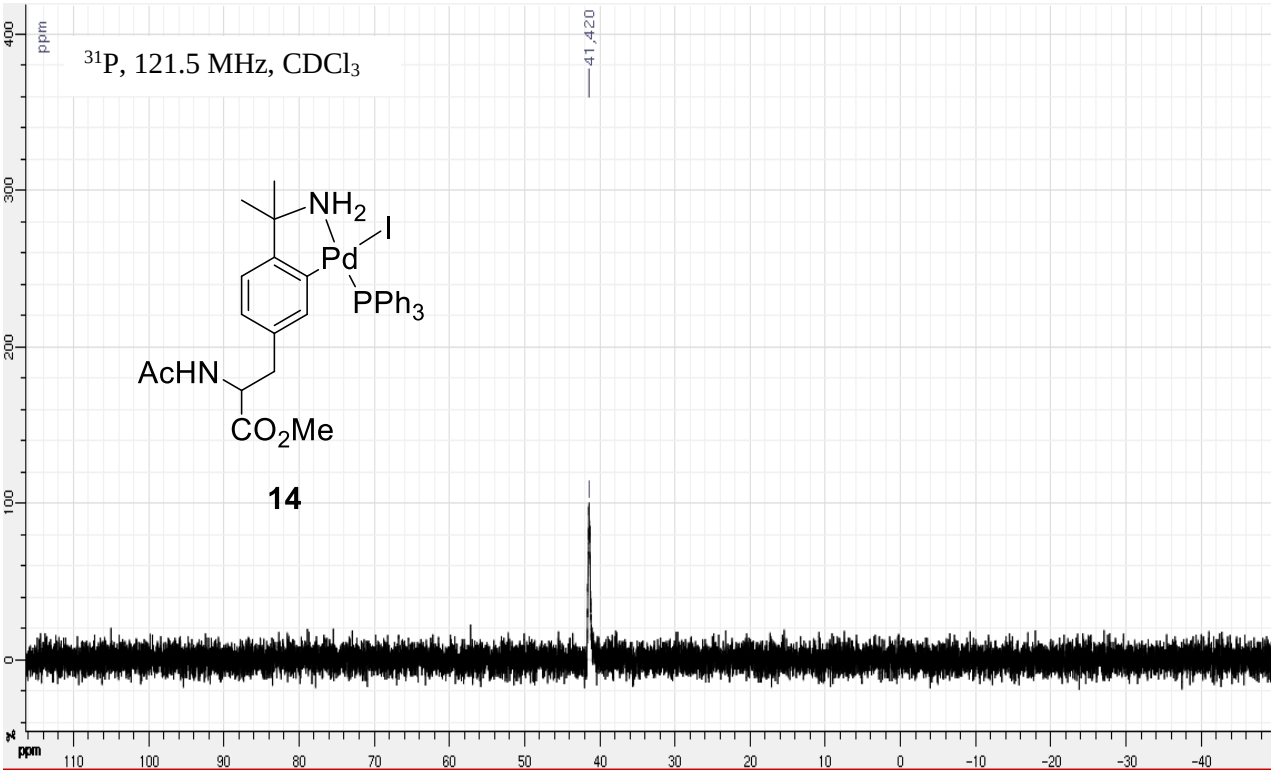
*g. Compound **13***

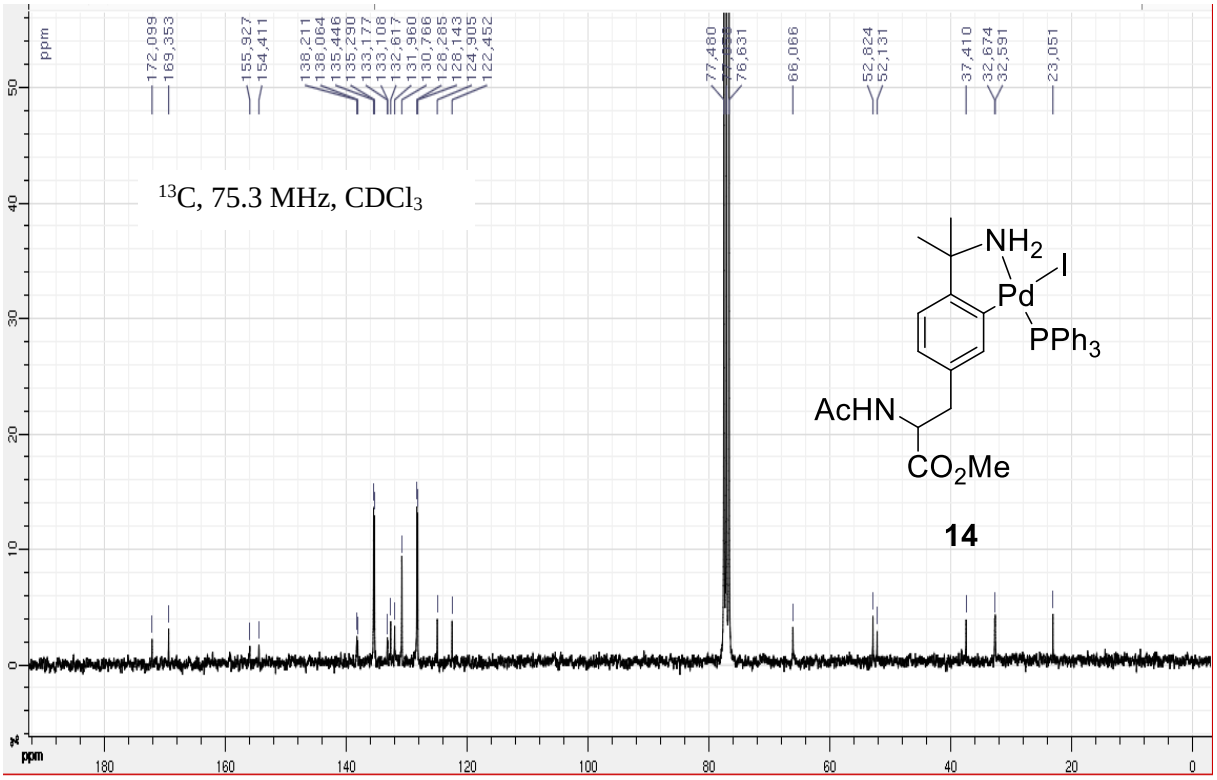




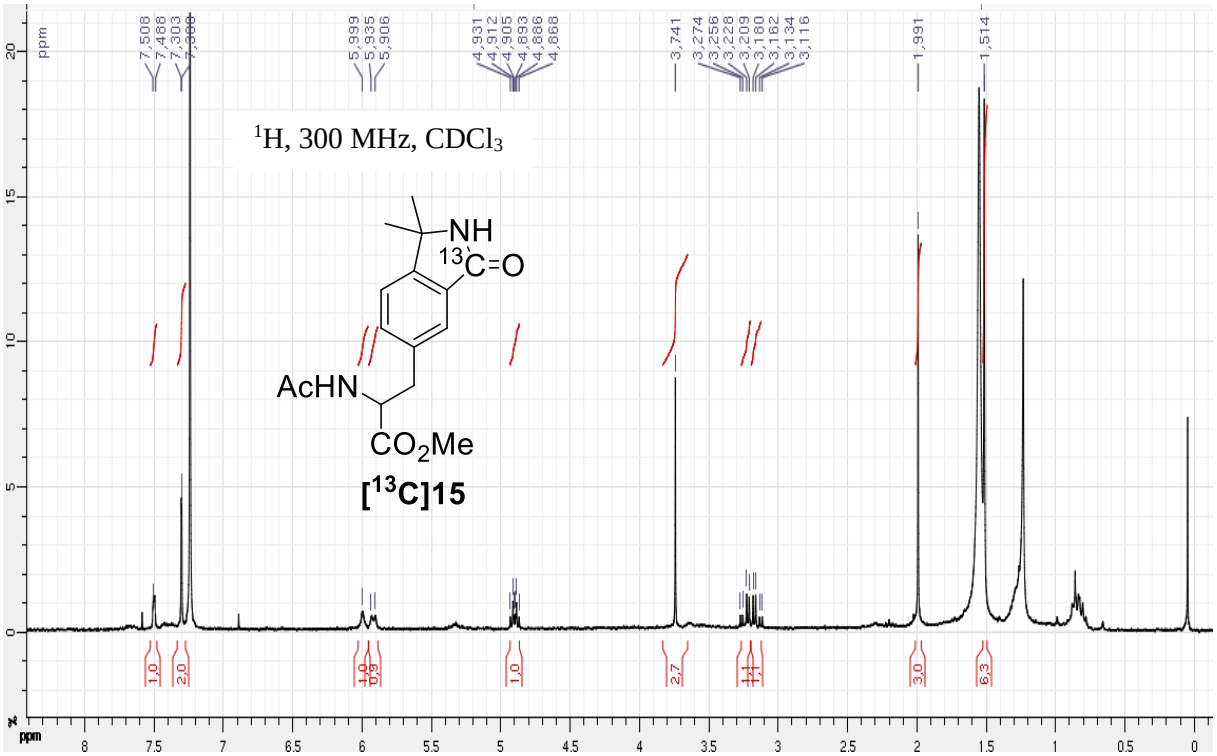
*h. Complex **14***

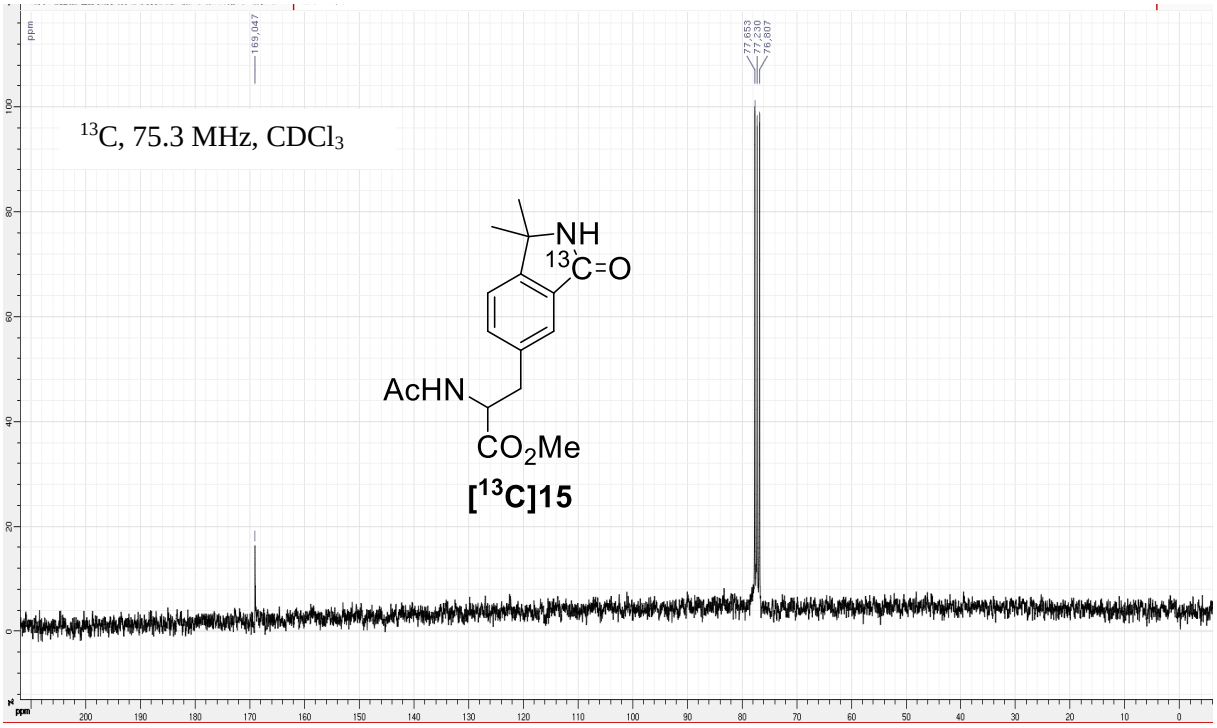

^{1}H, 300 MHz, $CDCl_3$
NH_2
I
Pd
PPh_3
AcHN
CO_2Me
14


^{31}P, 121.5 MHz, $CDCl_3$
41,420
NH_2
I
Pd
PPh_3
AcHN
CO_2Me
14


172,099
169,353
155,927
154,411
138,211
138,064
135,446
135,290
133,177
133,108
132,617
131,960
130,766
128,285
128,143
124,905
122,452
77,480
76,631
66,066
52,824
52,131
37,410
32,674
32,591
23,051
ppm
^{13}C, 75.3 MHz, $CDCl_3$
NH_2
I
Pd
PPh_3
AcHN
CO_2Me
14

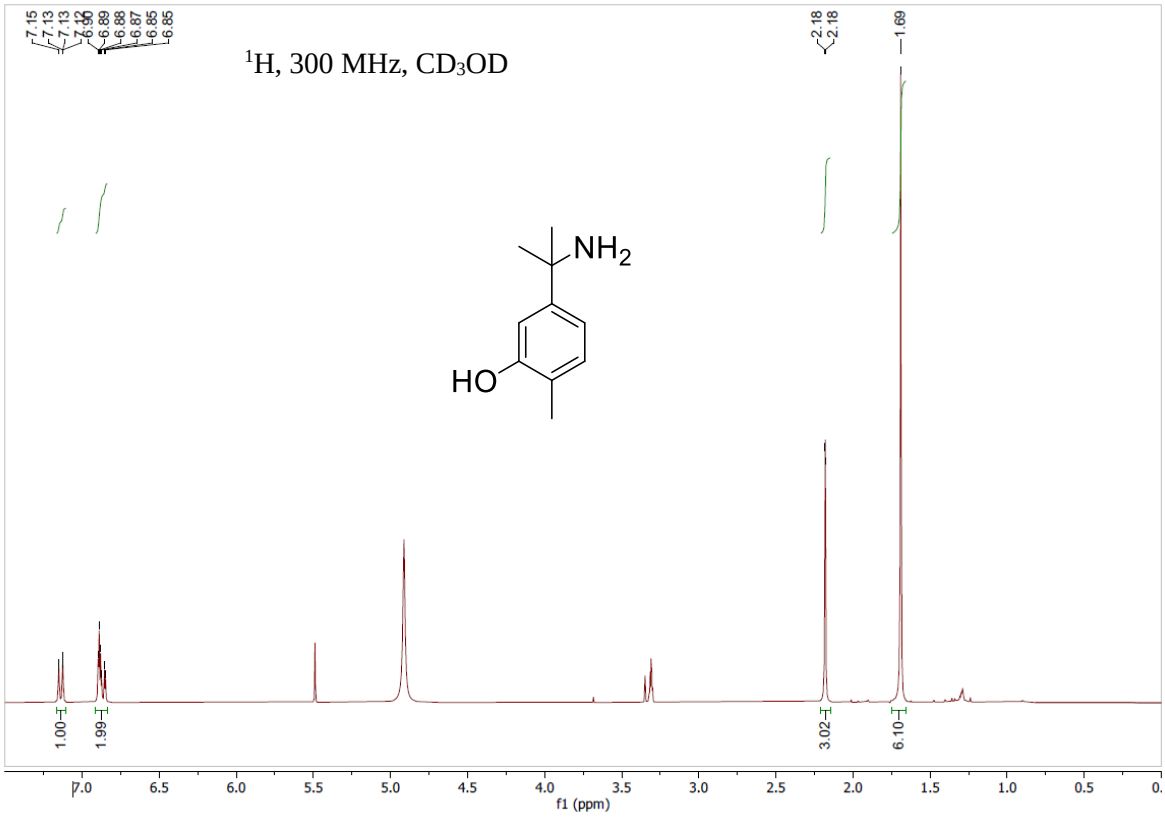
i. Compound ***[^{13}C]15***



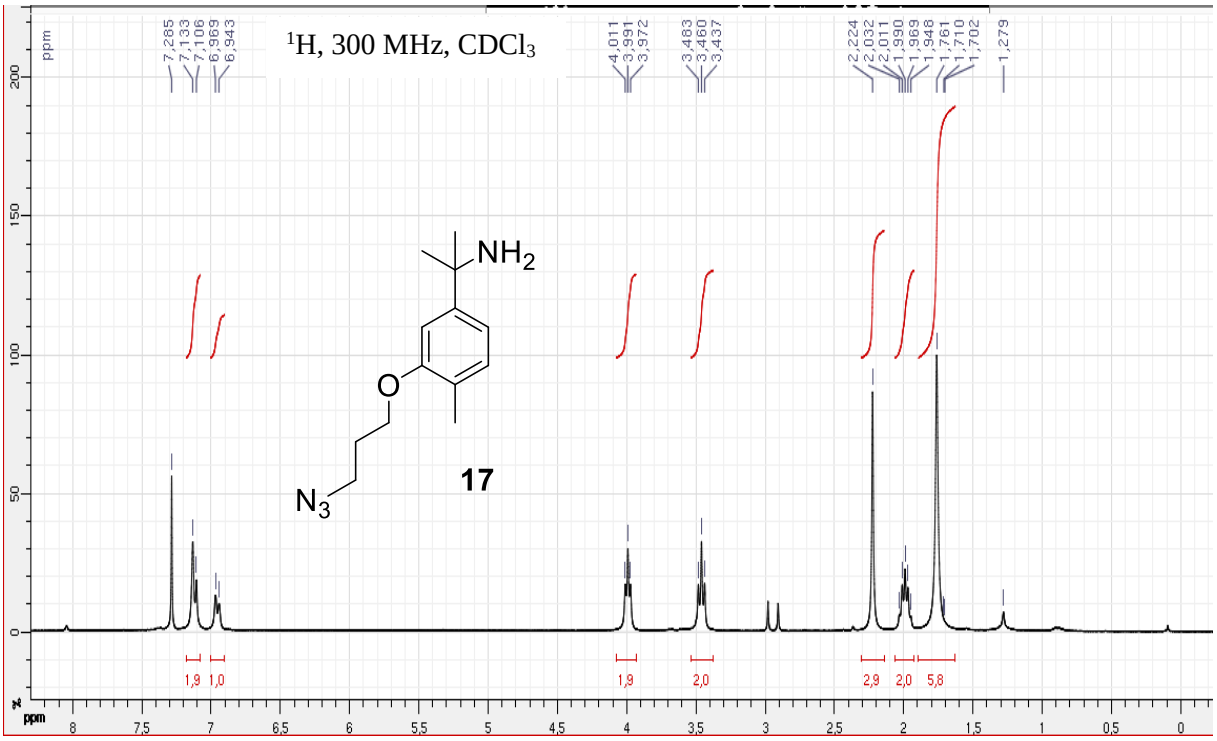


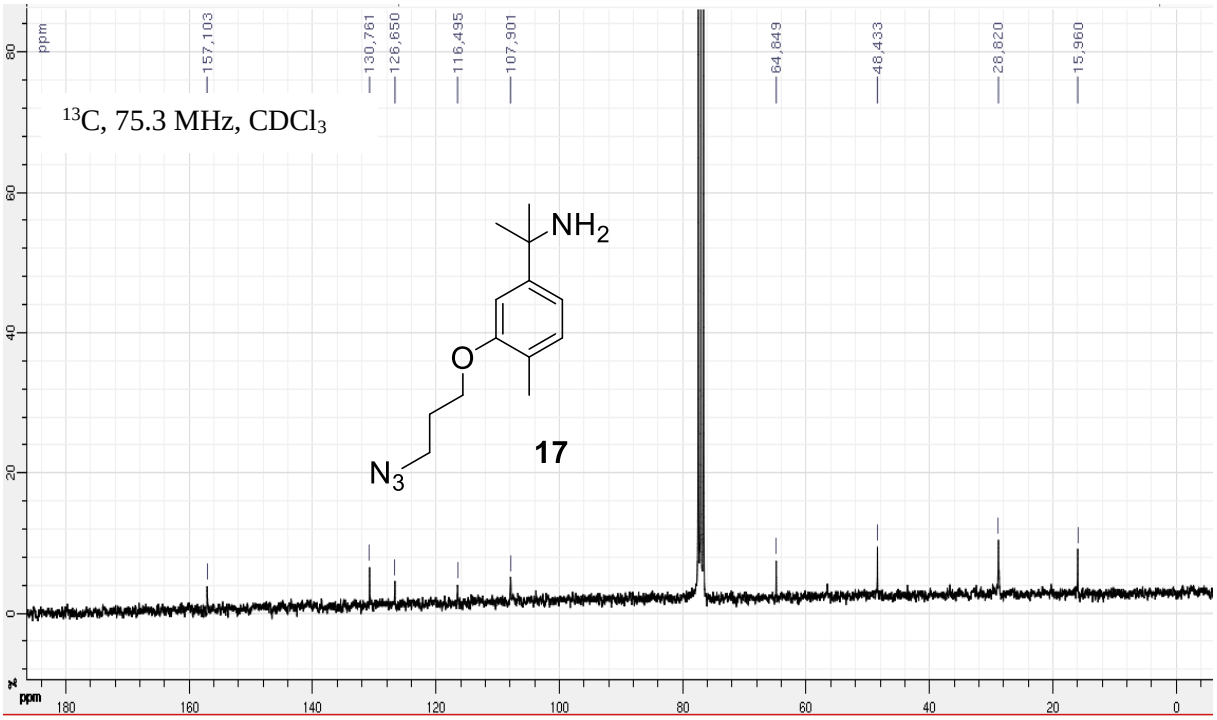
j. *Compound **17***

2-(3-hydroxy-4-methylphenyl)propan-2-amine

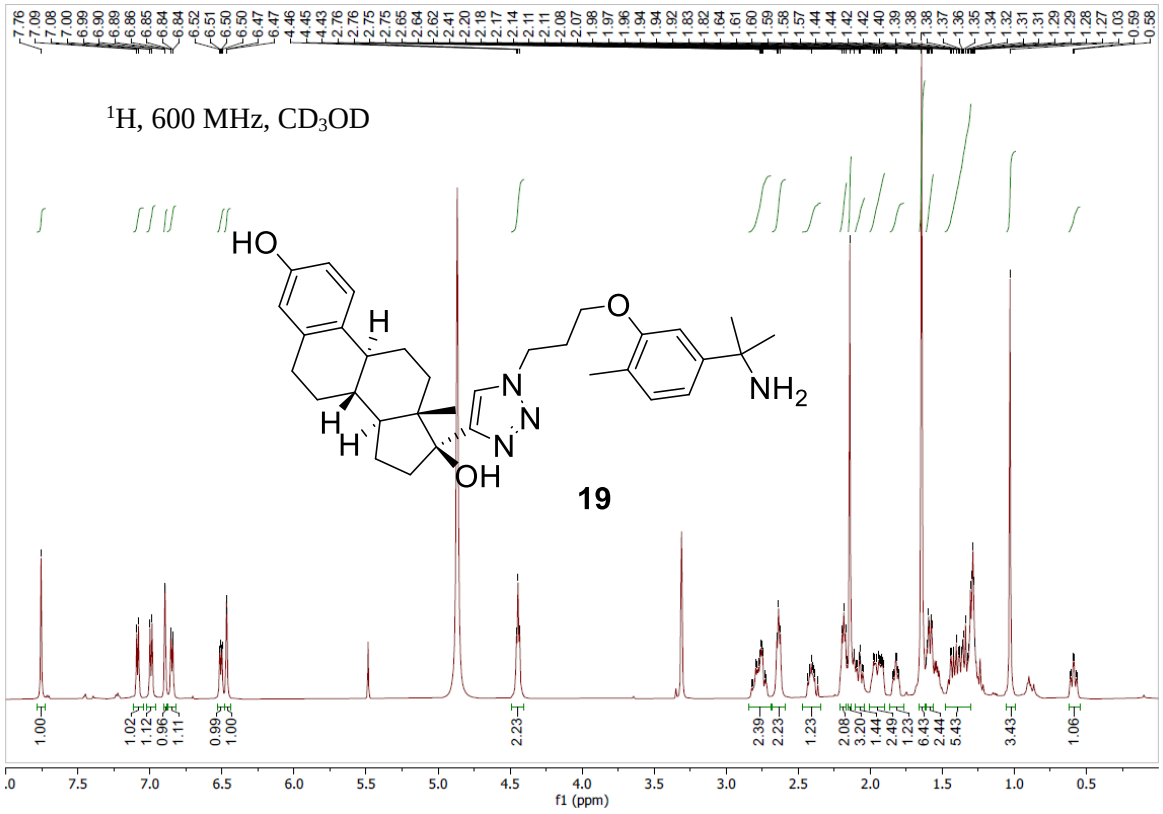


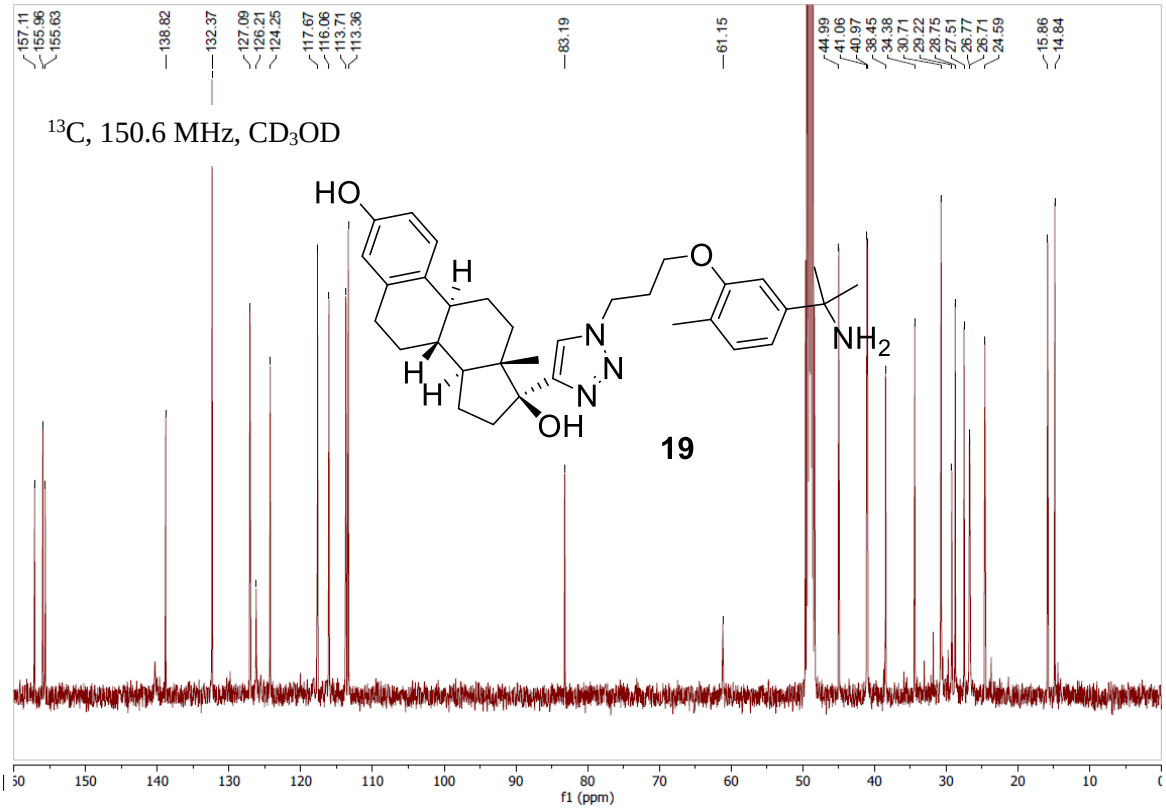
Compound 17


^{1}H, 300 MHz, $CDCl_3$
7,285
7,133
7,106
6,969
6,943
4,011
3,991
3,972
3,483
3,460
3,437
2,224
2,032
2,011
1,990
1,969
1,948
1,761
1,710
1,702
1,279
NH2
O
N3
17
1,9
1,0
1,9
2,0
2,9
2,0
5,8
ppm

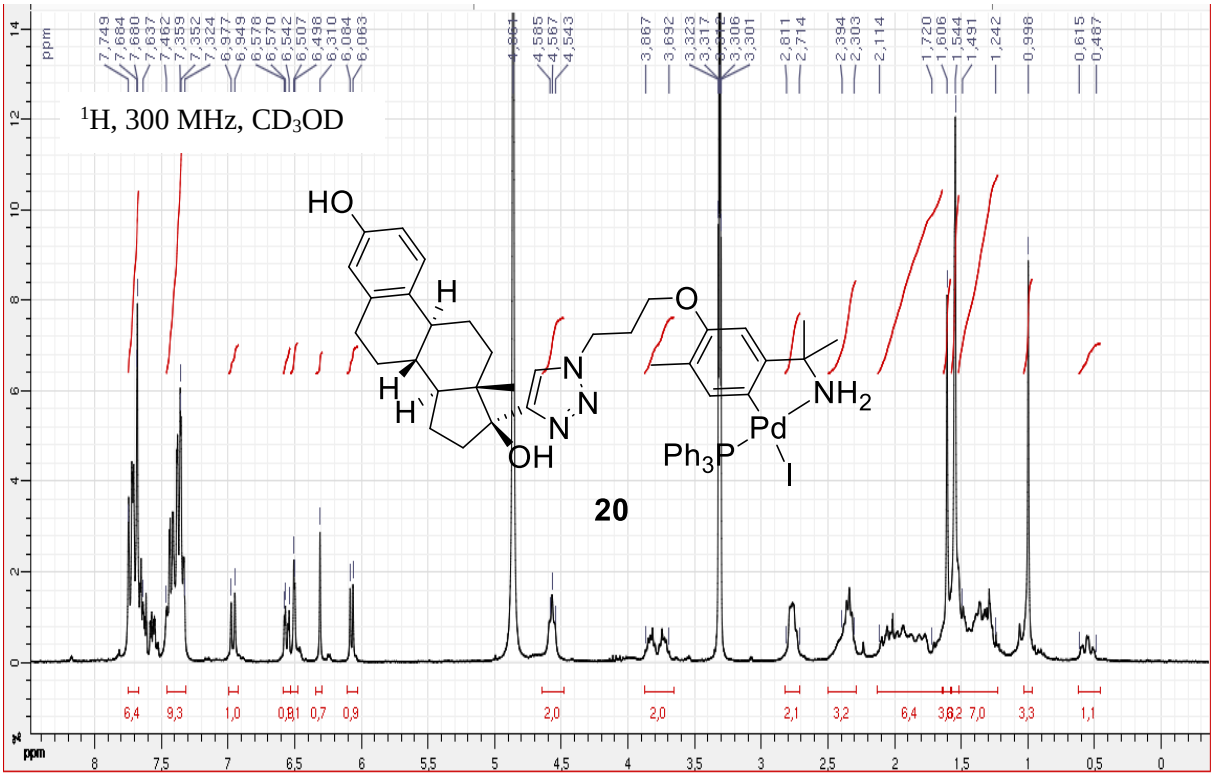

^{13}C, 75.3 MHz, $CDCl_3$
157,103
130,761
126,650
116,435
107,901
64,849
48,433
28,820
15,960
NH2
O
N3
17
ppm

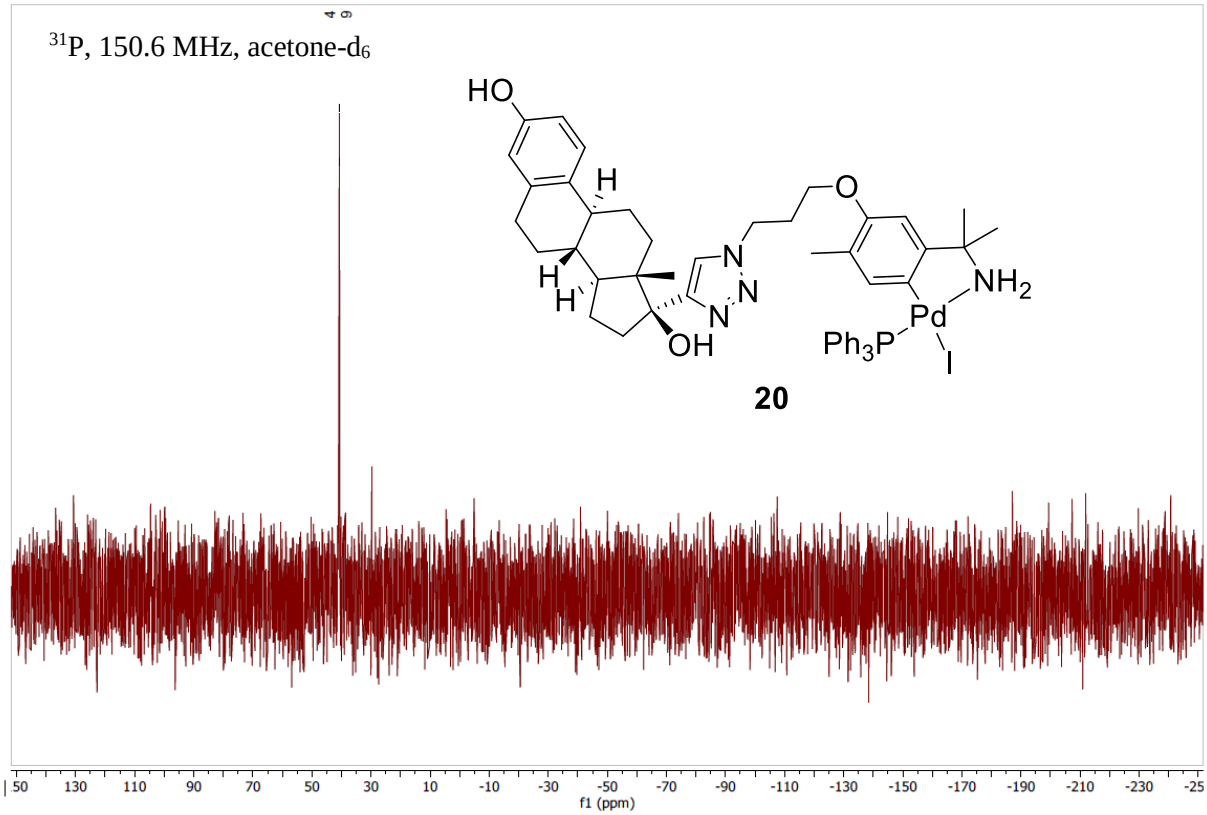
*k. Compound **19***

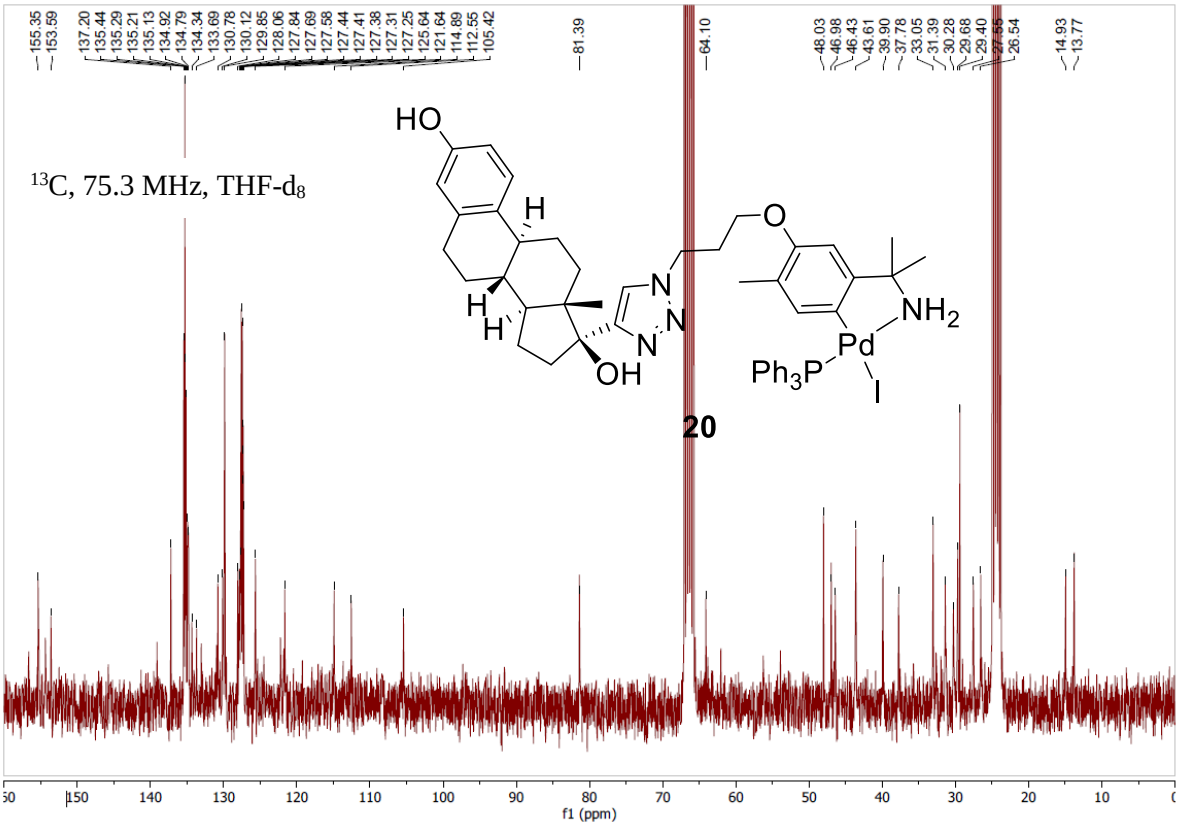




*l. Complex **20***


^{1}H, 300 MHz, CD_3OD
HO
H
H
H
OH
N
N
N
O
NH$_2$
Pd
Ph$_3$P
I
20


^{31}P, 150.6 MHz, acetone-d$_6$
HO
H
H
H
OH
N
N
N
O
NH$_2$
Pd
Ph$_3$P
I
20
f1 (ppm)


155.35
153.59
137.20
135.44
135.29
135.21
135.13
134.92
134.79
134.34
133.69
130.78
130.12
129.85
128.06
127.84
127.69
127.58
127.44
127.41
127.38
127.31
127.25
125.64
121.64
114.89
112.55
105.42
81.39
64.10
48.03
46.98
46.43
43.61
39.90
37.78
33.05
31.39
30.28
29.68
29.40
27.55
26.54
14.93
13.77
13C, 75.3 MHz, THF-d8
HO
H
H
H
N
N
N
OH
O
NH2
Pd
Ph3P
I
20
f1 (ppm)

*m. Compound **[^{13}C]21** (From **20-PS**, after filtration)*