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Solving the Challenging Synthesis of Highly Cytotoxic Silver Complexes bearing Sterically Hindered NHC Ligands with Mechanochemistry

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I. General Information

All reagents were purchased from Sigma Aldrich, Fluka, Acros or Alfa Aesar. The milling treatments were carried out either in a vibrating Retsch Mixer Mill 200 or 400 (vbm) operated at up to 30 Hz, in a planetary ball-mill Retsch PM100 (pbm) operated at 450 rpm or in a planetary ball-mill Fritsch pulverisette 7 operated at 650 rpm or 800 rpm. Milling load (ML) is defined as the ratio between the mass of the reactants over the free volume of the jar. All of reaction mixtures were recovered with a solvent and filtrated over celite to remove metallic particles lost by the reactor during ball milling. Imidazolium salts **1a-1c**[1] and **1f-1i**[2] were prepared according to literature procedures.

NMR Analyses were performed at the 'Laboratoire de Mesures Physiques' (IBMM, Université de Montpellier). ^{1}H NMR spectra were recorded on a Bruker AVANCE 400 MHz, a Bruker AVANCE III 500 MHz or a Bruker AVANCE III 600 MHz and are reported in ppm using deuterated solvent ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm, acetone-d_6 at 2.05 ppm or $MeOD_4$ at 3.49 ppm) as internal standards. Data are reported as s = singlet, d = doublet, t = triplet, q = quadruplet, qt = quintuplet, sept = septuplet, m = multiplet ; coupling constant in Hz; integration. ^{13}C-{^{1}H} NMR spectra were recorded on a Bruker AVANCE 101 MHz, a Bruker AVANCE III 126 MHz or a Bruker AVANCE III 151 MHz and are reported in ppm using deuterated deuterated solvent ($CDCl_3$ at 77.2 ppm or DMSO-d_6 at 39.5 ppm or acetone-d_6 at 29.8 ppm or MeOD-d_4 at 50.4 ppm) as internal standards.

Solid-State NMR spectra were recorded on a Varian VNMRS600 spectrometer (Larmor frequencies: $\nu^{1}H$ = 599.818 MHz and $\nu^{13}C$ = 150.839 MHz) using a 3.2 mm magic angle spinning (MAS) probe (T3 Wide Bore HX). Values of the isotropic chemical shifts of ^{1}H and ^{13}C are given using a secondary reference: Adamantane (1.8 ppm for ^{1}H and 38.5 ppm for ^{13}C). For the imidazolium salt, the studies were carried out with a $\pi/2$ pulse length of 4 µs, and a recycle delay of 10 s for 1H and 5 s for 13C. The used contact time is 2 ms. For the silver complex, the studies were carried out with a $\pi/2$ pulse length of 7 µs, and a recycle delay of 1 s for ^{1}H and 2 s for ^{13}C. The used contact time is 1 ms.

Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer and wavelength numbers of the relevant bands are reported in cm^{-1}.

Mass spectra were obtained by LC-MS with ESI using a Water Alliance 2695 as LC, coupled to a Waters ZQ spectrometer with electrospray source, a simple quadrupole analyzer and a UV Waters 2489 detector. HRMS analyses were performed on UPLC Acquity H-Class from Waters hyphenated to a Synapt G2-S mass spectrometer with a dual ESI source from Waters. ASAP analysis were performed on Synapt G2-S mass spectrometer from Waters, in a positive mode. HPLC conversion was measured on an Agilent technologies 1220 Infinity LC using a Chromolith® high resolution RP-18^{e} 50-4.6 mm column and a linear gradient of 0 to 100% CH_3CN/0.1% TFA in H_2O/0.1% TFA over 3 min (detection at 214 nm, flow rate: 1 ml/min).

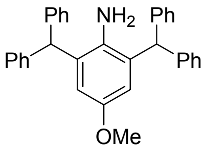
Human HCT116 cancer cell line was obtained from the American type Culture Collection (ATCC, Rockville, MD) and was grown in Gibco McCoy's 5A supplemented with 10% fetal calf serum (FCS) and 1% glutamine according to the supplier's instructions. Cell line was maintained at 37°C in a humidified atmosphere containing 5% CO_2. Cell viability was determined by a luminescent assay according to the manufacturer's instructions (Promega, Madison, WI, USA). For IC_{50} determination, the cells were seeded in 96-well plates (3×10^3 cells/well) containing 100 μL of growth medium. After 24 h of culture, the cells were treated with the tested compounds at 10 different final concentrations. Each concentration was obtained from serial dilutions in culture medium starting from the stock solution. Control cells were treated with the vehicle. Experiments were performed in triplicate. After 72 h of incubation, 100 μL of CellTiter Glo Reagent was added for 15 min before recording luminescence with a spectrophotometric plate reader PolarStar Omega (BMG LabTech). The dose-response curves were plotted with Graph Prism software and the IC_{50} values were calculated using the Graph Prism software from polynomial curves (four or five-parameter logistic equations).

II. General procedure for the synthesis of imidazolium salts

A. Synthesis of halogenated imidazolium salts

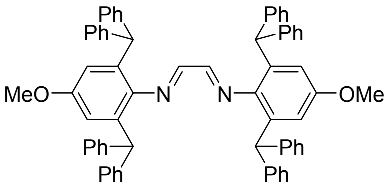
1. IPr*^{OMe}.HCl **1d**

[1,3-Bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazolium chloride



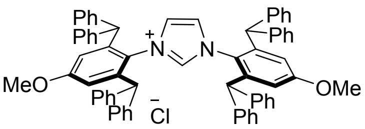
Following the reported procedure by Markó[3] and using diphenylmethanol (22.7 g, 123.2 mmol, 2.00 eq), 4-anisidine (7.39 g, 60.0 mmol, 1.00 eq) and a premade solution of HCl/ZnCl$_2$ (37% HCl in water, 5.6 mL, 60.0 mmol, 1.00 eq; ZnCl$_2$, 4.1 g, 30.0 mmol, 0.50 eq), the pure 4-methoxy-2,6-bis(diphenylmethyl)aniline (21.1 g, 46.3 mmol, 77%) was obtained as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28 (t, *J* = 8.2 Hz, 8H), 7.21 (t, *J* = 8.2 Hz, 4H), 7.10 (d, *J* = 8.1 Hz, 8H), 6.19 (s, 2H), 5.48 (s, 2H), 3.42 (s, 3H), 3.17 – 3.08 (*br* s, 2H). All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[4]



Following reported procedure[5] and using glyoxal (0.22 mL, 1.92 mmol, 1.00 eq), 4-methoxy-2,6-bis(diphenylmethyl)aniline (1.75 g, 3.83 mmol, 2.00 eq), few drops of formic acid and MeOH (100 mL), the pure *N*,*N'*-bis(4-methoxy-2,6-(diphenylmethyl)phenyl)ethane-1,2-diimine (1.59 g, 1.70 mmol, 89%) was obtained as a yellow powder.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18 (m, 26H), 7.24 (d, 16H), 6.42 (s, 4H), 5.26 (s, 4H), 3.51 (s, 6H). All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[4]

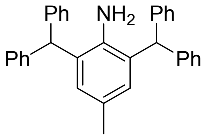


Following the procedure reported by Nolan *et al.*[6] and using *N*,*N'*-bis(4-methoxy-2,6-(diphenylmethyl)phenyl)ethane-1,2-diimine (8.0 g, 8.57 mmol, 1.00 eq) in THF (275 mL), and HCl/ZnCl$_2$/paraformaldehyde (HCl 4M in dioxane, 3.4 mL, 13.54 mmol, 1.50 eq; ZnCl$_2$, 1.17 g, 8.58 mmol, 1.00 eq; paraformaldehyde, 211.2 mg, 9.09 mmol, 1.05 eq), the pure [1,3-bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazolium chloride (2.1 g, 2.14 mmol, 25%) was obtained as an off white powder.

^{1}H NMR (400 MHz, CDCl$_3$) δ 12.89 (s, 1H), 7.31-7.11 (m, 34H,), 7.15 (d, *J* = 7.1 Hz, 8H), 6.47 (s, 4H), 5.42 (s, 2H), 5.31 (s, 4H), 3.52 (s, 6H). All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[4]

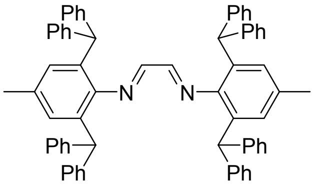
2. IPr*.HCl **1e**

[1,3-Bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazolium chloride



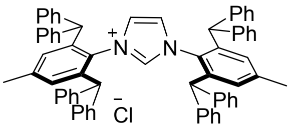
Following the reported procedure by Markó and co-worker[3] and using diphenylmethanol (22.7 g, 123.0 mmol, 2.00 eq) and 4-toluidine (6.43 g, 60.0 mmol, 1.00 eq) and a solution of HCl/ZnCl$_2$ (37% HCl in water, 5.6 mL, 60 mmol, 1.00 eq; $ZnCl_2$, 4.1 g, 30 mmol , 0.50 eq), the 4-methyl-2,6-diphenylmethylaniline (20.1 g, 45.7 mmol, 76%) was obtained as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 8H), 7.22 (t, *J* = 7.0 Hz, 8H), 7.10 (d, *J* = 6.8 Hz, 8H), 6.39 (s, 2H), 5.46 (s, 2H), 2.03 (s, 3H). All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[3]



Following the reported procedure by Markó and co-worker[3] and using 40% glyoxal in water (0.85 mL, 7.50 mmol, 1.00 eq), 4-methyl-2,6-diphenylmethylaniline (6.6 g, 15.0 mmol, 2.00 eq), formic acid (0.1 ml) and dichloromethane (150 mL), the pure *N*,*N'*-bis[(4-methyl-2,6-diphenylmethyl)phenyl]ethane-1,2-diimine (5.87 g, 6.51 mmol, 87%) was obtained as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 6.6 Hz, 16H), 7.23-7.12 (m, 26H), 6.66 (s, 4H), 5.22 (s, 4H), 2.12 (s, 6H). All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[3]



Following the procedure reported by Markó and co-worker[3] and using *N*,*N'*-bis[(4-methyl-2,6-diphenylmethyl)phenyl]ethane-1,2-diimine (2.5 g, 2.77 mmol, 1.00 eq) in $CHCl_3$ (30 mL), and a solution of HCl/$ZnCl_2$/paraformaldehyde (37% HCl in water, 0.60 mL, 6.72 mmol, 2.40 eq), $ZnCl_2$ (458 mg, 3.36 mmol, 1.20 eq) and paraformaldehyde (100.9 mg, 3.36 mmol, 1.20 eq), the pure [1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazolium chloride (1.35 g, 1.42 mmol, 51%) was obtained as an off white powder.

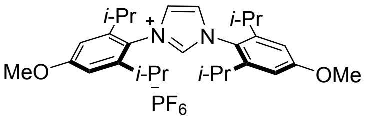
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.92 – 13.06 (*br* s, 1H), 7.28 – 7.08 (m, 24H), 6.88 – 6.65 (m, 12H), 5.46 (s, 2H), 5.29 (s, 4H), 2.18 (s, 6H). All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[3]

B. Synthesis of hexafluorophosphate imidazolium salts

General procedure A: Imidazolium (1.00 eq) was dissolved in water and potassium hexafluorophosphate (1.20 eq) was added. The resulting suspension was stirred for 30 minutes and filtrated under vacuum. The solid was washed with water and diethyl ether and dried under vacuum to afford the product.

General procedure B : Imidazolium (1.00 eq) and potassium hexafluorophosphate (1.05 eq) were introduced in a 13 mL PTFE grinding bowl with one stainless steel ball (1 cm diameter). Total mass of the reagents has been calculated so that milling load equals 19.2 mg/mL. The bowl was closed and subjected to grinding in the vibratory ball mill. Reaction mixture was recovered with dichloromethane, filtrated over celite and the solvent was evaporated under vacuum. The residue was then washed with water three times and diethyl ether twice. The product was dried under vacuum to afford hexafluorophosphate imidazolium salt.

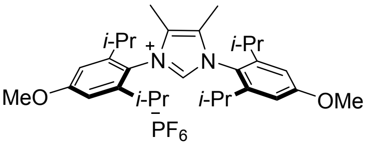
[1,3-Bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate 3a



General procedure A was followed with [1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium chloride (300 mg, 0.618 mmol) and potassium hexafluorophosphate (136.6 mg, 0.742 mmol) to afford [1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate (328.3 mg, 0.552 mmol, 89%) as a white solid.

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.03 (t, *J* = 1.5 Hz, 1H), 8.43 (s, 1H), 8.43 (s, 1H), 7.00 (s, 4H), 3.87 (s, 6H), 2.31 (sept, *J* = 6.8 Hz, 4H), 1.25 (d, *J* = 6.8 Hz, 12H), 1.15 (d, *J* = 6.8 Hz, 12H); **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 161.5, 146.6, 140.0, 126.5, 122.9, 109.9, 55.7, 28.9, 24.0, 23.0; **^{31}P NMR (202 MHz, DMSO-*d*$_6$)** δ -144.2 (sept, *J* = 711.3 Hz); **HRMS** calcd for $C_{29}H_{41}N_2O_2$ $[M - PF_6^-]^+$: 449.3168; found: 449.3167.

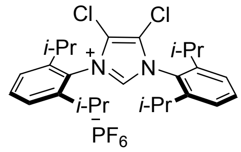
[4,5-Dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate 3b



General procedure A was followed with [4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium chloride (300.0 mg, 0.585 mmol) and potassium hexafluorophosphate (129.1 mg, 0.702 mmol) to afford [4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate (287.0 mg, 0.461 mmol, 79%) as a white solid.

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 9.86 (s, 1H), 7.02 (s, 4H), 3.88 (s, 6H), 2.26 (sept, *J* = 6.8 Hz, 4H), 2.06 (s, 6H), 1.25 (d, *J* = 6.8 Hz, 12H), 1.11 (d, *J* = 6.8 Hz, 12H); **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 161.6, 147.0, 137.4, 129.1, 120.6, 110.2, 55.7, 28.7, 24.6, 22.5, 8.4; **^{31}P NMR (202 MHz, DMSO-*d*$_6$)** δ -144.19 (sept, *J* = 711.2 Hz); **^{19}F NMR (376 MHz, DMSO-*d*$_6$)** δ -70.18 (d, *J* = 711.3 Hz); **HRMS** calcd for $C_{31}H_{45}N_2O_2$ $[M - PF_6^-]^+$: 477.3481; found: 477.3485.

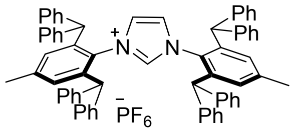
[1,3-Bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium hexafluorophosphate 3c



General procedure A was followed with [1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium chloride (300.0 mg, 0.607 mmol) and potassium hexafluorophosphate (134.1 mg, 0.729 mmol) to afford [1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium hexafluorophosphate (315.5 mg, 0.523 mmol, 86%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.74 (t, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 4H), 2.53 – 2.47 (m, 4H) signal corresponding to the C**H**(CH$_3$)$_2$ under the residual signal of DMSO-d_6, 1.27 (d, *J* = 6.8 Hz, 12H), 1.13 (d, *J* = 6.8 Hz, 12H); **^{13}C NMR (126 MHz, DMSO-d_6)** δ 145.8, 138.1, 133.1, 126.8, 125.3, 122.4, 28.5, 24.5, 22.8; **^{31}P NMR (202 MHz, DMSO-d_6)** δ -144.2 (sept, *J* = 711.2 Hz); **^{19}F NMR (376 MHz, DMSO-d_6)** δ -70.2 (d, *J* = 711.2 Hz); **HRMS** calcd for $C_{27}H_{35}N_2Cl_2$ [M – PF_6^-]$^+$: 457.2177; found: 457.2181.

[1,3-Bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazolium hexafluorophosphate 3d

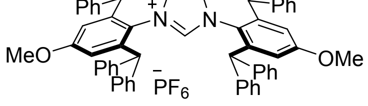


General procedure B was followed with [1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazolium chloride (350.0 mg, 0.369 mmol) and potassium hexafluorophosphate (81.5 mg, 0.369 mmol) to afford [1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazolium hexafluorophosphate (303.9 mg, 0.287 mmol, 78%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.29 – 7.23 (m, 24H), 6.97 (s, 4H), 6.95 – 6.91 (m, 8H), 6.85 – 6.81 (m, 8H), 6.75 (d, *J* = 1.4 Hz, 2H), 4.89 (s, 4H), 2.23 (s, 6H); **^{13}C NMR (126 MHz, DMSO-d_6)** δ 141.7, 141.5, 141.3, 140.03, 139.99, 130.0, 129.6, 129.0, 128.85, 128.80, 128.7, 127.4, 127.2, 125.4, 51.0, 21.3; **^{31}P NMR (202 MHz, DMSO-d_6)** δ -144.2 (sept, *J* = 711.2 Hz); **^{19}F NMR (376 MHz, DMSO-d_6)** δ -70.2 (d, *J* = 711.2 Hz); **HRMS** calcd for $C_{69}H_{57}N_2$ [M – PF_6^-]$^+$: 913.4522; found: 913.4526.

^{1}H solid state NMR (600 MHz, none) δ 9.53, 9.05 – 4.83, 4.23, 3.55, 2.03, 1.21; **^{13}C solid state NMR (151 MHz, none)** δ 145.6, 144.3, 143.5, 142.8, 142.1, 139.7, 133.6, 131.9, 130.8, 129.9, 129.5, 129.2, 127.9, 126.5, 52.7, 52.2, 51.9, 22.2, 20.9.

[1,3-Bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazolium hexafluorophosphate 3e

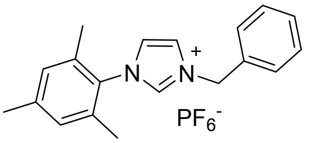


General procedure A was followed with [1,3-bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazolium chloride (400 mg, 0.422 mmol) and potassium hexafluorophosphate (93.1 mg, 0.506 mmol). 10 mL stainless steel jar was used and subjected to grinding in a vibratory ball mill operated at 30 Hz for 0.5 h to afford [1,3-bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazolium hexafluorophosphate (410 mg, 0.357 mmol, 92%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.29 – 7.22 (m, 24H), 6.94 – 6.90 (m, 8H), 6.83 – 6.79 (m, 8H), 6.54 (d, *J* = 1.4 Hz, 2H), 6.53 (s, 4H), 4.84 (s, 4H), 3.52 (s, 6H); **^{13}C NMR (126 MHz, DMSO-d_6)**

δ 160.9, 142.5, 141.6, 141.5, 140.9, 129.4, 129.3, 129.2, 129.1, 127.9, 127.8, 125.7, 125.1, 115.1, 55.8, 51.6; **HRMS** calcd for $C_{69}H_{57}N_2O_2$ [M – PF_6^-]$^+$: 945.4420; found: 945.4423.

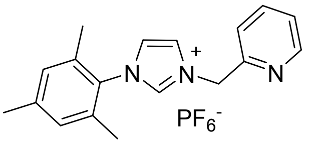
1-Benzyl-3-mesitylimidazolium hexafluorophosphate 3f



General procedure B was used with 1-benzyl-3-mesitylimidazolium bromide (155 mg, 0.44 mmol, 1.00 eq) and potassium hexafluorophosphate (84 mg, 0.46 mmol, 1.05 eq). The milling jar was subjected to grinding in the vibratory ball mill operated at 25 Hz for 0.5 h to afford 1-benzyl-3-mesitylimidazolium hexafluorophosphate (165 mg, 0.39 mmol, 89 %) as a pale brown solid.

^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ 9.57 (s, 1H), 8.07 (s, 1H), 7.96 (t, *J* = 1.7 Hz, 1H), 7.45 (s, 5H), 7.16 (s, 2H), 5.53 (s, 2H), 2.34 (s, 3H), 2.01 (s, 6H) ; **^{13}C NMR (101 MHz, DMSO-*d$_6$*)** δ 140.3, 137.6, 134.7, 134.2, 131.1, 129.2, 128.8, 128.0, 124.3, 123.2, 52.4, 20.5, 16.8; **^{31}P NMR (162 MHz, DMSO- *d$_6$*)** δ -144.2 (hept, *J* = 710.6 Hz) ; **^{19}F NMR (376 MHz, DMSO- *d$_6$*)** δ -70.1 (d, *J* = 710.6 Hz).

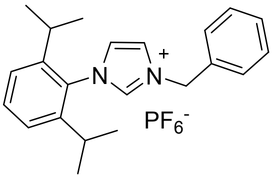
1-mesityl-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium hexafluorophosphate 3g



General procedure B was used with 1-mesityl-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium bromide (155 mg, 0.44 mmol, 1.00 eq) and potassium hexafluorophosphate (84 mg, 0.46 mmol, 1.05 eq). The milling jar was subjected to grinding in the vibratory ball mill operated at 25 Hz for 0.5 h to afford 1-mesityl-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium hexafluorophosphate (151 mg, 0.36 mmol, 81 %) as a pale brown solid.

^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ 9.46 (s, 1H), 8.47 (d, *J* = 4.2 Hz, 1H), 7.96 (s, 1H), 7.88 – 7.81 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.08 (s, 2H), 5.60 (s, 2H), 2.26 (s, 3H), 1.97 (s, 6H) ; **^{13}C NMR (101 MHz, DMSO-*d$_6$*)** δ 153.3, 149.7, 140.4, 138.6, 137.6, 134.4, 131.2, 129.3, 124.0, 123.9, 123.8, 122.4, 53.3, 20.6, 16.9 ; **^{31}P NMR (162 MHz, DMSO- *d$_6$*)** δ -139.5 (hept, *J* = 711.3 Hz) ; **^{19}F NMR (376 MHz, DMSO- *d$_6$*)** δ -65.4 (d, *J* = 711.4 Hz).

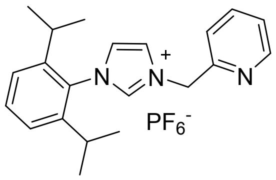
3-benzyl-1-(2,6-diisopropylphenyl)-1H-imidazol-3-ium hexafluorophosphate 3h



General procedure B was used with 3-benzyl-1-(2,6-diisopropylphenyl-1H-imidazol-3-ium bromide (161 mg, 0.41 mmol, 1.00 eq) and potassium hexafluorophosphate (78.3 mg, 0.43 mmol, 1.05 eq). The milling jar was subjected to grinding in the vibratory ball mill operated at 25 Hz for 0.5 h. to afford 3-benzyl-1-(2,6-diisopropylphenyl-1H-imidazol-3-ium hexafluorophosphate (182 mg, 0.39 mmol, 96 %) as a white solid.

^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 9.74 (s, 1H), 8.15 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.51 – 7.42 (m, 7H), 5.57 (s, 2H), 2.23 (dt, *J* = 13.6, 6.8 Hz, 2H), 1.14 (dd, *J* = 7.7, 7.1 Hz, 12H). ; **^{13}C NMR (125 MHz, DMSO-*d$_6$*)** δ 145.0, 140.2, 129.2, 129.1, 128.9, 128.7, 127.9, 127.9, 125.5, 125.4, 124.4, 124.4, 123.6, 52.6, 28.1, 23.8, 23.6 ; **^{31}P NMR (202 MHz, DMSO- *d$_6$*)** δ -144.2 (hept, *J* = 711.0 Hz) ; **^{19}F NMR (470 MHz, DMSO- *d$_6$*)** δ -70.2 (d, *J* = 711.0 Hz).

1-(2,6-diisopropylphenyl)-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium hexafluorophosphate 3i



General procedure B with 1-(2,6-diisopropylphenyl)-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium bromide (162 mg, 0.40 mmol, 1.00 eq) and potassium hexafluorophosphate (78.2 mg, 0.42 mmol, 1.05 eq). The milling jar was subjected to grinding in the vibratory ball mill operated at 25 Hz for 0.5 h. to afford 1-(2,6-diisopropylphenyl)-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium hexafluorophosphate (119 mg, 0.26 mmol, 64 %) as a pale red solid.

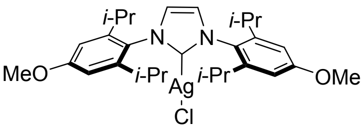
^{1}H NMR (500 MHz, DMSO-*d_6*) 9.65 (s, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 8.09 (dt, *J* = 10.7, 1.8 Hz, 2H), 7.92 (d, *J* = 1.8 Hz, 1H), 7.64 – 7.61 (t, J = 4.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.41 (dd, *J* = 7.1, 5.3 Hz, 1H), 5.70 (s, 2H), 2.38 – 2.35 (m, 1H), 1.17 – 1.12 (m, 12H) ; **^{13}C NMR (125 MHz, DMSO-*d_6*)** δ 153.2, 149.5, 145.2, 139.4, 137.6, 131.5, 130.7, 124.9, 124.4, 124.2, 123.7, 122.2, 53.2, 28.1, 23.9, 23.7 ; **^{31}P NMR (202 MHz, DMSO- *d_6*)** δ -144.2 (hept, *J* = 711.3 Hz) ; **^{19}F NMR (377 MHz, DMSO- *d_6*)** δ -70.2 (d, *J* = 711.3).

III. Synthesis of Silver(I)-carbene complexes in a ball-mill

A. Heteroleptic Silver(I)-carbene complexes mono-NHC

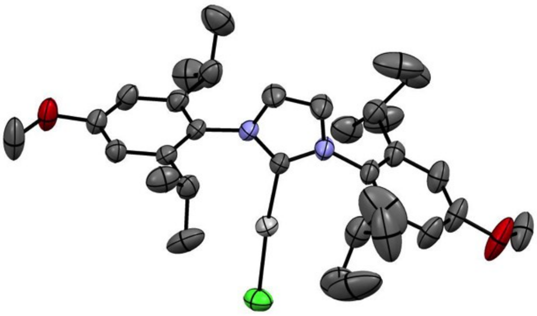
General procedure C : Imidazolium (1.00 eq) and silver oxide (0.55 eq) were introduced in a 10 mL stainless steel grinding bowl with one stainless steel ball (1 cm diameter). Total mass of the reagents was calculated so that a milling load equals 19.2 mg/mL. The bowl was closed and subjected to grinding. The powder was recovered with dichloromethane, the suspension was filtrated over celite and the filtrate was concentrated under vacuum. The solid was washed with diethyl ether and dried to afford the product.

[[1,3-Bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver chloride 2a



General procedure C was followed with [1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium chloride (144.1 mg, 0.297 mmol) and silver oxide (37.9 mg, 0.163 mmol). Reaction mixture was grinded for 3 hours at 30 Hz to afford [[1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver chloride (143.3 mg, 0.242 mmol, 81%) as a white solid.

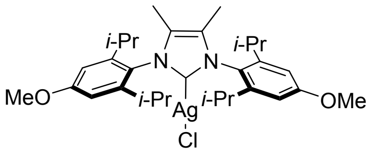
A mixture of [AgCl(IPr^{OMe})] and [AgCl(IPr^{OMe})$_2$] were obtained in 87:13 ratio. Below, peaks for the [AgCl(IPr^{OMe})] (major product) are reported: **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.16 (s, 1H), 7.16 (s, 1H), 6.77 (s, 4H), 3.89 (s, 6H), 2.51 (sept, *J* = 6.9 Hz, 4H), 1.26 (d, *J* = 6.9 Hz, 12H), 1.20 (d, *J* = 6.9 Hz, 12H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ 185.5 (d, $J_{C\text{-}Ag109}$ = 274.6 Hz), 185.5 (d, $J_{C\text{-}Ag107}$ = 238.0 Hz), 161.0, 147.2, 127.8, 124.1, 124.0, 109.8, 55.5, 29.0, 24.8, 24.1. Below, peaks for the [AgCl(IPr^{OMe})$_2$] (minor product) are reported: **^{1}H NMR (500 MHz, CDCl$_3$)** 7.06 (d, *J* = 1.2 Hz, 4H), 6.60 (s, 8H), 3.95 (s, 12H), 2.24 (sept, *J* = 7.0 Hz, 8H), 1.07 (d, J = 7.0 Hz, 24H), 0.80 (d, *J* = 7.0 Hz, 24H); **^{13}C NMR (126 MHz, CDCl$_3$)** 184.1 (d, $J_{C\text{-}Ag109}$ = 218.3 Hz), 184.1 (d, $J_{C\text{-}Ag107}$ = 189.5 Hz), 160.9, 146.8, 127.6, 125.21, 125.17, 109.6, 55.6, 28.8, 24.3, 24.1; **HRMS** calcd for $C_{29}H_{40}N_2O_2Ag$ [M – Cl$^-$]$^+$: 555.2141; found: 555.2145.



ORTEPs (at 50% probability level) of **2a**

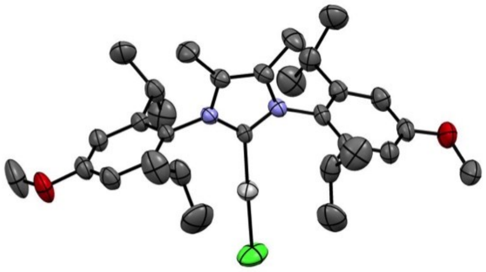
CCDC 1977192	**[AgCl(IPrOMe)] 2a**
Formula	$C_{29}H_{40}AgClN_2O_2$
M /g.mol^{-1}	591.95
Crystal system	monoclinic
Space group	P 2(1)/n
a/ Å	12.6677 (5)
b/ Å	12.5262 (6)
c/ Å	19.5459 (8)
α/ °	90
β/ °	103.521 (4)
γ/ °	90
V/ Å^3	3015.5 (2)
Z	4
ρ_{calcd}/g.cm^{-3}	1.304
μ (Mo Kα)/ mm^{-1}	0.783
T/ K	293 (2)
Number of reflections	46230
Number of unique reflections	7986
R_{int}	0.0403
R1, wR2 (I > 2σ(I))	0.0294, 0.0712
R1, wR2 (all data)	0.0434, 0.0765
GOF	1.033

[[4,5-Dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver chloride 2b



General procedure C was followed with [4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium chloride (145.8 mg, 0.284 mmol) and silver oxide (36.2 mg, 0.156 mmol). Reaction mixture was grinded for 3 hours at 30 Hz to afford [[4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver chloride (151.0 mg, 0.244 mmol, 86%) as a white solid.

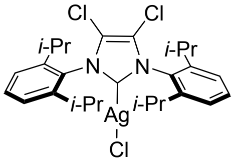
A mixture of [AgCl(MeIPr.OMe)] and [AgCl(MeIPr.OMe)$_2$] were obtained in 87:13 ratio. Below, peaks for the [AgCl(MeIPr.OMe)] (major product) are reported: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 6.78 (s, 4H), 3.89 (s, 6H), 2.40 (sept, J = 6.9 Hz, 4H), 1.93 (s, 6H), 1.25 (d, J = 6.9 Hz, 12H), 1.21 (d, J = 6.9 Hz, 12H) ; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 181.3 (d, $J_{C\text{-}Ag109}$ = 277.6 Hz), 181.3 (d, $J_{C\text{-}Ag107}$ = 240.4 Hz), 160.9, 147.5, 126.92, 126.87, 126.2, 109.9, 55.5, 28.9, 25.5, 23.4, 9.8. Below, peaks for the [AgCl(MeIPr.OMe)$_2$] (minor product) are reported: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 6.61 (s, 8H), 3.97 (s, 12H), 2.16 – 2.11 (m, 8H), 1.75 (s, 12H), 1.06 (d, J = 6.9 Hz, 24H), 0.74 (d, J = 6.9 Hz, 24H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 180.7 (d, $J_{C\text{-}Ag109}$ = 219.5 Hz), 180.7 (d, $J_{C\text{-}Ag107}$ = 190.1 Hz), 160.7, 147.0, 127.73, 127.68, 126.2, 109.9, 55.5, 28.6, 25.3, 23.1, 9.9; **HRMS** calcd for $C_{31}H_{44}N_2O_2Ag$ [M – Cl$^-$]$^+$: 583.2454; found: 583.2460.



ORTEPs (at 50% probability level) of **2b**

CCDC 1977193	**[AgCl(^{Me}IPr^{OMe})] 2b**
Formula	$C_{31}H_{44}AgClN_2O_2$, $C_4H_{10}O$
M /g.mol^{-1}	694.12
Crystal system	monoclinic
Space group	P 2(1)/n
a/ Å	13.1039 (7)
b/ Å	21.2304 (10)
c/ Å	14.5112 (9)
α/ °	90
β/ °	112.345 (7)
γ/ °	90
V/ Å^3	3733.9 (4)
Z	4
ρ_{calcd}/g.cm^{-3}	1.235
μ (Mo Kα)/ mm^{-1}	0.644
T/ K	293 (2)
Number of reflections	51104
Number of unique reflections	9691
R_{int}	0.0666
R1, wR2 (I > 2σ(I))	0.0485, 0.1122
R1, wR2 (all data)	0.0752, 0.1224
GOF	1.039

[[1,3-Bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazol-2-ylidene]silver chloride 2c

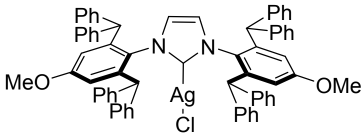


General procedure C was followed with [1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium chloride (144.6 mg, 0.293 mmol) and silver oxide (37.3 mg, 0.161 mmol). Reaction mixture was grinded for 3 hours at 30 Hz to afford [[1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazol-2-ylidene]silver chloride (158.7 mg, 0.264 mmol, 90%) as a white solid.

A mixture of [AgCl(Cl.IPr)] and [AgCl(Cl.IPr)$_2$] were obtained in 95:5 ratio. Below, peaks for the [AgCl(Cl.IPr)] (major product) are reported: **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.57 (t, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 4H), 2.46 (sept, J = 6.3 Hz, 4H), 1.28 (t, J = 6.3 Hz, 24H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ

183.9 (d, $J_{C\text{-}Ag109}$ = 273.6 Hz), 183.9 (d, $J_{C\text{-}Ag107}$ = 237 Hz), 146.1, 131.85, 131.79, 124.9, 119.8, 119.7, 29.2, 25.1, 23.5. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[9]

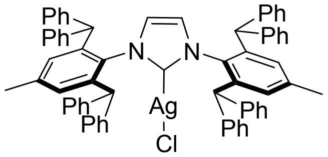
[[1,3-Bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazol-2-ylidene]silver chloride 2d



General procedure C was followed with [1,3-bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazolium chloride (161.0 mg, 0.164 mmol) and silver oxide (20.9 mg, 0.090 mmol). Reaction mixture was grinded for 3 hours at 30 Hz to afford [[1,3-bis(4-methoxy-2,6-diphenylmethyl)phenyl]imidazol-2-ylidene]silver chloride (159.5 mg, 0.146 mmol, 89%) as a white solid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.22 – 7.15 (m, 24H), 6.96 – 6.90 (m, 16H), 6.55 (s, 4H), 5.91 (s, 1H), 5.91 (s, 1H), 5.12 (s, 4H), 3.59 (s, 6H) ; **^{13}C NMR (126 MHz, CDCl$_3$)** δ 185.4 (d, $J_{C\text{-}Ag109}$ = 269.3 Hz), 185.4 (d, $J_{C\text{-}Ag107}$ = 233.3 Hz), 160.2, 143.1, 142.8, 142.0, 129.9, 129.54, 129.47, 129.0, 128.6, 127.0, 123.94, 123.88, 115.2, 55.3, 51.5; **HRMS** calcd for $C_{69}H_{56}N_2O_2Ag$ [M – Cl$^-$]$^+$: 1051.3393; found: 1051.3392.

[[1,3-Bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazol-2-ylidene]silver chloride 2e



General procedure C was followed with [1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazolium chloride (160.4 mg, 0.169 mmol) and silver oxide (21.6 mg, 0.093 mmol). Reaction mixture was grinded for 3 hours at 30 Hz to afford [[1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazol-2-ylidene]silver chloride (144.4 mg, 0.137 mmol, 81%) as a white solid.

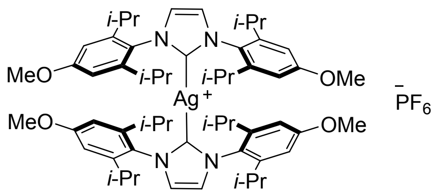
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.21 – 7.16 (m, 24H), 6.94 – 6.90 (m, 16H), 6.84 (s, 4H), 5.96 (s, 1H), 5.95 (s, 1H), 5.12 (s, 4H), 2.23 (s, 6H) ; **^{13}C NMR (126 MHz, CDCl$_3$)** δ 184.6 (d, $J_{C\text{-}Ag109}$ = 269.4 Hz), 184.6 (d, $J_{C\text{-}Ag107}$ = 233.2 Hz), 143.3, 142.2, 140.9, 140.4, 134.5, 130.4, 129.6, 128.9, 128.6, 126.90, 126.86, 123.77, 123.71, 51.3, 21.9. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[3]

B. Homoleptic Silver (I)-carbene complexes

General procedure D: Imidazolium (1.00 eq), sodium hydroxide (1.10 eq) and silver oxide (0.50 eq) were introduced in a 10 mL stainless steel grinding bowl with one stainless steel ball (10 mm diameter). Total mass of the reagents was calculated so that milling load equals 19.2 mg/mL. The bowl was closed and subjected to grinding in the vibratory ball mill operated at 30 Hz. The powder was recovered with dichloromethane and the suspension was filtrated over celite. The filtrate was concentrated under vacuum. The solid was washed with diethyl ether and dried under vacuum to afford the product.

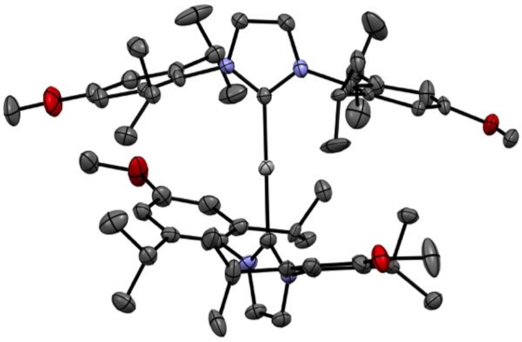
General procedure E: Hexafluorophosphate imidazolium salt (1.00 eq), silver oxide (0.75 eq) and sodium hydroxide (1.1 eq) were introduced in a 12 mL Stainless Steel grinding bowl with fifty stainless steel balls (0.5 cm diameter). Total mass of the reagents has been calculated so that milling load equals 19.2 mg/mL. The bowl was closed and subjected to grinding in the planetary ball mill operated at 450 rpm for 5 h. Reaction mixture was recovered with dichloromethane, dried with magnesium sulfate and filtrated over celite. The solvent was evaporated under vacuum to afford the desired homoleptic silver(I)-carbene complex.

Bis[(1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver hexafluorophosphate 4a



General procedure D was followed with [1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate (141.2 mg, 0.238 mmol), sodium hydroxide (10.4 mg, 0.261 mmol) and silver oxide (30.3 mg, 0.131 mmol). Reaction mixture was grinded for 3 hours to afford bis[(1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver hexafluorophosphate (132.3 mg, 0.115 mmol, 97%) as a white solid.

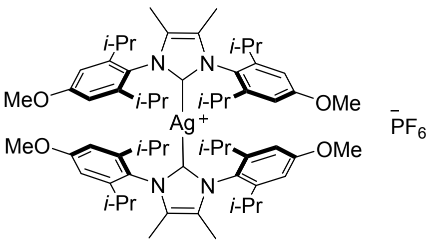
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (s, 2H), 7.68 (s, 2H), 6.65 (s, 8H), 3.90 (s, 12H), 2.18 (sept, J = 6.9 Hz, 8H), 1.01 (d, J = 6.8 Hz, 24H), 0.77 (d, J = 6.9 Hz, 24H); **^{13}C NMR (126 MHz, DMSO-d_6)** δ 183.1 (d, $J_{C\text{-}Ag109}$ = 215.7 Hz), 183.1 (d, $J_{C\text{-}Ag107}$ = 186.9 Hz), 160.6, 146.7, 128.0, 126.35, 126.31, 109.6, 55.8, 28.7, 24.1, 24.0; **^{31}P NMR (202 MHz, DMSO-d_6)** δ -144.2 (sept, J = 711.2 Hz); **^{19}F NMR (376 MHz, DMSO-d_6)** δ -70.2 (d, J = 711.2 Hz); **HRMS** calcd for $C_{58}H_{80}N_4O_4Ag$ [M – PF_6^-]$^+$: 1003.5231; found: 1003.5240.



ORTEPs (at 50% probability level) of **4a**

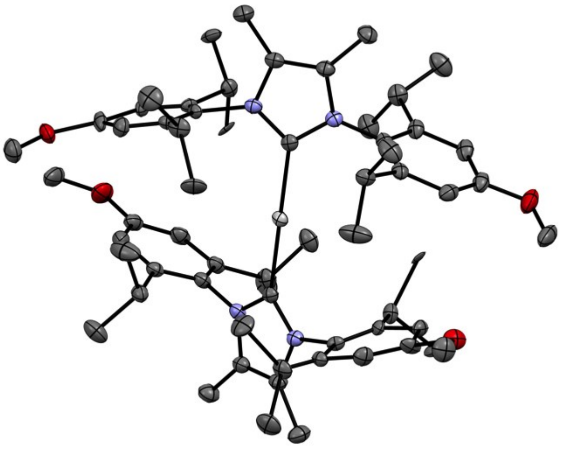
CCDC 1977190	**$[Ag(IPrOMe)_2]PF_6$ 4a**
Formula	$C_{58}H_{80}AgN_4O_4$, PF_6, 1/4CH_2Cl_2
M /g.mol^{-1}	1192.56
Crystal system	Triclinic
Space group	P -1
a/ Å	12.5248 (4)
b/ Å	13.1434 (4)
c/ Å	20.5413 (6)
α/ °	82.614 (3)
β/ °	84.230 (2)
γ/ °	64.618 (3)
V/ Å^3	3025.82 (18)
Z	2
ρ_{calcd}/g.cm^{-3}	1.309
μ (Mo Kα)/ mm^{-1}	0.469
T/ K	100 (2)
Number of reflections	39130
Number of unique reflections	13985
R_{int}	0.0608
R1, wR2 (I > 2σ(I))	0.0460, 0.1137
R1, wR2 (all data)	0.0672, 0.1222
GOF	1.057

Bis[(4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate 4b



General procedure D was followed with [4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate (142.7 mg, 0.229 mmol), sodium hydroxide (10.1 mg, 0.252 mmol) and silver oxide (29.2 mg, 0.126 mmol). Reaction mixture was grinded for 3h to afford bis[(4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl)imidazole-2-ylidene]silver hexafluorophosphate (138.2 mg, 0.115 mmol, 100%) as a white solid.

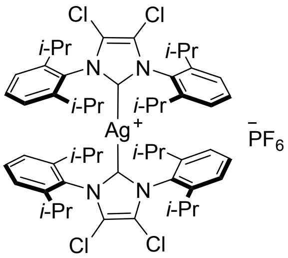
^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 6.66 (s, 8H), 3.93 (s, 12H), 2.11 (sept, *J* = 6.9 Hz, 8H), 1.71 (s, 12H), 1.01 (d, *J* = 6.9 Hz, 24H), 0.71 (d, *J* = 6.9 Hz, 24H); **^{13}C NMR (126 MHz, DMSO-*d$_6$*)** δ 179.8 (d, $J_{C\text{-}Ag109}$ = 218.9 Hz), 179.8 (d, $J_{C\text{-}Ag107}$ = 189.5 Hz), 160.1, 146.4, 127.4, 127.3, 125.7, 109.5, 55.3, 28.1, 24.7, 22.6, 9.3; **^{31}P NMR (202 MHz, DMSO-*d$_6$*)** δ -144.2 (sept, *J* = 711.2 Hz); **^{19}F NMR (376 MHz, DMSO-*d$_6$*)** δ -70.2 (d, *J* = 711.2 Hz); **HRMS** calcd for $C_{63}H_{84}N_8O_4Ag$ $[M - PF_6^-]^+$: 1059.5870; found: 1059.5861.



ORTEPs (at 50% probability level) of **4b**

CCDC 1977191	**[Ag(^{Me}IPr^{OMe})$_2$]PF$_6$ 4b**
Formula	$C_{62}H_{88}AgN_4O_4$, PF_6, CH_2Cl_2, 0.72 ($C_4H_{10}O$)
M /g.mol^{-1}	1291.12
Crystal system	orthorhombic
Space group	Ibca
a/ Å	20.9271 (5)
b/ Å	25.5794 (6)
c/ Å	25.7948 (6)
α/ °	90
β/ °	90
γ/ °	90
V/ Å^3	13808.0 (6)
Z	8
ρ_{calcd}/g.cm^{-3}	1.242
μ (Mo Kα)/ mm^{-1}	0.453
T/ K	100
Number of reflections	140570
Number of unique reflections	9669
R_{int}	0.0580
R1, wR2 (I > 2σ(I))	0.0331, 0.0748
R1, wR2 (all data)	0.0482, 0.0806
GOF	1.054

Bis[(1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro)imidazol-2-ylidene]silver hexafluorophosphate 4c



General procedure D was followed with [1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium hexafluorophosphate (141.7 mg, 0.235 mmol), sodium hydroxide (10.3 mg, 0.258 mmol) and silver oxide (29.9 mg, 0.129 mmol). Reaction mixture was grinded for 3 hours to afford bis[(1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro)imidazol-2-ylidene]silver hexafluorophosphate (116.1 mg, 0.0994 mmol, 85%) as a white solid.

Procedure in solution:

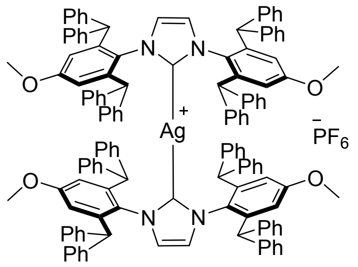
Protocol 1: In a solution of [1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium hexafluorophosphate (50.0 mg, 82.9 µmol, 1.00 eq) in chloroform (830 µL), silver oxide (9.6 mg, 41.4 µmol, 0.50 eq) was added. The resulting suspension was stirred at reflux.

Protocol 2: In a solution of [1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium hexafluorophosphate (50.0 mg, 82.9 µmol, 1.00 eq) in dichloromethane (830 µL), silver oxide (9.6 mg, 41.4 µmol, 0.50 eq) and sodium hydroxide (3.4 mg, 91.2 µmol, 1.10 eq) was added. The resulting suspension was stirred at room temperature for 24h to afford bis[(1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro)imidazol-2-ylidene]silver hexafluorophosphate (21.9 mg, 18.8 µmol, 45%) as a white solid.

Entry	Procedure	Reaction time (h)	Conversion (%)	Yield (%)
1	Procedure in the ball-mill	3	100	85
2	Protocol 1	24	31	-
		48	90	-
3	Protocol 2	24	100	45

^{1}H NMR (500 MHz, DMSO-*d_6*) δ 7.63 (t, *J* = 7.8 Hz, 4H), 7.28 (d, *J* = 7.8 Hz, 8H), 2.13 (sept, J = 6.9 Hz, 8H), 1.06 (d, *J* = 6.9 Hz, 24H), 0.73 (d, *J* = 6.9 Hz, 24H); **^{13}C NMR (126 MHz, DMSO-*d_6*)** δ 180.9 (d, $J_{C-Ag109}$ = 227.5 Hz), 180.9 (d, $J_{C-Ag107}$ = 197.3 Hz), 145.0, 131.8, 130.9, 124.9, 120.4, 120.3, 28.3, 24.6, 22.7; **^{31}P NMR (202 MHz, DMSO-*d_6*)** δ -144.2 (sept, *J* = 711.2 Hz); **^{19}F NMR (376 MHz, DMSO-*d_6*)** δ -70.2 (d, *J* = 711.2 Hz); **HRMS** calcd for $C_{54}H_{68}N_4Cl_4Ag$ [M – PF_6^-]$^+$: 1019.3249; found: 1019.3256.

Bis[(1,3-bis(4-methoxy-2,6-diphenyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate 4d

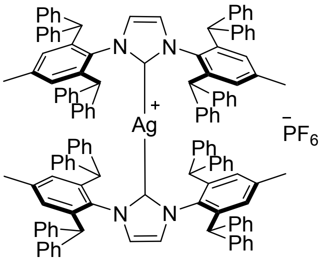


General procedure D was followed with [1,3-bis(4-methoxy-2,6-diphenyl)phenyl]imidazolium hexafluorophosphate (158.7 mg, 0.145 mmol), sodium hydroxide (6.4 g, 0.160 mmol) and silver oxide (16.9 mg, 0.073 mmol). Reaction mixture was grinded for 3h. Protocol 2 was followed to afford bis[(1,3-bis(4-methoxy-2,6-diphenyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate (142.5 mg, 0.0685 mmol, 94%) as a white solid.

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.25 – 7.12 (m, 24H), 7.00 – 6.89 (m, 16H), 6.58 (s, 4H), 5.96 (s, 2H), 5.12 (s, 4H), 3.57 (s, 6H); **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 165.1, 147.7, 147.1, 134.3, 134.2, 133.7, 133.4, 131.8, 131.7, 128.8, 119.9, 60.1, 56.4; **^{31}P NMR (202 MHz, $CDCl_3$)** δ -144.2 (sept, *J* = 713.1 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -73.1 (d, *J* = 713.1 Hz).

Of note, the carbenic carbon of **4d** (expected as two doublets) could not be observed, even with prolonged relaxation time.

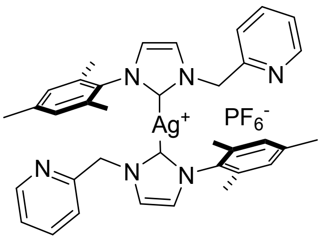
Bis[(1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate 4e



General procedure D was followed with [1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl]imidazolium hexafluorophosphate (158.1 mg, 0.149 mmol), sodium hydroxide (6.6 mg, 0.164 mmol) and silver oxide (17.3 mg, 0.075 mmol). Reaction mixture was grinded for 3h. Protocol 2 was followed to afford bis[(1,3-bis(4-methyl-2,6-diphenylmethyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate (139.4 mg, 0.069 mmol, 93%) as a white solid.

^{1}H solid state NMR (600 MHz, none) δ 8.95 – 4.12, 6.13, 2.99 – 0.55; **^{13}C solid state NMR (600 MHz, none)** 182.4, 149.5 – 138.0, 135.3, 133.7 – 120.5, 52.0, 22.0.

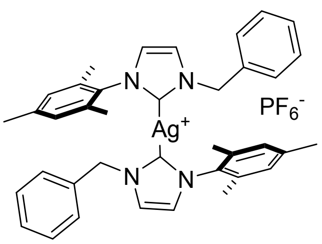
Bis[(1-(2-pyridyl)methylene-3-mesityl)imidazol-2-ylidene]silver hexafluorophosphate 4f



General procedure E was applied with 1-mesityl-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium (111 mg, 0.26 mmol, 1.00 eq), silver oxide (45.4 mg, 0.20 mmol, 0.75 eq) and sodium hydroxide (11.5 mg, 0.29 mmol, 1.1 eq) to afford Bis[(1-(2-pyridyl)methylene-3-mesityl)imidazol-2-ylidene]silver(I) hexafluorophosphate(V) (83.8 mg, 0.25 mmol, 80 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d_6*) δ 8.49 (d, *J* = 4.3 Hz, 2H), 7.78 (td, *J* = 7.7, 1.7 Hz, 2H), 7.72 (t, *J* = 3.0 Hz, 2H), 7.45 (d, *J* = 1.6 Hz, 2H), 7.35 (dd, *J* = 6.8, 4.9 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.94 – 6.92 (m, 2H), 5.39 (s, 4H), 2.34 (s, 7H), 1.66 (s, 12H). **^{13}C NMR (126 MHz, DMSO-*d_6*)** δ 181.98 (d, $J_{C\text{-}Ag109}$ = 207.9 Hz), 181.98 (d, $J_{C\text{-}Ag107}$ = 183.9 Hz), 156.2, 149.5, 138.5, 137.3, 135.5, 134.3, 128.8, 123.2, 121.4, 55.5, 20.7, 17.0. **^{31}P NMR (162 MHz, DMSO- *d_6*)** δ -144.3 (hept, *J* = 712.7 Hz) ; **^{19}F NMR (376 MHz, DMSO- *d_6*)** δ -73.1 (d, *J* = 712.7 Hz). **HRMS** calcd for $C_{36}H_{38}N_6Ag$ [M – PF_6^-]$^+$: 661.2203; found: 661.2312.

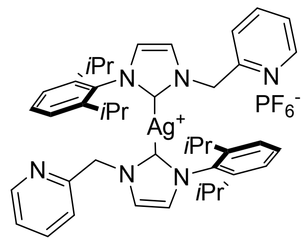
Bis[(1-benzyl-3-mesityl)imidazol-2-ylidene]silver hexafluorophosphate 4g



General procedure E was applied with 1-benzyl-3-mesitylimidazolium hexafluorophosphate (111 mg, 0.26 mmol, 1.00 eq), silver oxide (45.5 mg, 0.20 mmol, 0.75 eq) and sodium hydroxide (11.5 mg, 0.29 mmol, 1.1 eq) to afford bis[(1-benzyl-3-mesityl)imidazol-2-ylidene)silver(I) hexafluorophosphate(V) (103 mg, 0.25 mmol, 97 %) as a white solid.

^{1}H NMR (500 MHz, DMSO-*d_6*) δ 7.70 (t, *J* = 1.5 Hz, 2H), 7.44 (t, *J* = 1.4 Hz, 2H), 7.32 (dd, *J* = 5.0, 1.8 Hz, 5H), 7.12 – 7.09 (m, 4H), 6.94 (s, 4H), 5.21 (s, 4H), 2.30 (s, 6H), 1.64 (s, 12H); **^{13}C NMR (126 MHz, DMSO-*d_6*)** 181.28 (d, $J_{C\text{-}Ag109}$ = 210.4 Hz), 181.28 (d, $J_{C\text{-}Ag107}$ = 180.2 Hz), 139.0, 137.7, 135.9, 134.7, 129.24 (d, *J* = 8.9 Hz), 128.5, 127.6, 123.9 (d, *J* = 6.4 Hz), 123.2 (d, *J* = 6.2 Hz), 54.29, 21.10, 17.39 ; **^{31}P NMR (162 MHz, DMSO-*d_6*)** δ -145.2 (hept, *J* = 712.7 Hz) **^{19}F NMR (377 MHz, DMSO- *d_6*)** δ -70.16 (d, J = 711.3 Hz). **HRMS** calcd for $C_{38}H_{40}N_4Ag$ [M – PF_6^-]$^+$: 659.2298; found: 659.2304.

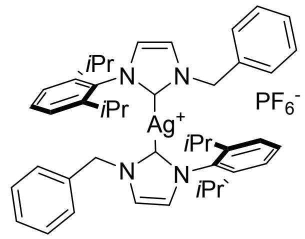
Bis[(1-(2-pyridyl)methylene-3-(2,6-diisopropylphenyl))imidazol-2-ylidene]silver hexafluorophosphate 4h



General procedure E was applied with 1-(2,6-diisopropylphenyl)-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium hexafluorophosphate (114 mg, 0.25 mmol, 1.00 eq), silver oxide (42.6 mg, 0.18 mmol, 0.75 eq) and sodium hydroxide (10.8 mg, 0.27 mmol, 1.1 eq) to afford bis[(1-(2-pyridyl)methylene-3-(2,6-diisopropylphenyl))imidazol-2-ylidene]silver(I) hexafluorophosphate(V) (78 mg, 0.25 mmol, 70 %) as a white solid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (t, 2H), 7.29 (dd, 6H), 7.21 (t, 2H), 7.13 (d, 4H), 6.99 – 6.96 (m, 6H), 5.05 (s, 4H), 2.24 (sept, 4H), 1.06 (d, 12H), 0.89 (d, 12H); **^{13}C NMR (126 MHz, CDCl$_3$)** δ 182.9 (d, $J_{C\text{-}Ag109}$ = 213.3 Hz), 182.9 (d, $J_{C\text{-}Ag107}$ = 184.5 Hz), 154.9, 149.5, 145.8, 137.4, 134.7, 130.3, 123.9, 123.3, 122.4, 122.4, 122.2, 56.4, 28.1, 24.6, 23.9 ; **^{31}P NMR (162 MHz, CDCl$_3$)** δ -144.4 (hept, *J* = 712.9 Hz) ; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -73.4 (d, *J* = 712.9 Hz). **HRMS** calcd for $C_{42}H_{50}N_6Ag$ $[M - PF_6^-]^+$: 745.3148; found: 745.3262.

Bis[(1-benzyl-3-(2,6-diisopropylphenyl)imidazol-2-ylidene]silver hexafluorophosphate 4i



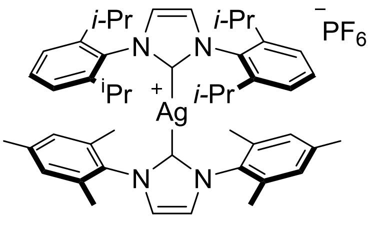
General procedure E was applied with 3-benzyl-1-(2,6-diisopropylphenyl)-1H-imidazol-3-ium hexafluorophosphate (114 mg, 0.25 mmol, 1.00 eq), silver oxide (42.7 mg, 0.18 mmol, 0.75 eq) and sodium hydroxide (10.8 mg, 0.29 mmol, 1.1 eq) to afford Bis[(1-benzyl-3-(2,6-diisopropylphenyl)imidazol-2-ylidene]silver(I) hexafluorophosphate(V) (98 mg, 0.25 mmol, 88 %) as a white solid.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.35 (t, *J* = 7.8 Hz, 2H), 7.29 (dd, *J* = 4.9, 1.7 Hz, 6H), 7.21 (t, *J* = 1.6 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 4H), 6.99 – 6.96 (m, 6H), 5.05 (s, 4H), 2.24 (dt, *J* = 13.8, 6.9 Hz, 4H), 1.06 (d, *J* = 6.9 Hz, 12H), 0.89 (d, *J* = 6.9 Hz, 12H) **^{13}C NMR (151 MHz, CDCl$_3$)** δ 181.97 (d, $J_{C\text{-}Ag109}$ = 211.5 Hz), 181.97 (d, $J_{C\text{-}Ag107}$ = 181.5 Hz), 146.0, 136.0, 134.7, 130.6, 12.4, 129.1, 129.0, 128.5, 127.8, 127.0, 124.5, 124.5, 124.2, 122.9, 122.4, 122.4 ; **^{31}P NMR (162 MHz, CDCl$_3$)** δ -144.4 (hept, *J* = 712.6 Hz) ; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -73.4 (d, *J* = 712.6 Hz). **HRMS** calcd for $C_{44}H_{52}N_4Ag$ $[M - PF_6^-]^+$: 743.3243; found: 743.3248.

C. Heteroleptic silver-carbene complexes bis-NHC

General procedure F: [AgCl(IPr)] (1.00 eq), sodium hydroxide (1.10 eq) and corresponding imidazolium hexafluorophosphate (1.00 eq) were introduced in a 10 mL stainless steel grinding bowl with one stainless steel ball (10 mm diameter). Total mass of the reagents was calculated so that milling load equals 19.2 mg/mL. The bowl was closed and subjected to grinding in the vibratory ball mill operated at 30 Hz for 1 h. The powder was recovered with dichloromethane and the suspension was filtrated over celite. The filtrate was concentrated under vacuum. The solid was washed with diethyl ether and dried under vacuum to afford the pure product.

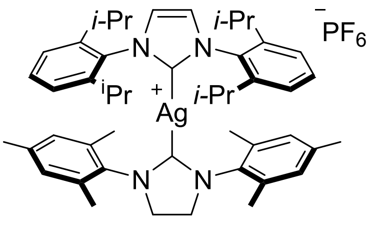
[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene]silver hexafluorophosphate 5a



General procedure F was followed with [AgCl(IPr)] (94.3 mg, 0.18 mmol, 1.00 eq), sodium hydroxide (7.8 mg, 0.20 mmol, 1.10 eq) and [1,3-Bis(2,4,6-trimethylphenyl)]imidazolium hexafluorophosphate (79.9 mg, 0.18 mmol, 1.00 eq) to afford [[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene]silver hexafluorophosphate (151.5 mg, 0.16 mmol, 90 %) as a solid.

^{1}H NMR (500 MHz, CD$_2$Cl$_2$) δ 7.54 (t, *J* = 7.7 Hz, 2H), 7.19 (m, 4H), 6.99 (s, 2H), 6.81 (s, 4H), 2.39 (s, 6H), 2.25 (dt, *J* = 13.5, 6.9 Hz, 4H), 1.68 (s, 12H), 1.12 (d, *J* = 6.8 Hz, 12H), 0.81 (d, *J* = 6.8 Hz, 12H); **^{13}C NMR (126 MHz, CD$_2$Cl$_2$)** δ 184.505 (d, $J_{C\text{-}Ag109}$ = 212.9 Hz), 184.505 (d, $J_{C\text{-}Ag107}$ = 185.2 Hz), 181.67 (d, $J_{C\text{-}Ag109}$ = 211.7 Hz), 181.67 (d, $J_{C\text{-}Ag107}$ = 182.7 Hz), 145.8, 139.7, 135.1, 134.7, 134.6, 131.0, 130.1, 124.4, 124.3, 123.8, 28.9, 24.7, 23.9, 21.4, 17.4; **^{31}P NMR (202 MHz, CD$_2$Cl$_2$)** δ -144.6 (sept, *J* = 710.4 Hz); **^{19}F NMR (376 MHz, CD$_2$Cl$_2$)** δ -73.7 (d, *J* = 710.3 Hz); **HRMS** calcd for $C_{48}H_{62}N_4Ag$ [M – PF_6^-]$^+$: 799.3863; found: 799.3864.

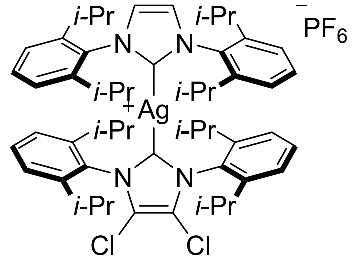
[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]silver hexafluorophosphate 5b



General procedure F was followed with [AgCl(IPr)] (94.1 mg, 0.18 mmol, 1.00 eq), sodium hydroxide (7.8 mg, 0.20 mmol, 1.10 eq) and [1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydro]imidazolium hexafluorophosphate (80.1 mg, 0.18 mmol, 1.00 eq) to afford [[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]silver hexafluorophosphate (153.2 mg, 0.16 mmol, 91 %) as a solid.

^{1}H NMR (500 MHz, CD$_2$Cl$_2$) δ 7.55 (t, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 4H), 7.15 (d, *J* = 1.0 Hz, 2H), 6.75 (s, 4H), 3.77 (s, 4H), 2.34 (s, 6H), 2.23 (sept, *J* = 6.9 Hz, 4H), 1.90 (s, 12H), 1.11 (d, *J* = 6.9 Hz, 12H), 0.81 (d, *J* = 6.9 Hz, 12H); **^{13}C NMR (126 MHz, CD$_2$Cl$_2$)** δ 205.95 (d, $J_{C\text{-}Ag109}$ = 201.6 Hz), 205.95 (d, $J_{C\text{-}Ag107}$ = 176.4 Hz), 184.35 (d, $J_{C\text{-}Ag109}$ = 211.6 Hz), 184.35 (d, $J_{C\text{-}Ag107}$ = 183.7 Hz), 145.6, 138.7, 135.4, 134.9, 134.5, 131.0, 130.4, 124.4, 124.3, 124.2, 51.8, 51.7, 28.8, 24.5, 23.8, 21.3, 17.6; **^{31}P NMR (202 MHz, CD$_2$Cl$_2$)** δ -144.5 (sept, *J* = 710.3 Hz); **^{19}F NMR (376 MHz, CD$_2$Cl$_2$)** δ -73.6 (d, *J* = 710.3 Hz); **HRMS** calcd for $C_{48}H_{62}N_4Ag$ [M – PF_6^-]$^+$: 801.4020 ; found : 801.4039.

[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,6-di*iso*propyl)phenyl]-4,5-dichloroimidazol-2-ylidene]silver hexafluorophosphate 5c

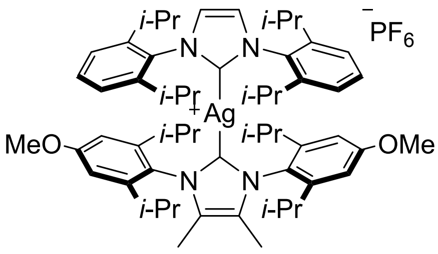


General procedure F was followed with [AgCl(IPr)] (82.1 mg, 0.15 mmol, 1.00 eq), sodium hydroxide (6.8 mg, 0.17 mmol, 1.10 eq) and 1,3-Bis(2,6-di*iso*propyl)phenyl]-4,5-dichloroimidazolium hexafluorophosphate (93.1 mg, 0.15 mmol, 1.00 eq) to afford [[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,6-

di*iso*propyl)phenyl]-4,5-dichloroimidazol-2-ylidene]silver hexafluorophosphate (148.7 mg, 0.14 mmol, 88 %) as a solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.56 (t, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 4H), 7.16 (d, *J* = 7.8 Hz, 4H), 7.07 (s, 1H), 7.07 (s, 1H), 2.26 (sept, J = 6.8 Hz, 4H), 2.15 (sept, *J* = 6.8 Hz, 4H), 1.11 (d, *J* = 6.8 Hz, 12H), 1.04 (d, *J* = 6.8 Hz, 12H), 0.79 (d, *J* = 7.0 Hz, 12H), 0.77 (d, *J* = 7.0 Hz, 12H); **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 182.25 (d, $J_{C\text{-}Ag109}$ = 219.7 Hz), 182.25 (d, $J_{C\text{-}Ag107}$ = 189.2 Hz), 181.9 (d, $J_{C\text{-}Ag109}$ = 226.4 Hz), 181.9 (d, $J_{C\text{-}Ag107}$ = 197.5 Hz), 146.2, 145.6, 134.9, 132.2, 131.8, 131.2, 125.44, 125.39, 125.2, 124.9, 121.0, 120.9, 29.2, 29.0, 25.4, 24.7, 24.2, 23.1; **^{31}P NMR (202 MHz, CD_2Cl_2)** δ -144.5 (sept, *J* = 710.2 Hz); **^{19}F NMR (376 MHz, CD_2Cl_2)** δ -73.6 (d, *J* = 710.2 Hz); **HRMS** calcd for $C_{54}H_{70}N_4Cl_2Ag$ [M – PF_6^-]$^+$: 951.4023; found : 951.4019.

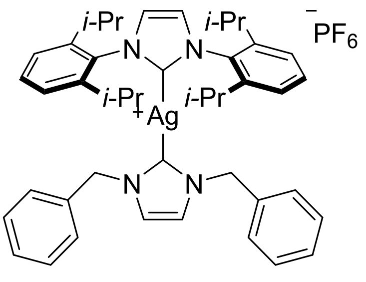
[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][(4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate 5d



<u>General procedure F</u> was followed with [AgCl(IPr)] (34.5 mg, 0.06 mmol, 1.00 eq), sodium hydroxide (2.9 mg, 0.07 mmol, 1.10 eq) and (4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl)imidazolium hexafluorophosphate (40.4 mg, 0.06 mmol, 1.00 eq) with a milling load equal to 8.3 mg/mL to afford [[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][(4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate (64.3 mg, 0.06 mmol, 89 %) as a solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.57 – 7.52 (m, 2H), 7.21 (dd, *J* = 7.5, 3.7 Hz, 4H), 7.10 (s, 1H), 7.10 (s, 1H), 6.66 (d, *J* = 3.4 Hz, 4H), 3.97 (s, 3H), 3.97 (s, 3H), 2.38 – 2.30 (m, 4H), 2.21 – 2.12 (m, 4H), 1.76 (d, *J* = 3.4 Hz, 6H), 1.11 (d, *J* = 6.9 Hz, 12H), 1.09 (d, *J* = 6.9 Hz, 12H), 0.89 (d, *J* = 3.5 Hz, 6H), 0.87 (d, *J* = 4.0 Hz, 6H), 0.77 (d, *J* = 3.5 Hz, 6H), 0.76 (d, *J* = 4.0 Hz, 6H); **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 183.55 (d, $J_{C\text{-}Ag109}$ = 213.1 Hz), 183.55 (d, $J_{C\text{-}Ag107}$ = 185.0 Hz), 180.05 (d, $J_{C\text{-}Ag109}$ = 222.3 Hz), 180.05 (d, $J_{C\text{-}Ag107}$ = 193.1 Hz), 161.0, 147.4, 145.7, 135.2, 131.1, 128.05, 128.01, 126.3, 125.31, 125.27, 124.7, 110.1, 55.7, 28.9, 25.8, 24.4, 24.2, 22.9, 9.8; **^{31}P NMR (202 MHz, CD_2Cl_2)** δ -144.5 (sept, *J* = 710.4 Hz); **^{19}F NMR (376 MHz, CD_2Cl_2)** δ -73.57 (d, *J* = 710.4 Hz); **HRMS** calcd for $C_{58}H_{80}N_4Ag$ [M – PF_6^-]$^+$: 971.5327; found : 971.5330.

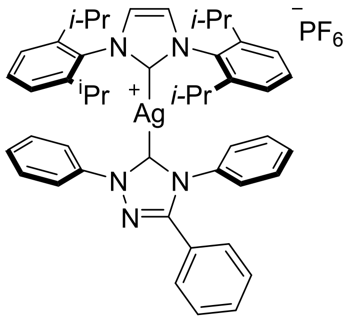
[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][*N,N*-dibenzylimidazolium]silver hexafluorophosphate 5e



General procedure E was followed with [AgCl(IPr)] (99.8 mg, 0.19 mmol, 1.00 eq), sodium hydroxide (8.3 mg, 0.21 mmol, 1.10 eq) and *N,N*-dibenzylimidazolium hexafluorophosphate (73.9 mg, 0.19 mmol, 1.00 eq) to afford [[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][*N,N*-dibenzylimidazolium]silver hexafluorophosphate (164.1 mg, 0.18 mmol, 99 %) as a solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.46 – 7.41 (m, 4H), 7.37 – 7.29 (m, 10H), 6.93 (s, 1H), 6.92 (s, 1H), 6.82 (d, *J* = 7.2 Hz, 4H), 4.69 (s, 4H), 2.57 (sept, *J* = 6.9 Hz, 4H), 1.27 (d, *J* = 6.9 Hz, 12H), 1.20 (d, *J* = 6.9 Hz, 12H); **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 184.68 (d, $J_{C\text{-}Ag109}$ = 211.6 Hz), 184.68 (d, $J_{C\text{-}Ag107}$ = 183.0 Hz), 179.65 (d, $J_{C\text{-}Ag109}$ = 212.2 Hz), 179.65 (d, $J_{C\text{-}Ag107}$ = 183.5 Hz), 146.2, 135.5, 134.7, 131.3, 129.4, 128.9, 127.4, 124.7, 124.64, 124.59, 122.6, 122.5, 55.5, 29.1, 25.0, 24.0; **^{31}P NMR (202 MHz, CD_2Cl_2)** δ -144.5 (sept, *J* = 710.4 Hz); **^{19}F NMR (376 MHz, CD_2Cl_2)** δ -73.4 (d, *J* = 710.4 Hz) ; **HRMS** calcd for $C_{44}H_{52}N_4Ag$ $[M – PF_6^-]^+$: 743.3237; found : 743.3235.

[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3,4-triphenyl-1,2,4-triazolium]silver hexafluorophosphate 5f

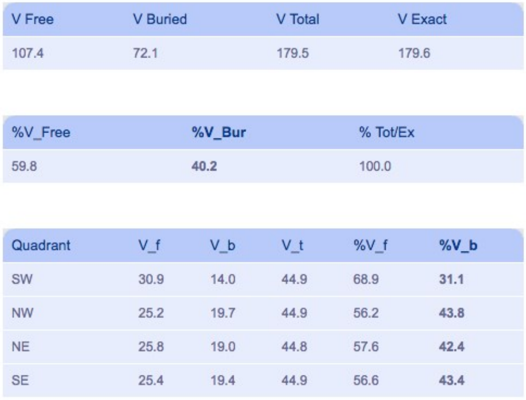


General procedure E was followed with [Ag(IPr)Cl] (102.6mg, 0.19 mmol, 1.00 eq), sodium hydroxide (8.5 mg, 0.21 mmol, 1.10 eq) and 1,3,4-triphenyl-1,2,4-triazolium hexafluorophosphate (70.8 mg, 0.21 mmol, 1.00 eq) to afford [[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3,4-triphenyl-1,2,4-triazolium]silver hexafluorophosphate (172.9 mg, 0.18 mmol, 95 %) as a solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.58 (t, *J* = 7.8 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.44 – 7.41 (m, 1H), 7.41 – 7.38 (m, 2H), 7.31 – 7.19 (m, 14H), 6.98 (dd, *J* = 8.4, 1.0 Hz, 2H), 2.39 (sept, *J* = 6.8 Hz, 4H), 1.17 (d, *J* = 6.9 Hz, 12H), 0.96 (d, *J* = 6.9 Hz, 12H); **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 182.84 (d, $J_{C\text{-}Ag109}$ = 225.9 Hz), 182.84 (d, $J_{C\text{-}Ag107}$ = 195.5 Hz), 182.05 (d, $J_{C\text{-}Ag109}$ = 207.1 Hz), 182.05 (d, $J_{C\text{-}Ag107}$ = 179.0 Hz), 154.64, 154.59, 145.89, 139.1, 135.9, 134.5, 131.7, 131.5, 131.0, 130.8, 130.4, 130.0, 129.24, 129.21, 126.5, 124.95, 124.90, 124.78, 124.1, 123.4, 28.9, 25.1, 23.7; **^{31}P NMR (202 MHz, CD_2Cl_2)** δ -144.5 (sept, *J* = 710.1 Hz). **^{19}F NMR (376 MHz, CD_2Cl_2)** δ -73.7 (d, *J* = 710.1 Hz) ; **HRMS** calcd for $C_{47}H_{51}N_5Ag$ $[M – PF_6^-]^+$: 792.3190; found : 792.3189.

IV. %V_{Bur} calculations

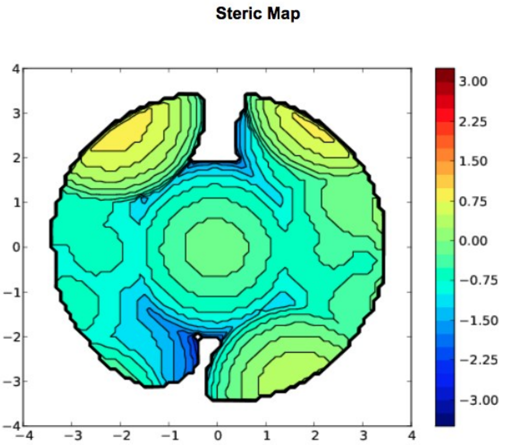
A. %VBur for **2a** with real C-Ag distance, sphere radius of 3.5 Å.



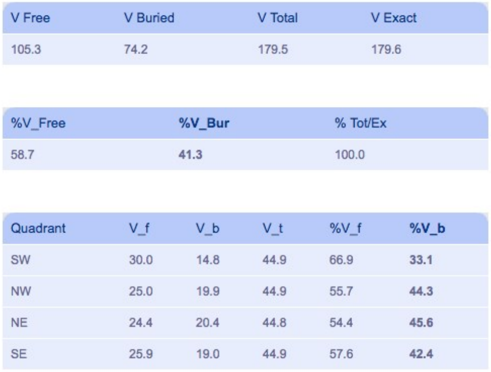
V Free	V Buried	V Total	V Exact
107.4	72.1	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
59.8	**40.2**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	30.9	14.0	44.9	68.9	**31.1**
NW	25.2	19.7	44.9	56.2	**43.8**
NE	25.8	19.0	44.8	57.6	**42.4**
SE	25.4	19.4	44.9	56.6	**43.4**



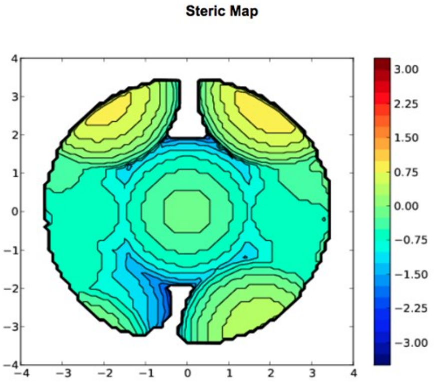
B. %VBur for **2a** with distance C-Ag normalized at 2.1 Å, sphere radius 3.5 Å.



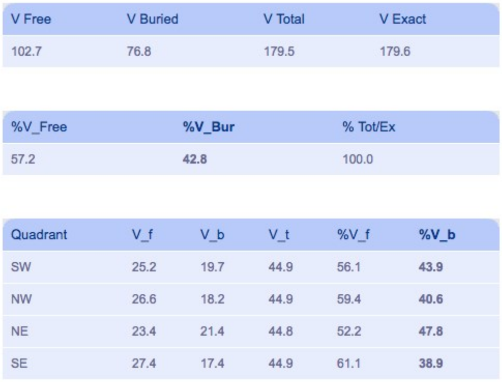
V Free	V Buried	V Total	V Exact
105.3	74.2	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
58.7	**41.3**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	30.0	14.8	44.9	66.9	**33.1**
NW	25.0	19.9	44.9	55.7	**44.3**
NE	24.4	20.4	44.8	54.4	**45.6**
SE	25.9	19.0	44.9	57.6	**42.4**



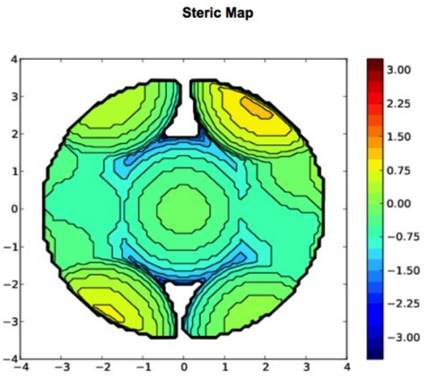
C. %VBur for **2b** with real C-Ag distance, sphere radius of 3.5 Å.



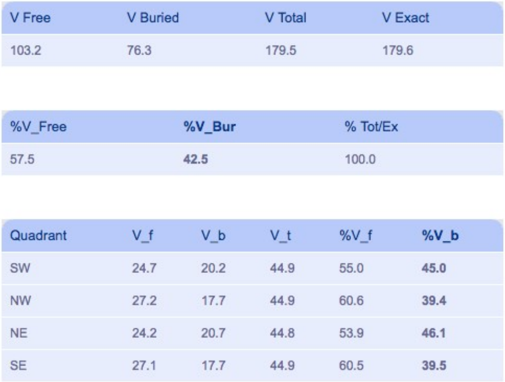
V Free	V Buried	V Total	V Exact
102.7	76.8	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
57.2	**42.8**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	25.2	19.7	44.9	56.1	**43.9**
NW	26.6	18.2	44.9	59.4	**40.6**
NE	23.4	21.4	44.8	52.2	**47.8**
SE	27.4	17.4	44.9	61.1	**38.9**



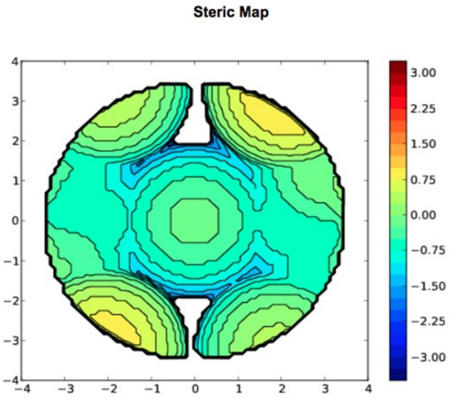
D. %VBur for **2b** with distance C-Ag normalized at 2.1 Å, sphere radius 3.5 Å.



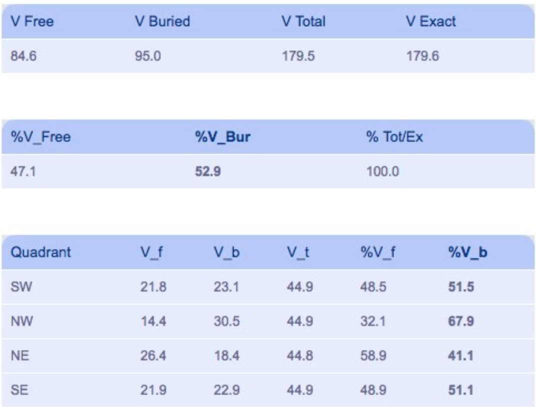
V Free	V Buried	V Total	V Exact
103.2	76.3	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
57.5	**42.5**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	24.7	20.2	44.9	55.0	**45.0**
NW	27.2	17.7	44.9	60.6	**39.4**
NE	24.2	20.7	44.8	53.9	**46.1**
SE	27.1	17.7	44.9	60.5	**39.5**



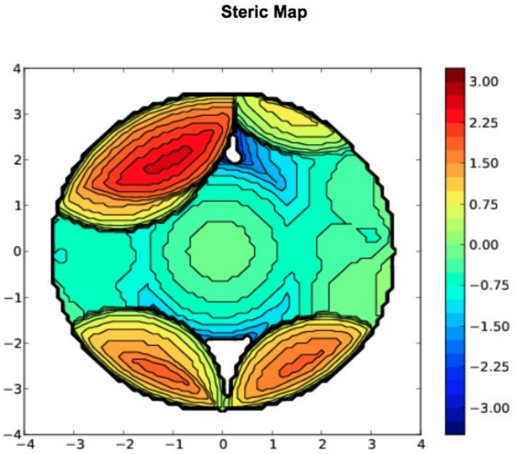
E. %VBur for **2e** with real C-Ag distance, sphere radius of 3.5 Å.



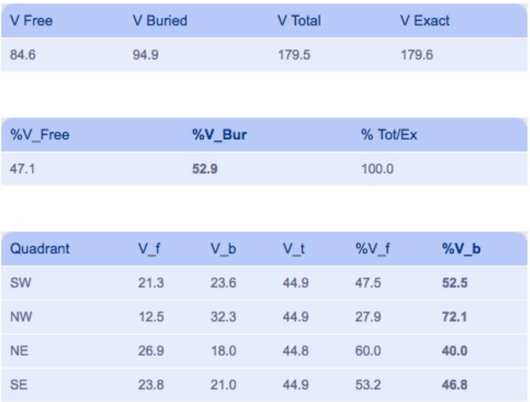
V Free	V Buried	V Total	V Exact
84.6	95.0	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
47.1	**52.9**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	21.8	23.1	44.9	48.5	**51.5**
NW	14.4	30.5	44.9	32.1	**67.9**
NE	26.4	18.4	44.8	58.9	**41.1**
SE	21.9	22.9	44.9	48.9	**51.1**



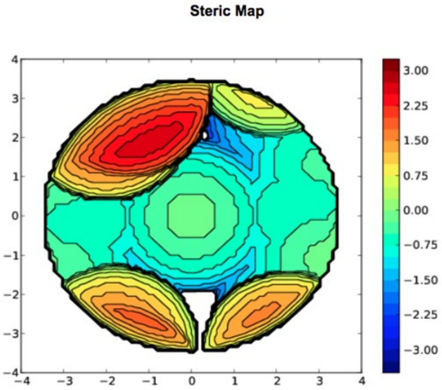
F. %VBur for **4a** with distance C-Ag normalized at 2.1 Å, sphere radius 3.5 Å.



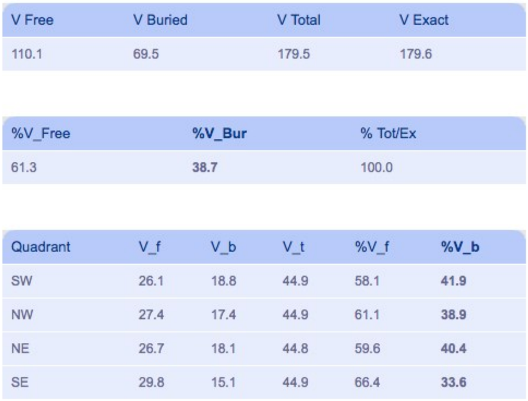
V Free	V Buried	V Total	V Exact
84.6	94.9	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
47.1	**52.9**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	21.3	23.6	44.9	47.5	**52.5**
NW	12.5	32.3	44.9	27.9	**72.1**
NE	26.9	18.0	44.8	60.0	**40.0**
SE	23.8	21.0	44.9	53.2	**46.8**



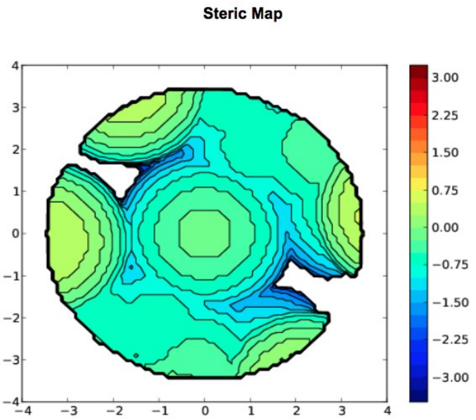
G. %VBur for **4a** with real C-Ag distance, sphere radius of 3.5 Å.



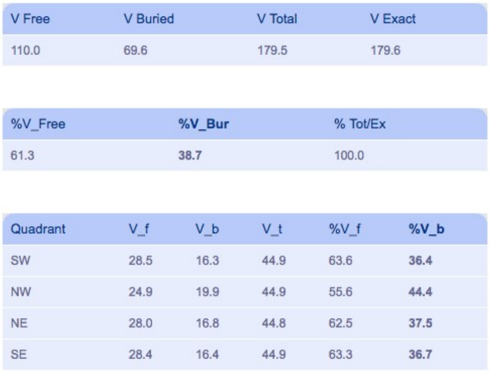
V Free	V Buried	V Total	V Exact
110.1	69.5	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
61.3	**38.7**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	26.1	18.8	44.9	58.1	**41.9**
NW	27.4	17.4	44.9	61.1	**38.9**
NE	26.7	18.1	44.8	59.6	**40.4**
SE	29.8	15.1	44.9	66.4	**33.6**



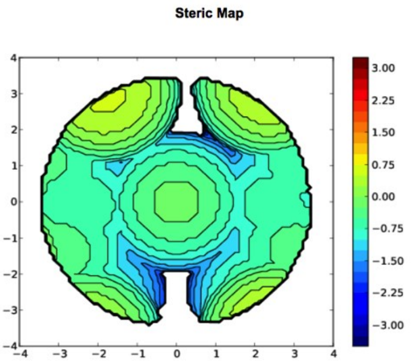
H. %VBur for **4a** with distance C-Ag normalized at 2.1 Å, sphere radius 3.5 Å.



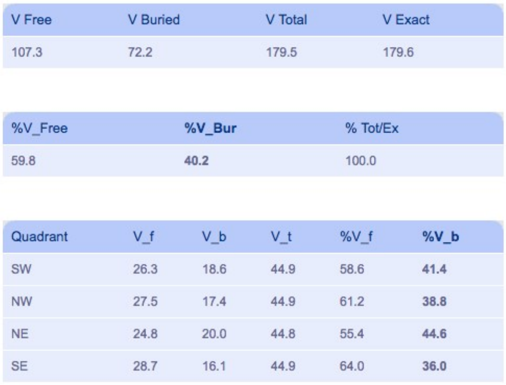
V Free	V Buried	V Total	V Exact
110.0	69.6	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
61.3	**38.7**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	28.5	16.3	44.9	63.6	**36.4**
NW	24.9	19.9	44.9	55.6	**44.4**
NE	28.0	16.8	44.8	62.5	**37.5**
SE	28.4	16.4	44.9	63.3	**36.7**



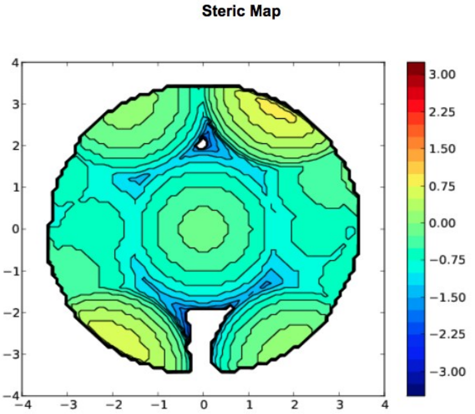
I. %VBur for **4b** with real C-Ag distance, sphere radius of 3.5 Å.



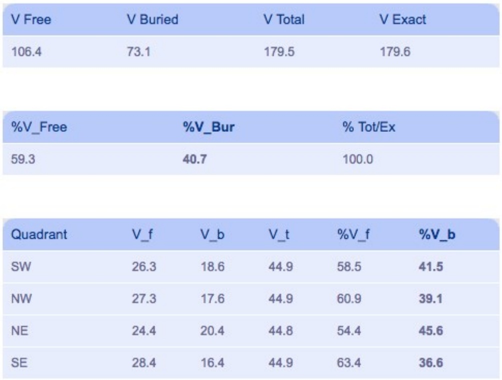
V Free	V Buried	V Total	V Exact
107.3	72.2	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
59.8	**40.2**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	26.3	18.6	44.9	58.6	**41.4**
NW	27.5	17.4	44.9	61.2	**38.8**
NE	24.8	20.0	44.8	55.4	**44.6**
SE	28.7	16.1	44.9	64.0	**36.0**



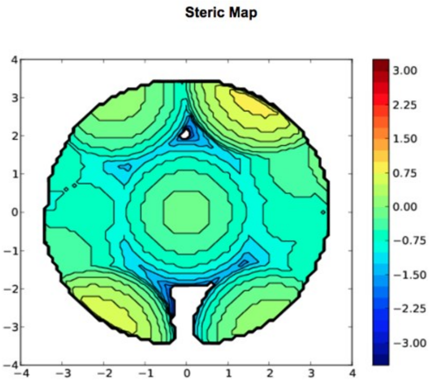
J. %VBur for **4b** with distance C-Ag normalized at 2.1 Å, sphere radius 3.5 Å.



V Free	V Buried	V Total	V Exact
106.4	73.1	179.5	179.6

%V_Free	**%V_Bur**	% Tot/Ex
59.3	**40.7**	100.0

Quadrant	V_f	V_b	V_t	%V_f	**%V_b**
SW	26.3	18.6	44.9	58.5	**41.5**
NW	27.3	17.6	44.9	60.9	**39.1**
NE	24.4	20.4	44.8	54.4	**45.6**
SE	28.4	16.4	44.9	63.4	**36.6**



V. Biological tests

Biological activity against HCT116 carcinoma cells

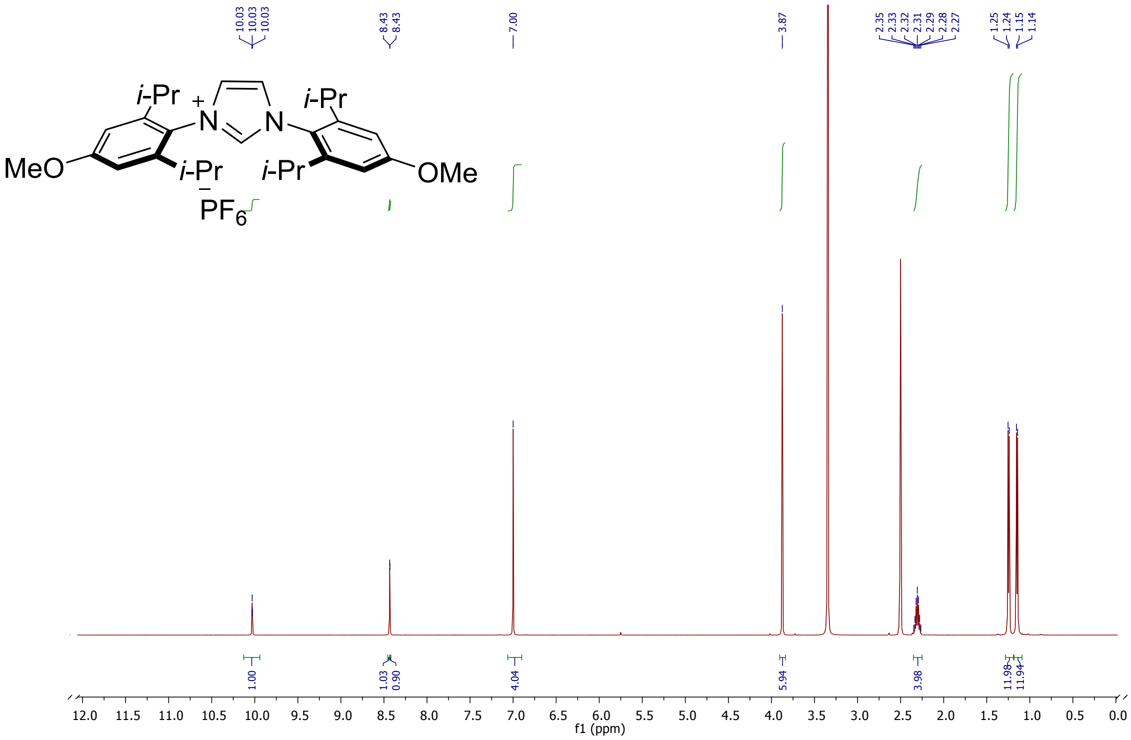
Entry	**Complex**	**% inhibition at** 10^{-5} **M**	10^{-6} **M**	**IC$_{50}$ (nM)**
1	**2a**	100 ± 0.1	88 ± 1	259 ± 37.3
2	**2b**	99 ± 0.1	91 ± 1	96.8 ± 2.9
3	**2c**	100 ± 0.1	88 ± 1	616 ± 5.3
4	**2d**	11 ± 2	11 ± 3	n.d.[a]
5	**2e**	8 ± 2	2 ± 1	n.d.[a]
6	**2f**	100 ± 0.1	90 ± 1	390 ± 20
7	**4a**	100 ± 0.1	83 ± 1	35.4 ± 0.9
8	**4b**	100 ± 0.1	85 ± 0.9	24.9 ± 3.2
9	**4c**	99 ± 0.3	91 ± 0.4	174 ± 48.8
10	**4f**	27 ± 1	9 ± 1	n.d.[a]
11	**4g**	98 ± 0.3	12 ± 1	2181 ± 276
12	**4h**	100 ± 1	39 ± 3	293 ± 60
13	**4i**	99 ± 0.1	8 ± 1	n.d.[a]
14	**4j**	86 ± 0.6	87 ± 1	140 ± 10
15	**5a**	93 ± 0.2	88 ± 0.6	35.6 ± 2
16	**5b**	86 ± 0.2	89 ± 1	42.2 ± 2.4
17	**5c**	76 ± 4	23 ± 5	n.d.[a]
18	**5d**	95 ± 0.6	86 ± 1	21 ± 1.6
19	**5e**	99 ± 0.1	40 ± 5	n.d.[a]
20	**5f**	100 ± 0.1	71 ± 3	163 ± 44
21	Doxorubicin			810 ± 110
22	cisplatin			5370 ± 150

[a] n.d.= not determined.

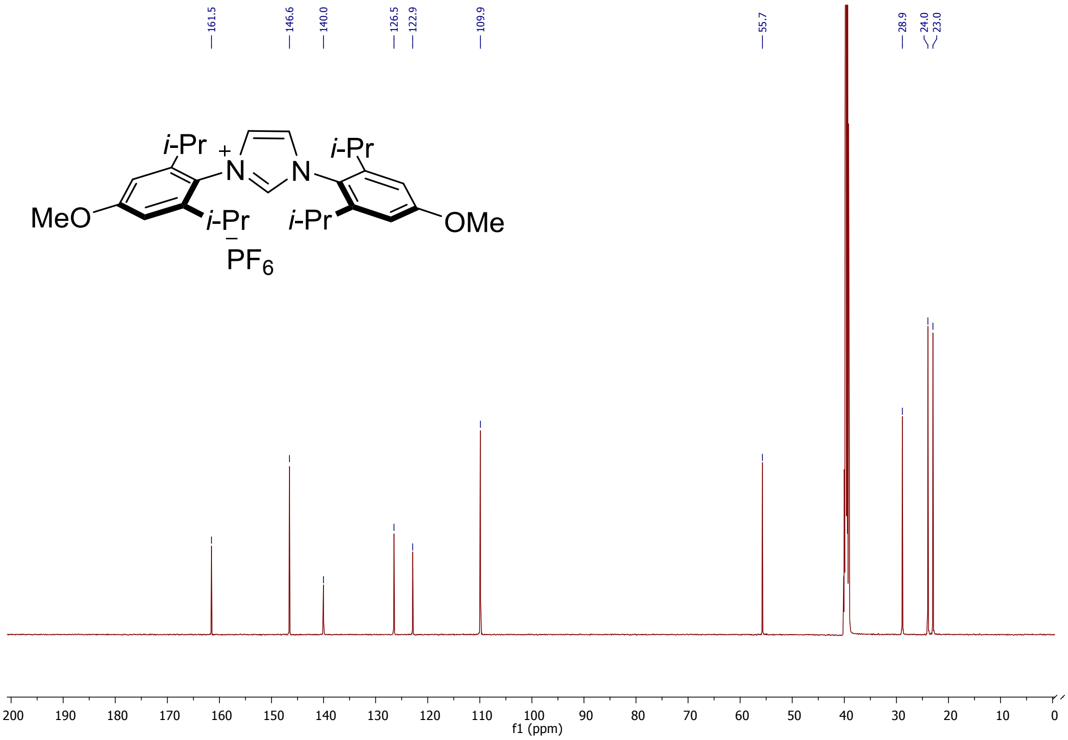
VI. SPECTRA

[1,3-Bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate 3a

^{1}H NMR (500 MHz, DMSO-d_6)

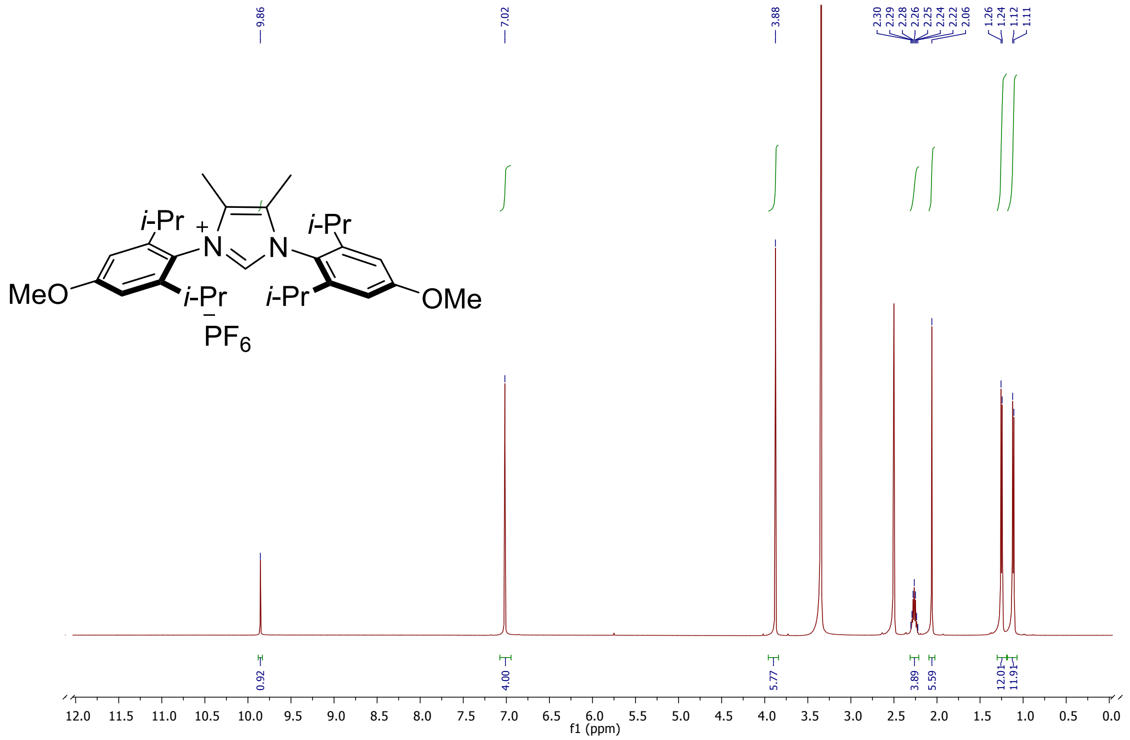


^{13}C NMR (126 MHz, DMSO-d_6)

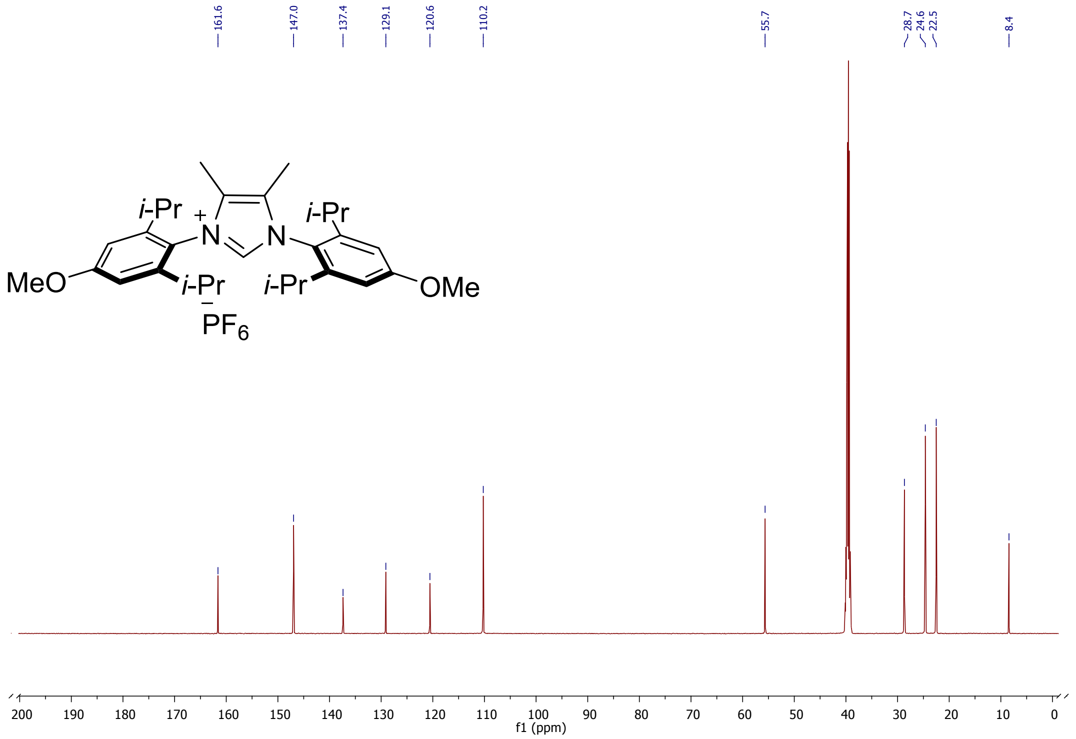


[4,5-Dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazolium hexafluorophosphate 3b

^{1}H NMR (500 MHz, DMSO-d_6)

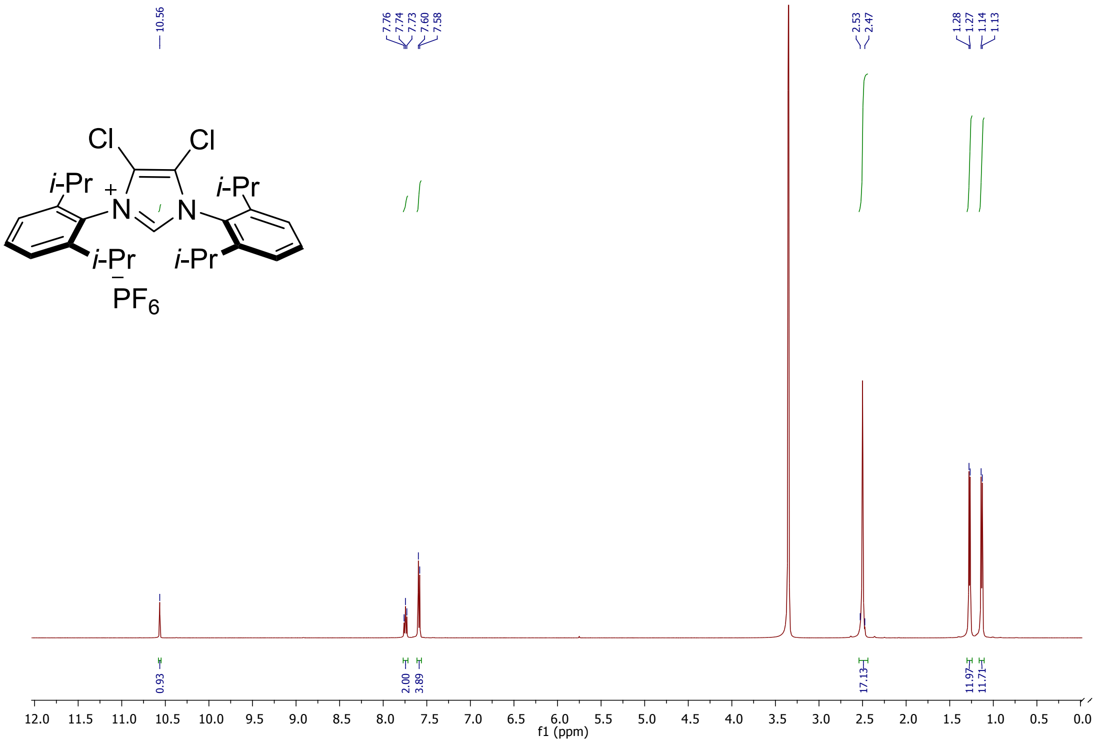


^{13}C NMR (126 MHz, DMSO-d_6)

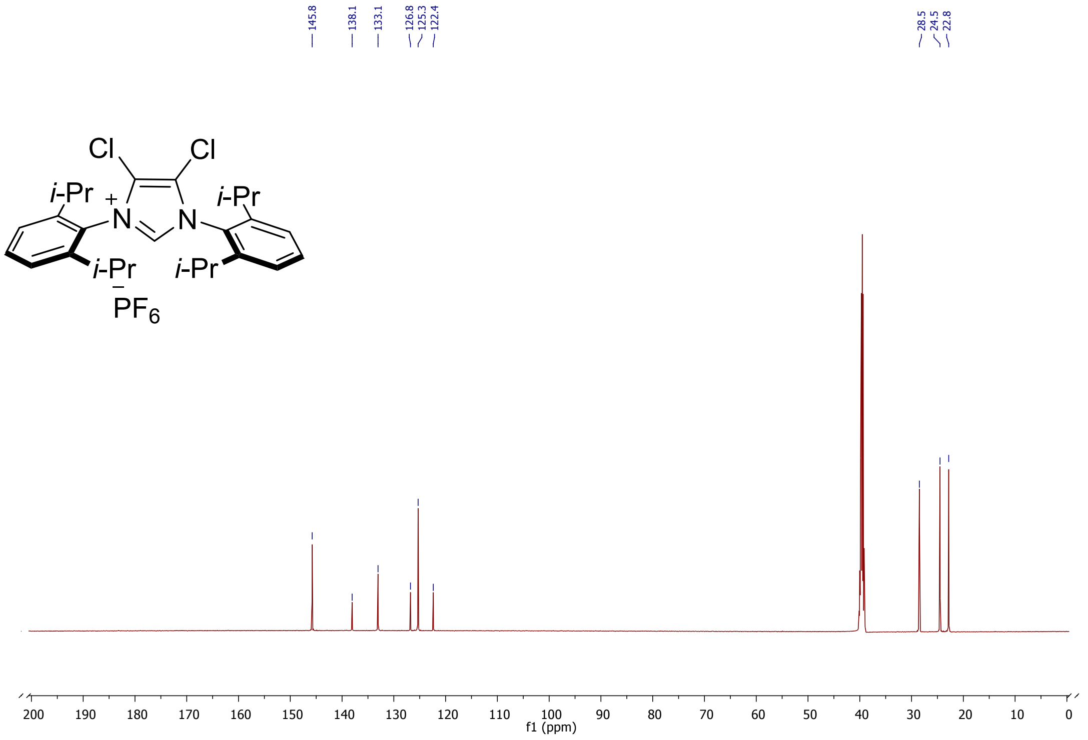


[1,3-Bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazolium hexafluorophosphate 3c

^{1}H NMR (500 MHz, DMSO-*d$_6$*)

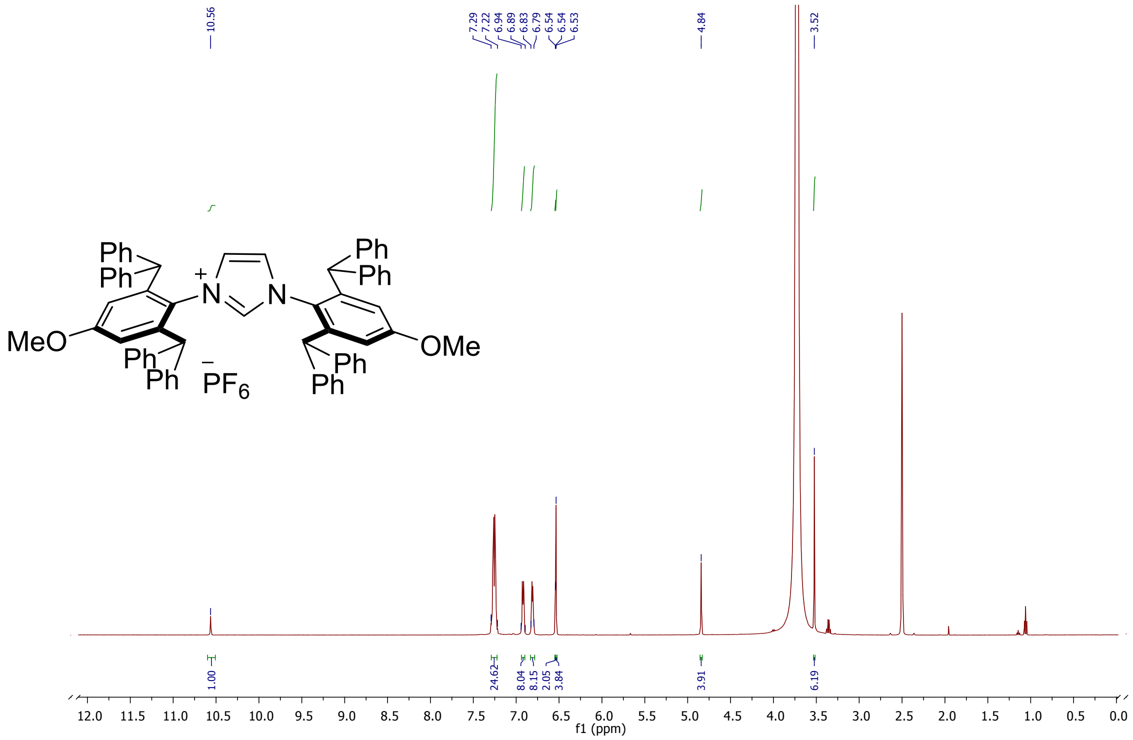


^{13}C NMR (126 MHz, DMSO-*d$_6$*)

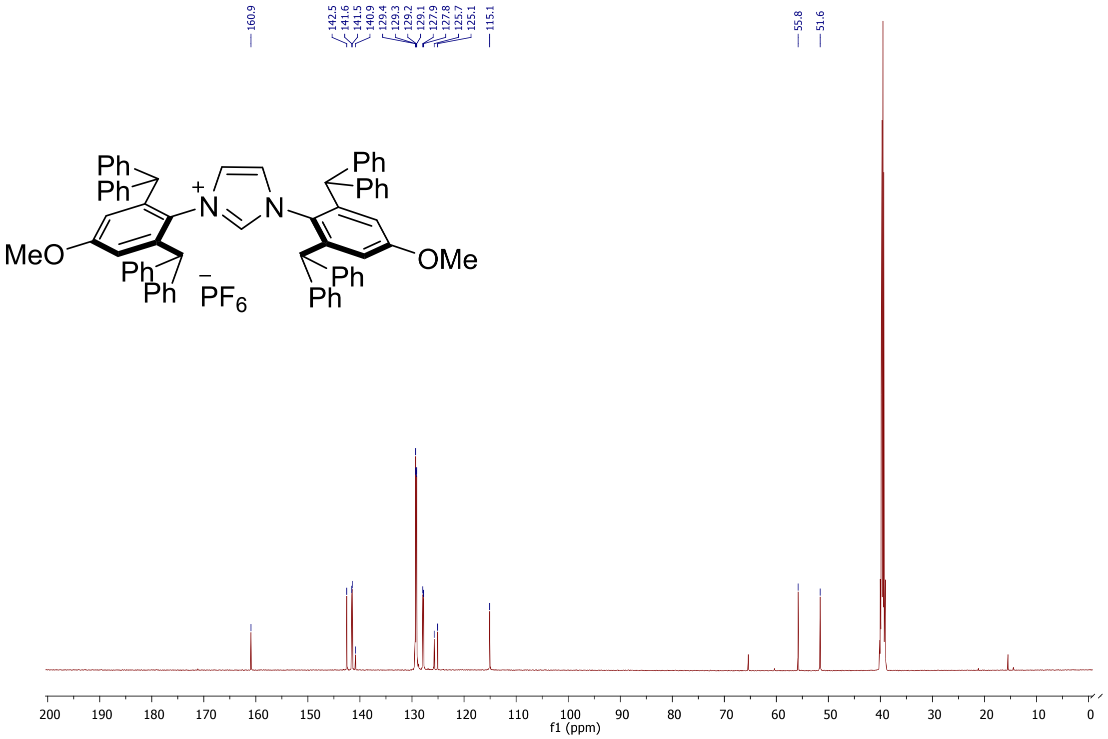


[1,3-Bis(4-methoxy-2,6-diphenyl)phenyl]imidazolium hexafluorophosphate 3d

^{1}H NMR (500 MHz, DMSO-d_6)

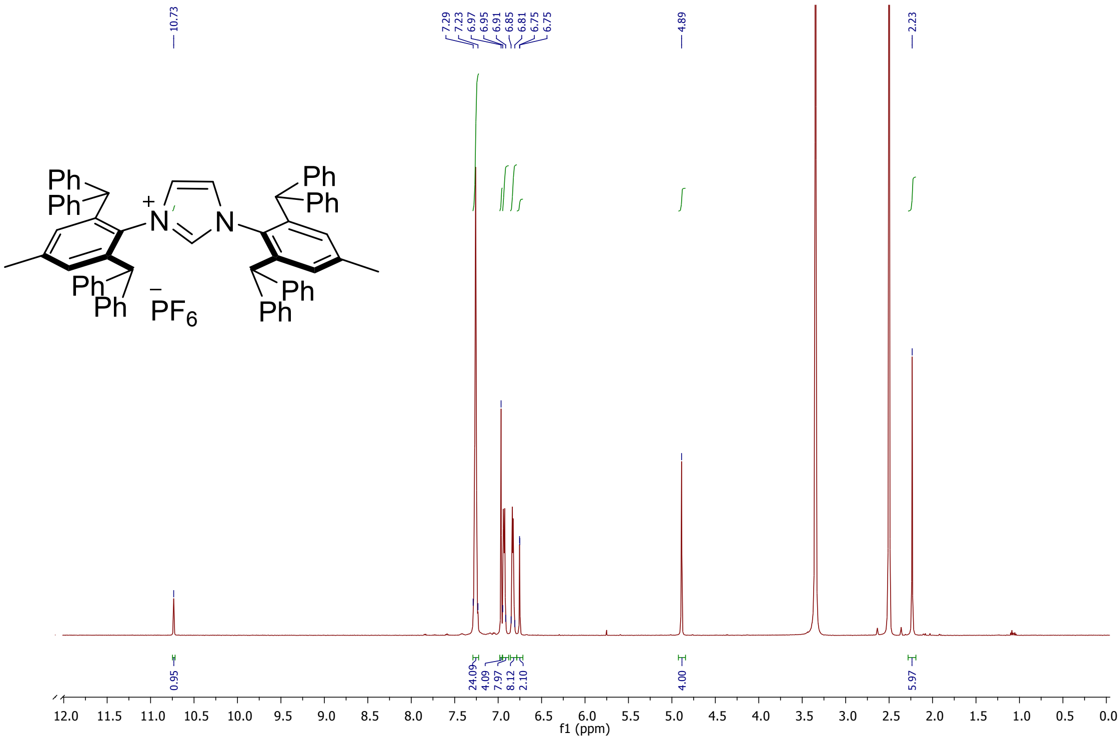


^{13}C NMR (126 MHz, DMSO-d_6)

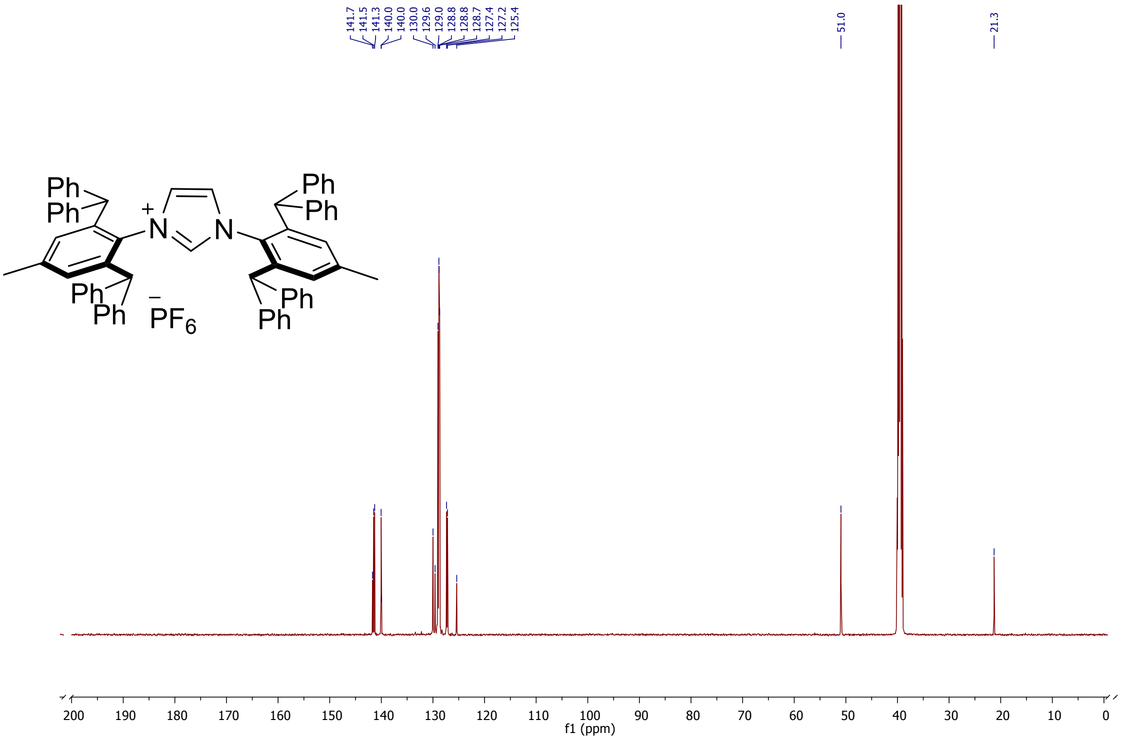


[1,3-Bis(4-methyl-2,6-diphenyl)phenyl]imidazolium hexafluorophosphate 3e

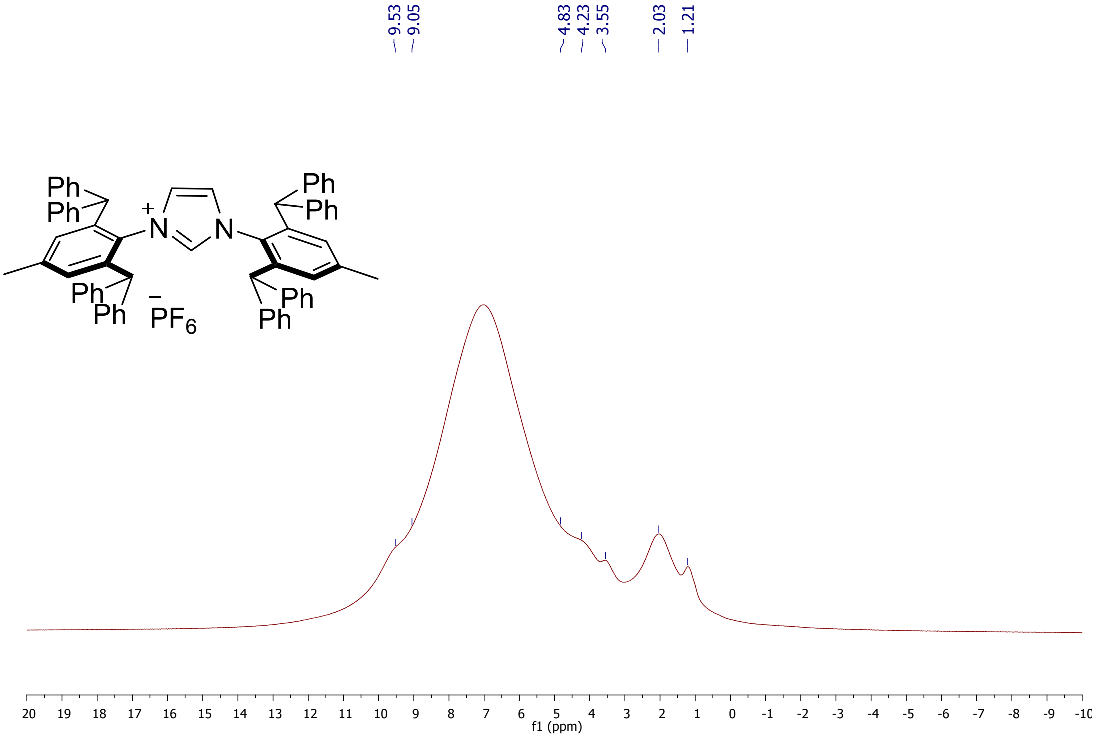
^{1}H NMR (500 MHz, DMSO-d_6)



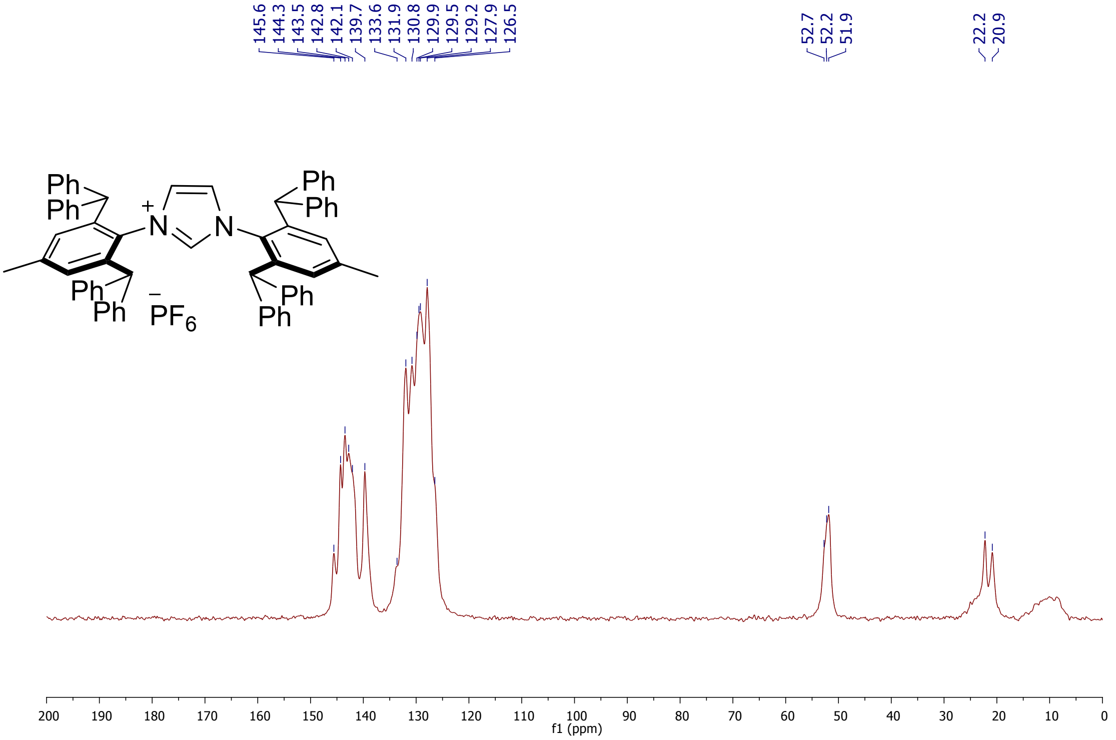
^{13}C NMR (126 MHz, DMSO-d_6)



^{1}H solid state HR-MAS NMR (600 MHz)

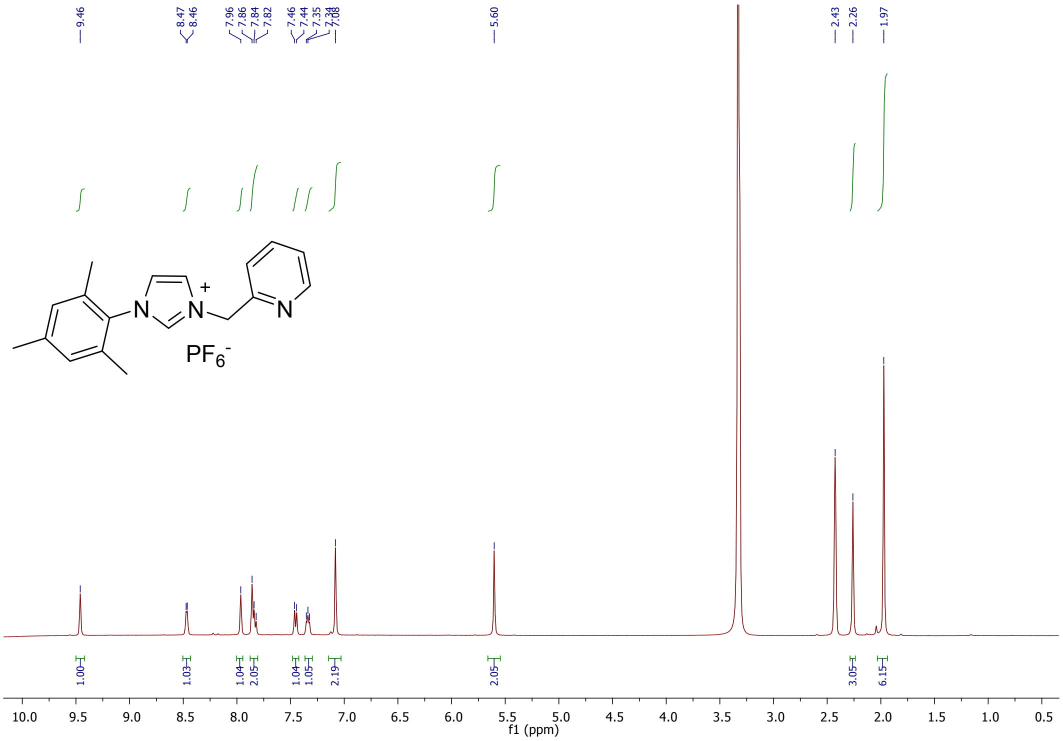


^{13}C solid state HR-MAS NMR (151 MHz)

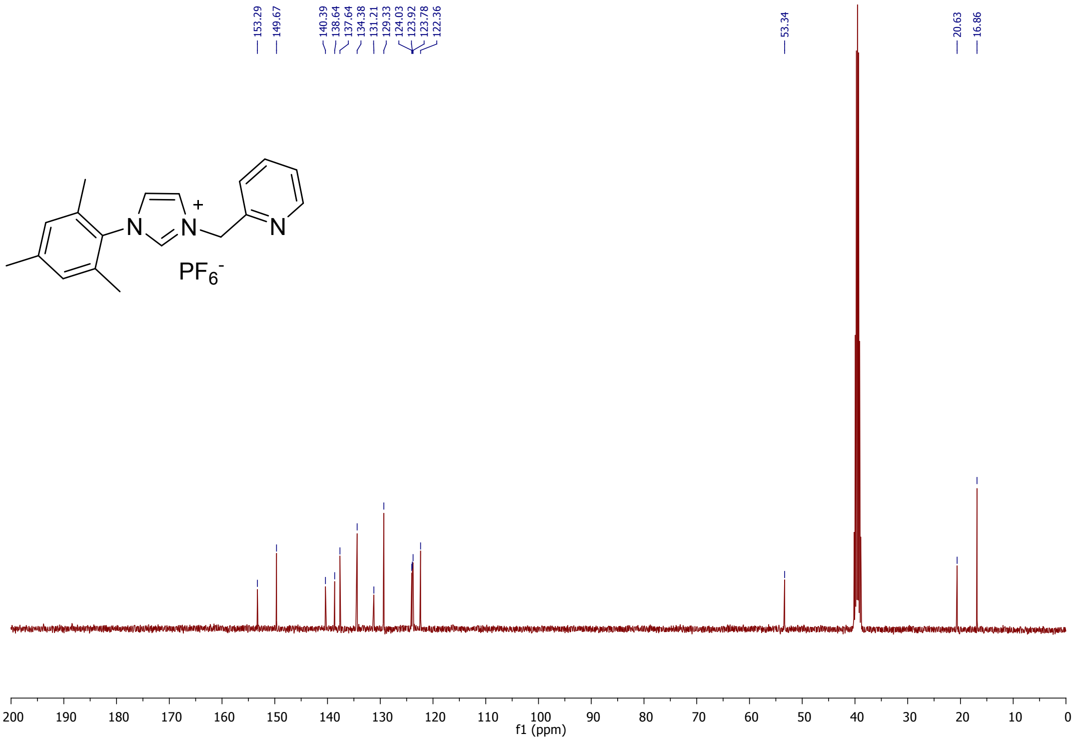


1-mesityl-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium hexafluorophosphate(V) 3f

^{1}H NMR (400 MHz, DMSO-d_6)

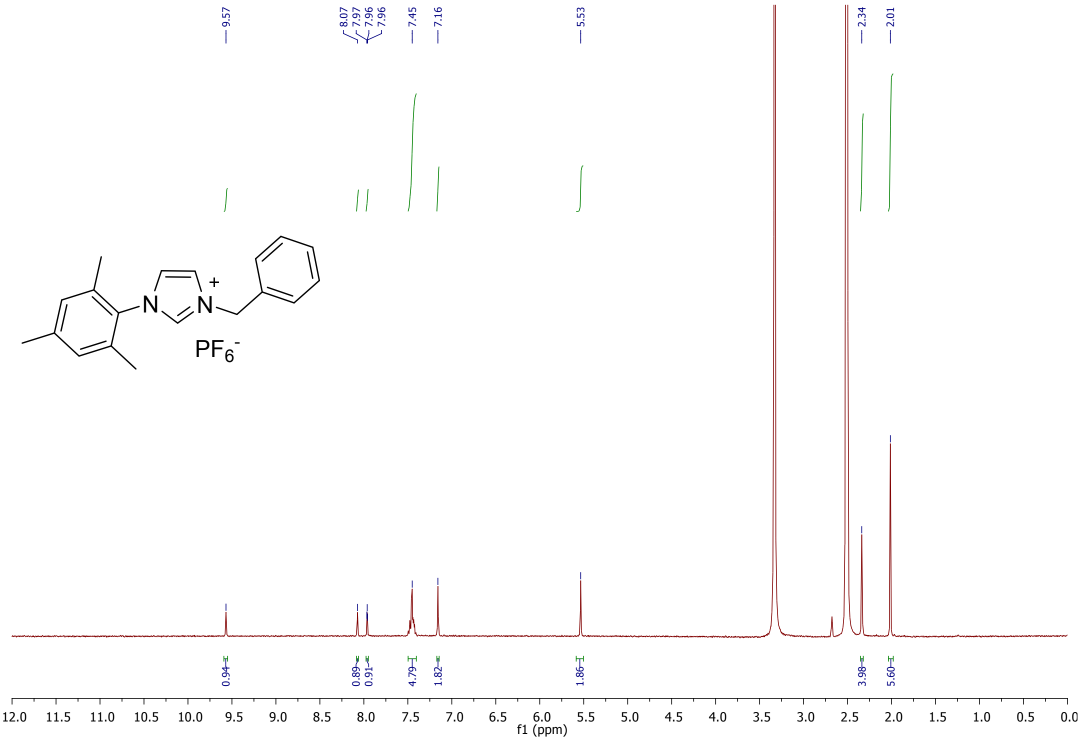


^{13}C NMR (101 MHz, DMSO-d_6)

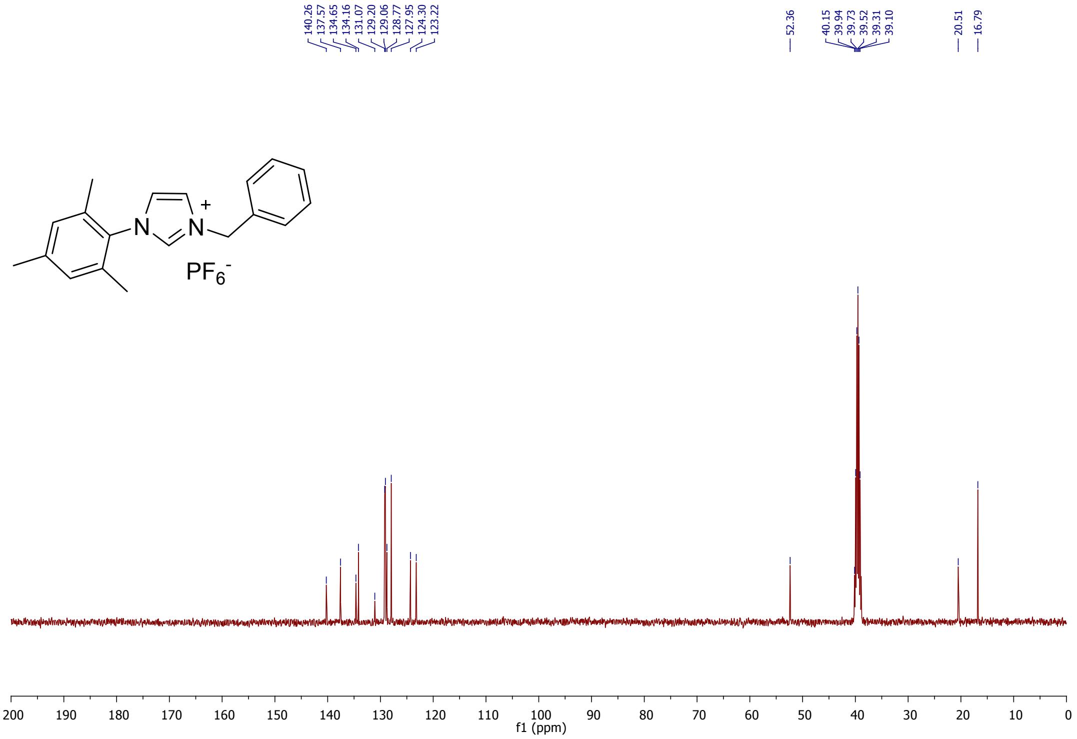


1-Benzyl-3-mesitylimidazolium hexafluorophosphate(V) 3g

^{1}H NMR (400 MHz, DMSO-d_6)

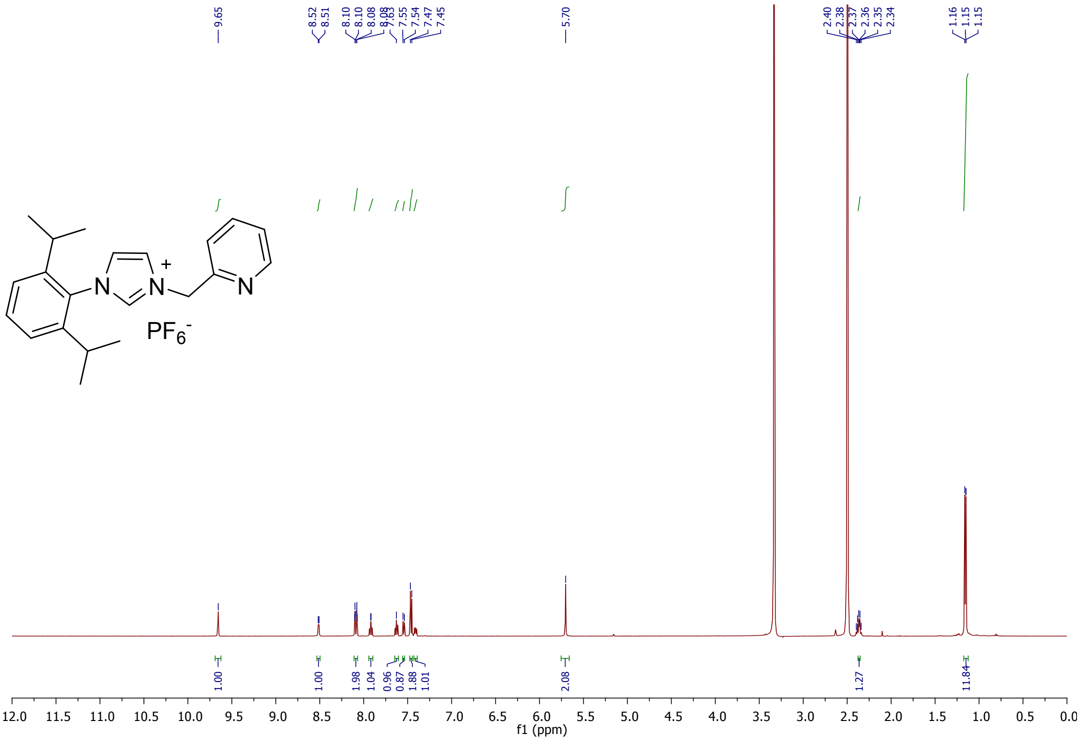


^{13}C NMR (101 MHz, DMSO-d_6)

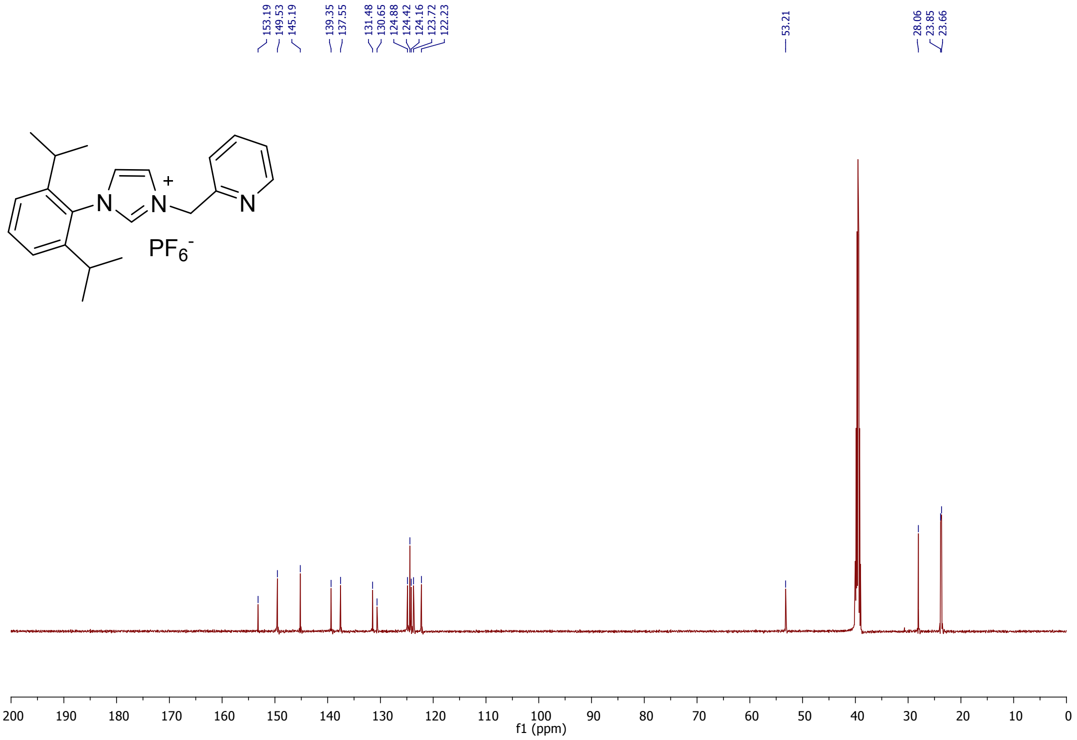


1-(2,6-diisopropylphenyl)-3-(pyridin-2-ylmethyl)-1H-imidazol-3-ium hexafluorophosphate(V) 3h

^{1}H NMR (500 MHz, DMSO-d_6)

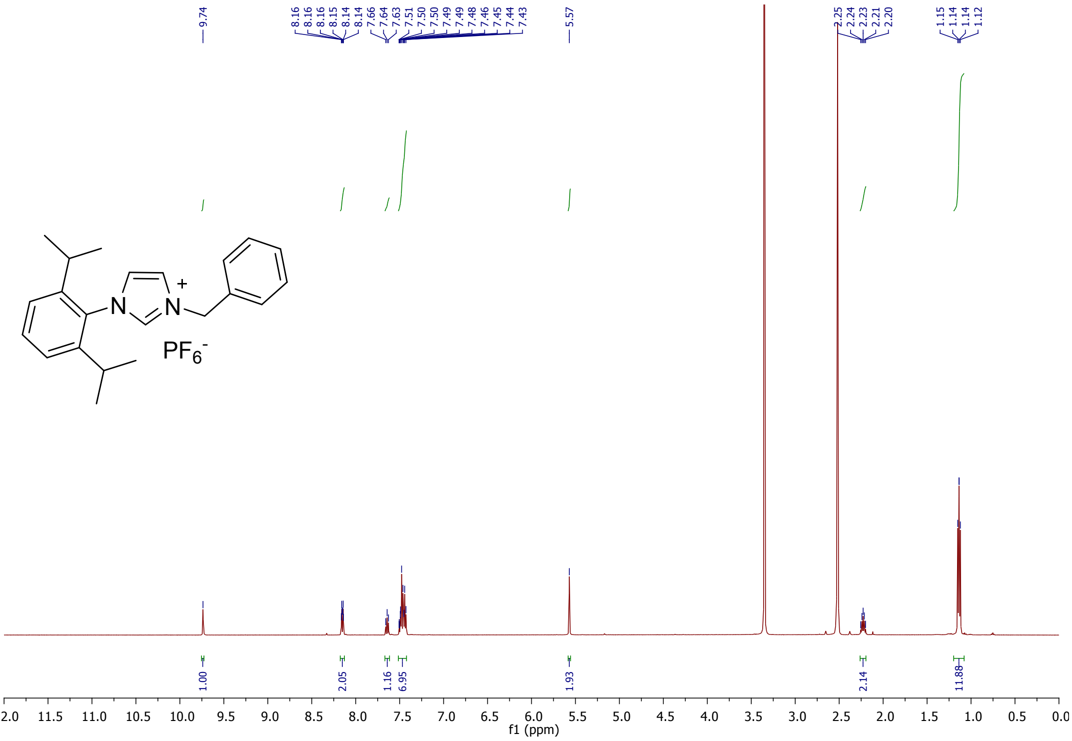


^{13}C NMR (125 MHz, DMSO-d_6)

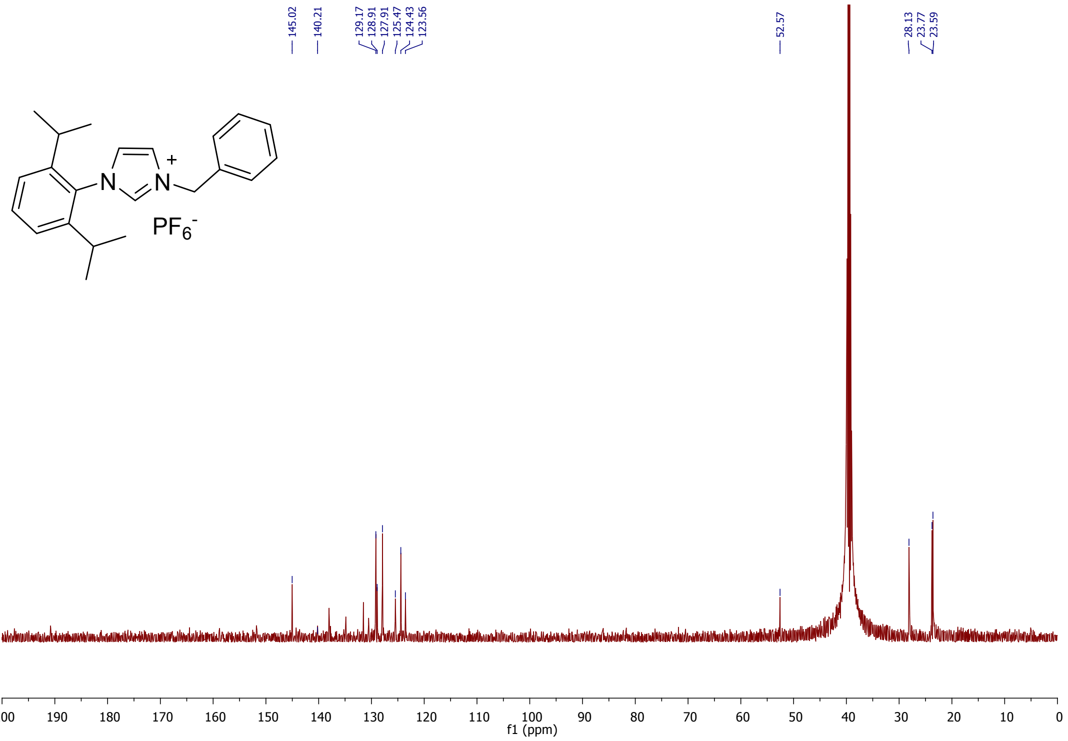


3-benzyl-1-(2,6-diisopropylphenyl)-1H-imidazol-3-ium hexafluorophosphate(V) 3i

^{1}H NMR (500 MHz, DMSO-d_6)

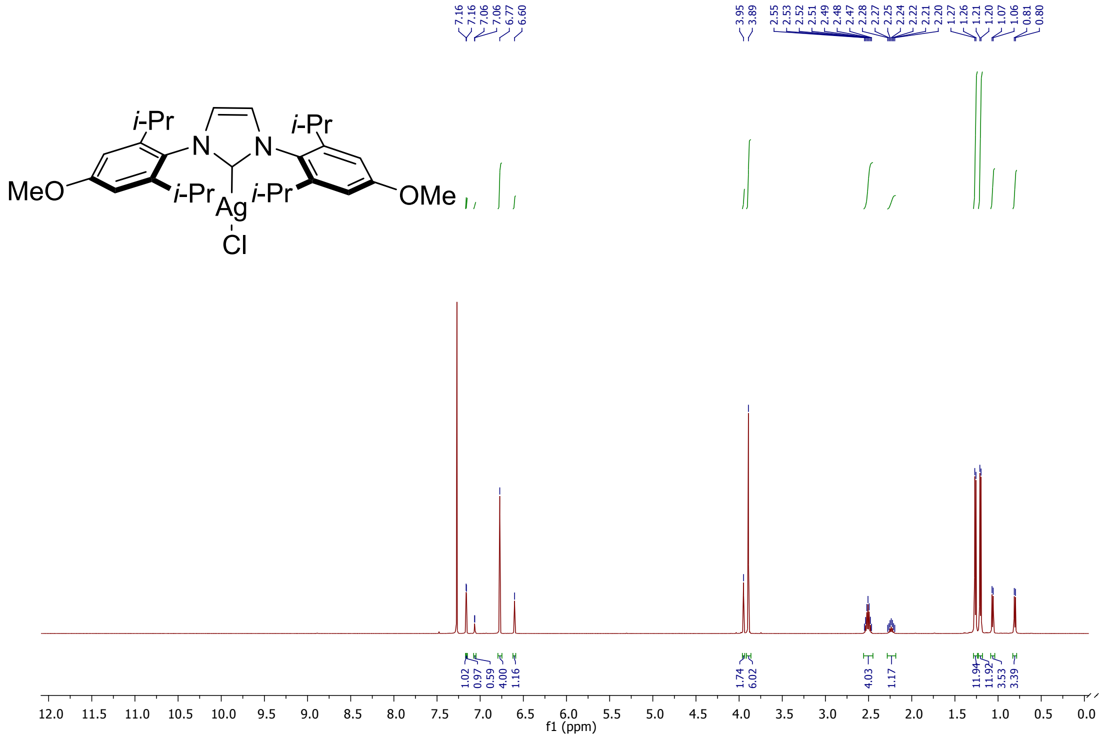


^{13}C NMR (125 MHz, DMSO-d_6)

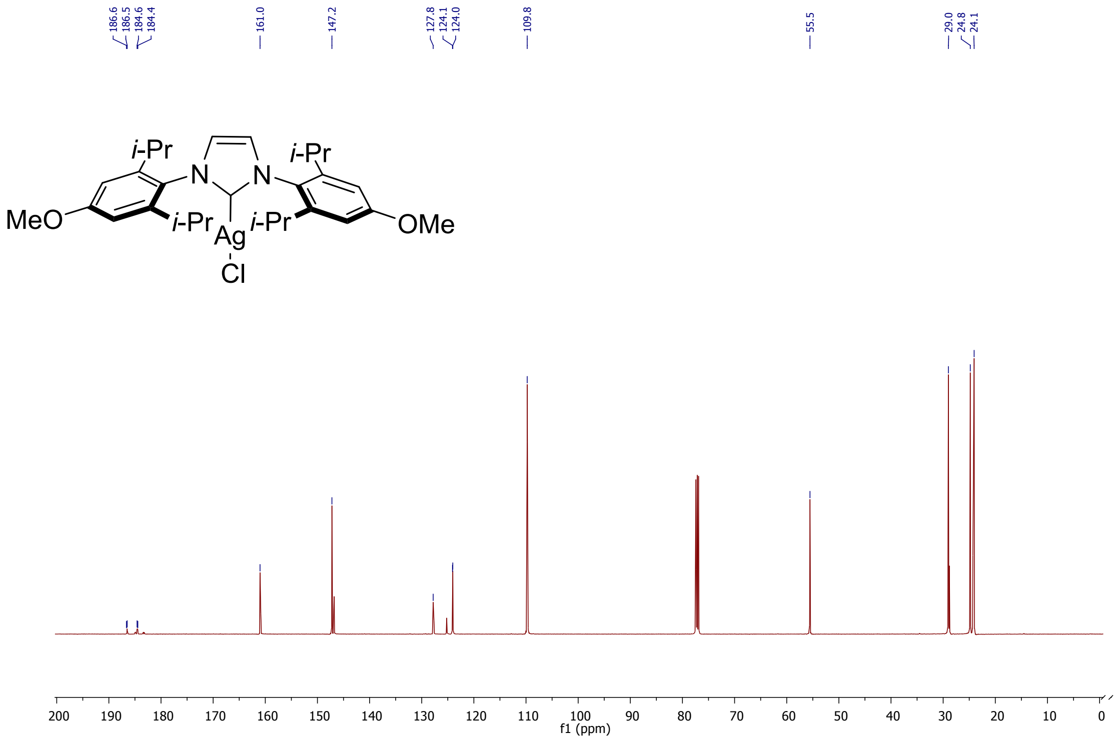


[[1,3-Bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver chloride 2a

^{1}H NMR (500 MHz, CDCl$_3$)

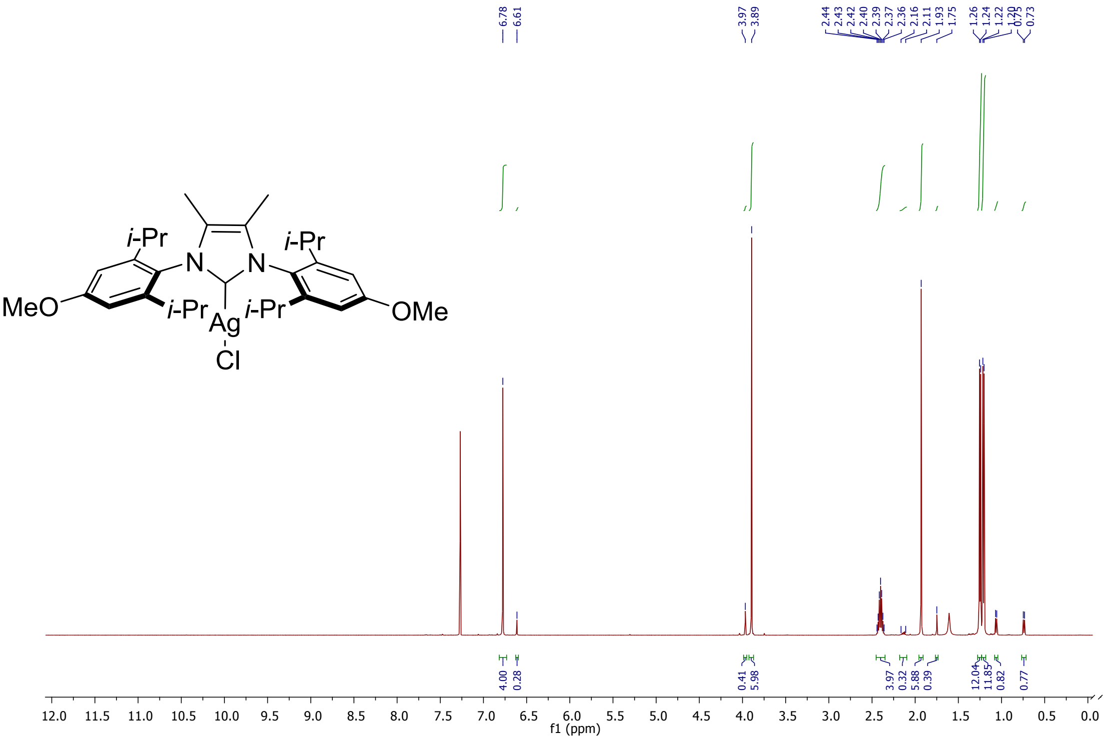


^{13}C NMR (126 MHz, CDCl$_3$)

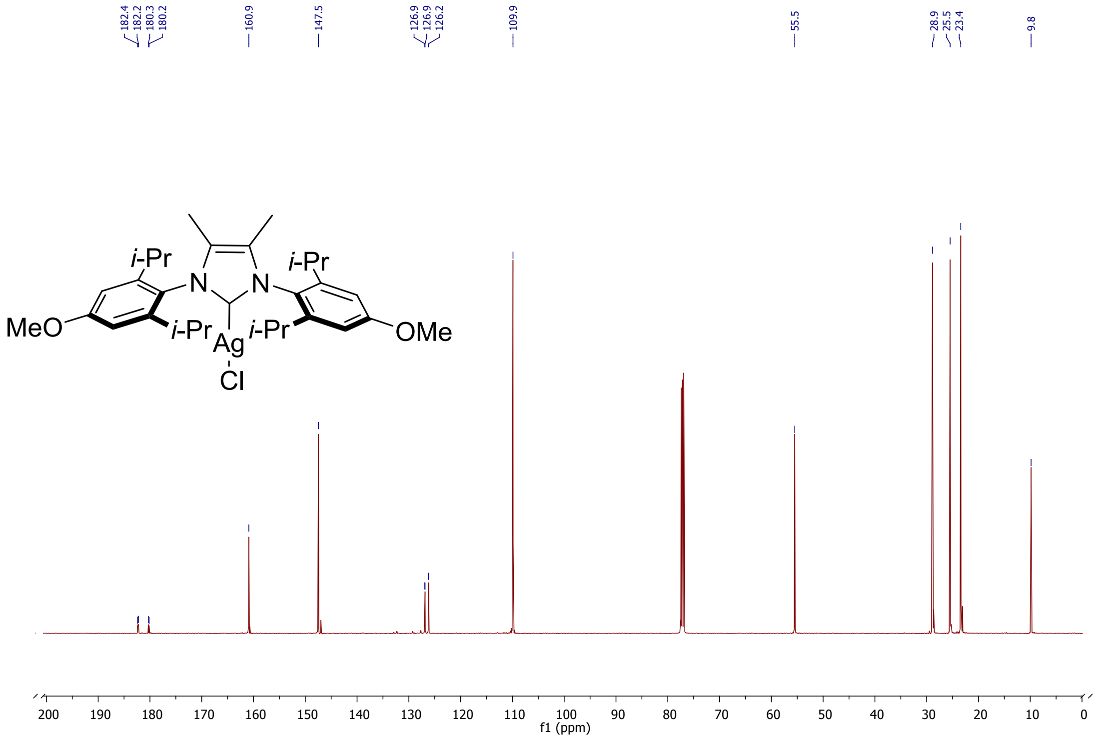


[[4,5-Dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver chloride 2b

^{1}H NMR (500 MHz, CDCl$_3$)

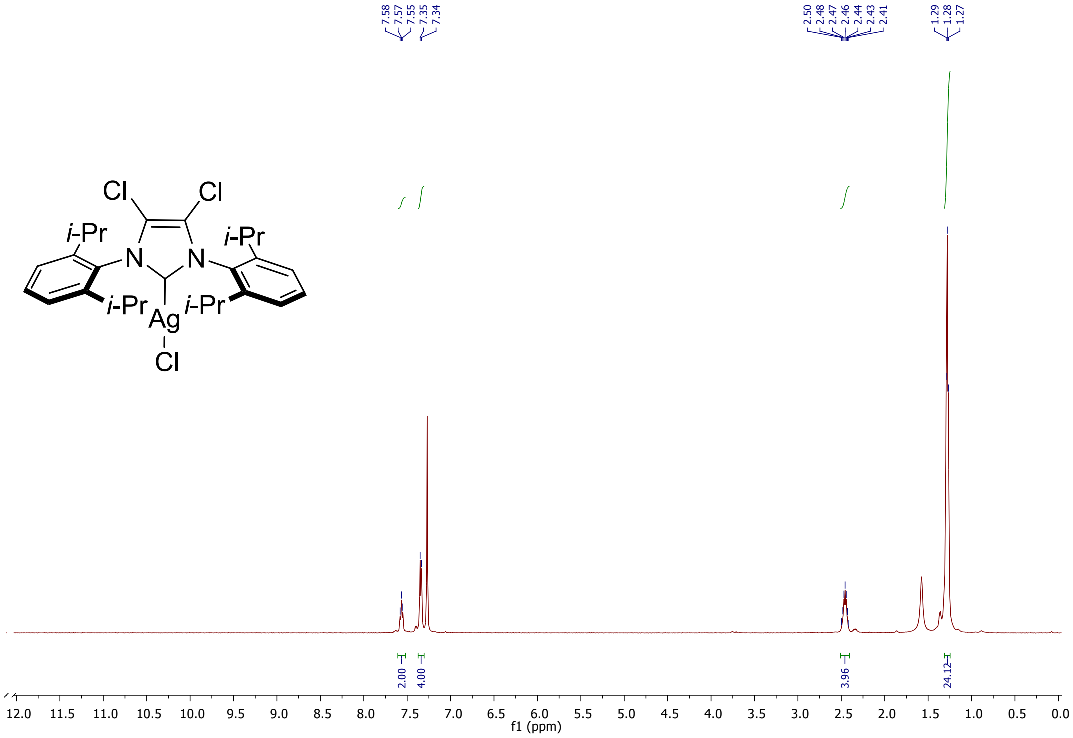


^{13}C NMR (126 MHz, CDCl$_3$)

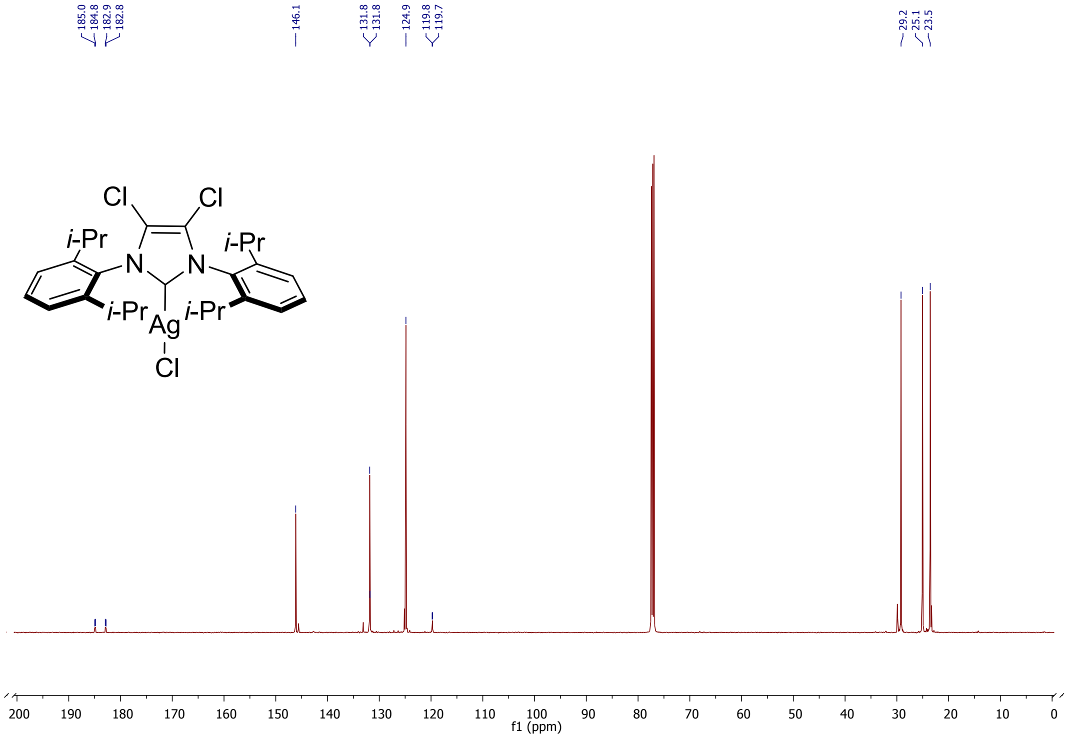


[[1,3-Bis(2,6-di*iso*propylphenyl)-4,5-dichloro]imidazol-2-ylidene]silver chloride 2c

^{1}H NMR (500 MHz, CDCl$_3$)

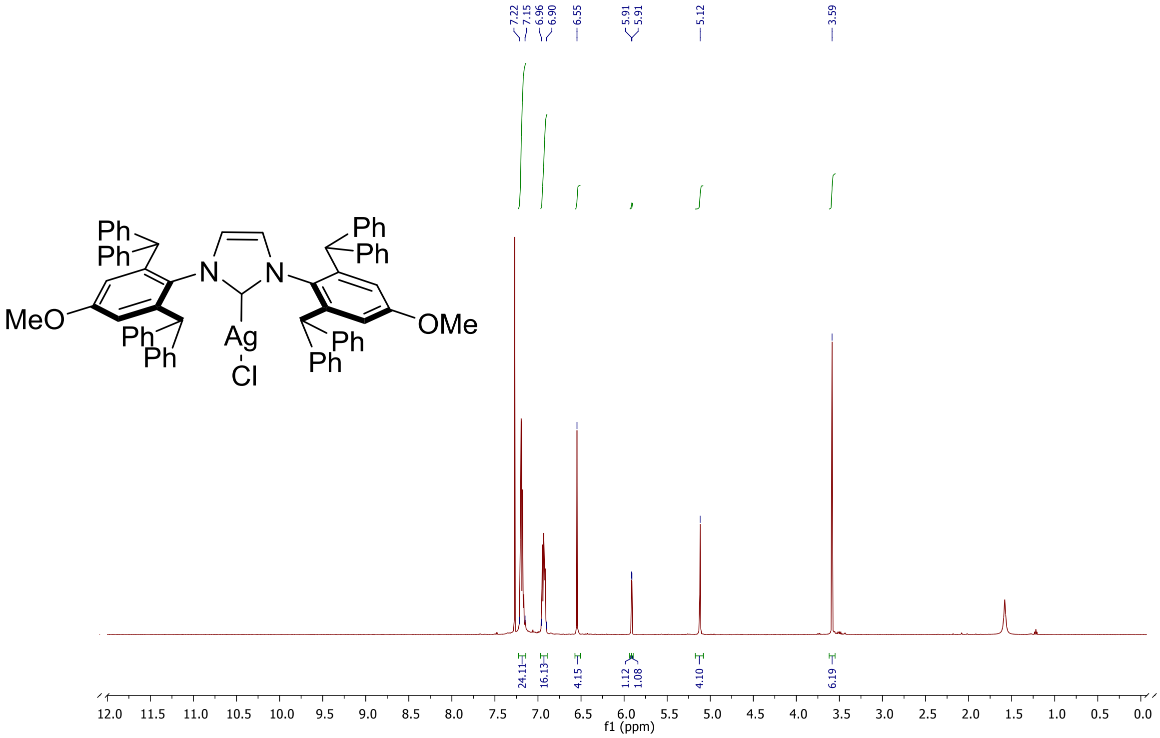


^{13}C NMR (126 MHz, CDCl$_3$)

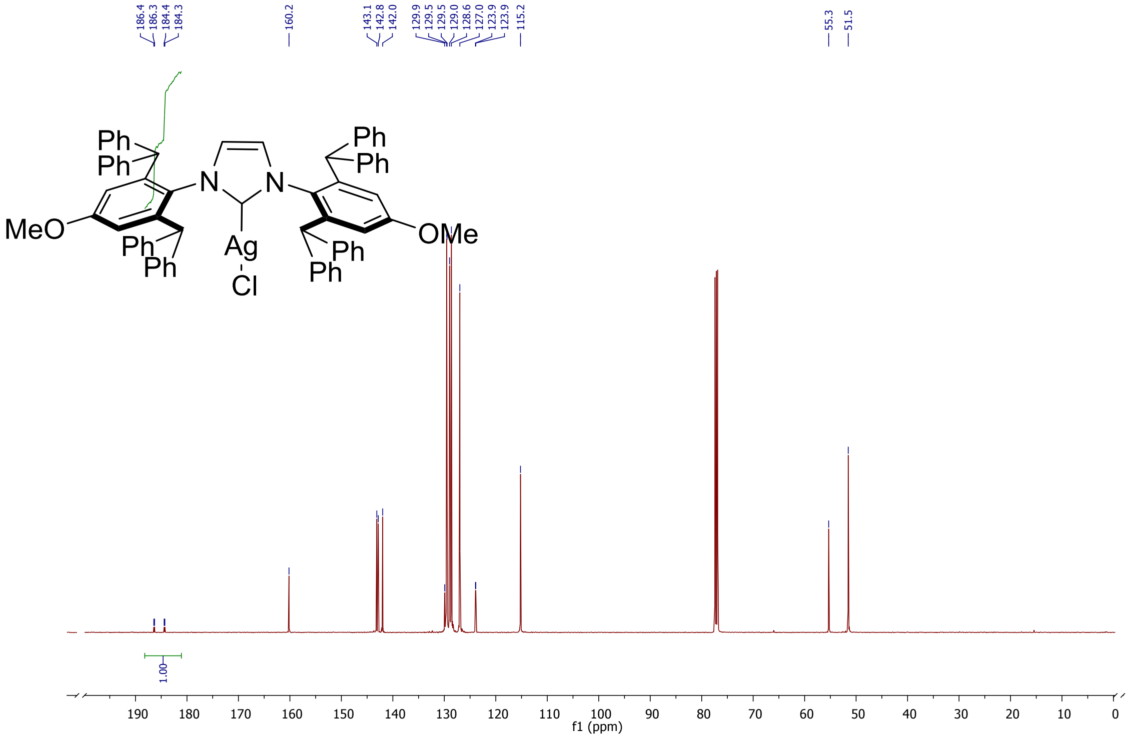


[[1,3-Bis(4-methoxy-2,6-diphenyl)phenyl]imidazol-2-ylidene]silver chloride 2d

^{1}H NMR (500 MHz, $CDCl_3$)

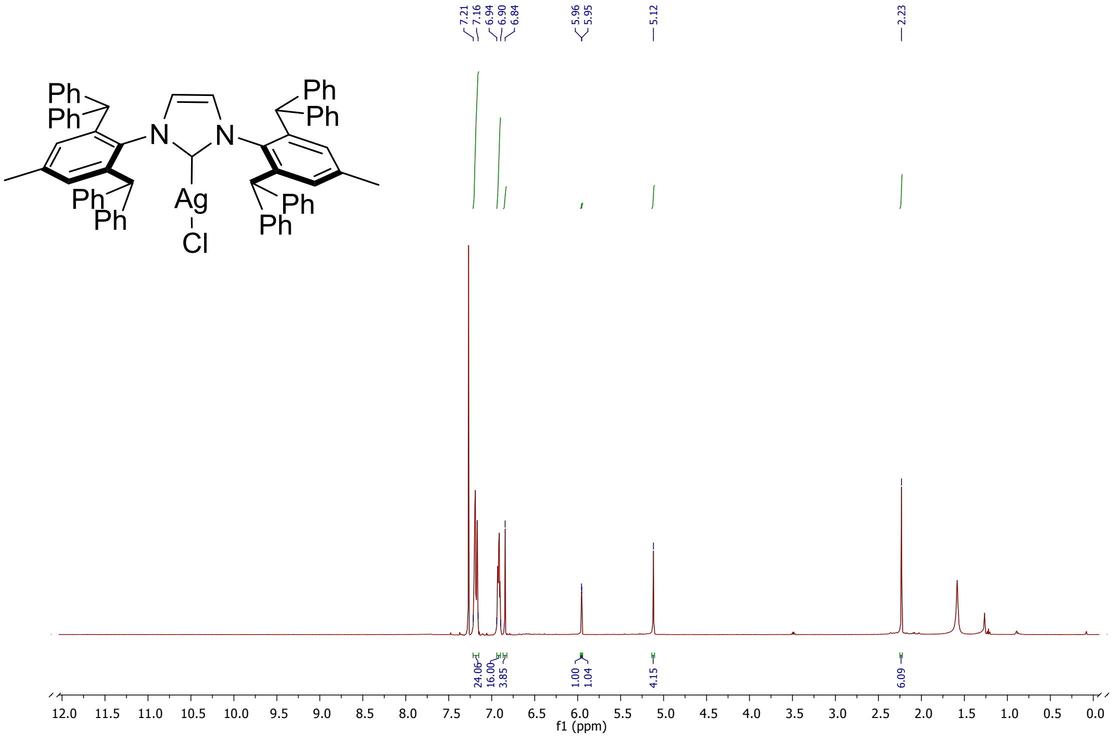


^{13}C NMR (126 MHz, $CDCl_3$)

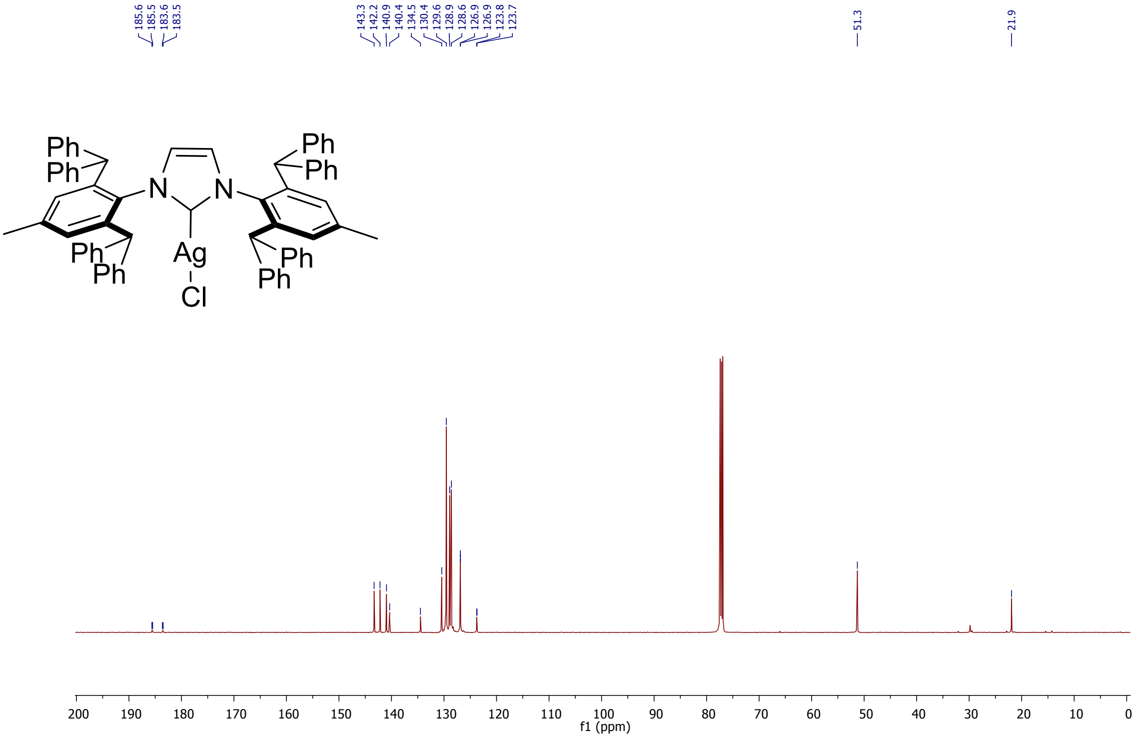


[[1,3-Bis(4-methyl-2,6-diphenyl)phenyl]imidazol-2-ylidene]silver chloride 2e

^{1}H NMR (500 MHz, CDCl$_3$)

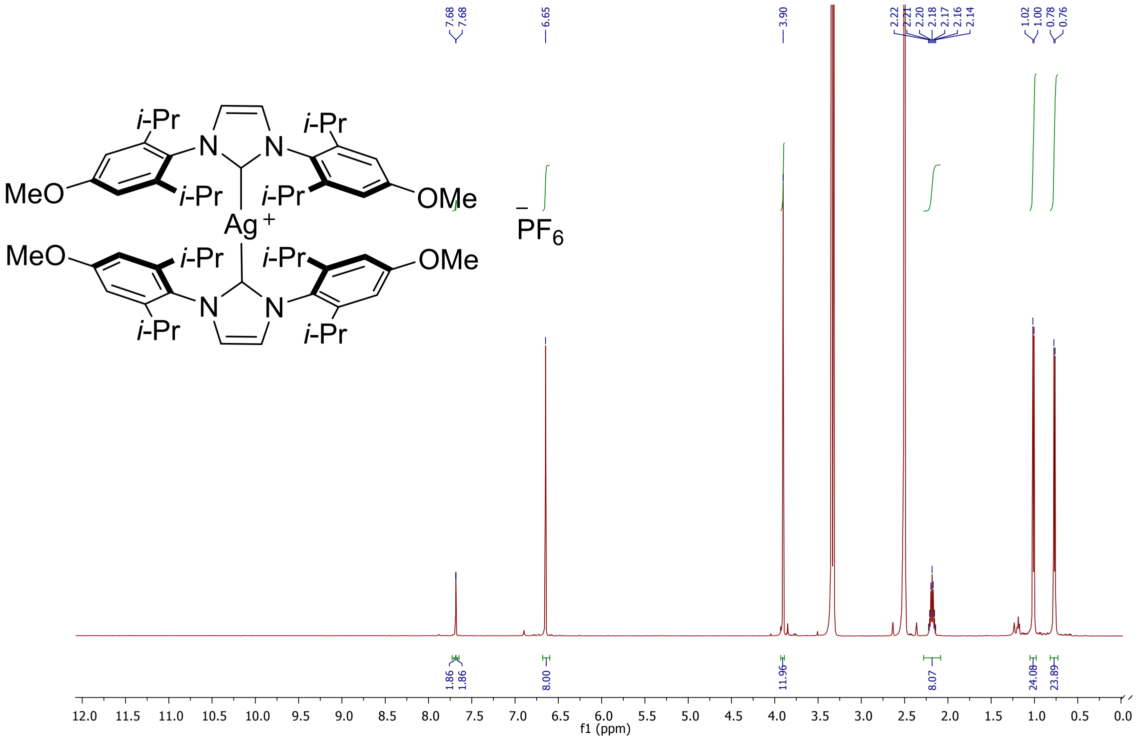


^{13}C NMR (126 MHz, CDCl$_3$)

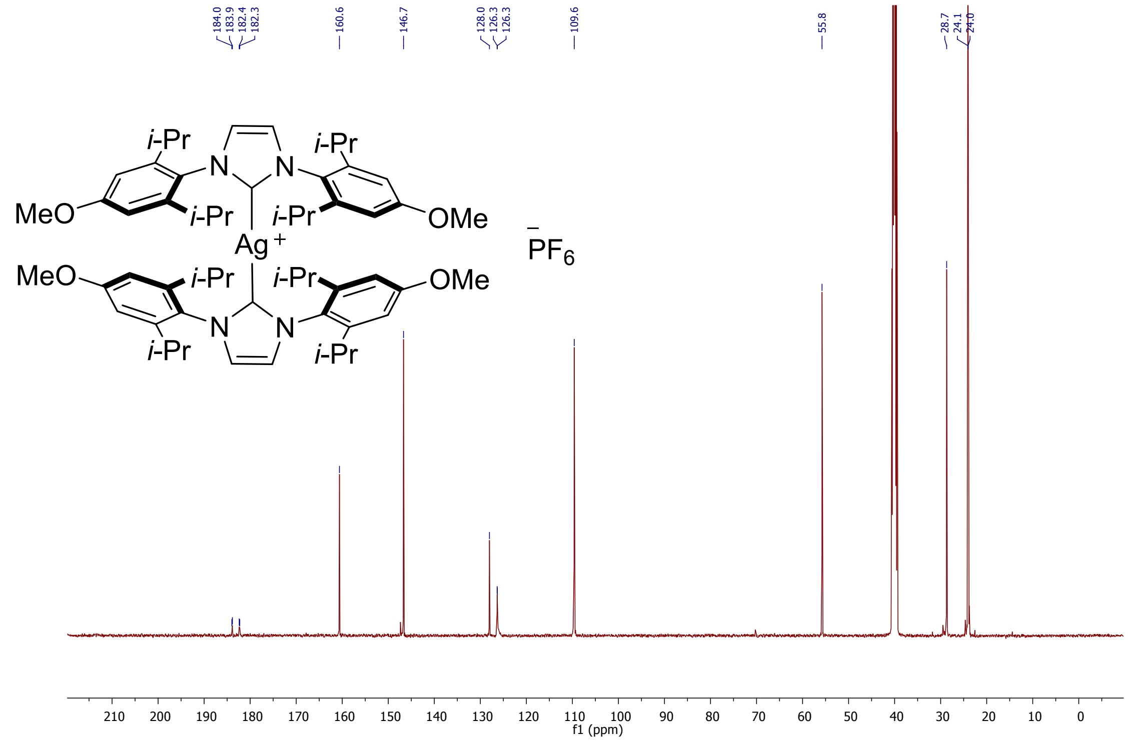


Bis[(1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl]imidazol-2-ylidene]silver hexafluorophosphate 4a

^{1}H NMR (500 MHz, DMSO-d_6)

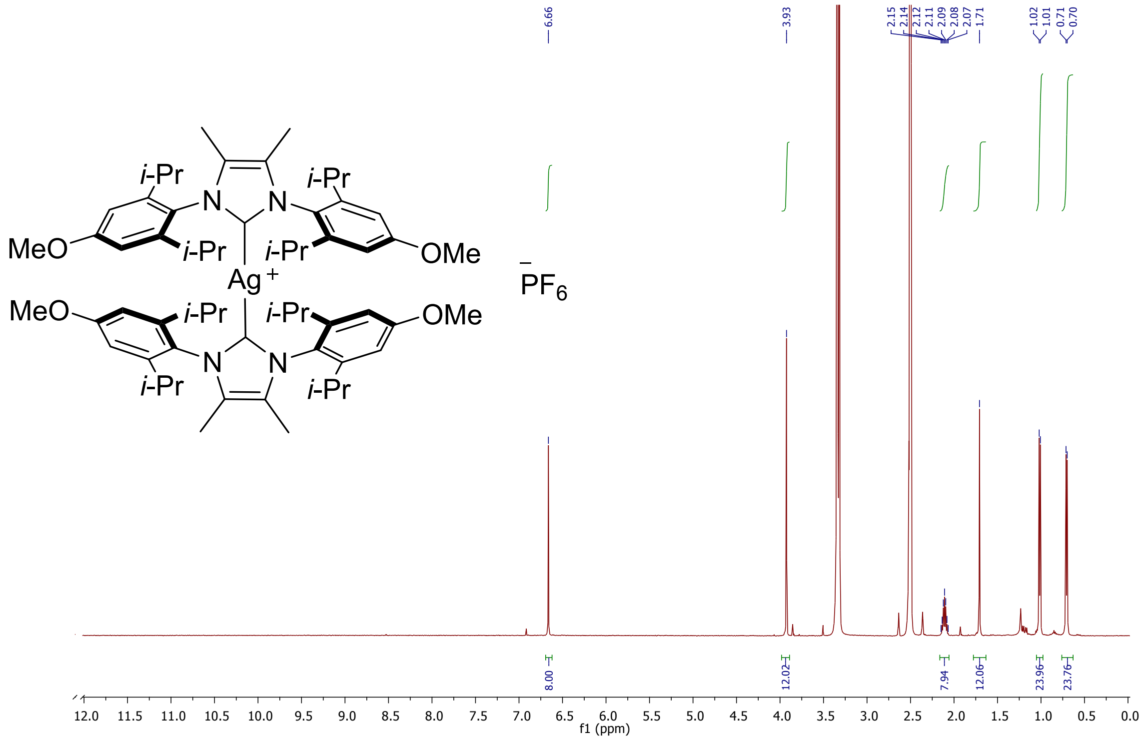


^{13}C NMR (126 MHz, DMSO-d$_6$)

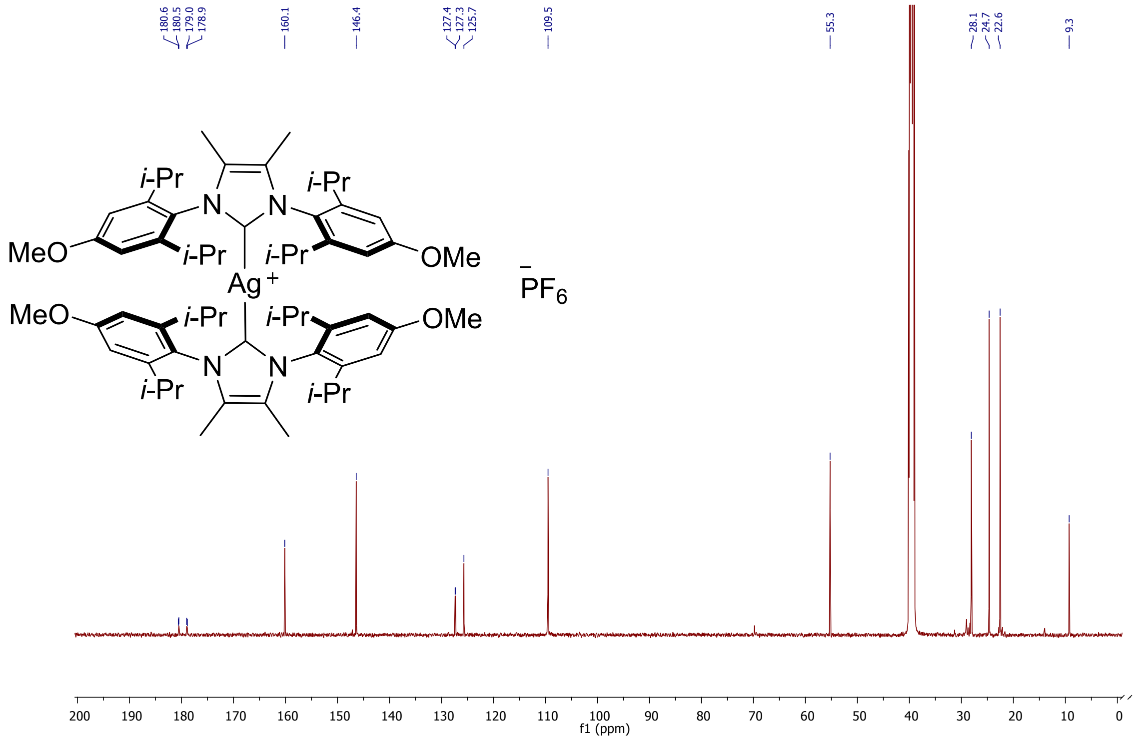


Bis[(4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl)imidazole-2-ylidene]silver hexafluorophosphate 4b

^{1}H NMR (500 MHz, DMSO-d_6)

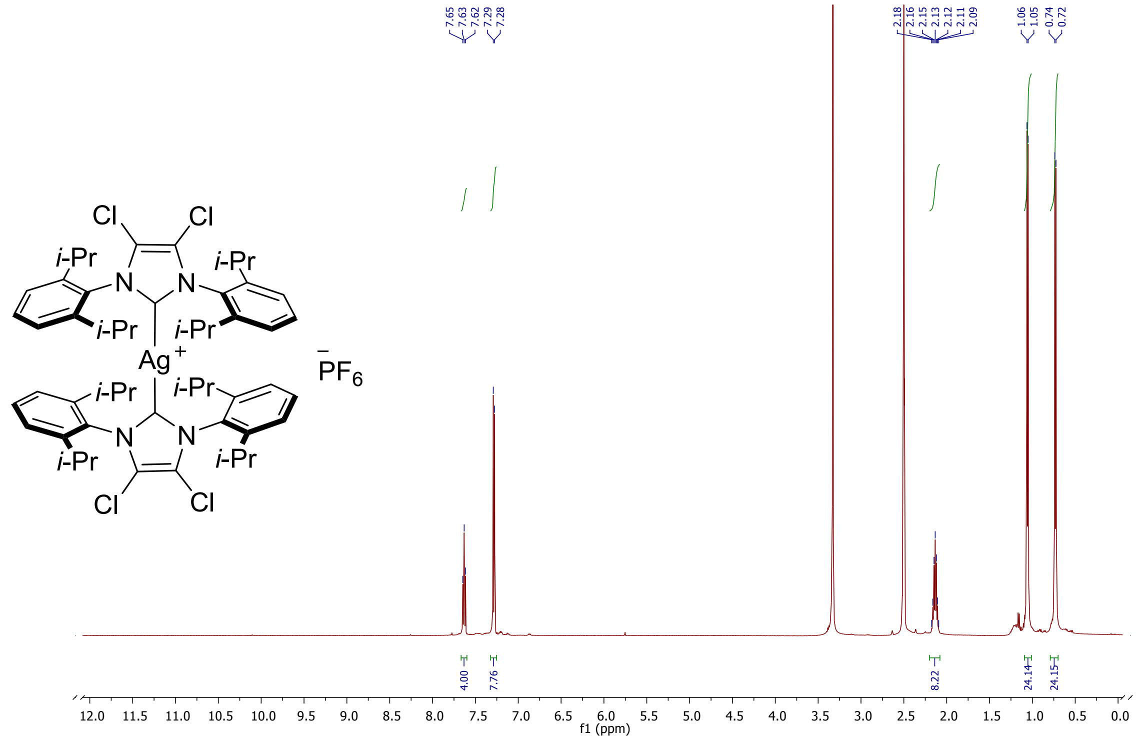


^{13}C NMR (126 MHz, DMSO-d_6)

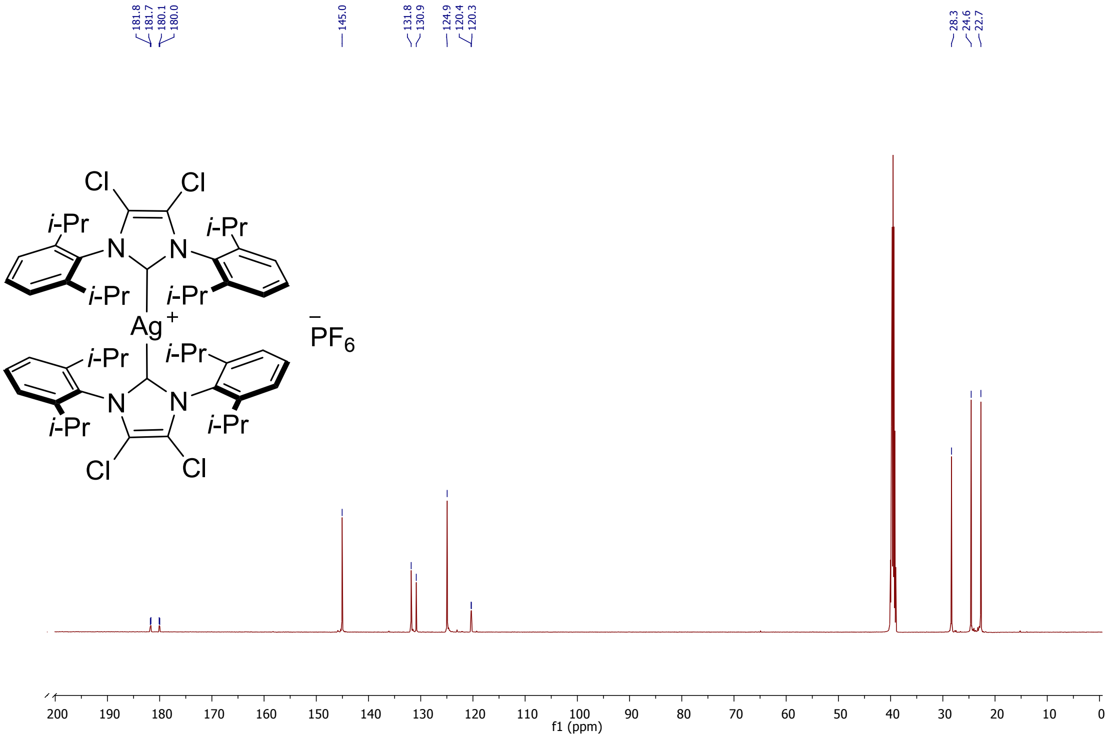


Bis[(1,3-bis(2,6-di*iso*propylphenyl)-4,5-dichloro)imidazol-2-ylidene] silver hexafluorophosphate 4c

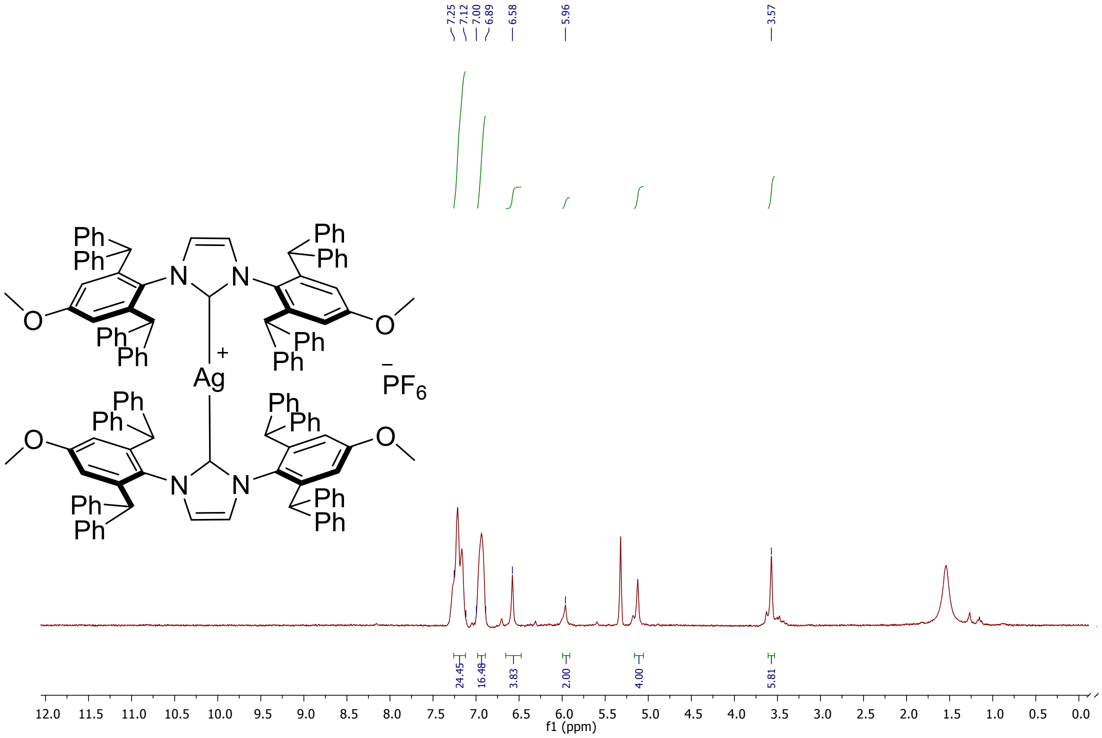
^{1}H NMR (500 MHz, DMSO-d_6)



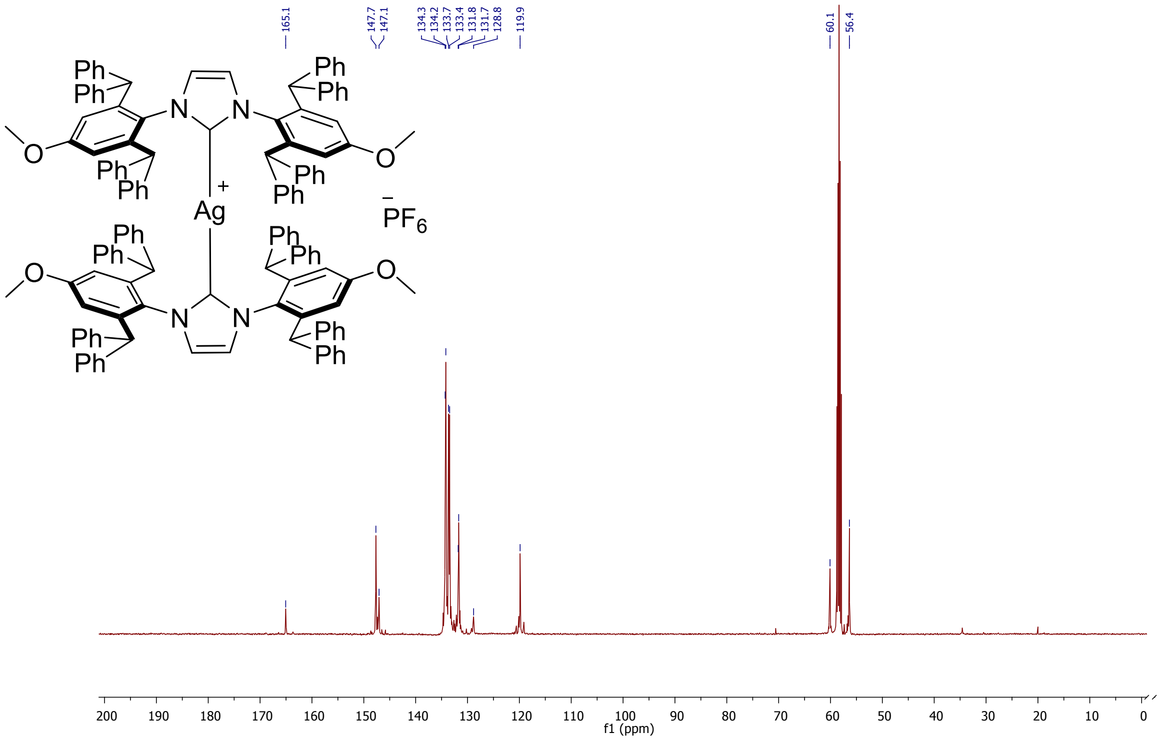
^{13}C NMR (126 MHz, DMSO-d_6)



Bis[(1,3-bis(4-methoxy-2,6-diphenyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate 4d
^{1}H NMR (300 MHz, CD_2Cl_2)

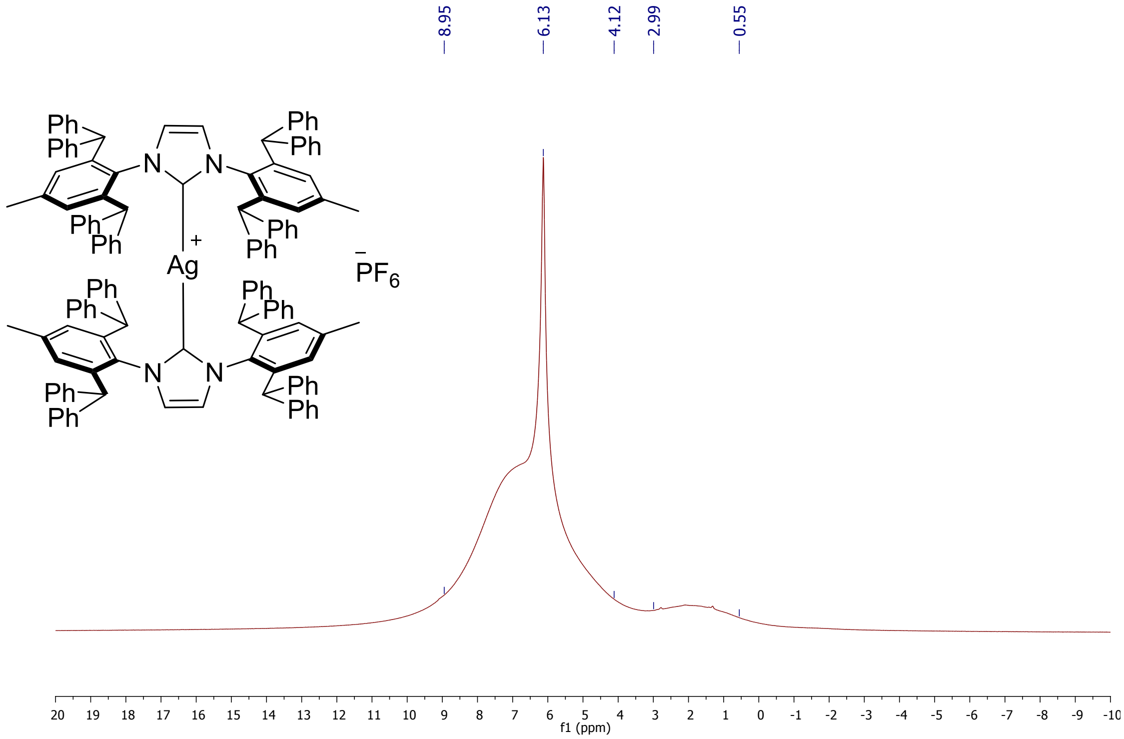


^{13}C NMR (126 MHz, CD_2Cl_2)

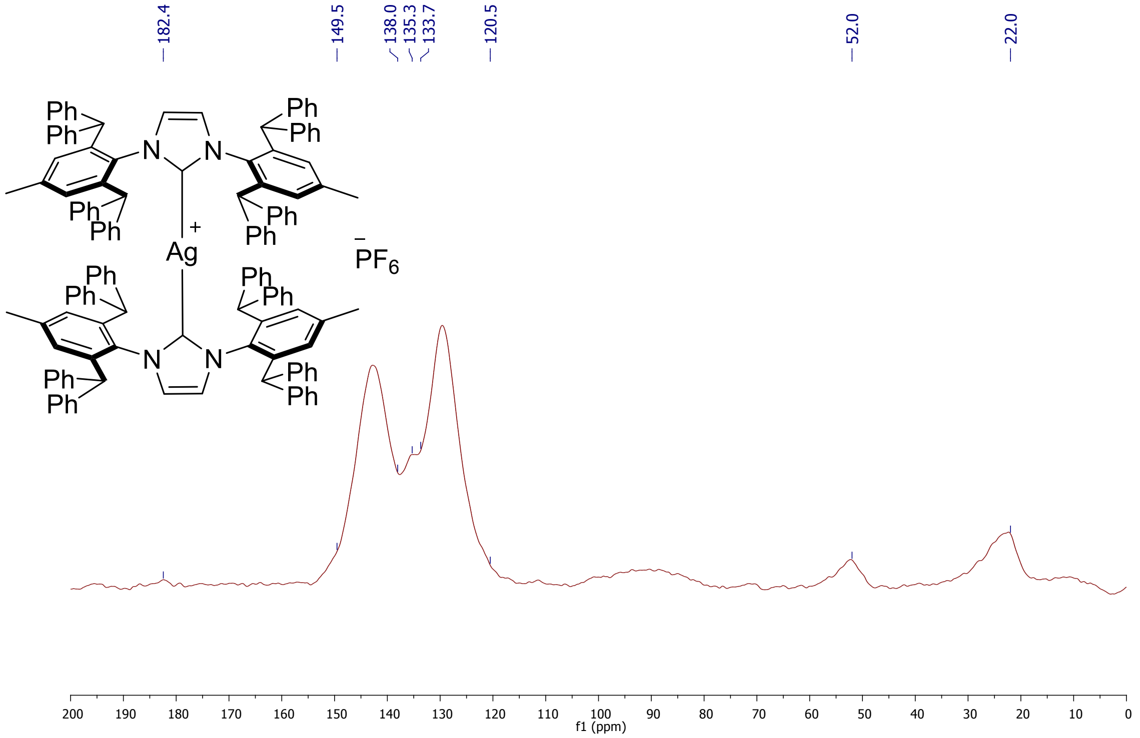


Bis[(1,3-bis(4-methyl-2,6-diphenyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate 4e

^{1}H solid state HR-MAS NMR (600 MHz)

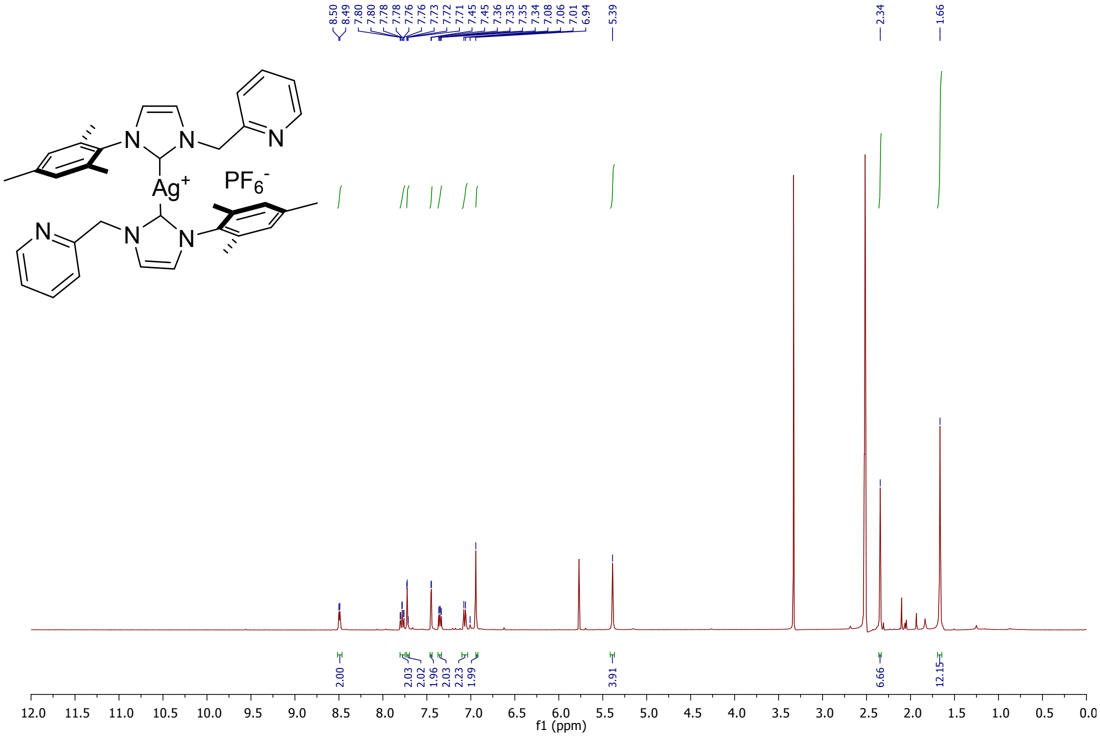


^{13}C solid state HR-MAS NMR (151 MHz)

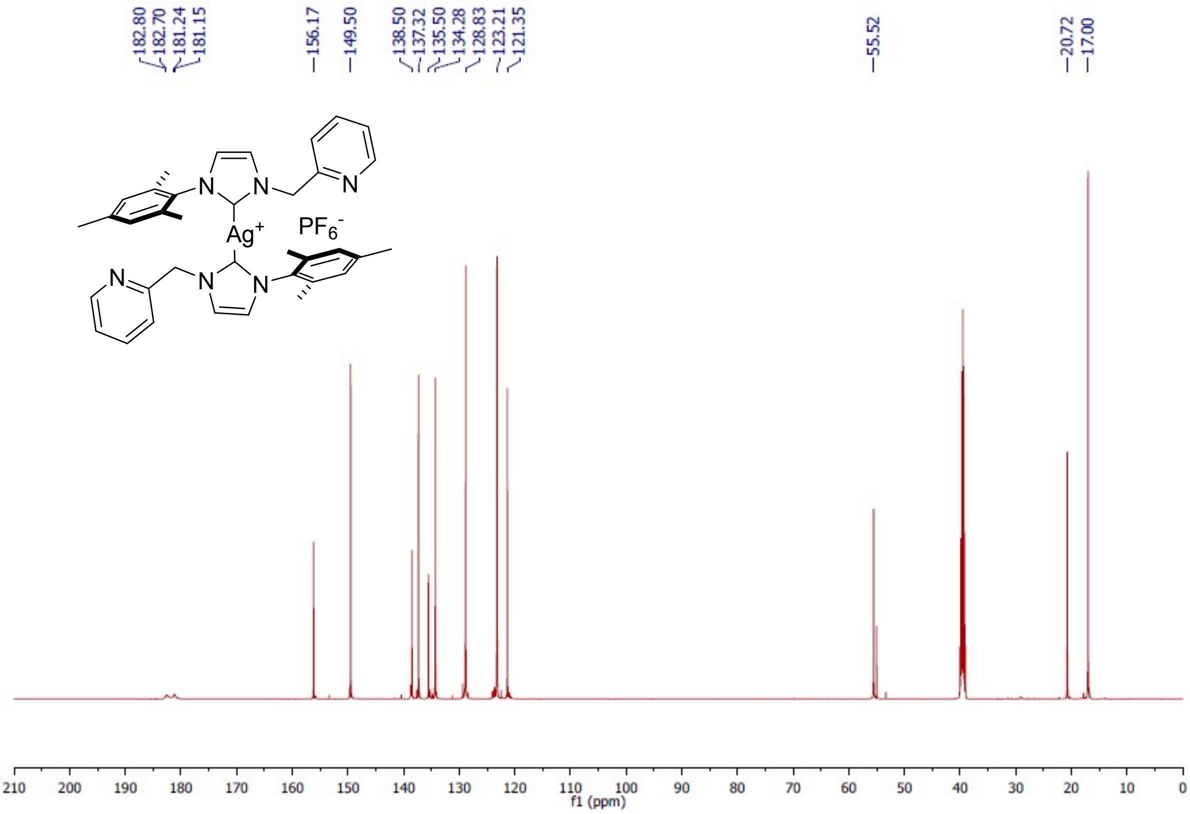


Bis[(1-(2-pyridyl)methylene-3-mesityl)imidazol-2-ylidene]silver hexafluorophosphate 4f

^{1}H NMR (400 MHz, DMSO-d_6)

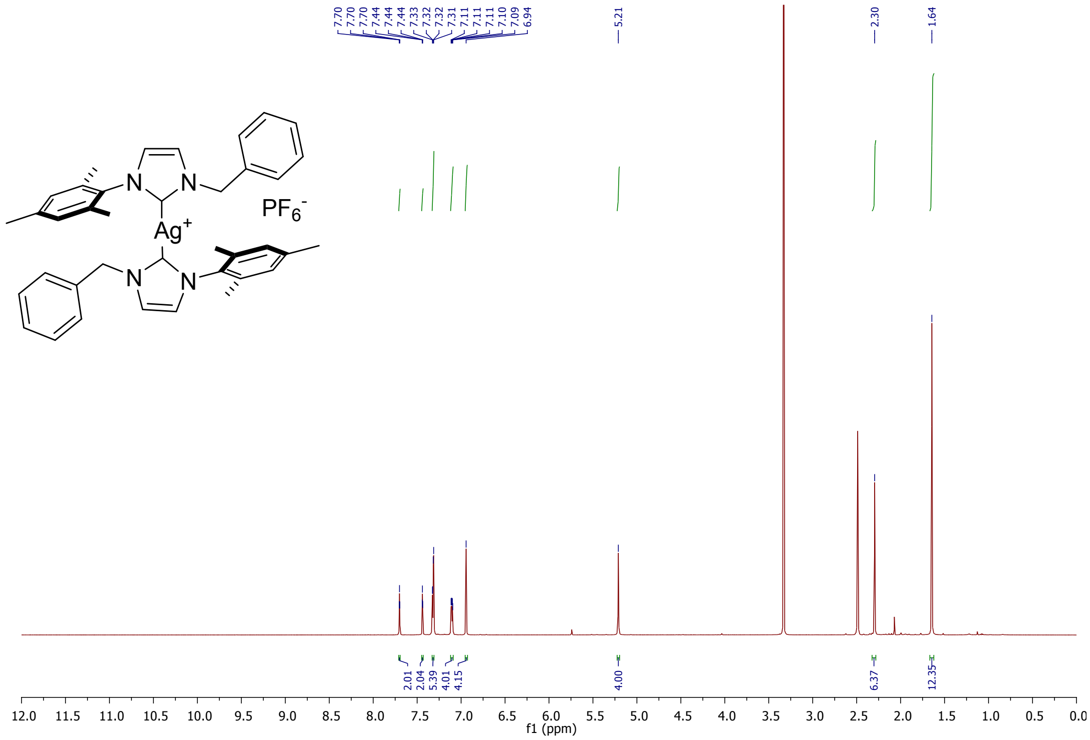


^{13}C NMR (126 MHz, DMSO-d_6)

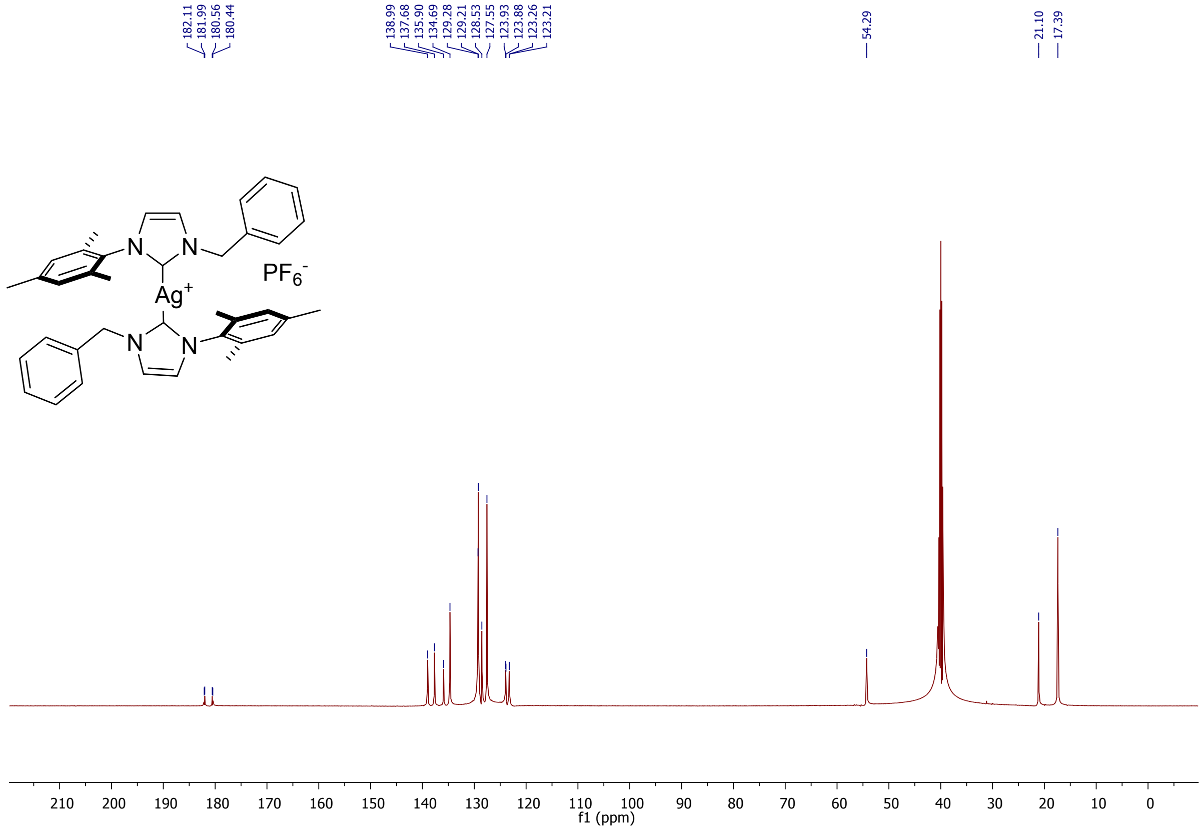


Bis[(1-benzyl-3-mesityl)imidazol-2-ylidene]silver hexafluorophosphate 4g

^{1}H NMR (500 MHz, DMSO-*d₆*)

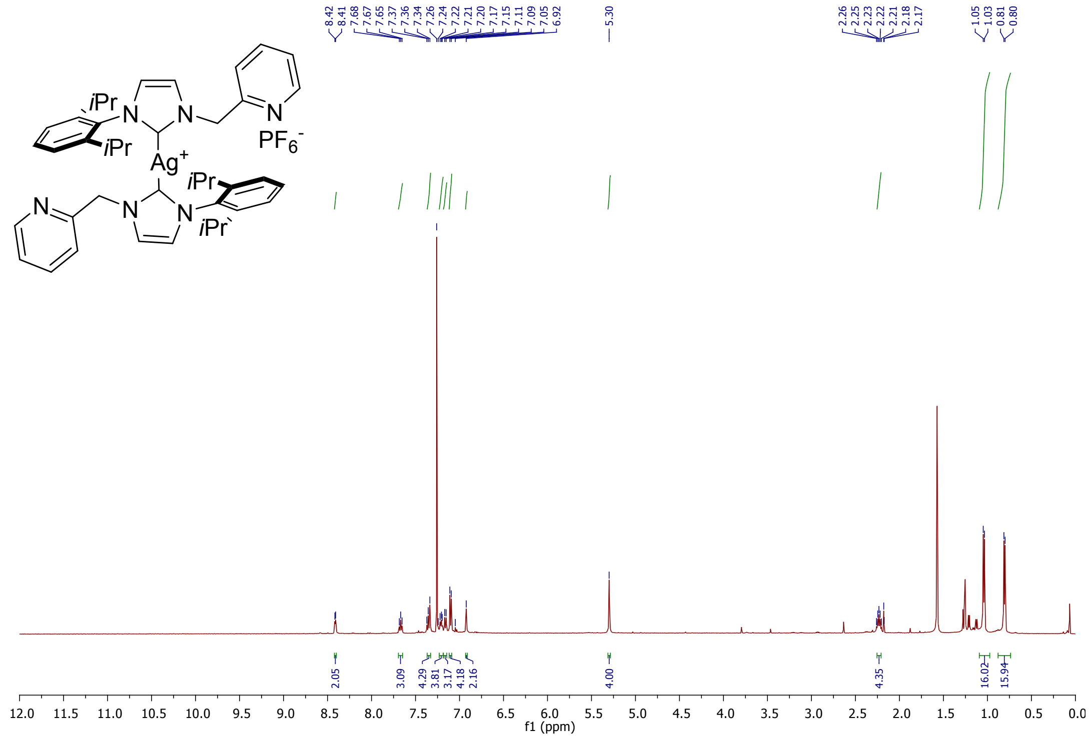


^{13}C NMR (126 MHz, DMSO-*d₆*)

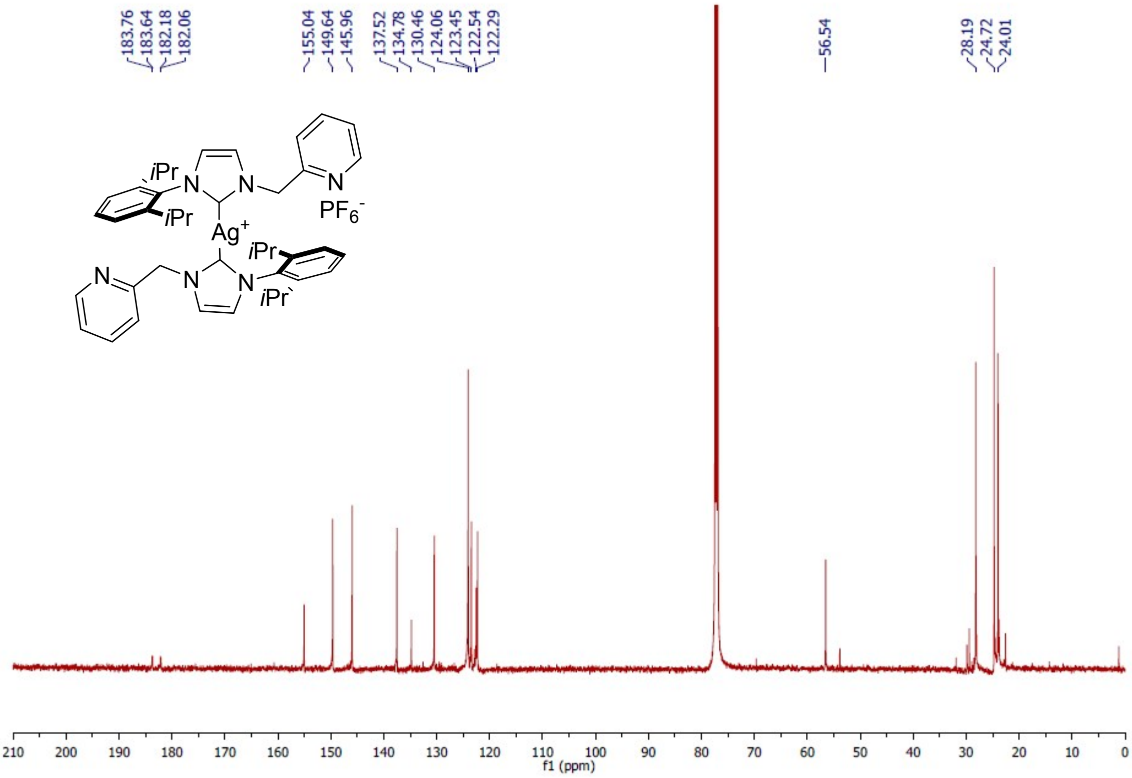


Bis[(1-(2-pyridyl)methylene-3-(2,6-diisopropylphenyl))imidazol-2-ylidene]silver hexafluorophosphate 4h

^{1}H NMR (500 MHz, CDCl$_3$)

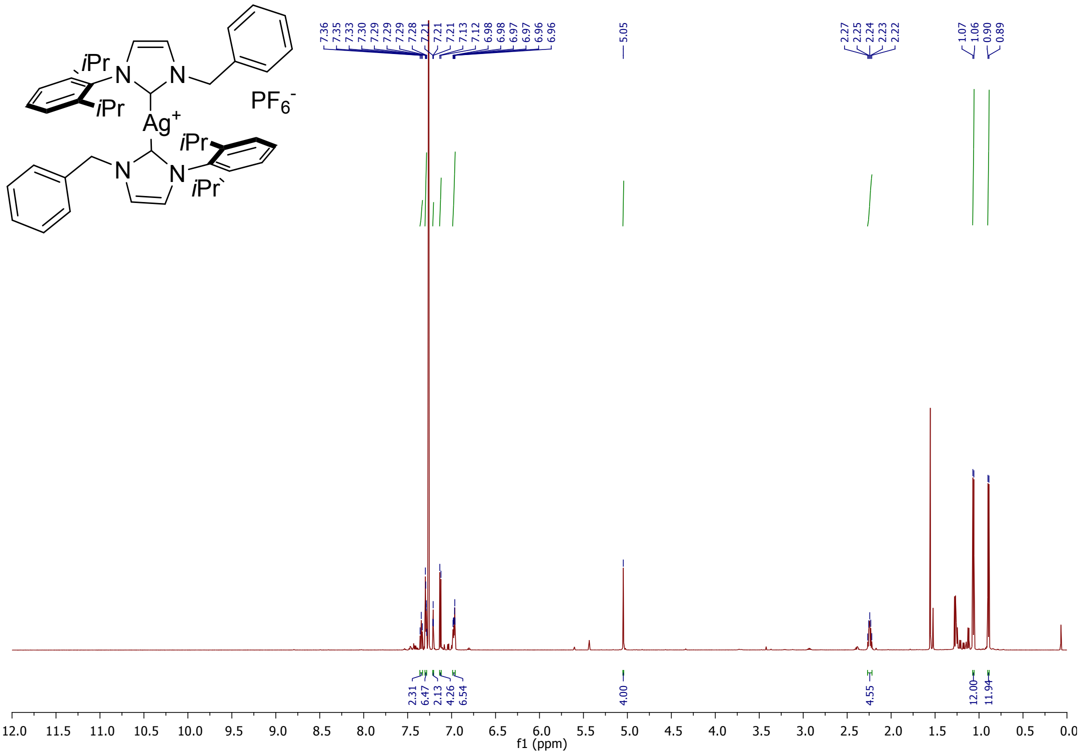


^{13}C NMR (126 MHz, CDCl$_3$)

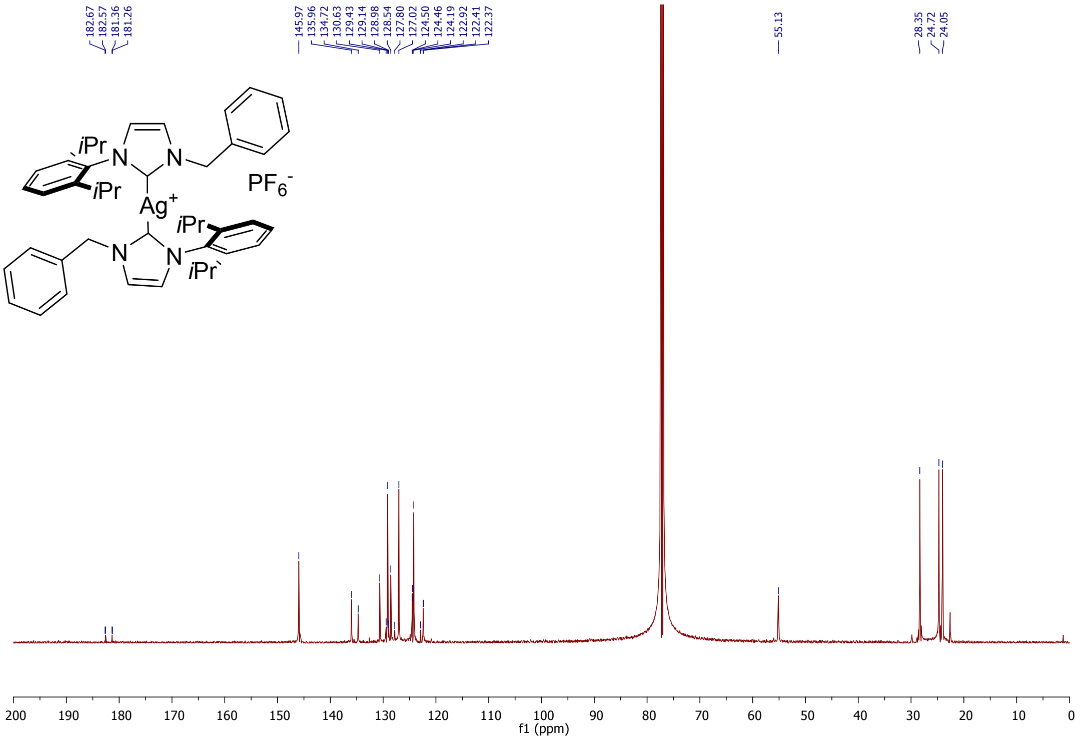


Bis[(1-benzyl-3-(2,6-diisopropylphenyl)imidazol-2-ylidene]silver hexafluorophosphate 4i

^{1}H NMR (600 MHz, CDCl$_3$)

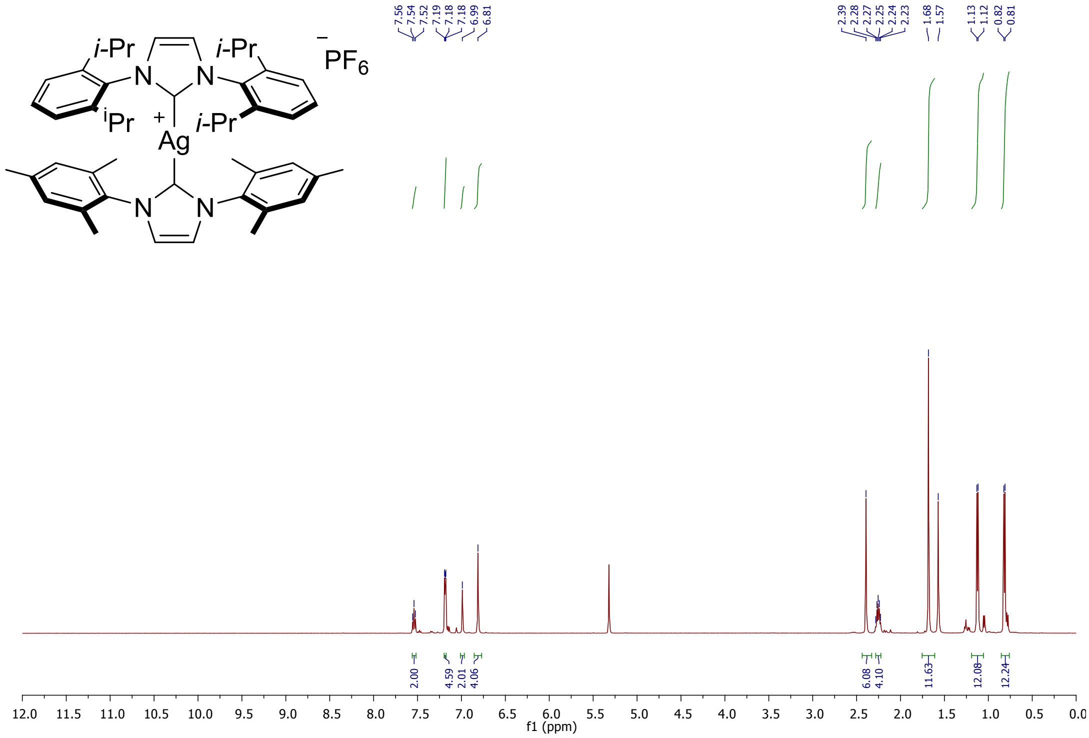


^{13}C NMR (151 MHz, CDCl$_3$)

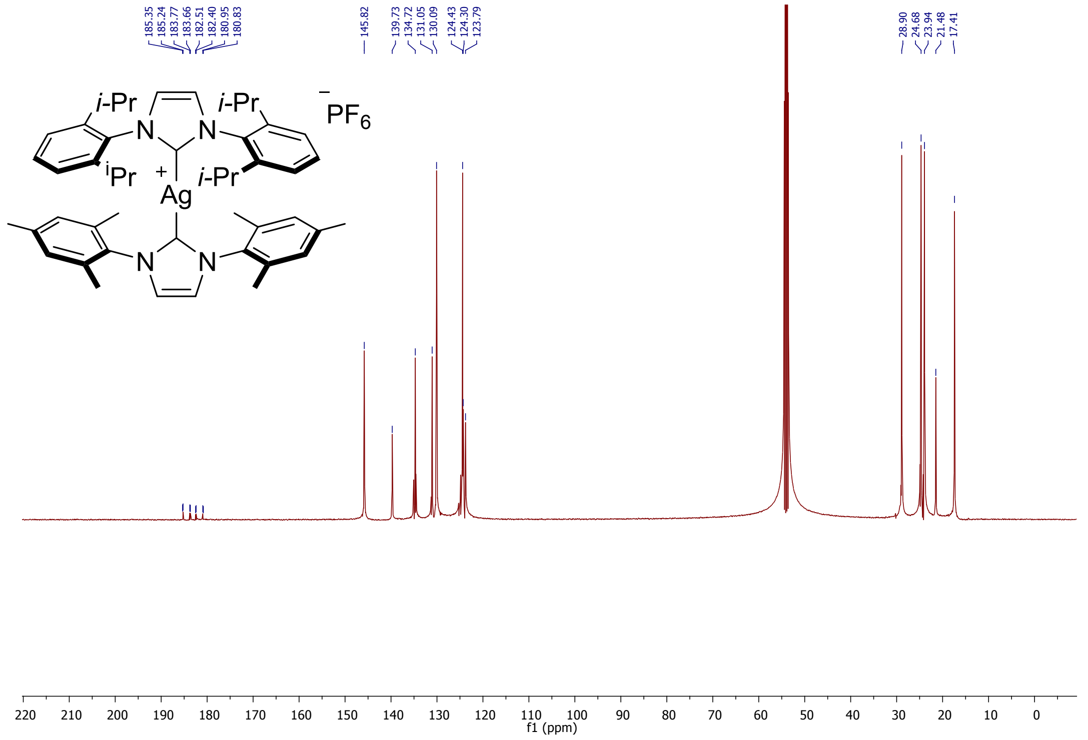


[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]silver chloride 5a

^{1}H NMR (500 MHz, CD$_2$Cl$_2$)

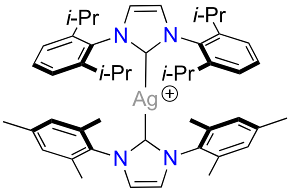


^{13}C NMR (126 MHz, CD$_2$Cl$_2$)



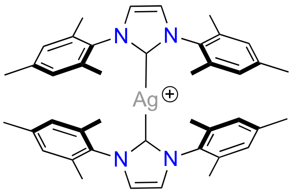
HRMS analysis

Expected molecule

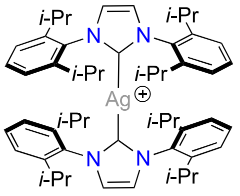


Chemical Formula: $C_{48}H_{60}AgN_4^+$
Exact Mass: 799.3863
Molecular Weight: 800.9037

Molecules resulting from ligand scrambling



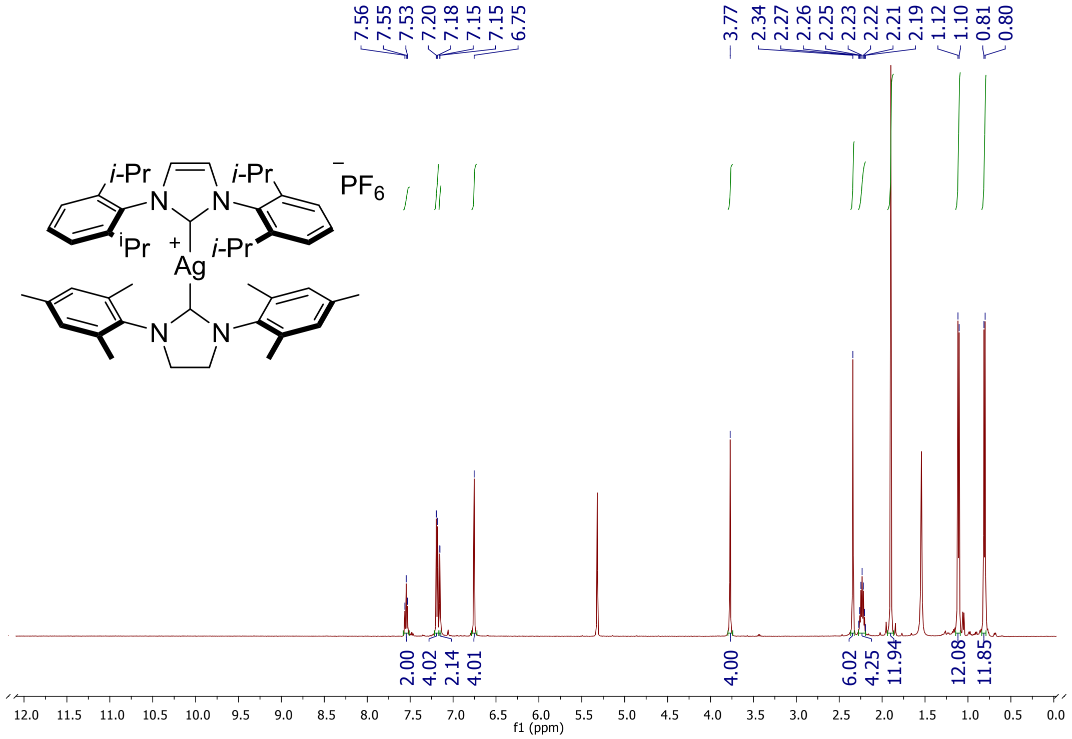
Chemical Formula: $C_{42}H_{48}AgN_4^+$
Exact Mass: 715.2924
Molecular Weight: 716.7417



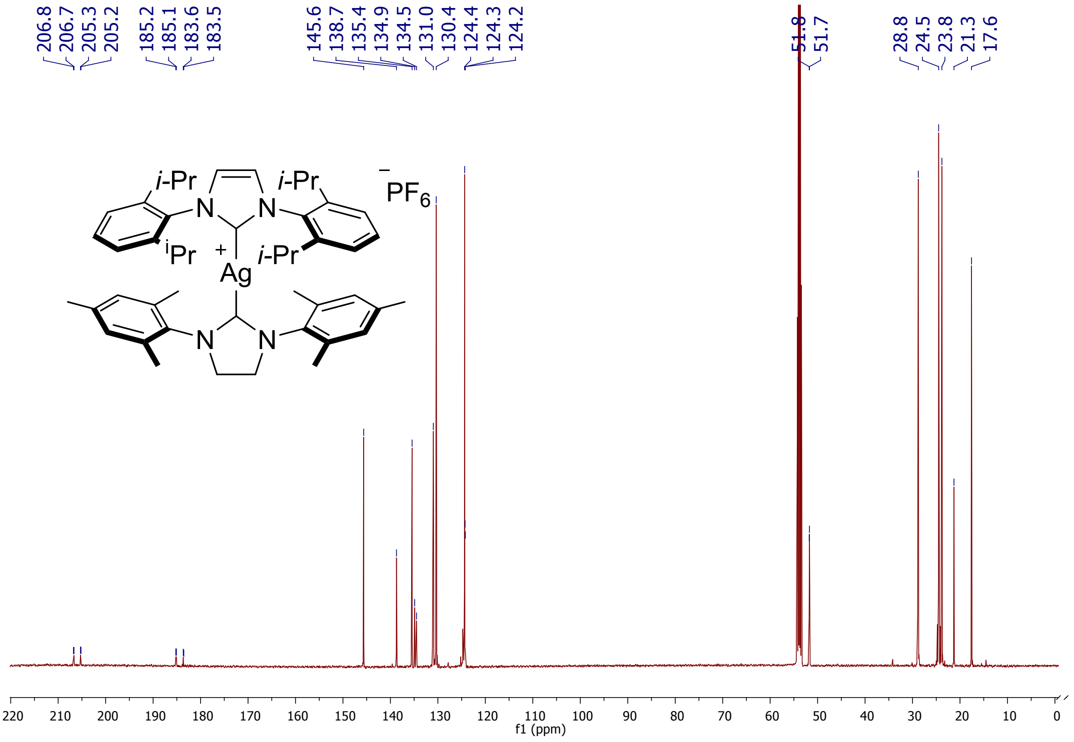
Chemical Formula: $C_{54}H_{72}AgN_4^+$
Exact Mass: 883.4802
Molecular Weight: 885.0657

[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]silver chloride 5b

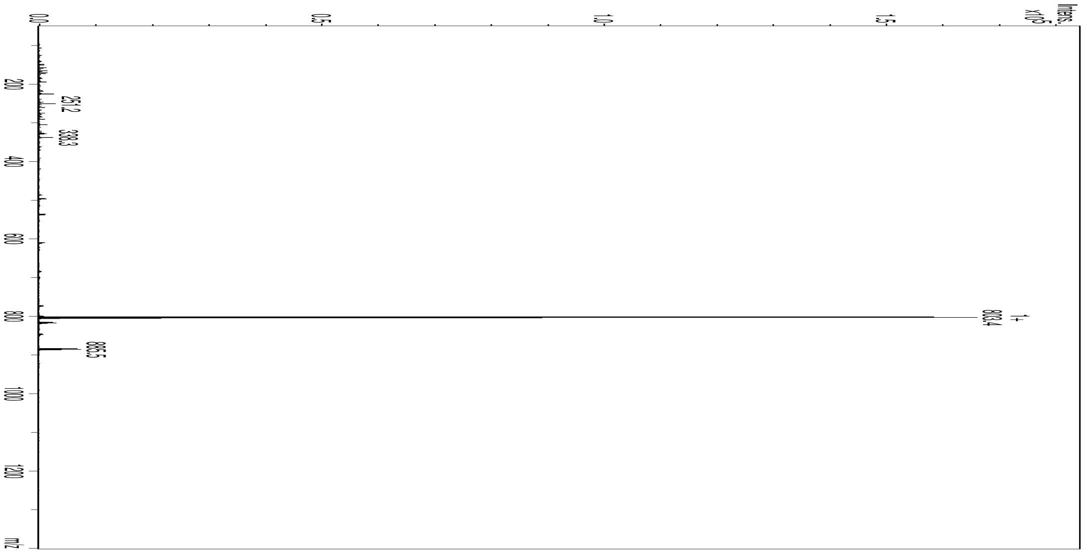
^{1}H NMR (500 MHz, CD_2Cl_2)



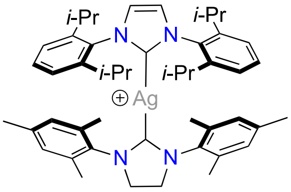
^{13}C NMR (126 MHz, CD_2Cl_2)



HRMS analysis

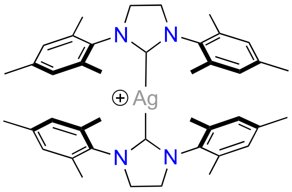


Expected molecule

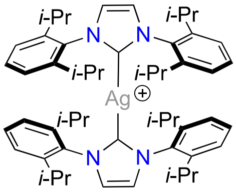


Chemical Formula: $C_{48}H_{62}AgN_4^+$
Exact Mass: 801.4020
Molecular Weight: 802.9197

Molecules resulting from ligand scrambling



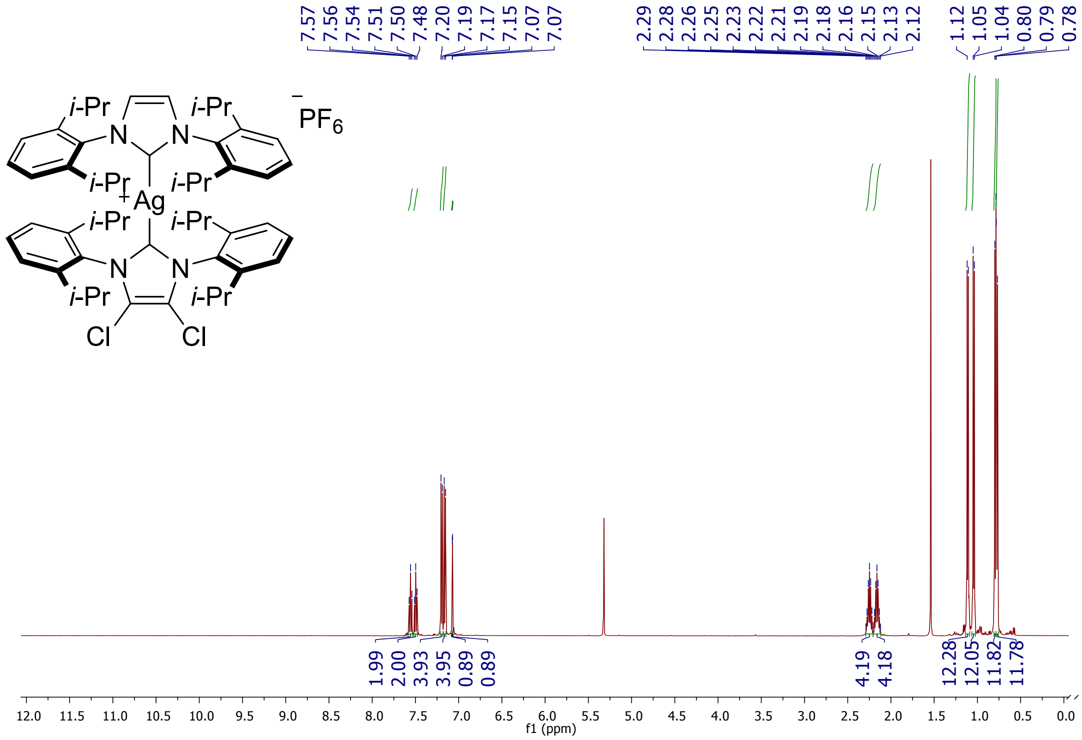
Chemical Formula: $C_{42}H_{52}AgN_4^+$
Exact Mass: 719.3237
Molecular Weight: 720.7737



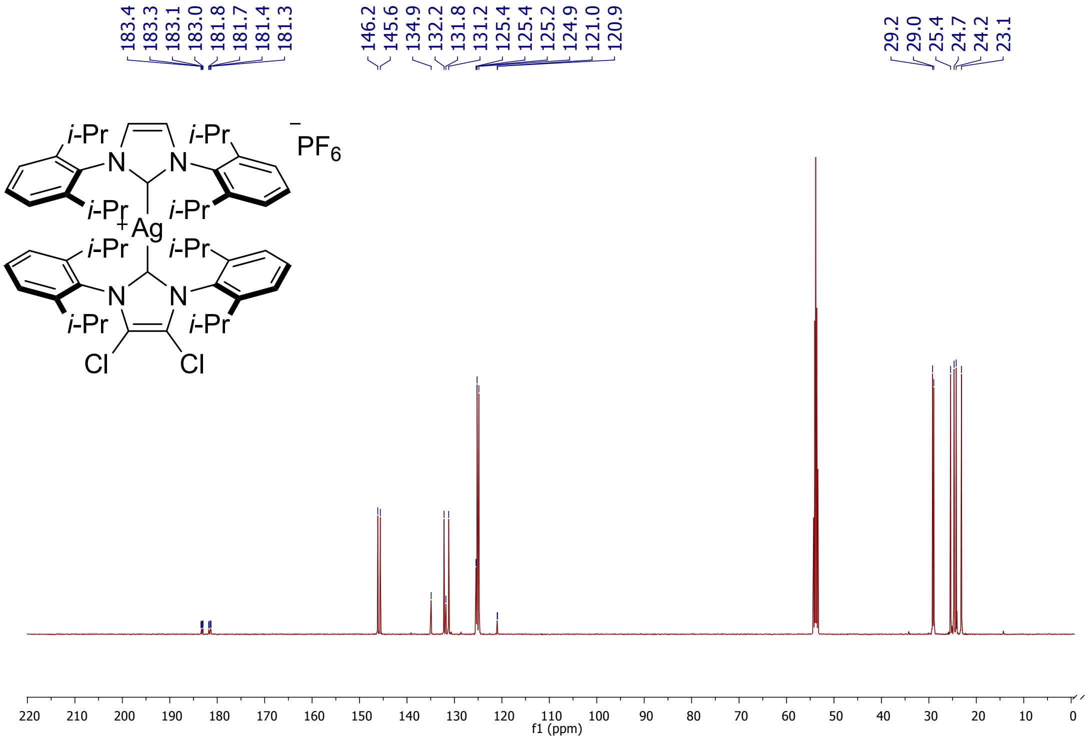
Chemical Formula: $C_{54}H_{72}AgN_4^+$
Exact Mass: 883.4802
Molecular Weight: 885.0657

[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3-Bis(2,6-di*iso*propyl)phenyl]-4,5-dichloroimidazol-2-ylidene]silver hexafluorophosphate 5c

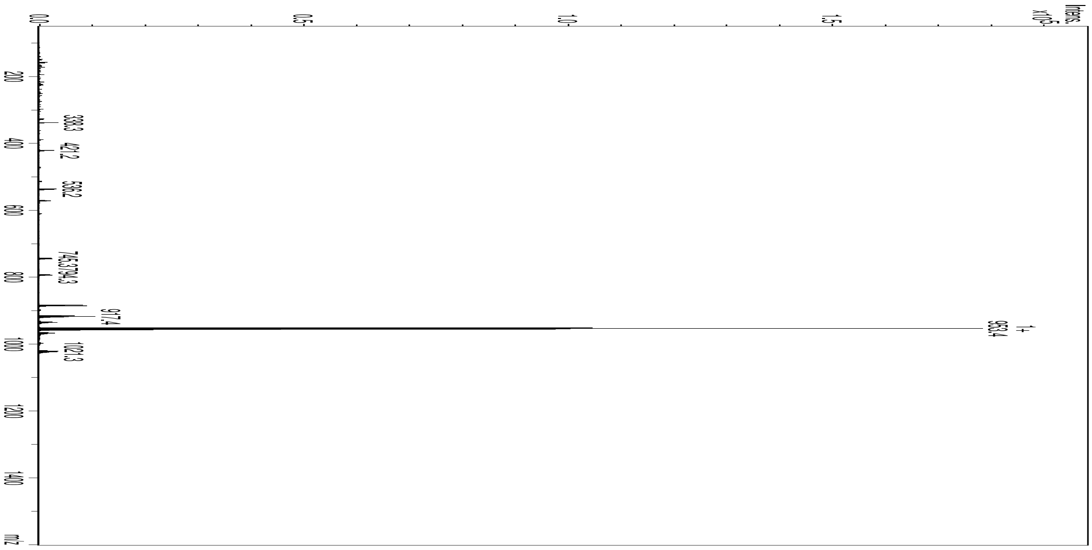
^{1}H NMR (500 MHz, CD$_2$Cl$_2$)



^{13}C NMR (126 MHz, CD$_2$Cl$_2$)

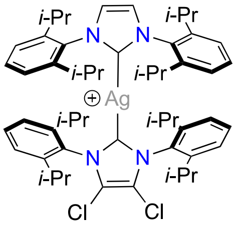


HRMS analysis

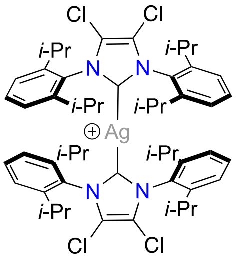


Expected molecule

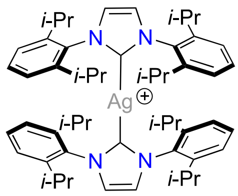
Molecules resulting from ligand scrambling



Chemical Formula: $C_{54}H_{70}AgCl_2N_4^+$
Exact Mass: 951.4023
Molecular Weight: 953.9497



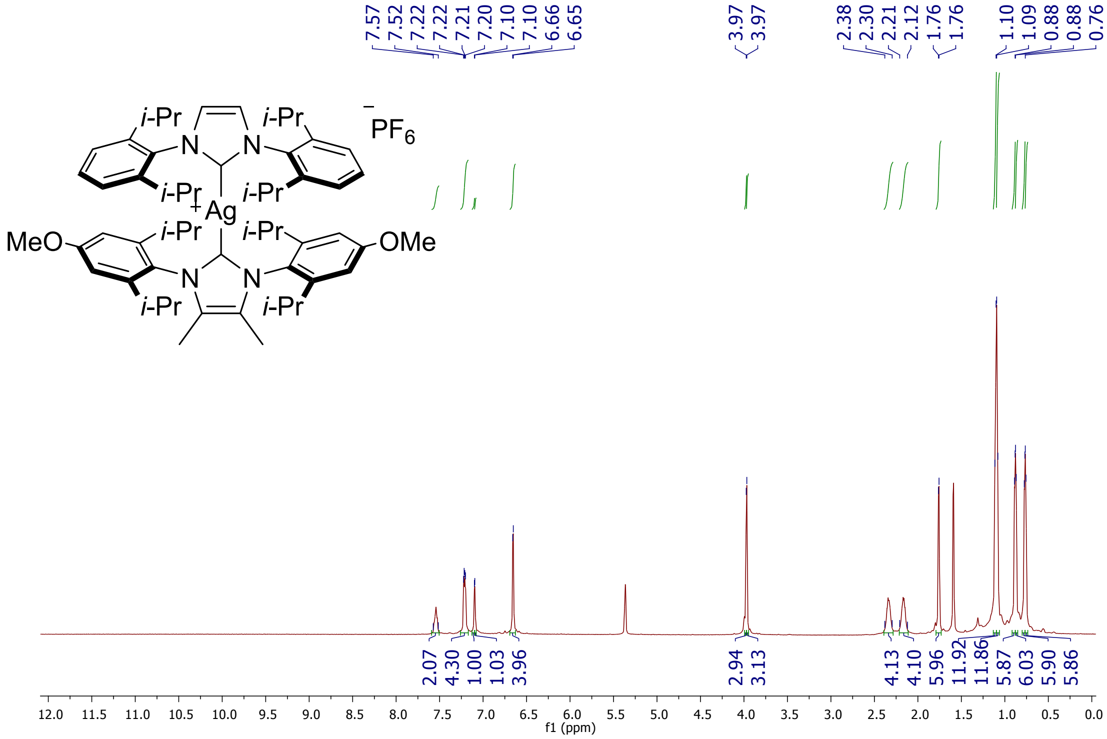
Chemical Formula: $C_{54}H_{68}AgCl_4N_4^+$
Exact Mass: 1019.3244
Molecular Weight: 1022.8337



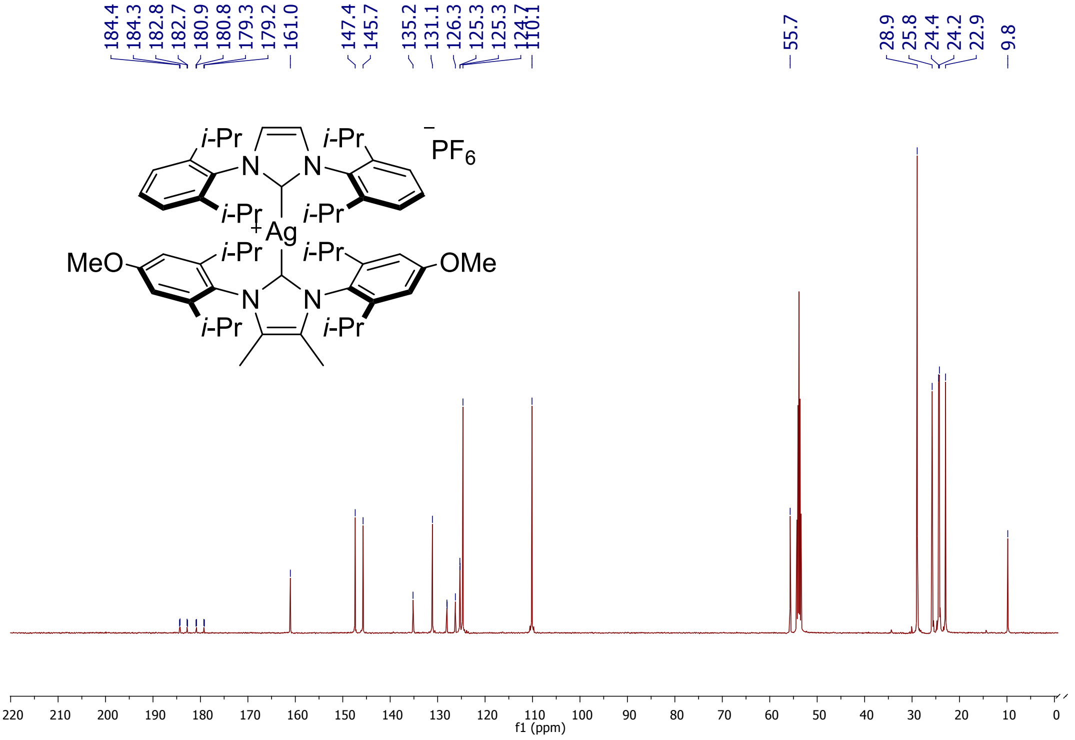
Chemical Formula: $C_{54}H_{72}AgN_4^+$
Exact Mass: 883.4802
Molecular Weight: 885.0657

[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][(4,5-dimethyl-1,3-bis(4-methoxy-2,6-di*iso*propyl)phenyl)imidazol-2-ylidene]silver hexafluorophosphate 5d

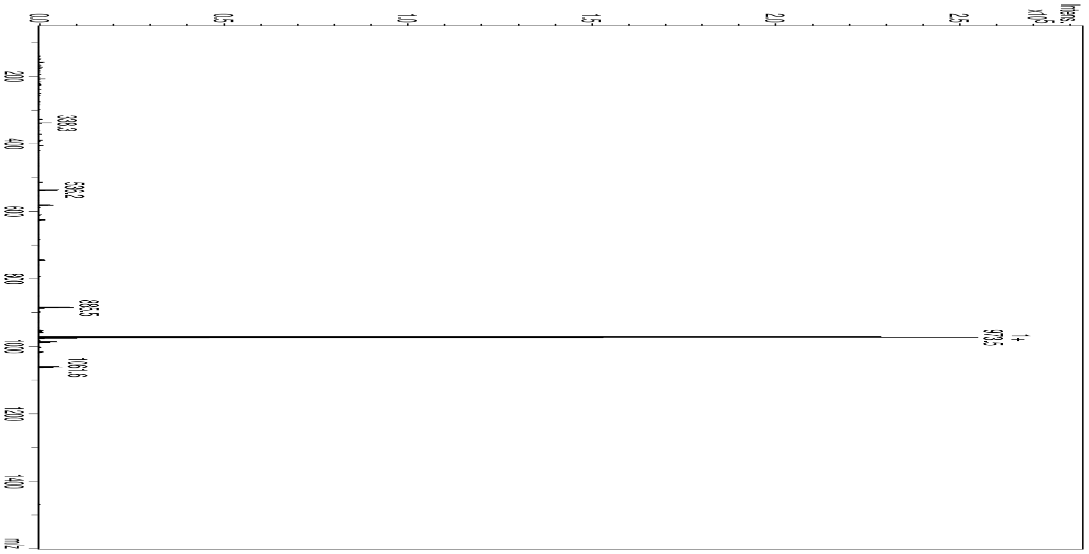
^{1}H NMR (500 MHz, CD_2Cl_2)



^{13}C NMR (126 MHz, CD_2Cl_2)

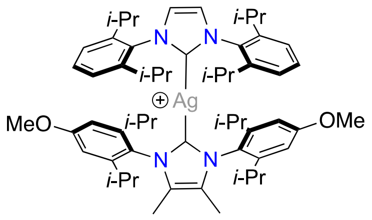


HRMS analysis

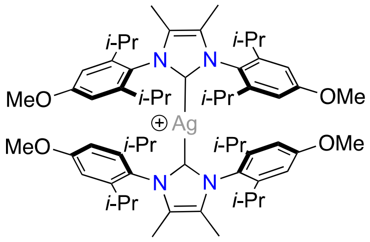


Expected molecule

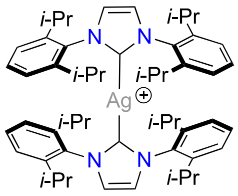
Molecules resulting from ligand scrambling



Chemical Formula: $C_{58}H_{80}AgN_4O_2^+$
Exact Mass: 971.5327
Molecular Weight: 973.1717



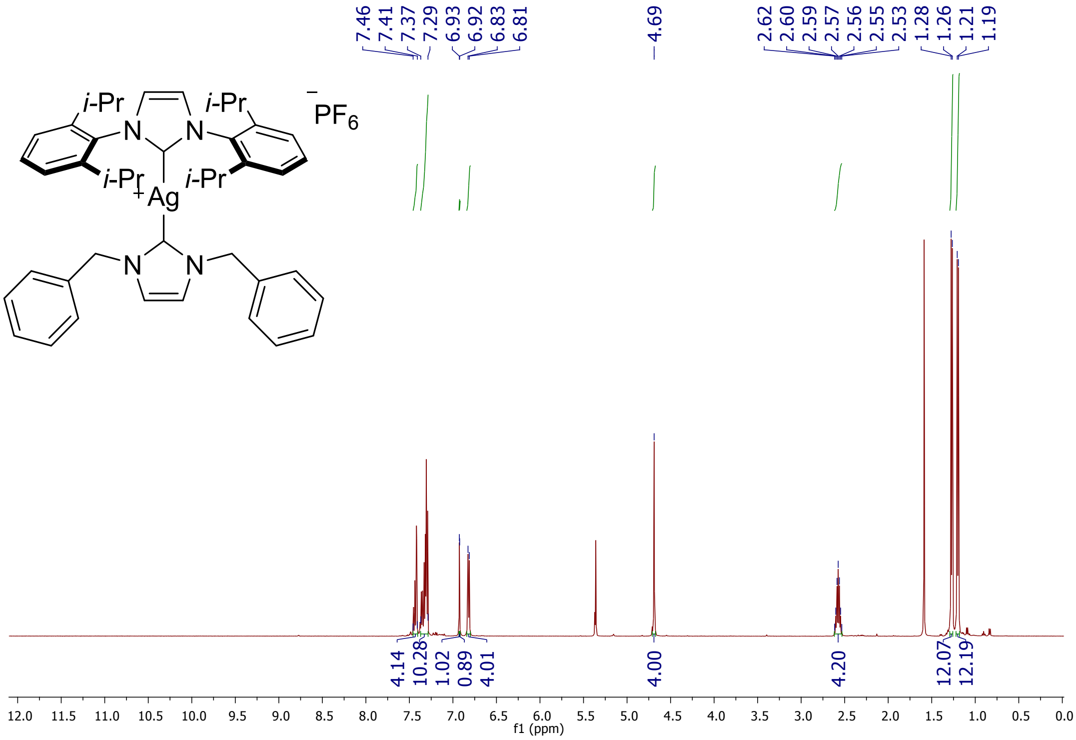
Chemical Formula: $C_{62}H_{88}AgN_4O_4^+$
Exact Mass: 1059.5851
Molecular Weight: 1061.2777



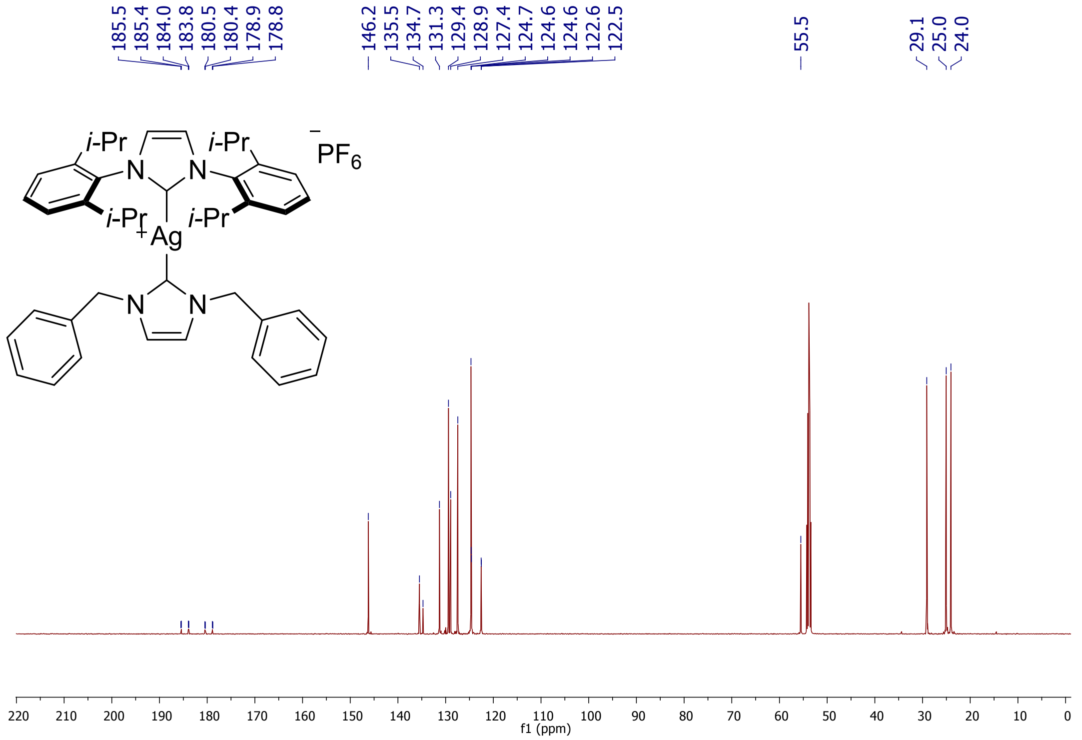
Chemical Formula: $C_{54}H_{72}AgN_4^+$
Exact Mass: 883.4802
Molecular Weight: 885.0657

[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][*N,N*-dibenzylimidazolium]silver hexafluorophosphate 5e

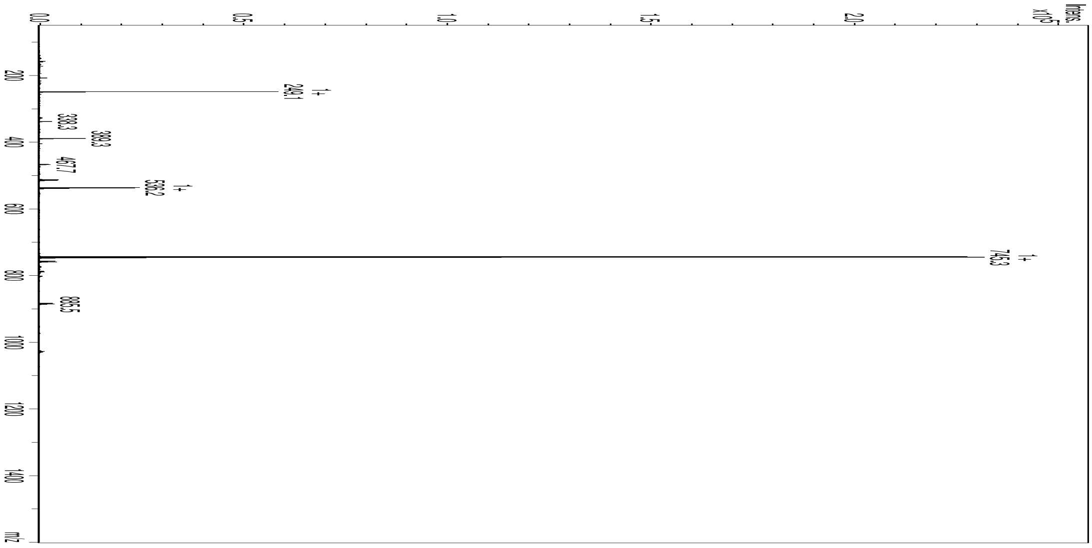
^{1}H NMR (500 MHz, CD_2Cl_2)



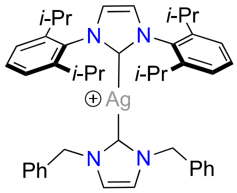
^{13}C NMR (126 MHz, CD_2Cl_2)



HRMS analysis

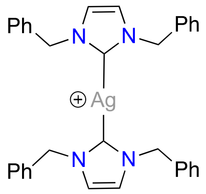


Expected molecule

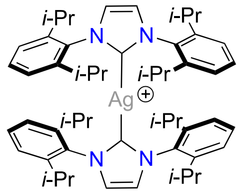


Chemical Formula: $C_{44}H_{52}AgN_4^+$
Exact Mass: 743.3237
Molecular Weight: 744.7957

Molecules resulting from ligand scrambling



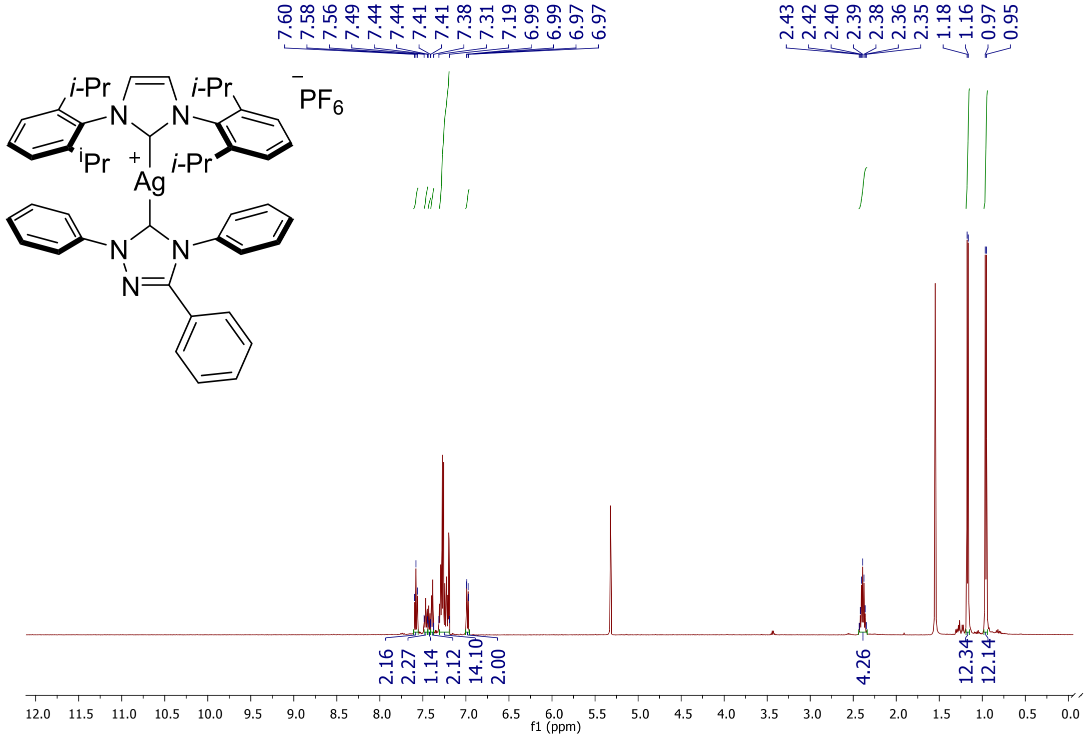
Chemical Formula: $C_{34}H_{32}AgN_4^+$
Exact Mass: 603.1672
Molecular Weight: 604.5257



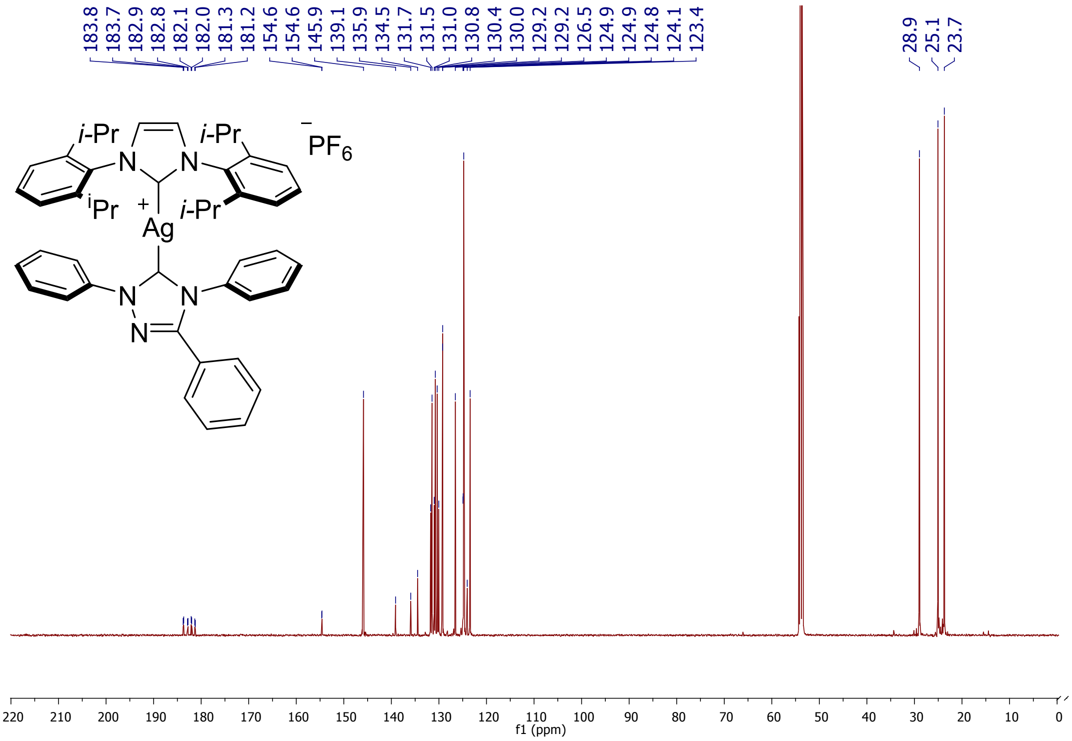
Chemical Formula: $C_{54}H_{72}AgN_4^+$
Exact Mass: 883.4802
Molecular Weight: 885.0657

[[1,3-Bis(2,6-di*iso*propyl)phenyl]imidazol-2-ylidene][1,3,4-triphenyl-1,2,4-triazolium]silver hexafluorophosphate 5f

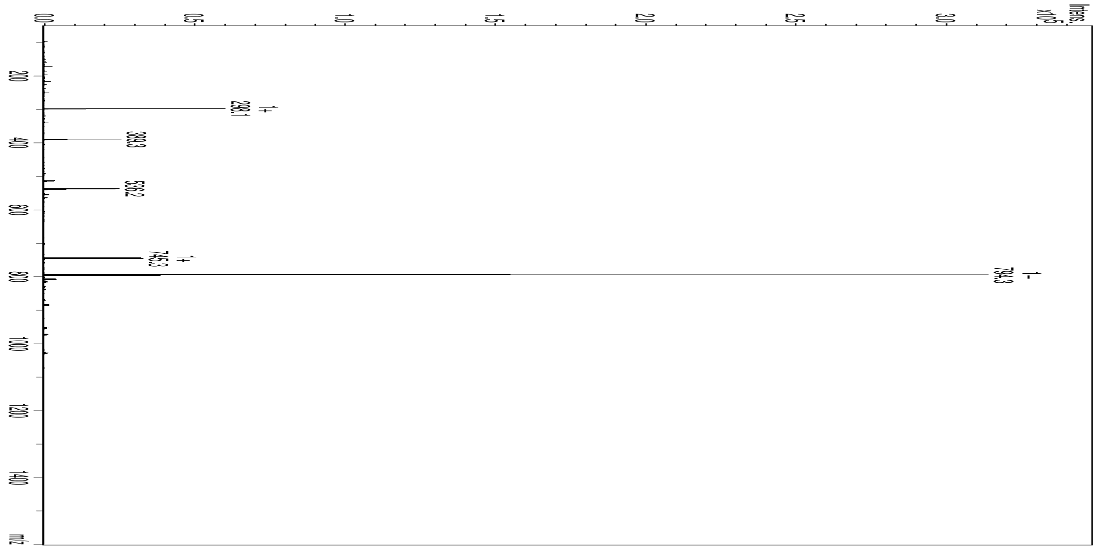
^{1}H NMR (500 MHz, CD_2Cl_2)



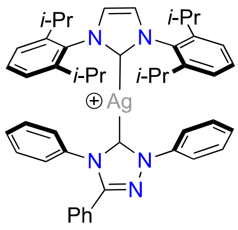
^{13}C NMR (126 MHz, CD_2Cl_2)



HRMS analysis

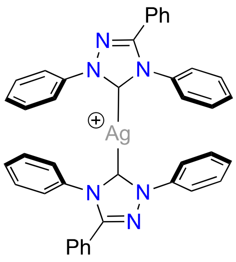


Expected molecule

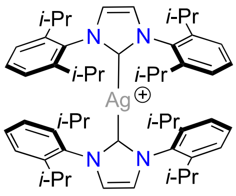


Chemical Formula: $C_{47}H_{51}AgN_5^+$
Exact Mass: 792.3190
Molecular Weight: 793.8277

Molecules resulting from ligand scrambling



Chemical Formula: $C_{40}H_{30}AgN_6^+$
Exact Mass: 701.1577
Molecular Weight: 702.5897



Chemical Formula: $C_{54}H_{72}AgN_4^+$
Exact Mass: 883.4802
Molecular Weight: 885.0657

VII. References

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