

Electronic Supplementary Information

Synthesis of carbon-11 radiolabelled transition metal complexes using ^{11}C - dithiocarbamates

Sara Cesarec,^a Fraser Edgar,^{a,b} Titan Lai,^a Christophe Plisson,^c Andrew J.P.
White^a and Philip W. Miller^a

^a Department of Chemistry, Imperial College London, Molecular Sciences Research Hub
White City Campus, Wood Lane, London, UK, W12 0BZ

^b School of Biomedical Engineering and Imaging Sciences, King's College London, 4th Floor
Lambeth Wing, St Thomas' Hospital, London, UK

^c Invicro, Burlington Danes Building, Hammersmith Hospital, Du Cane Road, London, UK

Email: philip.miller@imperial.ac.uk

Table of contents

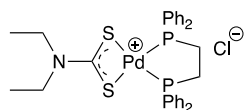
1. General radiochemistry and chemistry considerations
2. Synthesis of Pt(II) and Pd(II) dithiocarbamate Complexes
3. [^{11}C]Carbon disulfide production
4. Radiosynthesis of ^{11}C -labelled Au(III) and Au(I) complexes
5. Radiosynthesis of ^{11}C -labelled Pt(II) and Pd(II) complexes
6. X-Ray Crystallography
7. References

1. General radiochemistry and chemistry considerations

Radiolabelling reactions were performed in a lead-lined hot cell using a custom-built methylation apparatus consisting of an externally controlled valve array, heater block and magnetic stirrer. Analysis of crude radioactive reaction mixtures was performed via HPLC using an Agilent 1100 system with in-line radioactivity and diode array detectors (UV) and an Agilent Eclipse XDB-C18 column (5 μm , 4.6 x 150 mm). Eluent mixture of acetonitrile and ammonium formate pH 8.0 at a flow of 1.5 mL/min were used. Radioactivity measurements were performed using an Isomed 2000 dose calibrator. Reagents and anhydrous solvents were obtained from Sigma-Aldrich and used as received. Complexes: $[\text{AuCl}_2(\text{S}_2\text{CNEt}_2)]$, $[\text{AuCl}_2(\text{S}_2\text{CNBn}_2)]$ and $[\text{Au}(\text{S}_2\text{CNEt}_2)(\text{PPh}_3)]$ were prepared according to literature procedures.^{1,2}

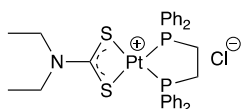
2. Synthesis of Pt(II) and Pd(II) Dithiocarbamate Complexes

Synthesis of $[\text{Pd}(\text{S}_2\text{CNEt}_2)(\text{dppe})]\text{Cl}$ (6)



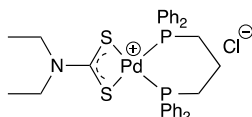
Pd(II) and Pt(II) dithiocarbamate complexes were prepared by a modified method initially reported by Steed and co-workers.^{3,4} Briefly, $[\text{PdCl}_2(\text{dppe})]$ (57 mg, 0.1 mmol) and sodium diethyldithiocarbamate (17 mg, 0.1 mmol) were heated in water (5 mL) to 60 °C for 1 hour. The solution was then extracted with chloroform (5 mL), dried over MgSO_4 and evaporated to dryness to obtain a white solid (41 mg, 59 %). ^1H NMR (400 MHz, CDCl_3): δ 7.93 – 7.87 (m, 2H), 7.80 – 7.75 (m, 6H), 7.58 – 7.48 (m, 12H), 3.82 (q, $J = 7.2$ Hz, 4H), 3.10 (dd, $J = 22.3, 6.5$ Hz, 4H), 1.32 (t, $J = 7.2$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 205.4 (s), 133.0 – 132.9 (m), 132.4 (s), 129.7 – 129.6 (m), 128.3 – 127.5 (m), 44.5 (s), 27.9 – 27.4 (m), 12.6 (s). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ 58.9 (s). IR (v/cm^{-1}): 3397, 1520, 1431, 1274, 1998, 1103, 991, 812, 756, 685. MS (ES⁺) m/z calculated for $[\text{C}_{31}\text{H}_{34}\text{NP}_2\text{PdS}_2]^+$ ($[\text{M}]^+$) 652.0643; found 652.0667 (100%).

Synthesis of $[\text{Pt}(\text{S}_2\text{CNEt}_2)(\text{dppe})]\text{Cl}$ (7)



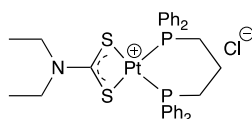
[PtCl₂(dppe)] (66 mg, 0.1 mmol) and sodium diethyldithiocarbamate (17 mg, 0.1 mmol) were heated in water (5 mL) to 60 °C for 1 hour. The solution was then extracted with chloroform (5 mL), dried over MgSO₄ and evaporated to dryness to obtain a white solid (43 mg, 55 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.89 – 7.82 (m, 2H), 7.74 (m, 6H), 7.67 – 7.55 (m, 12H), 3.69 (q, *J* = 7.2 Hz, 4H), 2.93 – 2.77 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 6H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 205.4 (s), 133.0 – 132.8 (m), 132.4 (s), 129.6 – 129.4 (mc), 129.0 – 127.0 (m), 44.9 (s), 27.8 – 27.4 (m), 12.6 (s). ³¹P{¹H} NMR (162 MHz, CDCl₃): δ 42.6 (s, *J*_{Pt,P} = 3127 Hz). IR (ν/cm⁻¹): 3347, 1535, 1446, 1283, 1212, 1162, 1095, 990, 787, 744, 671. MS (ES⁺) *m/z* calculated for [C₃₁H₃₄NP₂PtS₂]⁺ ([M]⁺) 741.1256; found 741.1260 (100%).

Synthesis of [Pd(S₂CNEt₂)(dppp)]Cl (8)



[PdCl₂(dppp)] (59 mg, 0.1 mmol) and sodium diethyldithiocarbamate (17 mg, 0.1 mmol) were heated in water (5 mL) to 60 °C for 1 hour. The solution was then extracted with chloroform (5 mL), dried over MgSO₄ and evaporated to dryness to obtain a white solid (48 mg, 68 %). Single crystals suitable for X-ray diffraction were obtained via diffusion of diethyl ether into a chloroform solution of the complex. ¹H NMR (400 MHz, CDCl₃): δ 7.64 – 7.53 (m, 8H), 7.50 – 7.37 (m, 12H), 3.58 (q, *J* = 7.2 Hz, 4H), 3.18 (m, 4H), 2.28 (ddt, *J* = 23.4, 17.0, 5.4 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 6H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 204.1 (s), 133.2 – 133.1 (m), 131.5 (s), 129.1 – 129.0 (m), 128.6 – 128.2 (m), 44.0 (s), 23.5 – 23.3 (m), 18.9 (s), 12.5 (s). ³¹P{¹H} NMR (162 MHz, CDCl₃): δ 10.2 (s). IR (ν/cm⁻¹): 3295, 1513, 1431, 1376, 1274, 1205, 1167, 1103, 995 (C-S), 798, 693. MS (ES⁺) *m/z* calculated for [C₃₂H₃₆NP₂PdS₂]⁺ ([M]⁺) 666.0799; found 666.0853 (100%).

Synthesis of [Pt(S₂CNEt₂)(dppp)]Cl (9)



[PtCl₂(dppp)] (68 mg, 0.1 mmol) and sodium diethyldithiocarbamate (17 mg, 0.1 mmol) were heated in water (5 mL) to 60 °C for 1 hour. The solution was then extracted with chloroform (5 mL), dried over MgSO₄ and evaporated to dryness to obtain a white solid (51 mg, 65 %). Single crystals suitable for X-ray diffraction were obtained via diffusion of diethyl ether into a chloroform solution of the complex. ¹H NMR (400 MHz, CDCl₃): δ 7.58 (m, 8H), 7.51 – 7.37 (m, 12H), 3.58 (q, *J* = 7.2 Hz, 4H), 3.15 – 2.99 (m, 4H), 2.42 – 2.23 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 6H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 203.3 (s), 133.0 – 132.9 (m), 131.8 (s), 129.0 – 128.9 (m), 128.0 – 127.4 (m), 44.6 (s), 23.6 – 23.2 (m), 19.3 (s), 12.5 (s). ³¹P{¹H} NMR (162 MHz, CDCl₃): δ -5.1 (s, *J*_{Pt,P} = 2981 Hz). IR (ν/cm⁻¹): 3373, 1537, 1435, 1279, 1202, 1155, 1099, 974 (C-S), 835, 799, 744, 694, 669. MS (ES⁺) *m/z* calculated for [C₃₂H₃₆NP₂PtS₂]⁺ ([M]⁺) 755.1412; found 755.1430 (100%).

3. [¹¹C]Carbon disulfide production

[¹¹C]carbon dioxide was produced using a Siemens Eclipse HP cyclotron via the ¹⁴N[p,α]¹¹C nuclear reaction of 11 MeV proton bombardment of a gaseous target containing nitrogen and 1% oxygen. Cyclotron bombardment was typically set at 15 μA for 5 minutes. [¹¹C]CH₃I was produced via [¹¹C]CO₂ the gas phase H₂ reduction reaction over Ni catalyst and high temperature free-radical iodination of [¹¹C]CH₄ using a commercially-available Synthra unit. Gas phase [¹¹C]CH₃I was delivered to the hotcell for in a stream of helium carrier gas for further reaction. [¹¹C]CS₂ was produced by in-line reaction of [¹¹C]CH₃I with elemental sulphur, by passing the [¹¹C]CH₃I/He gas stream at 20 mL/min through a quartz Omnifit column (10 x 300 mm) containing a mixture of sulphur (0.5 g) and chromatography sand (2.5 g), placed in a Carbolite oven at 450 °C. High radiochemical conversions (typically >99%) of [¹¹C]CH₃I to [¹¹C]CS₂ were observed as assessed by radio-HPLC analysis. [¹¹C]CS₂ was then typically trapped in acetonitrile (between 300 and 500 MBq) before other radiolabelling reactions take place. The production process of [¹¹C]CS₂, including the [¹¹C]CO₂ to [¹¹C]CH₃I conversion, was typically complete within 15 minutes. Trapping of [¹¹C]CS₂ was monitored by measuring radioactivity in the column and the vial using pin diodes placed beside these components (figure 1). Depletion of the radioactivity in the S₈/sand column, apparent by the dip in the green graph, is followed by a rise and eventual plateau in the purple graph indicating maximum trapping of [¹¹C]CS₂. Further details the production process and representative reference radio-HPLC traces have been previously reported by us.⁵

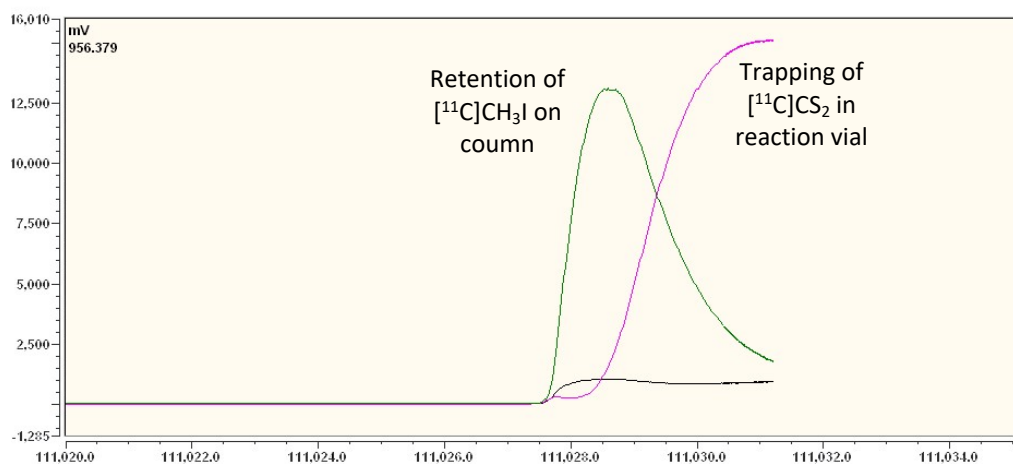


Figure 1S. Typical radioactivity transfer profile of of $[^{11}\text{C}]\text{CH}_3\text{I}$ to $[^{11}\text{C}]\text{CS}_2$ conversion as monitored by radiation detectors placed near the S_8/sand reaction column and the trapping vial. Retention of radioactivity in the S_8/sand column (green) and the reaction vial (purple). Note: The intensities of graphs are not quantified and correlated, as the detectors are not positioned at precisely the same distance from the column and reaction vial. Axes represent the arbitrary radioactivity units (mV) versus time (min).

4. Radiosynthesis of ^{11}C -labelled Au(III) and Au(I) complexes

Gaseous $[^{11}\text{C}]\text{CS}_2$ was produced as described above and passed into a solution of diethylamine or dibenzylamine (5 mg) in acetonitrile (1 mL) to generate $[^{11}\text{C}]$ diethyldithiocarbamate or $[^{11}\text{C}]$ dibenzylthiocarbamate in situ. The preparation and radioHPLC analysis of $[^{11}\text{C}]$ diethyldithiocarbamate (**1**) and $[^{11}\text{C}]$ dibenzylthiocarbamate (**2**) has been previously reported by us.⁵ When the radioactivity profile of the reaction vial reached a maximum, the gas flow was stopped and the vial allowed to stand at room temperature for two min. An aqueous solution of NaOH (0.8 M, 0.15 mL) was then added and the solution agitated to ensure mixing. This was followed by addition of a solution of either KAuCl_4 (5 mg in 0.15 mL water) or $\text{AuCl}(\text{PPh}_3)$ (5 mg in 0.4 mL THF) and stirred for five min at room temperature to generate the Au(III) or Au(I) complexes respectively. The crude mixture was analysed by radio- and UV-HPLC with spiked co-injection of the unlabelled reference compounds $[\text{AuCl}_2(\text{S}_2\text{CNEt}_2)]$, $[\text{AuCl}_2(\text{S}_2\text{CNBn}_2)]$ or $[\text{Au}(\text{S}_2\text{CNEt}_2)(\text{PPh}_3)]$ confirming the presence of the radiolabelled product.

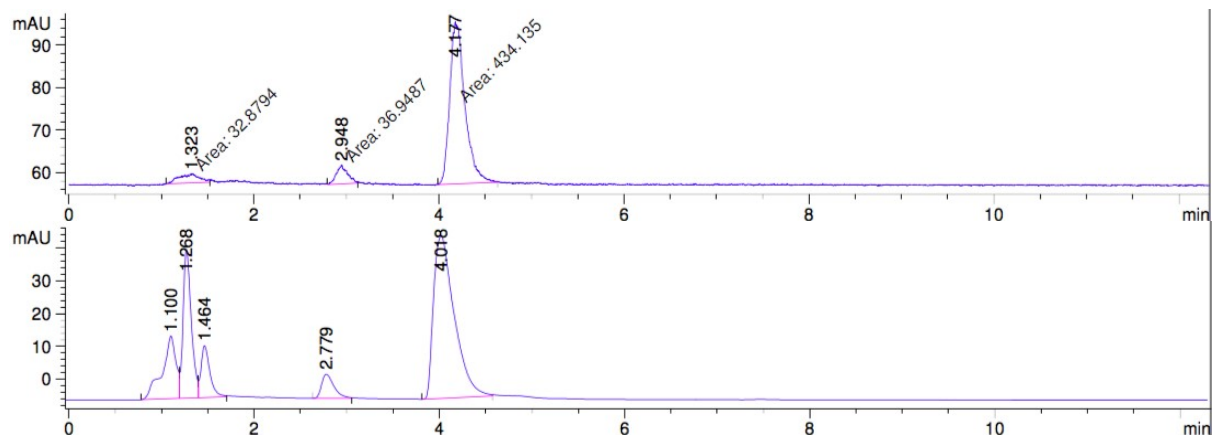
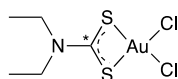


Figure 2S. Radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of $[\text{AuCl}_2([\text{}^{11}\text{C}]\text{S}_2\text{CNET}_2)]$. The crude reaction mixture was spiked with the unlabelled reference compound $[\text{AuCl}_2(\text{S}_2\text{CNET}_2)]$. HPLC eluent MeCN:AMF pH 8.0 (42:58).

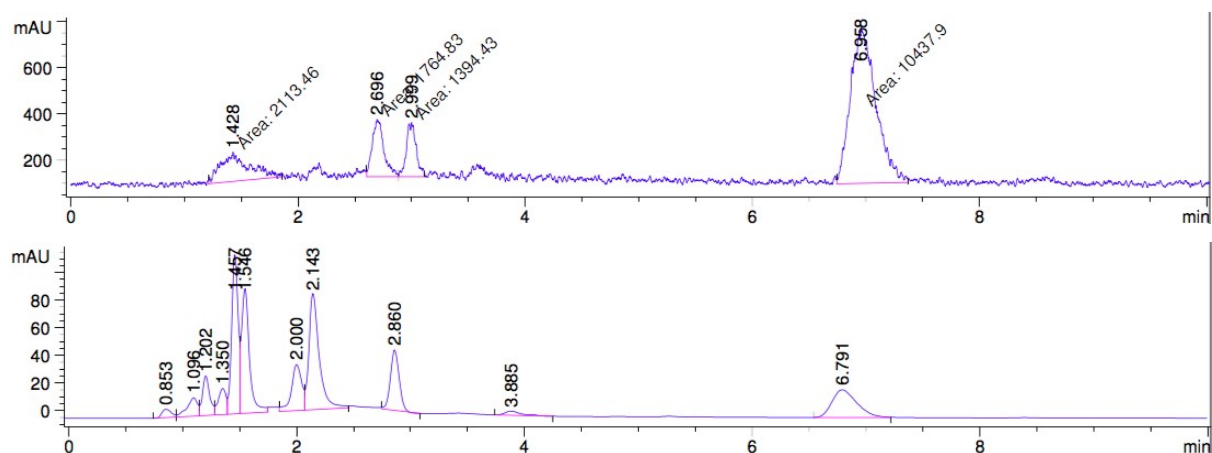
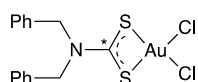
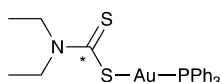


Figure 3S. Radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of $[\text{AuCl}_2([\text{}^{11}\text{C}]\text{S}_2\text{CNBn}_2)]$. The crude reaction mixture was spiked with the unlabelled reference compound $[\text{AuCl}_2(\text{S}_2\text{CNBn}_2)]$. HPLC eluent MeCN:AMF pH 8.0 (70:30).



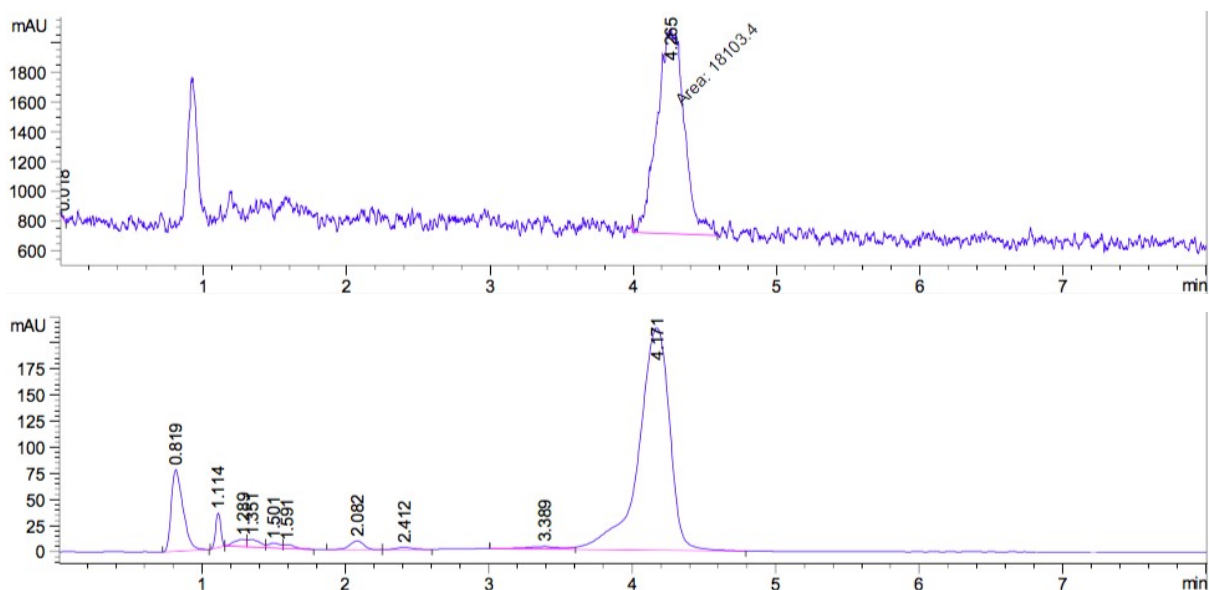
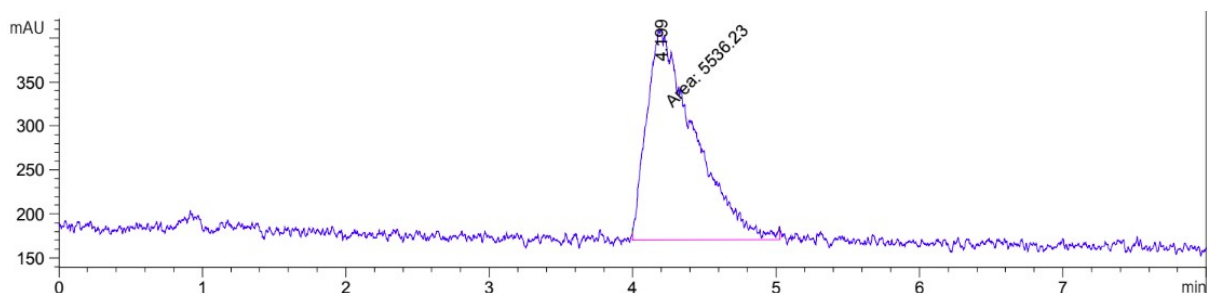
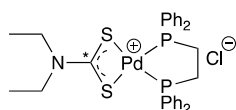


Figure 4S. Radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of $[\text{Au}([^{11}\text{C}]\text{S}_2\text{CNEt}_2)(\text{PPh}_3)]$. The crude reaction mixture was spiked with the unlabelled reference compound $[\text{Au}(\text{S}_2\text{CNEt}_2)(\text{PPh}_3)]$. HPLC eluent MeCN:AMF pH 8.0 (85:15).

5. Radiosynthesis of ^{11}C -labelled Pd(II) and Pt(II) complexes

$[^{11}\text{C}]$ Diethyldithiocarbamate (**1**) was prepared via the reaction $[^{11}\text{C}]\text{CS}_2$ with diethylamine (5 mg in acetonitrile 1 mL) as described above. A solution of metal precursor $[\text{MCl}_2(\text{dppe})]$ or $[\text{MCl}_2(\text{dppp})]$, $\text{M} = \text{Pd}$ or Pt , (5 mg in 0.2 mL DMF) was added and stirred for 5-10 min at 60 °C. The crude mixture was analysed by radio- and UV-HPLC with spiked co-injection of the unlabelled reference compounds $[\text{Pt}(\text{S}_2\text{CNEt}_2)(\text{dppe})]\text{Cl}$, $[\text{Pt}(\text{S}_2\text{CNEt}_2)(\text{dppp})]\text{Cl}$, $[\text{Pd}(\text{S}_2\text{CNEt}_2)(\text{dppe})]\text{Cl}$ or $[\text{Pt}(\text{S}_2\text{CNEt}_2)(\text{dppp})]\text{Cl}$ confirming the presence of the radiolabelled product.



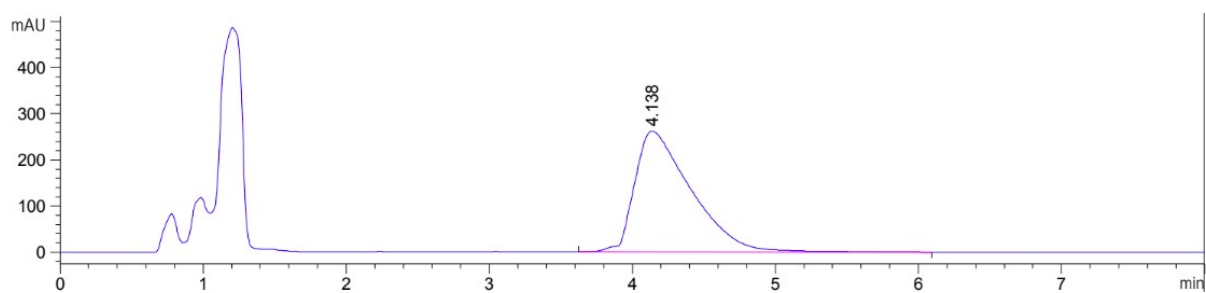


Figure 5S. Radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of $[\text{Pd}([\text{}^{11}\text{C}]\text{S}_2\text{CNEt}_2)(\text{dppe})]^+$. The crude reaction mixture was spiked with the unlabelled reference compound $[\text{Pt}(\text{S}_2\text{CNEt}_2)(\text{dppe})]\text{Cl}$. HPLC eluent MeCN:AMF pH 8.0 (70:30).

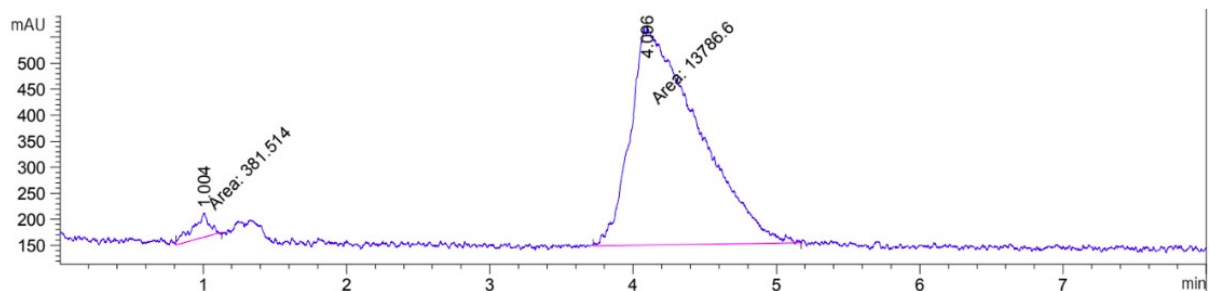
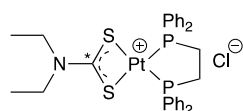
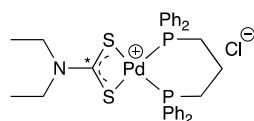


Figure 6S. Radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of $[\text{Pt}([\text{}^{11}\text{C}]\text{S}_2\text{CNEt}_2)(\text{dppe})]^+$. The crude reaction mixture was spiked with the unlabelled reference compound $[\text{Pt}(\text{S}_2\text{CNEt}_2)(\text{dppe})]\text{Cl}$. HPLC eluent MeCN:AMF pH 8.0 (70:30).



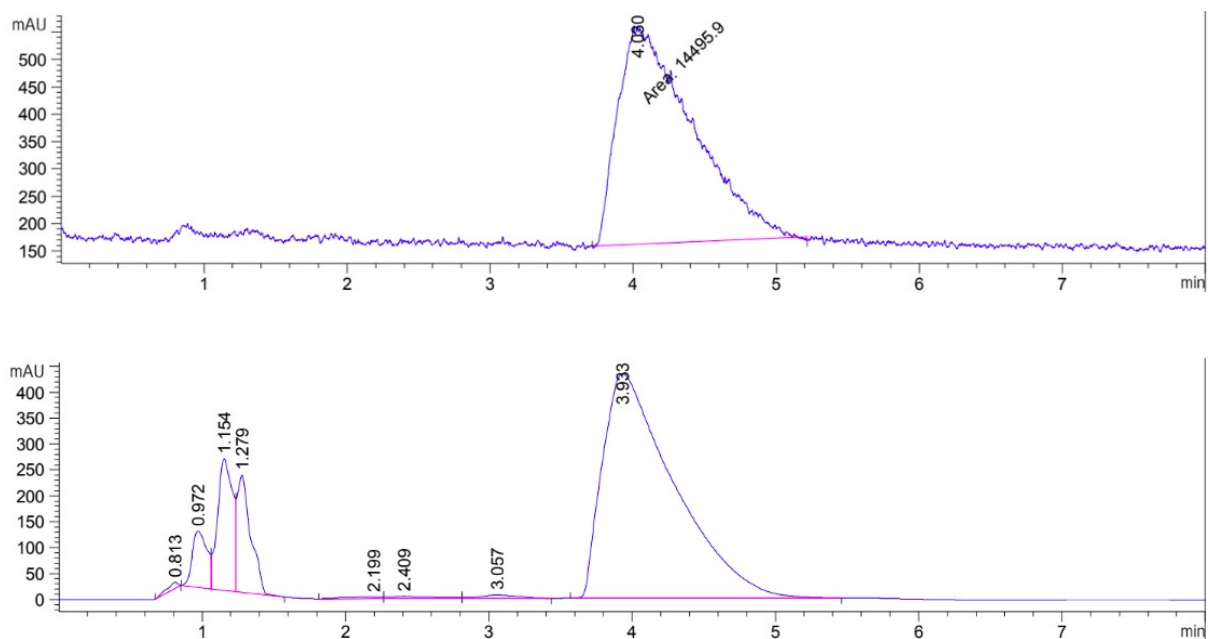


Figure 7S. Radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of $[\text{Pd}([\text{C}^{11}\text{S}_2\text{CNEt}_2)(\text{dppp})]^+$. The crude reaction mixture was spiked with the unlabelled reference compound $[\text{Pd}(\text{S}_2\text{CNEt}_2)(\text{dppp})]\text{Cl}$. HPLC eluent MeCN:AMF pH 8.0 (70:30).

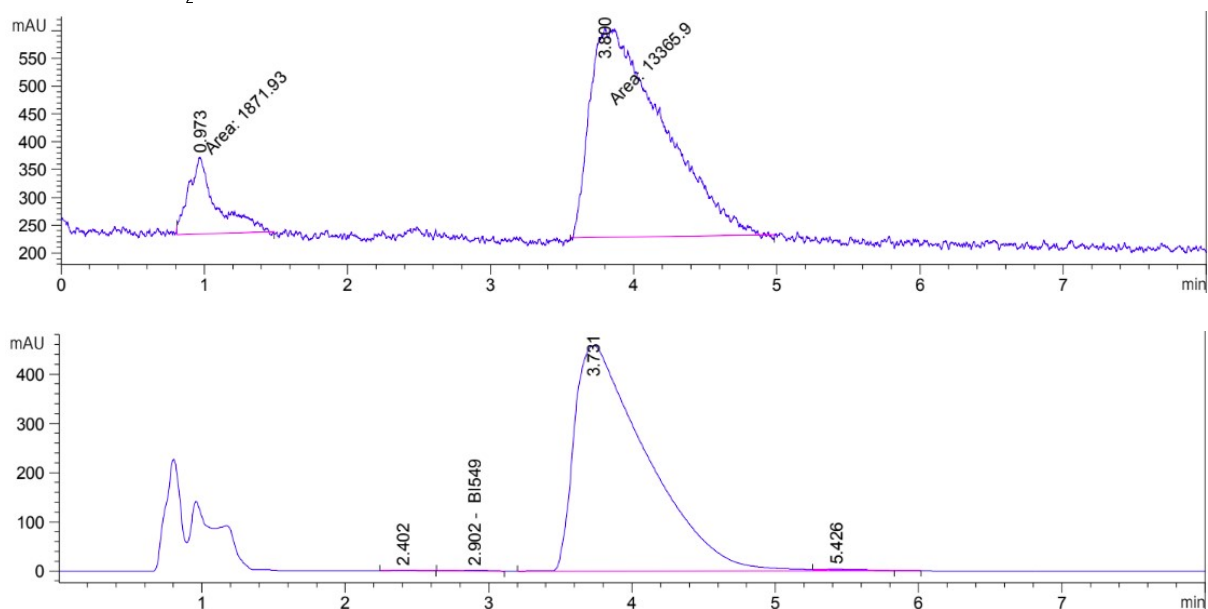
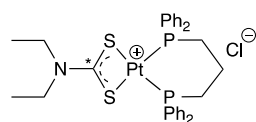


Figure 8S. Radio-HPLC trace (top) and UV-HPLC trace (bottom) of the crude reaction mixture for the formation of $[\text{Pt}([\text{C}^{11}\text{S}_2\text{CNEt}_2)(\text{dppp})]^+$. The crude reaction mixture was spiked with

the unlabelled reference compound [Pt(S₂CNEt₂)(dppp)]Cl. HPLC eluent MeCN:AMF pH 8.0 (70:30).

6. X-Ray Crystallography

The X-ray crystal structure of **8**

Crystal data for 8: [C₃₂H₃₆NP₂PdS₂][Cl]·2(CHCl₃), *M* = 941.26, triclinic, *P*-1 (no. 2), *a* = 15.3553(2), *b* = 15.3770(2), *c* = 17.2255(4) Å, α = 91.6478(16), β = 92.6572(16), γ = 92.2153(12)°, *V* = 4057.94(13) Å³, *Z* = 4 [two independent complexes], *D*_c = 1.541 g cm⁻³, μ (Mo-K α) = 1.126 mm⁻¹, *T* = 173 K, pale yellow blocks, Agilent Xcalibur 3 E diffractometer; 23485 independent measured reflections (*R*_{int} = 0.0505), *F*² refinement,^[X1,X2] *R*₁(obs) = 0.0350, *wR*₂(all) = 0.1075, 19348 independent observed absorption-corrected reflections [*|F_o*| > 4 σ (*|F_o*)], completeness to θ_{full} (25.2°) = 99.8%, 871 parameters. CCDC 2130302.

The crystal of **8** that was studied was found to be a two component twin in a *ca.* 52:48 ratio, with the two lattices related by the approximate twin law [-1.00 0.00 0.00 0.00 -1.00 0.00 0.09 -0.02 1.00]. The structure was found to contain two independent complex cations (**8-A** and **8-B**), two chloride anions, and four included chloroform solvent molecules in the asymmetric unit. The N4-based NEt₂ unit in the structure of complex **8-A** was found to be disordered. Two orientations were identified of *ca.* 81 and 19% occupancy, their geometries were optimised, the thermal parameters of adjacent atoms were restrained to be similar, and only the non-hydrogen atoms of the major occupancy orientation were refined anisotropically (those of the minor occupancy orientation were refined isotropically).

The X-ray crystal structure of **9**

Crystal data for 9: [C₃₂H₃₆NP₂PtS₂][Cl]·CHCl₃, *M* = 910.58, triclinic, *P*-1 (no. 2), *a* = 9.9905(4), *b* = 10.0596(3), *c* = 19.4585(10) Å, α = 79.965(3), β = 75.841(4), γ = 83.887(3)°, *V* = 1862.98(14) Å³, *Z* = 2, *D*_c = 1.623 g cm⁻³, μ (Mo-K α) = 4.275 mm⁻¹, *T* = 173 K, colourless blocks, Agilent Xcalibur 3 E diffractometer; 7303 independent measured reflections (*R*_{int} = 0.0226), *F*² refinement,^[X1,X2] *R*₁(obs) = 0.0298, *wR*₂(all) = 0.0515, 6484 independent observed absorption-corrected reflections [*|F_o*| > 4 σ (*|F_o*)], completeness to θ_{full} (25.2°) = 98.4%, 408 parameters. CCDC 2130303.

The C50-based included dichloromethane solvent molecule in the structure of **9** was found to be disordered. Two orientations were identified of *ca.* 83 and 17% occupancy, their geometries

were optimised, the thermal parameters of adjacent atoms were restrained to be similar, and only the non-hydrogen atoms of the major occupancy orientation were refined anisotropically (those of the minor occupancy orientation were refined isotropically).

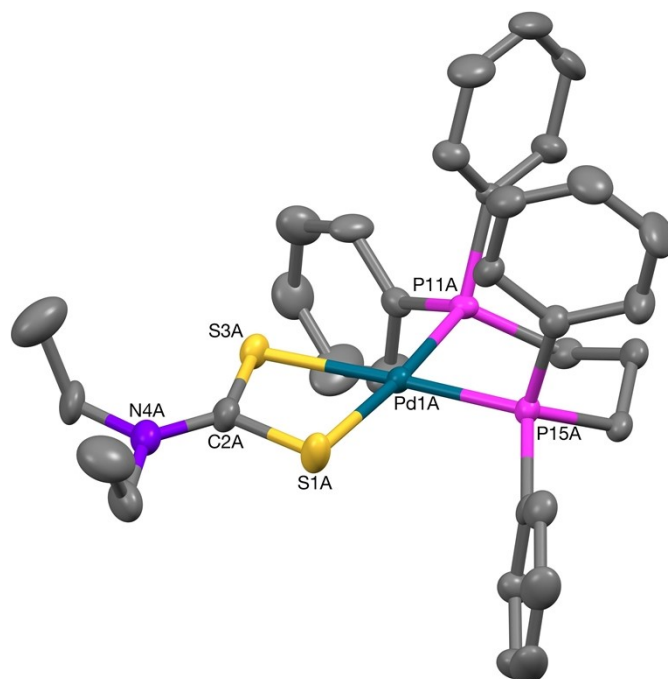


Figure S9. The structure of **8-A**, one of the two independent complex cations present in the crystal of **8** (50% probability ellipsoids).

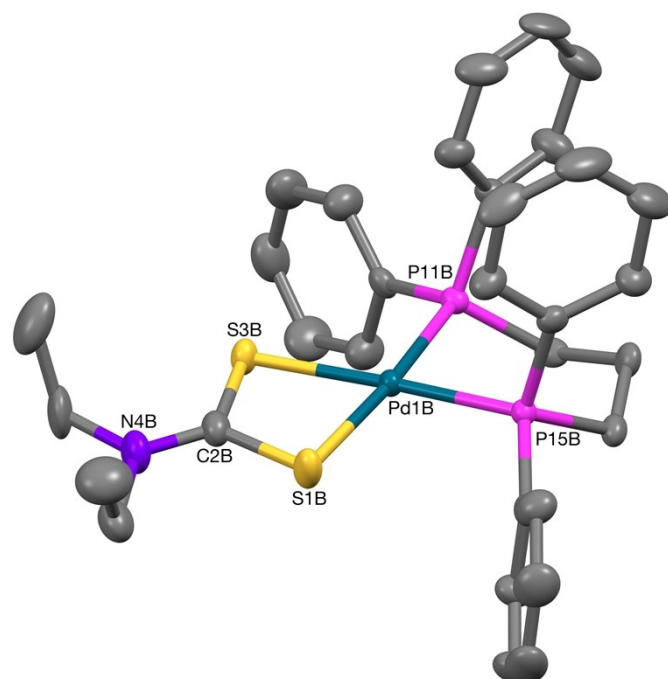


Figure S10. The structure of **8-B**, one of the two independent complex cations present in the crystal of **8** (50% probability ellipsoids).

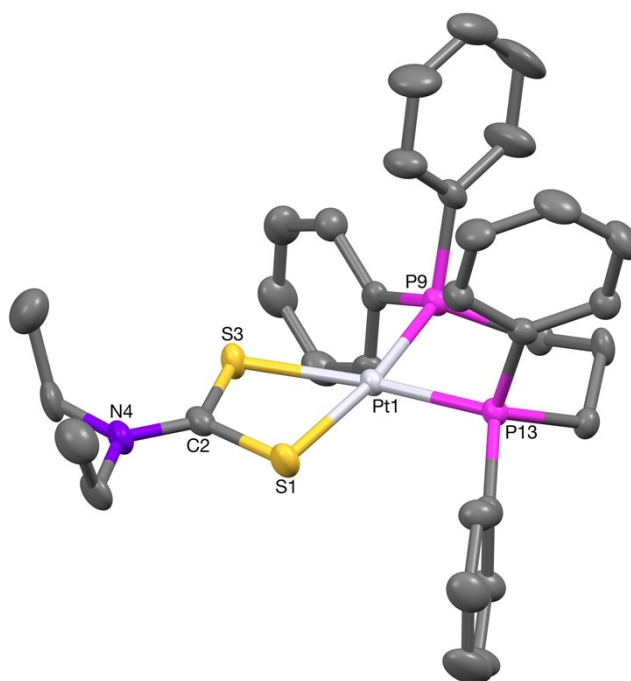


Figure S11. The structure of the complex cation present in the crystal of **9** (50% probability ellipsoids).

References

- [1] A. Megia-Fernandez, D. de la Torre-Gonzalez, J. Parada-Aliste, F. J. Lopez-Jaramillo, F. Hernandez-Mateo and F. Santoyo-Gonzalez, *Chem. Asian J.*, 2014, **9**, 620–631.
- [2] M. Altaf, A. A. Isab, J. Vančo, Z. Dvořák, Z. Trávníček and H. Stoeckli-Evans, *RSC Adv.*, 2015, **5**, 81599–81607.
- [3] G. Exarchos, S. D. Robinson and J. W. Steed, *Polyhedron*, 2001, **20**, 2951–2963.
- [4] G. Exarchos, S. D. Robinson and J. W. Steed, *Polyhedron*, 2000, **19**, 1511–1517.
- [5] T. Haywood, S. Kealey, S. Sanchez-Cabezas, J. J. Hall, L. Allott, G. Smith, C. Plisson and P. W. Miller, *Chem. Eur. J.*, 2015, **21**, 9034–9038.
- [6] SHELXTL v5.1, Bruker AXS, Madison, WI, 1998.
- [7] SHELX-2013, G.M. Sheldrick, *Acta Cryst.*, 2015, **C71**, 3-8.
- [8] A.L. Spek (2003, 2009) PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands. See also A.L. Spek, *Acta Cryst.*, 2015, **C71**, 9-18.

