Synthesis, characterization and cytotoxicity of some palladium(II), platinum(II), rhodium(I) and iridium(I) complexes of ferrocenylpyridine and related ligands. Crystal and molecular structure of *trans*-dichlorobis(3-ferrocenylpyridine)palladium(II)

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Abstract

The preparation of a series of ferrocenyl nitrogen donor ligands including ferrocenylpyridines, ferrocenylphenylpyridines and 1,1′-di(2-pyridyl)ferrocene is described. Coordination studies of the substituted pyridines (L) were carried out with platinum, palladium, rhodium and iridium. This resulted in the preparation of the following types of complexes: [MCl(CO)$_2$(L)] and [M(cod)(L)$_2$]ClO$_4$ where M = Rh or Ir, cod = 1,5-cyclooctadiene; [M′Cl$_2$(L)$_2$] where M′ = Pt or Pd. The X-ray crystal structure of *trans*-dichlorobis(3-ferrocenylpyridine)palladium was obtained. The complexes were screened for activity against two human cancer cell lines. At least two of the complexes displayed growth inhibition similar to that of the widely used chemotherapeutic agent, *cis*platin.
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1. Introduction

Several metal complexes most notably those containing platinum such as *cis*platin have shown promise in the treatment of various cancers [1]. Very recently, the development and cytotoxicity of multinuclear platinum complexes as anti-cancer drugs have been reviewed [2]. Several metallocenes, including complexes based on ferrocene [3], titanocene [4], vanadocene [5] and niobocene [6] have also been investigated for their potential anti-cancer activity. Three of the ferrocene derivatives that exhibit promising cytotoxic activity are shown in Scheme 1 and include a neutral ferrocene based on the anti-cancer drug tamoxifen, a ferrocenium tetraflouroborate salt containing two ferrocenyl groups and finally a ferrocene complex based on the anti-cancer drug *cis*platin [7]. Reviewing the literature in connection with the anti-cancer properties of ferrocenes, it becomes apparent that there are conflicting conclusions with regards to the important features that are required in the molecules to provide anti-cancer properties. In most cases, ferrocenium salts are reported to be more potent than the neutral molecules [8]. This effect could arise from the solubility difference although recent evidence by Osella et al. [9] suggests that the reduction of ferrocenium ions in vivo generates active oxygen radicals such as hydroxyl responsible for its anti-cancer activity through the formation of radical metabolites that are responsible for biological damage in the cancer cell.

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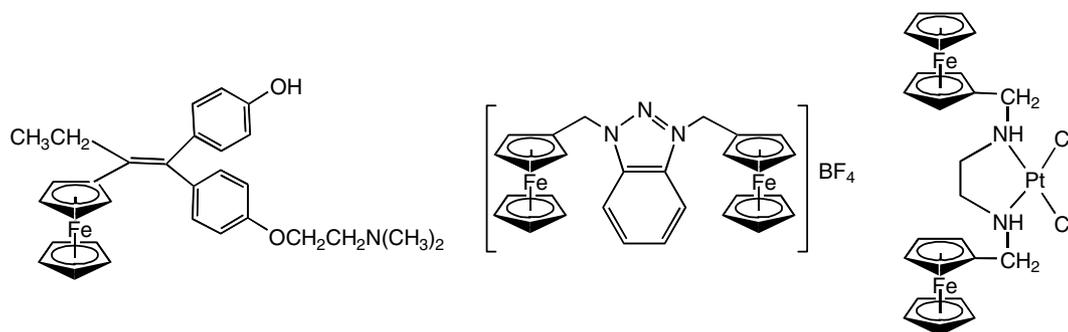
Scheme 1. Ferrocene derivatives with encouraging cytotoxic properties.

In a study combining ferrocene and platinum group metals, we report on the synthesis of metal complexes formed between ferrocenylpyridine and related nitrogen donor ligands and platinum, palladium, iridium and rhodium centres. The full details on the synthesis of the ferrocenylpyridine-type complexes of rhodium and iridium will be provided in a future publication that will report on their catalytic properties [10]. Cytotoxicity studies were carried out on a selection of the palladium, platinum, rhodium and iridium ferrocenylpyridine-type complexes. The complexes were screened for activity against oesophageal and cervical cancer cell lines. Complexes that exhibited significant activity in an initial screening assay, and which were fully soluble in the culture media, were further tested to determine their IC_{50} values. These were compared to the IC_{50} value of *cis*platin, determined in the same way and for the same cell line.

2. Results and discussion

2.1. Preparation of ligands

#### 2.1.1. Monosubstituted ferrocenylpyridine ligands

The key step in the synthetic route used in the preparation of monosubstituted ferrocenylpyridine ligands involved a nickel–phosphine catalysed cross-coupling reaction between a Grignard reagent and an aryl halide. This type of cross-coupling reaction has been reported to be particularly effective under relatively mild conditions, and offers comparatively good yields with respect to other synthetic methods [11]. The synthetic route to 4-ferrocenylpyridine **2** is illustrated in Scheme 2. A similar methodology was applied to the preparation of other ferrocenylpyridine compounds.

Bromoferrocene **1**, was obtained by the bromination of chloromercuriferrocene with *N*-bromosuccinimide [12]. The synthesis of chloromercuriferrocene was achieved through metallation of ferrocene with mercury(II) acetate followed by addition of lithium chloride [13]. The metallation of ferrocene in this case yields mono- and 1,1′-disubstituted chloromercuriferrocene, which were separated by Soxhlet extraction. Unreacted ferrocene was removed by sublimation, yielding chloromercuriferrocene as the unsublimed portion which was recrystallised to give a fine golden powder. Ferrocenylmagnesium bromide was formed in situ by gradual addition of 1,2-dibromoethane to magnesium in solution with **1** in diethyl ether. Once the Grignard reagent was generated, a mixture of the halogenated pyridine, together with the nickel catalyst, was added in diethyl ether. The reaction mixture was heated under reflux generating the product **2** which was purified by column chromatography. The product was obtained as yellow flakes in good yield and high purity.
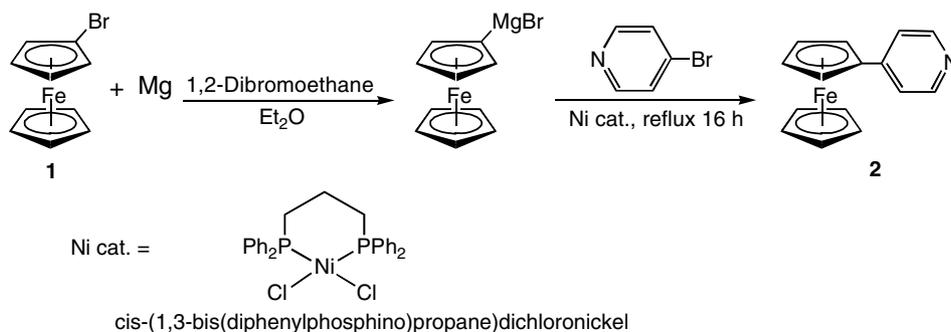
Scheme 2. Synthesis of 4-ferrocenylpyridine via the Grignard reaction.
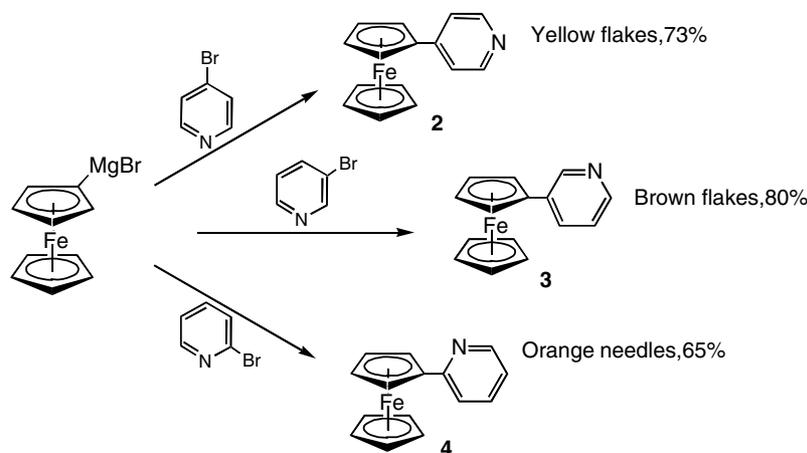
Scheme 3. Preparation of ferrocenylpyridine ligands via a Grignard reaction.
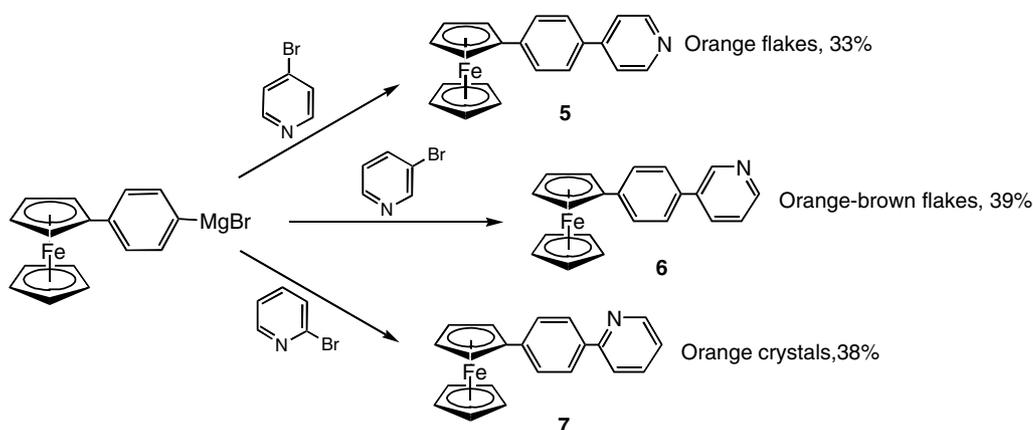
Scheme 4. Preparation of ferrocenylphenylpyridine ligands via a Grignard reaction.

Using this synthetic route, ligands **3**–**7** were prepared (Schemes 3 and 4). Moving the position of the substituents on the pyridyl ring from the 4- to 3- and 2-positions was performed with the intention of varying the number of bonds between the ferrocenyl substituent and the nitrogen donor atom, and consequently orientating the metals in the ligand-coordinated transition metal complexes spatially closer together. These types of complexes may allow electrochemical communication to occur through bond, as well as through space. Compounds **3** and **4** were similarly obtained from bromoferrocene and the appropriate halogenated pyridine. Although the preparation of **3** has been achieved previously by a diazonium reaction [14], the Grignard reaction described here consistently gave a higher yield.

The compounds **5**, **6** and **7** were obtained using the same synthetic route as for the preparation of **2**, **3** and **4**, starting from 4-bromophenylferrocene. The yields were

appreciably lower. The exact reason for this is unclear but may be related to the preparation of ferrocenylphenylmagnesium bromide in situ. Although compound **5** has previously been prepared via a palladium-catalysed cross-coupling reaction with an organozinc reagent [15], the synthetic route described here represents a relatively simple one-pot synthesis.

2.1.2. 1,1′-(2-Pyridyl)ferrocene ligand

Despite the fact that 1,1′-di(2-pyridyl)ferrocene **8** was prepared over three decades ago [16], its coordination behaviour has not been extensively investigated. Studies have been limited to the preparation and X-ray crystal structure analysis of novel rhodium and silver complexes [17]. Recent work has seen the preparation of palladium and platinum complexes of **8** [18]. The palladium complex has been further studied in carbonyl insertion reactions. This type of disubstituted ferrocene offers a ligand with a relatively flexible conformation and a large

bite angle. Compound **8** was prepared by a palladium catalysed cross-coupling reaction between a bis(chloro-zinc)ferrocene and a bromopyridine. The dilithioferro-cene–TMEDA complex was prepared in *n*-hexane and this resulted in a higher conversion to the desired dilithioferrocene than in the commonly used diethyl ether [16].

8
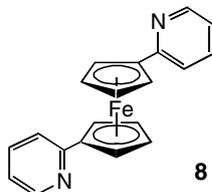
### 2.2. Preparation and properties of palladium complexes

The ligands investigated were soluble in dichlorome-thane, whereas the palladium starting material was not. The palladium complexes were prepared using a bi-phasic system with the ligands in a dichloromethane solution and the palladium starting material in an eth-anol–water mixture. The reaction mixture was stirred vigorously at room temperature to increase the interface of reaction between the solvent layers. A phase-transfer reaction was established between the layers, where the palladium product was found to be either soluble in the dichloromethane phase or formed as an insoluble pre-cipitate. The reaction could be monitored as the palla-dium layer was observed to lighten from dark brown to colourless. The use of this synthetic route gave a sub-stantial decrease in reaction time, with the longest re-action time being 10 h; this constitutes a decrease of more than half the reaction time when compared with the previously reported method [19]. Complexes **10–14**

were prepared using this synthetic route and were obtained in good yield.

The pyridyl proton chemical shifts for all complexes display downfield shifts on complexation of the palla-dium metal centre. The proton attached to the carbon atom adjacent to the nitrogen atom showed the largest shift on complexation of the palladium metal for com-plex **14**, contrary to the observed ferrocenyl shifts where very little difference was observed between the free li-gand and complex. Complexes **12** and **13** showed small downfield shifts for both α-H and β-H on complexation to the palladium metal centre (Scheme 5). Complex **10** was the only complex that displayed upfield shifts on complexation while complex **14** showed no difference between the free ligand and coordinated complex.

Cyclic voltammograms of the palladium complexes were obtained in acetonitrile using tetrabutylammonium perchlorate as the background electrolyte and a plati-num disk as the working electrode (Table 1). The vol-tammograms were recorded relative to ferrocene using a scan rate of 100 mV s^{-1} and the same conditions ($E_{1/2}$ = +75.5 mV). A single ferrocenyl wave was ob-served for all palladium complexes suggesting that no electrochemical communication occurred between the ferrocenyl groups of the complexes through the palla-dium metal centre.

With the exception of complex **14**, all samples dis-played a positive potential shift in $E_{1/2}$ indicating that the ferrocenyl group became harder to oxidise on coordi-nation of the palladium centre. Complex **13** gave the largest positive $E_{1/2}$ value as well as the most significant shift on comparison of the free ligand **3** and complex. Although the half-wave potential for complex **14** is puzzling, it is consistent with its spectroscopic properties.
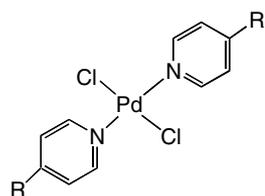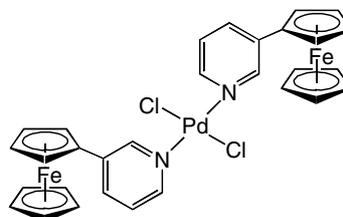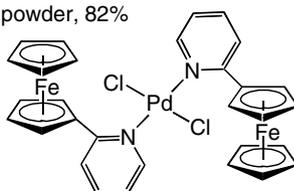

9 : R = H; yellow powder, 77%

10: R = Fc; red powder, 84%
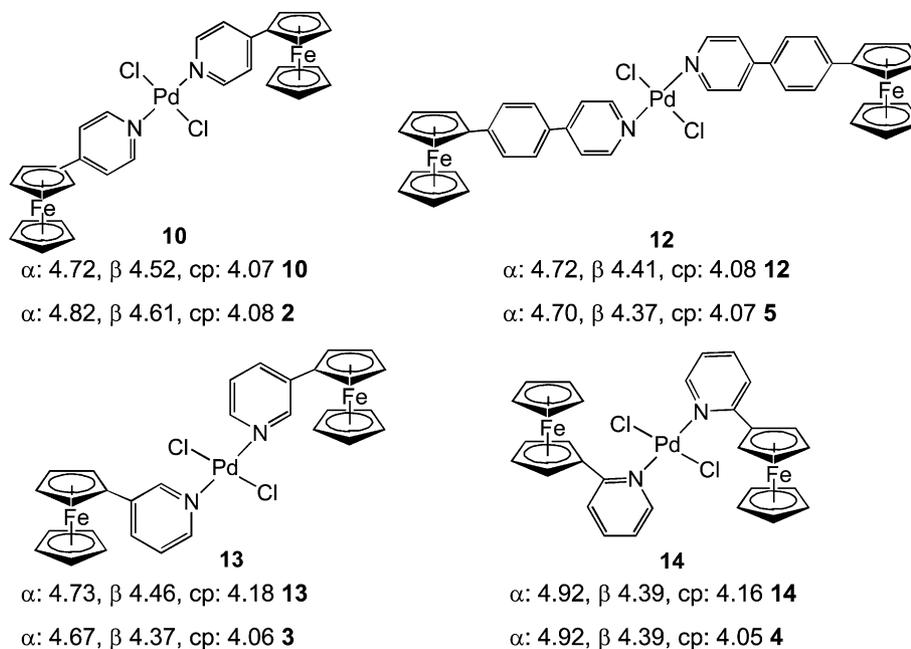
11: R = Ph; light yellow powder, 83%

12: R = (C$_6$H$_4$)Fc; maroon-brown powder, 82%

13: Mustard microcrystals, 84%

14: Dark red microcrystals, 78%

10
α: 4.72, β 4.52, cp: 4.07 **10**

α: 4.82, β 4.61, cp: 4.08 **2**

12
α: 4.72, β 4.41, cp: 4.08 **12**

α: 4.70, β 4.37, cp: 4.07 **5**

13
α: 4.73, β 4.46, cp: 4.18 **13**

α: 4.67, β 4.37, cp: 4.06 **3**

14
α: 4.92, β 4.39, cp: 4.16 **14**

α: 4.92, β 4.39, cp: 4.05 **4**

Scheme 5. Comparison of ^{1}H NMR chemical shifts (ppm) for complexes **10**, **12**, **13** and **14**.

Table 1
Electrochemical data for ferrocenyl palladium complexes **10**, **12**, **13** and **14** in acetonitrile

Complex number	Complex			Free ligand
	E_{pa} (mV)	E_{pc} (mV)	$E_{1/2}$ (mV)	$E_{1/2}$ (mV)
10	+253	+187	+220	+206
12	+176	+107	+142	+134
13	+256	+190	+223	+168
14	+136	+32	+84	+155

2.2.1. Crystal structure analysis of trans-dichlorobis(3-ferrocenylpyridine)palladium

The X-ray crystal structure of the palladium complex **13** was obtained using single crystals grown from a mixture of dichloromethane and pentane. The complex was observed to crystallise in the monoclinic space group $C2/c$ (Fig. 1).

The 3-ferrocenylpyridine ligands are equivalent from a crystallographic point of view, indicating a completely symmetrical structure. The X-ray analysis confirms the *trans* geometry of the complex. Selected bond lengths and angles are listed in Table 2. The observed bond lengths and angles around the palladium centre are similar to those reported for complex **9** [20]. The dihedral angle between the plane of the palladium centre and a pyridyl ring is 131°. The cyclopentadienyl rings in the ferrocenyl group are almost planar but tilt towards each other by an angle of 3.1°. The rings are not completely eclipsed and are observed to rotate by an angle of 5.7°. The pyridyl ring rotates away from the attached cyclopentadienyl ring by an angle of 12.5°. There are no

Table 2
Selected bond lengths (Å) and angles (°) for **13**

Pd(1)–Cl(1)	2.305 (9)	N(1)–Pd(1)–N′(1)	180.0 (1)
Pd(1)–N(1)	2.022 (2)	Cl(1)–Pd(1)–N(1)	89.8 (6)
N(1)–C(5)	1.343 (3)	Pd(1)–N(1)–C(1)	122.0 (2)
N(1)–C(1)	1.347 (3)	Pd(1)–N(1)–C(5)	119.0 (2)
C(5)–C(4)	1.390 (4)	C(3)–C(4)–C(6)–C(7)	15.7 (4)
C(1)–C(2)	1.380 (4)	C(5)–C(4)–C(6)–C(10)	12.5 (4)
C(2)–C(3)	1.384 (4)		
C(3)–C(4)	1.392 (4)		
C(4)–C(6)	1.464 (3)		
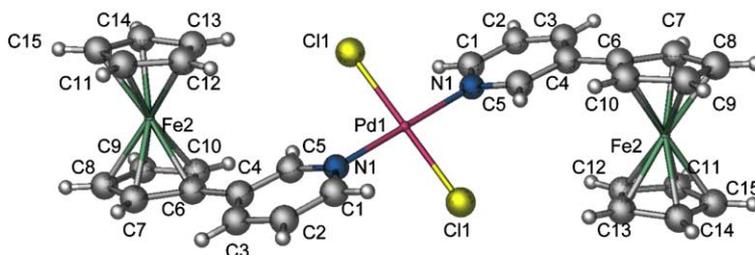
Fig. 1. Labelled perspective view of molecular structure for complex **13**.

significant intermolecular contacts between the molecules in the unit cell.

2.3. Preparation and properties of platinum complexes

Since the preparation of *cis*platin, a significant number of related platinum complexes have been synthesised in a bid to discover further platinum complexes exhibiting similar or enhanced anti-cancer activity. Both the *cis* and *trans* isomers of complex **15** have been prepared and their anti-cancer activity investigated [21].

The platinum complexes in this study, complexes **15**–**19**, were prepared using the synthetic route described in Scheme 6. This methodology is the same as that described for the synthesis of the palladium complex **9** where the product was formed as a precipitate over time. The preparation of the ferrocenyl complexes **18** and **19** was repeated using the biphasic route devised for the related palladium complexes. The biphasic route provided faster reaction times usually in the order of 5–10 h, as opposed to 24 h using the former route. The complexes were all obtained in good yield. Downfield shifts were observed for the pyridyl protons on complexation of the platinum metal, for all complexes. No shifts were observed in the ferrocenyl protons for complex **19** while upfield shifts were observed for complex **18.**

2.4. Preparation of rhodium and iridium complexes

An outline of the general synthetic methods used in the preparation of a series of rhodium(I) complexes is shown in Scheme 7. The full description of the syntheses and spectroscopic properties of the rhodium and iridium complexes will be published elsewhere along with a study on their catalytic properties [10]. The rhodium(I) carbonyl monosubstituted pyridyl coordination complex in this study was prepared through a bridge-splitting reaction of the rhodium carbonyl dimer **20**. The complex **21** was prepared using the synthetic route shown in Scheme 7(a). A bridge-splitting reaction of the

dimer was carried out in a low coordinating solvent with solvation of the monosubstituted rhodium leading to the formation of a monomeric species. This was followed by addition of the ligand with the product formed by displacement of the solvent molecule.

The rhodium cyclooctadienyl dimer, chloro(1,5-cyclooctadiene)rhodium(I) **22** was readily prepared by the reaction of excess cyclooctadiene and rhodium trichloride trihydrate. Several nitrogen-donor ligands were coordinated to the rhodium metal centre using by bridge splitting of the rhodium cyclooctadienyl dimer followed by addition of the ligand to give a series of complexes **23**–**28** (Scheme 7(b) and (c)).

Square planar rhodium(I) cationic complexes were also prepared. Cationic rhodium complexes are well-known primarily for their application in the field of catalysis [22]. The complexes examined in this study **29**–**32** contain two pyridyl ligands and in the case of those containing ferrocenylpyridyl ligands constitute the preparation of trimetallic complexes. The cationic rhodium(I) complexes were prepared using the general synthetic route described in Scheme 7(d). Silver perchlorate was added to a solution of the rhodium dimer in acetone, yielding a solvated complex of general formula $[Rh(COD)(Me_2CO)_x]ClO_4$. The addition of a nitrogen-donor ligand to this complex produced a cationic complex by displacement of the solvent from the rhodium coordination sphere. Complexes were obtained in good yield through concentration of the reaction mixture followed by addition of solvents such as diethyl ether or pentane to precipitate the product. The iridium complexes **33** and **34** are the iridium equivalents of complex **25** in which the H substituent is replaced by Ph and Fc, respectively, and were prepared in the same manner.

2.5. Cytotoxicity

Initial screening of complexes for cytotoxic activity was carried out by means of crystal violet staining of
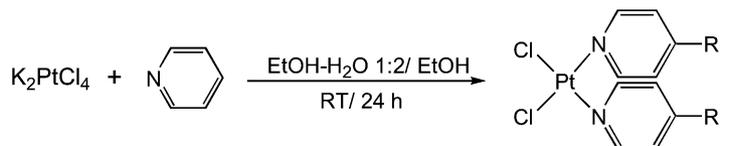
15: R = H; white powder, 72%
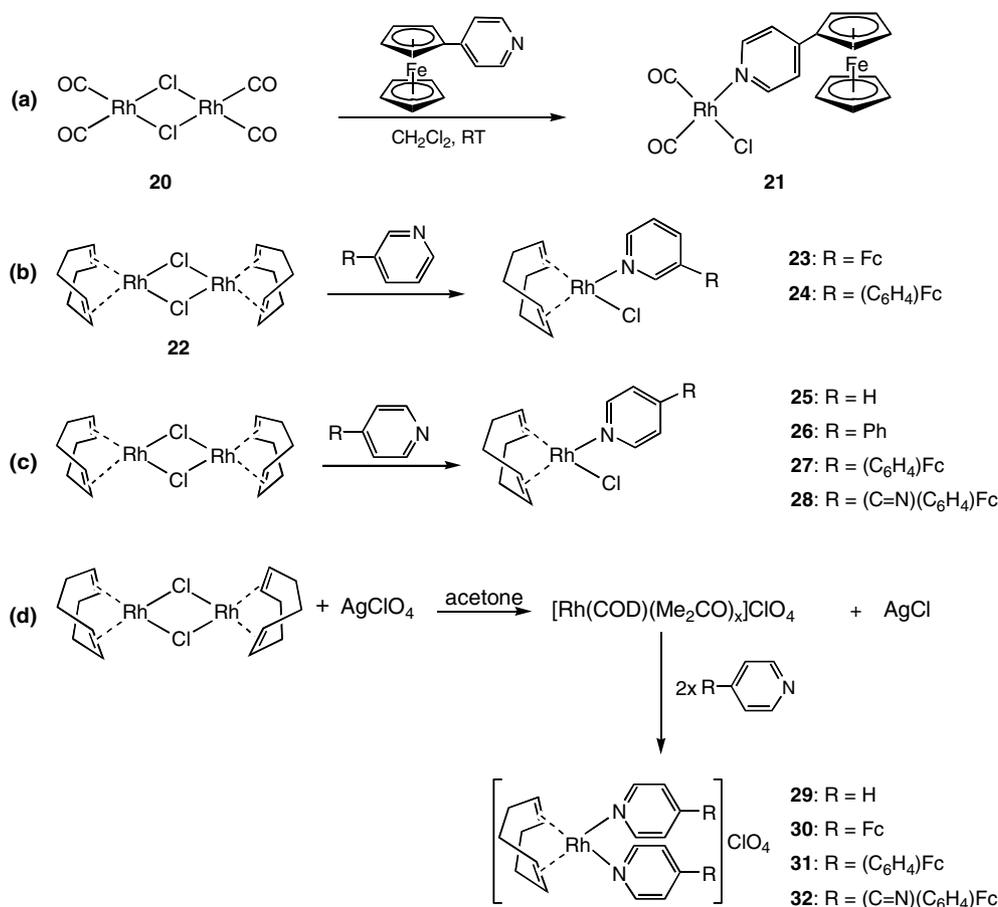
16: R = Ph; cream powder, 75%

17: R = (C=N)-Ph; mustard-yellow powder, 70%

18: R = Fc; orange-red powder, 72%

19: R = (C$_6$H$_4$)Fc; dark red microcrystals, 65%

Scheme 6. Synthesis of platinum complexes **15–19.**

Scheme 7. Preparation of rhodium complexes.

treated cells [23]. Complexes were tested at three different concentrations, and the results of the crystal violet assays are presented as percentage of untreated cells (see Table 3). In principle, an active compound would cause a decrease in cell number (and hence absorbance) with increasing drug concentration. Some complexes were not completely soluble, which occasionally resulted in an increased absorbance reading because the undissolved solid contributed to the absorbance. All cells were carefully examined microscopically prior to staining to determine the presence of precipitates and also to estimate cell density.

The next step involved determining the IC_{50} values of those compounds that were readily soluble. This was accomplished by treating cells with serial dilutions of each complex of interest, then assessing for cell viability with the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay [24]. An IC_{50} value was obtained, indicating the concentration of complex (in μM) which resulted in a 50% decrease in the number of cells. This approach allowed a direct comparison of various metal centres and various substituents on the activity of the synthesized complexes. The IC_{50} for

cisplatin was also determined so that the activity of the complexes described here could be compared to this widely used chemotherapeutic agent (see Table 4).

The use of platinum in anti-cancer drugs has been well established and cisplatin is the most prominent member of this class [25]. This drug is known to be 70–90% effective in cases of testicular cancer and is also used in the treatment of ovarian cancer. At least two of the complexes tested here displayed growth inhibitory activities similar to that of cisplatin (15 and 20 μM for complexes 23 and 32, respectively, compared to 13 μM for cisplatin) (Table 4). This is of interest as these were the only two complexes tested which have ferrocenyl substituents, the other complexes with ferrocenyl-containing ligands being too insoluble.

Although palladium complexes have generally been found to be less biologically active than related platinum complexes [26], we found that complex 9 (containing trans ligands with a palladium centre) was approximately twofold more active than complex 15 (an identical complex with cis ligands and a platinum centre).

Systematic substitution or modification of complex 25 allowed a functional comparison of an interesting

Table 3
Cytotoxic activity as determined by crystal violet assay[a]

Concentration (µg/ml)	WHCO1[b]			ME180[b]			Precipitate[c]		
	1	10	50	1	10	50	1	10	50
Pd complexes									
9	57	71	11	133	94	15			*
10	108	89	181	176	130	221	*	*	*
11	93	116	116	111	123	121	*	*	*
13	48	98	272	133	112	200	*	*	*
Pt complexes									
15	107	80	41	113	62	26			
16	61	31	51	67	21	24		*	*
18	103	67	57	131	67	47			*
Ir complexes									
33	113	133	25	100	83	16			
34	107	74	28	85	85	11			*
Rh complexes (one py ligand)									
21	70	74	28	77	57	24			*
23	149	53	30	176	55	15			
24	140	48	30	118	136	61		*	*
25	93	107	77	72	90	34			
26	100	57	38	136	70	16			
27	62	108	121	136	127	30		*	*
28	66	98	43	85	33	33			*
Rh complexes (two py ligands)									
29	90	84	97	103	100	57			
30	112	21	16	124	36	24			*
31	80	94	98	148	97	152	*	*	*
32	62	34	34	76	15	0		*	*

[a] Results are expressed as $[OD_{595\,nm}(\text{treated})/OD_{595\,nm}(\text{untreated})] \times 100$.

[b] Complexes were screened against two cancer cells lines (WHCO1 – oesophageal and ME180 – cervical) at three concentrations (1, 10 and 50 µg/ml).

[c] An asterisk indicates the presence of a precipitate at that concentration.

Table 4
IC_{50} values for soluble complexes against WHCO1 cells[a]

Complex	IC_{50} (µM)
9	33
15	78
23	15
25	253
26	33
29	147
32	19
33	59
cisplatin	13

[a] Values were determined from a dose response curve (assayed with MTT), and the IC_{50} is the concentration at which $OD_{595\,nm}$ is half that of untreated cells.

series of complexes containing a rhodium centre. Adding a phenyl substituent to the 4-position of the pyridyl ligand in complex **25**, generating complex **26**, substantially increased the growth inhibitory effect (by a factor of almost eight). Introducing a ferrocenyl substituent in the 3-position generated complex **23**, the most active complex tested in this series (approximately 17 times more active than complex **25**). Preliminary evidence suggests that replacing the chloride ligand in complex **23** with a second ferrocenyl pyridine ligand would result in

a complex with growth inhibitory activity similar or better than that displayed by cisplatin. In fact, the crystal violet results for the cationic complex **30** indicate that this complex is significantly more active than complex **23**, even with a reduced solubility. It is clear that relatively small structural changes to these complexes result in significant differences in cytotoxicity. Although the rhodium complexes (**21**, **23–28**) were generally more active in vitro relative to the platinum complexes (**15**, **16** and **18**), it is difficult at this stage given our limited study to comment on this difference.

3. Conclusion

In this paper, a series of new multinuclear complexes containing ferrocenyl groups and platinum group metals were successfully prepared and characterized using an array of analytical techniques. Some of the new complexes were tested for cytotoxic activity and a comparison was made to that of cisplatin. Several of the complexes displayed significant cytotoxic activity against the cancer cell line WHCO1 and two of the complexes particularly **23** and **32** displayed growth inhibitory activities similar to that of cisplatin. We are

currently exploring approaches to increase the water solubility of complexes such as **23**, **26**, **30** and **32** so that the growth inhibitory activity of the complexes can be determined more accurately, as well as investigating the synthesis and activity of related organometallic compounds.

4. Experimental

4.1. Purification and characterization of the materials

All manipulations, unless otherwise stated were carried out under an inert atmosphere of nitrogen using standard Schlenk techniques. Glass syringes were stored at 60 °C and all other glassware thoroughly dried at 210 °C for at least four hours prior to use. For the most part, reaction solvents were purified, dried and distilled prior to use according to literature methods. Less commonly used reagents and solvents such as *N,N*-dimethylformamide, pyridine and triethylamine were purified, dried, and then stored under nitrogen in dry glass storage vessels equipped with Teflon valve stopcocks. Chromatography solvents were of analytical grade and used without purification, with the exception of dichloromethane and hexane which were of chemically pure grade and distilled in air prior to use. *n*-Butyllithium (1.6 M in hexanes), Superhydride® (1.0 M in tetrahydrofuran) and *N,N,N′,N′*-tetramethylethylenediamine were purchased from Sigma–Aldrich and transferred under nitrogen into a glass storage vessel with a Teflon stopcock. All other commercial reagents were used as obtained without further purification. Rhodium, iridium, platinum, and palladium were obtained as chloride salts on loan from Johnson–Matthey and ferrocene was obtained commercially from Sigma–Aldrich. The rhodium complexes **20–32** used in this study were prepared and fully characterized by us and this work will be published elsewhere [10].

Thin layer chromatography was performed on aluminium backed silica gel or aluminium oxide 60 F_{254} plates in a variety of solvent systems using the ascending technique. Plates were analysed under ultraviolet light. Column chromatography was conducted either on silica gel 60, particle size 0.063–0.200 mm (70–230 mesh ASTM) or neutral alumina, particle size 0.063–0.200 mm (70–230 mesh ASTM). Columns were generally prepared with 1:100 ratio product to chromatographic material. Melting points were determined on a Kofler hotstage microscope (Reichart Thermovar). Microanalyses were obtained on a Carlo Erba EA 1108 elemental analyser. Fast atom bombardment (FAB) and high resolution (EI) mass spectra were recorded on a VG-70SEQ mass spectrometer at the mass spectrometry unit, Cape Technikon. In all cases the isotopic distribution was checked against the theoretical distribution.

Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer, with solid samples prepared as potassium bromide disks and solution samples in sodium chloride solution cells. Thermal analyses were conducted on Perkin Elmer Thermogravimetric analyser TGA7 and Differential Scanning Calorimeter DSC7. NMR spectra were recorded on either a Varian Unity-400 (^{1}H: 400 MHz; ^{13}C: 100.6 MHz) or Varian Mercury-300 (^{1}H: 300 MHz; ^{13}C: 75.5 MHz) spectrometer at ambient temperatures. ^{1}H NMR spectra were referenced internally using residual protons in the deuterated solvent (CDCl$_3$: δ 7.27; C$_6$D$_6$: δ 7.24, CD$_3$OD: δ 5.84, CD$_3$COCD$_3$: δ 2.09) and values reported relative to tetramethylsilane (δ 0.00). ^{13}C NMR spectra were similarly referenced internally to the solvent resonance (CDCl$_3$: δ 77.0; C$_6$D$_6$: δ 128.1, CD$_3$OD: δ 49.1, CD$_3$COCD$_3$: δ 30.60 and 205.87) with values reported relative to tetramethylsilane (δ 0.0). UV–Vis spectra were recorded on a Hewlett–Packard 8452A diode array spectrophotometer in a range of solvents. Cyclic voltammograms were obtained on a BAS 100B electrochemical analyser with a one compartment three-electrode system consisting of a Ag/AgNO$_3$ (0.01 M) reference electrode, platinum wire auxiliary electrode and platinum disc working electrode. Samples (1–2 mM) were prepared and run at a scan rate of 100 mV s^{-1} under argon at ambient temperature, in anhydrous acetonitrile with tetrabutylammonium perchlorate (0.1 M) as background electrolyte. Solutions were saturated with argon by bubbling for several minutes prior to each run. The system gave ferrocene $E_{1/2} = +75.5$ mV. The platinum disc working electrode was polished between runs as a standard protocol.

4.2. Cytotoxicity determinations

4.2.1. Cell culture

Cells were routinely maintained at 37 °C, 5% CO$_2$. WHCO1 cells were cultured in DMEM supplemented with 10% fetal calf serum, 100 U/ml penicillin and 100 μg/ml streptomycin. ME180 cells (ATCC #HTB-33) were maintained in McCoy's 5A supplemented with 10% fetal calf serum, 100 U/ml penicillin and 100 μg/ml streptomycin.

4.2.2. Crystal violet assay [23]

Initial screening for cytotoxicity was carried out by plating cells at 1500 cells/well in 90 μl medium in Cell-Star 96 well plates. After 24 h incubation to allow cell settling, complexes were added in 10 μl medium to a final concentration of 1, 10 and 50 μg/ml, with solvent (DMSO) at 0.2%. Following 48 h incubation, observations of cell number and morphology were made, and the plates were then processed for staining.

Media were discarded, the plates allowed to drain, and 100 μl absolute methanol applied to each well for 10

min. Methanol was discarded and replaced with staining solution (1% crystal violet, 50% methanol) for 20 min. Plates were rinsed with water, and 100 μl water added to each well for 1 h. The water was discarded and replaced with a further 100 μl water. Plates were read at 595 nm on an Anthos microplate reader 2001.

4.2.3. MTT assay [24]

IC_{50} determinations were carried out using the MTT kit from Roche (Cat #1465007), according to manufacturer's instructions. Briefly, 1500 cells were seeded per well in 90 μl medium in Cellstar 96 well plates. Cells were incubated for 24 h, then complexes were plated at a range of concentrations in 10 μl medium, with a final concentration of 0.2% DMSO. After 48 h incubation, observations were made, and 10 μl MTT solution was added to each well. After a further 4 h incubation, 100 μl solubilization solution was added to each well, and the plates incubated again overnight. The following morning, plates were read at 595 nm on an Anthos microplate reader 2001.

4.3. Preparation of ferrocenyl ligands

4.3.1. 4-Pyridylimine-4′-phenylferrocene

Pyridine-4-carboxaldehyde (0.12 g, 1.08 mmol) was added to a solution of 4-ferrocenylaniline (0.20 g, 0.72 mmol) in methanol (20 ml) with 4 Å molecular sieves (1 g). The reaction mixture was heated under reflux overnight. The reaction mixture was then filtered and concentrated. The concentrate was cooled to 0 °C to precipitate the product. The product was collected via vacuum filtration and obtained as maroon crystalline flakes (0.24 g, 90%), m.p. 195–196 °C; Anal. Calc. for $C_{22}H_{18}FeN_2$: M^+ 366.08194. Found: M^+ 366.08140; IR (KBr cm^{-1}) 3506, 1623, 1408, 1105, 846 and 823; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.77 (2H, d, $J = 5.9$ Hz, C$_5$H$_4$N), 8.54 (1H, s, N=CH), 7.79 (2H, dd, $J = 5.9$ Hz, C$_5$H$_4$N), 7.55 (2H, dd, $J = 6.7$ Hz, C$_6$H$_4$), 7.22 (2H, d, $J = 8.5$ Hz, C$_6$H$_4$), 4.68 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.36 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.06 (5H, s, C$_5$H$_5$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 156.71 (N=C), 150.80 (C$_5$H$_4$N), 148.61 (C$_5$H$_4$N), 143.26 (C$_6$H$_4$), 139.07 (C$_5$H$_4$N), 127.00 (C$_5$H$_4$N), 122.38 (C$_5$H$_4$N), 121.48 (C$_6$H$_4$), 69.88 (C$_5$H$_5$), 69.42 (C$_5$H$_4$) and 66.70 (C$_5$H$_4$); MS (EI) m/z 366 (M$^+$, 100%), 301 (8), 245 (9), 139 (8), 121 (8) and 56 (3).

4.3.2. 4-Ferrocenylpyridine 2

Diethyl ether (5 ml) was added to previously dried and weighed magnesium (396.0 mg, 16.0 mmol) in a two-necked 50 ml round bottom flask fitted with a condenser and dropping funnel. A solution of 1,2-dibromoethane (0.7 ml, 7.9 mmol) and bromoferrocene (792.0 mg, 4.0 mmol) in diethyl ether (10 ml) was added dropwise. On complete addition, two layers were ob-

served with a small amount of unreacted magnesium. A mixture of 4-bromopyridine (462.2 mg, 2.6 mmol) and *cis*-(1,3-bis(diphenylphosphino)propane)dichloronickel (16.7 mg, 31 μmol) in diethyl ether (10 ml) was added to the freshly prepared Grignard reagent. The reaction mixture was heated under reflux under nitrogen for 23 h, changing to a deep red solution over time. Upon cooling the reaction mixture, distilled water was added slowly to destroy any active Grignard reagent remaining. The two-layer reaction mixture was poured into a separating funnel and the aqueous layer extracted repeatedly with diethyl ether. The organic fractions were combined, washed with brine, dried over anhydrous magnesium sulfate and the solvent removed in vacuo yielding an orange residue. The residue was purified by column chromatography on silica gel. The product was eluted with 5% methanol in diethyl ether and isolated as golden yellow flakes (450 mg, 73%), m.p. 137–139 °C (lit. 136–138 °C [11]); IR (KBr cm^{-1}) 3104, 3069, 3033, 3047, 1612, 1569, 1478, 1436, 1348, 1105, 1093, 1033, 823, 486; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.45 (2H, d, $J = 6.0$ Hz, C$_5$H$_4$N), 7.51 (2H, dd, $J = 6.3$ Hz, C$_5$H$_4$N), 4.82 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.61 (2H, t, $J = 1.9$ Hz, C$_5$H$_4$), 4.08 (5H, s, C$_5$H$_5$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 150.78 (C$_5$H$_4$N), 123.85 (C$_5$H$_4$N), 72.02 (C$_5$H$_5$), 70.46 (C$_5$H$_4$) and 67.96 (C$_5$H$_4$).

4.3.3. 3-Ferrocenylpyridine 3

3-Ferrocenylpyridine was prepared according to the general procedure described in Section 4.3.2. Magnesium (183.7 mg, 7.55 mmol), 4-bromoferrocene (500.0 mg, 1.89 mmol), 1,2-dibromoethane (702.0 mg, 0.32 ml, 3.74 mmol), 3-bromopyridine (194.0 mg, 0.12 ml, 1.23 mmol) and *cis*-(1,3-bis(diphenylphosphino)propane)dichloronickel (8.0 mg, 14.7 μmol) in diethyl ether (25 ml) was heated under reflux for 19 h. The product was obtained as large flat brown crystals from dichloromethane–hexane (258.0 mg, 80%), m.p. 60-62 °C (lit. 57-59 °C [27]); IR (KBr cm^{-1}) 3853, 3743, 1699, 1652, 1569, 1495, 1419, 1305, 1282, 1215, 1103, 1088, 1007, 887, 808, 702, 668, 523, 498, 404; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.75 (1H, br s, C$_5$H$_4$N), 8.42 (1H, d, $J = 4.3$ Hz, C$_5$H$_4$N), 7.73 (1H, dd, $J = 8.0$ Hz, C$_5$H$_4$N), 7.21 (1H, dd, $J = 12.7$ Hz, C$_5$H$_4$N), 4.67 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.37 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.06 (5H, s, C$_5$H$_5$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 145.87 (C$_5$H$_4$N), 145.40 (C$_5$H$_4$N), 131.41 (C$_5$H$_4$N), 121.63 (C$_5$H$_4$N), 68.05 (C$_5$H$_5$), 67.85 (C$_5$H$_4$) and 64.87 (C$_5$H$_4$).

4.3.4. 2-Ferrocenylpyridine 4

2-Ferrocenylpyridine was prepared by the general procedure described in Section 4.3.2. Magnesium (220.6 mg, 9.06 mmol), bromoferrocene (600.9 mg, 2.26 mmol), 1,2-dibromoethane (840.0 mg, 0.39 ml, 4.48 mmol), 2-bromopyridine (200.0 mg, 0.12 ml, 1.28 mmol) and *cis*-(1,3-bis(diphenylphosphino)propane)dichloronickel (6.9

mg, 12.8 µmol) in diethyl ether (27 ml) were heated under reflux for 44.4 h. The product was obtained as orange rod-like microcrystals from dichloromethane–hexane (218.9 mg, 65%), m.p. 85–87 °C (lit. 87–89 °C [28]); Anal. Calc. for $C_{15}H_{13}FeN$: M$^+$ 263.1; Found: M$^+$ 263.0; IR (KBr cm^{-1}) 3608, 3565, 2324, 1843, 1767, 1698, 1622, 1587, 1558, 1495, 1423, 1275, 1106, 892, 824, 788, 741, 667, 518, 496, 441, 403; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.49 (1H, br s, C_5H_4N), 7.57 (1H, d, C_5H_4N), 7.41 (1H, dd, $J = 7.8$ Hz, C_5H_4N), 7.06 (1H, t, C_5H_4N), 4.92 (2H, t, $J = 1.8$ Hz, C_5H_4), 4.39 (2H, t, $J = 1.8$ Hz, C_5H_4), 4.05 (5H, s, C_5H_5); ^{13}C NMR (75 MHz, CDCl$_3$): δ 149.30 (C_5H_4N), 135.87 (C_5H_4N), 120.45 (C_5H_4N), 120.04 (C_5H_4N), 69.87 (C_5H_4), 69.56 (C_5H_5), 67.23 (C_5H_4); MS (FAB) m/z 264 (58%), 263 (M$^+$, 100), 198 (M − Cp, 39), 121 (Cp, 5), 56 (Fe, 6).

4.3.5. 4-Ferrocenylphenyl-4′-pyridine 5

4-Ferrocenylphenyl-4′-pyridine was prepared by the general procedure described in Section 4.3.2. Magnesium (178.2 mg, 7.33 mmol), 4-bromophenylferrocene (625.4 mg, 1.83 mmol), 1,2-dibromoethane (682.0 mg, 0.31 ml, 3.63 mmol), 4-bromopyridine (188.2 mg, 1.19 mmol) and *cis*-(1,3-bis(diphenylphosphino)propane)dichloronickel (7.8 mg, 14.3 µmol) in diethyl ether (36 ml) were heated under reflux for 21.8 h. The product was obtained as an orange powder (134.0 mg, 33%), m.p. 225-226 °C; IR (KBr cm^{-1}) 3085, 3023, 1645, 1610, 1545, 1500, 1435, 1401, 1105, 1087, 1000, 842, 810, 656, 498, 409; ^{1}H NMR (400 MHz; CDCl$_3$): δ 8.66 (2H, dd, $J = 5.9$ Hz, C_5H_4N), 7.59 (4H, s, C_6H_4), 7.54 (2H, dd, $J = 6.1$ Hz, C_5H_4N), 4.70 (2H, t, $J = 1.8$ Hz, C_5H_4), 4.37 (2H, t, $J = 1.8$ Hz, C_5H_4), 4.07 (5H, s, C_5H_5); ^{13}C NMR (101 MHz, CDCl$_3$): δ 150.45 (C_5H_4N), 127.09 (C_6H_4), 126.86 (C_6H_4), 121.35 (C_5H_4N), 66.83 (C_5H_4), 69.56 (C_5H_4), 69.92 (C_5H_5).

4.3.6. 4-Ferrocenylphenyl-3′-pyridine 6

4-Ferrocenylphenyl-3′-pyridine was prepared by the general procedure described in Section 4.3.2. Diethyl ether (5 ml) was added to previously dried and weighed magnesium (179.4 mg, 7.38 mmol) in a two-necked 50 ml round bottom flask fitted with a condenser and dropping funnel. A solution of 1,2-dibromoethane (682.0 mg, 0.31 ml, 3.63 mmol) and 4-bromophenylferrocene (625.3 mg, 1.83 mmol) in diethyl ether (10 ml) was added dropwise. On complete addition, two layers were observed with a small amount of unreacted magnesium. A mixture of 3-bromopyridine (188.2 mg, 0.11 ml, 1.19 mmol) and *cis*-(1,3-bis(diphenylphosphino)propane)dichloronickel (7.8 mg, 14.3 µmol) in diethyl ether (15 ml) was added to the freshly prepared Grignard reagent. The reaction mixture was heated under reflux under nitrogen for 20.5 h, changing to a bright orange solution over time. Upon cooling the reaction mixture, distilled water was added slowly to de-

stroy any active Grignard reagent remaining. The two-layer reaction mixture was poured into a separating funnel and the aqueous layer extracted repeatedly with diethyl ether. The organic fractions were combined, washed with brine, dried over anhydrous magnesium sulfate and the solvent removed in vacuo yielding an orange residue, which was subjected to column chromatography on silica gel. The product was eluted with 5% methanol in diethyl ether and isolated as an orange solid (156.0 mg, 39%), m.p. 144–147 °C; Anal. Calc. for $C_{21}H_{17}FeN$: C, 74.3; H, 5.1; N, 4.1%; M$^+$ 339.1. Found: C, 74.44; H, 5.06; N, 3.79%; M$^+$ 339.1; IR (KBr cm^{-1}) 3083, 3022, 2913, 2329, 1645, 1609, 1542, 1498, 1436, 1401, 1105, 1087, 1000, 842, 809, 668, 498, 409; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.89 (1H, br s, C_5H_4N), 8.58 (1H, d, $J = 4.8$ Hz, C_5H_4N), 7.89 (1H, dt, $J = 1.8$ and 11.7 Hz, C_5H_4N), 7.58 (2H, d, $J = 8.4$ Hz, C_6H_4), 7.52 (2H, d, $J = 8.8$ Hz, C_6H_4), 7.36 (1H, dd, $J = 12.4$ Hz, C_5H_4N), 4.69 (2H, t, $J = 1.8$ Hz, C_5H_4), 4.36 (2H, t, $J = 2.2$ Hz, C_5H_4), 4.07 (5H, s, C_5H_5); ^{13}C NMR (101 MHz, CDCl$_3$): δ 148.16 (C_5H_4N), 139.98 (C_5H_4N), 133.81 (C_5H_4N), 126.96 (C_6H_4), 126.65 (C_6H_4), 123.51 (C_5H_4N), 69.61 (C_5H_5), 69.14 (C_5H_4), 66.51 (C_5H_4); MS (EI) m/z 340 (24%), 339 (M$^+$, 100), 218 (M$^+$ − Cp–Fe, 18), 189 (4), 169 (4), 121 (Cp–Fe, 31) and 56 (Fe, 15).

4.3.7. 4-Ferrocenylphenyl-2′-pyridine 7

4-Ferrocenylphenyl-2′-pyridine was prepared by the general procedure described in Section 4.3.2. Diethyl ether (5 ml) was added to previously dried and weighed magnesium (129.0 mg, 5.28 mmol) in a two-necked 50 ml round bottom flask fitted with a condenser and dropping funnel. A solution of 1,2-dibromoethane (490.0 mg, 0.24 ml, 2.61 mmol) and 4-bromophenylferrocene (450.0 mg, 1.32 mmol) in diethyl ether (10 ml) was added dropwise. On complete addition, two layers were observed with a small amount of unreacted magnesium. A mixture of 2-bromopyridine (136.0 mg, 82.0 µl, 0.86 mmol) and *cis*-(1,3-bis(diphenylphosphino)propane)dichloronickel (5.6 mg, 10.3 µmol) in diethyl ether (16 ml) was added to the freshly prepared Grignard reagent. The reaction mixture was heated under reflux under nitrogen for 20.1 h, changing to a bright orange-red solution over time. Upon cooling the reaction mixture, distilled water was added slowly to destroy any active Grignard reagent remaining. The two-layer reaction mixture was poured into a separating funnel and the aqueous layer extracted repeatedly with diethyl ether. The organic fractions were combined, washed with brine, dried over anhydrous magnesium sulfate and the solvent removed in vacuo yielding an orange residue, which was subjected to column chromatography on silica gel. The product was eluted with 5% methanol in diethyl ether and isolated as a bright orange-red solid (112.0 mg, 38%), m.p. 37–39 °C; Anal. Calc. for $C_{21}H_{17}FeN$: C, 74.3; H, 5.0; N, 4.1%; M$^+$ 339.1. Found:

C, 74.54; H, 5.25; N, 4.10%; M^+ 339.1; IR (KBr cm^{-1}) 1585, 1467, 1434, 1105, 818, 782, 492, 441, 418, 411, 404; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.69 (1H, dd, $J = 4.8$ Hz, C$_5$H$_4$N), 7.93 (2H, dd, $J = 8.4$ Hz, C$_6$H$_4$), 7.74 (2H, dd, $J = 6.2$ Hz, C$_5$H$_4$N), 7.57 (2H, dd, $J = 8.8$ Hz, C$_6$H$_4$), 7.21 (1H, dd, $J = 6.6$ Hz, C$_5$H$_4$N), 4.71 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.35 (2H, t, $J = 2.2$ Hz, C$_5$H$_4$), 4.05 (5H, s, C$_5$H$_5$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 149.60 (C$_5$H$_4$N), 136.58 (C$_5$H$_4$N), 126.22 (C$_6$H$_4$), 126.77 (C$_6$H$_4$), 121.70 (C$_5$H$_4$N), 120.05 (C$_5$H$_4$N), 69.60 (C$_5$H$_5$), 69.12 (C$_5$H$_4$), 66.49 (C$_5$H$_4$); MS (FAB) m/z 340 (56%), 339 (M$^+$, 100), 274 (M − Cp, 5), 121 (Cp, 3), 56 (Fe, 3).

4.3.8. 1,1′-Bis(2-pyridyl)ferrocene 8

n-Butyllithium (6.23 ml, 9.97 mmol, 1.6 M in hexanes) was added slowly to a solution of $N,N,N′,N′$-tetramethylethylenediamine (1.16 g, 1.50 ml, 9.97 mmol) in hexane (5 ml). The mixture was stirred under nitrogen for at least 10 min at room temperature to allow butyllithium–TMEDA to form. A solution of ferrocene (0.743 g, 4.0 mmol) in hexane (35 ml) was added slowly and the mixture further stirred at room temperature for 6 h. Hexane was then removed and the residue taken up in tetrahydrofuran (30 ml) and cooled to 0 °C. A cold solution of zinc chloride (1.09 g, 8.0 mmol) in tetrahydrofuran (20 ml) was added to the dark solution, which was further stirred at room temperature for at least an hour. Meanwhile Superhydride$^{\circledR}$ (0.40 ml, 0.40 mmol, 1 M in tetrahydrofuran) was added to a suspension of dichlorobis(triphenylphosphine)palladium (0.140 g, 0.20 mmol) in tetrahydrofuran (10 ml), forming a dark solution that was added via cannula to the ferrocene reaction mixture. 2-Bromopyridine (1.58 g, 0.95 ml, 9.97 mmol) was added dropwise to the reaction mixture. An aqueous solution of sodium hydroxide (25 ml, 2.5 M) was added after 25 h. The two-layer reaction mixture was poured into a separating funnel. The aqueous phase was extracted repeatedly with dichloromethane. The organic fractions were combined and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue further purified by column chromatography on alumina. Elution with diethyl ether yielded a yellow band of 2-ferrocenylpyridine (575.5 mg, 55%). Elution with dichloromethane yielded an orange band of the product. The product was obtained as a pinkish-red powder (114.0 mg, 10%), m.p. 180–182 °C (lit. 179–180 °C [16]); IR (KBr cm^{-1}) 3568, 2323, 1773, 1700, 1636, 1617, 1586, 1562, 1507, 1457, 1425, 1100, 1025, 984, 668, 420, 405; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.35 (2H, d, $J = 5.3$ Hz, C$_5$H$_4$N), 7.67 (2H, t, $J = 7.8$ Hz, C$_5$H$_4$N), 7.50 (2H, dd, $J = 6.7$ Hz, C$_5$H$_4$N), 7.08 (2H, dd, $J = 11.6$ Hz, C$_5$H$_4$N), 4.91 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.36 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 156.97 (C$_5$H$_4$N), 136.51 (C$_5$H$_4$N),

131.90 (C$_5$H$_4$N), 128.39 (C$_5$H$_4$N), 120.30 (C$_5$H$_4$N), 71.48 (C$_5$H$_4$), 68.73 (C$_5$H$_4$).

4.4. Palladium complexes

4.4.1. Dichlorobis(pyridine)palladium 9

The reaction mixture was observed to change from a light brown solution to opaque yellow on addition of a solution of pyridine (54.0 mg, 55.0 μl, 0.68 mmol) in ethanol (5 ml) to a solution of sodium tetrachloropalladate(II) (100.0 mg, 0.34 mmol) in (1:2) ethanol/water (3 ml). The reaction mixture was further stirred at room temperature for 24 h. A precipitate was observed during this time. The product was collected via vacuum filtration as a light yellow powder (88.1 mg, 77%); IR (KBr cm^{-1}) 3629, 1636, 1604, 1474, 769, 668, 472; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.84 (4H, dd, $J = 8.1$ and 5.1 Hz, C$_5$H$_5$N), 7.78 (2H, tt, $J = 7.7$ Hz, C$_5$H$_5$N), 7.34 (4H, t, $J = 7.7$ Hz, C$_5$H$_5$N); ^{13}C NMR (101 MHz, CDCl$_3$): δ 153.65 (C$_5$H$_5$N), 138.96 (C$_5$H$_5$N), 124.95 (C$_5$H$_5$N).

4.4.2. Dichlorobis(4-phenylpyridine)palladium 11

A light yellow precipitate was observed to occur immediately on addition of a solution of 4-phenylpyridine (0.21 g, 1.36 mmol) in dichloromethane (5 ml) to a solution of sodium tetrachloropalladate(II) (0.20 g, 0.68 mmol) in (1:2) ethanol/water (6 ml). The reaction mixture was further stirred at room temperature for 6 h. The product was collected as a light yellow powder by vacuum filtration (0.27 g, 83%); Anal. Calc. for C$_{22}$H$_{18}$Cl$_2$N$_2$Pd: C, 54.2; H, 3.7; N, 5.7%. Found: C, 54.52; H, 3.55; N, 5.58%; IR (KBr cm^{-1}) 3626, 1760, 1699, 1634, 1609, 1480, 667, 503, 431; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.69 (4H, d, $J = 5.8$ Hz, C$_5$H$_4$N), 7.48 (4H, d, $J = 5.8$ Hz, C$_5$H$_4$N), 7.32 (10H, m, C$_6$H$_5$).

4.4.3. Dichlorobis(4-ferrocenylpyridine)palladium 10

Dichlorobis(4-ferrocenylpyridine)palladium was prepared according to the procedure described in Section 4.4.2. A red precipitate was observed to occur immediately on addition of a solution of 4-ferrocenylpyridine (0.50 g, 1.9 mmol) in dichloromethane (5 ml) to a solution of sodium tetrachloropalladate(II) (0.28 g, 0.95 mmol) in (1:2) ethanol–water (6 ml). The reaction mixture was further stirred at room temperature for 8 h. The product was collected as a red powder by vacuum filtration (0.56 g, 84%); m.p. 250–253 °C dec.; Anal. Calc. for C$_{30}$H$_{26}$Cl$_2$Fe$_2$N$_2$Pd: C, 51.2; H, 3.7; N, 4.0%; M^+ 703.65268. Found: C, 50.76; H, 3.52; N, 4.02%; M^+ 703.92108; IR (KBr cm^{-1}) 3568, 1700, 1636, 1611, 1499, 1215, 1107, 1039, 825, 494; ^{1}H NMR (CDCl$_3$): δ 8.59 (4H, d, $J = 6.7$ Hz, C$_5$H$_4$N), 7.30 (4H, br s, C$_5$H$_4$N), 4.72 (4H, s, C$_5$H$_4$), 4.52 (4H, s, C$_5$H$_4$), 4.07 (10H, s, C$_5$H$_5$); MS (FAB) m/z 703.9 (M$^+$, 28%), 667 (M − Cl, 14), 613 (9), 482 (7), 460 (25), 371 (8), 329 (32), 307 (75), 289 (60), 263 (ligand, 77), 176 (58), 107 (70), 89 (86).

4.4.4. Dichlorobis(3-ferrocenylpyridine)palladium 13

Dichlorobis(3-ferrocenylpyridine)palladium was prepared according to the procedure described in Section 4.4.2. A yellow precipitate was observed to occur immediately on addition of a solution of 3-ferrocenylpyridine (0.30 g, 1.2 mmol) in dichloromethane (5 ml) to a solution of sodium tetrachloropalladate(II) (0.17 g, 0.59 mmol) in (1:2) ethanol–water (6 ml). The reaction mixture was further stirred at room temperature for 6 h. The product was collected as a fine mustard-yellow crystalline powder by vacuum filtration (0.35 g, 84%), m.p. 148–150 °C dec.; Anal. Calc. for $C_{30}H_{26}Cl_2$ Fe_2N_2Pd requires C, 51.2; H, 3.7; N, 4.0%; M^+ 703.65268. Found: C, 50.86; H, 3.64; N, 3.92%; M^+ 703.92108; IR (KBr cm^{-1}) 3626, 1699, 1634, 1615, 1495, 1106, 815, 667, 498; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.91 (2H, br s, C$_5$H$_4$N), 8.62 (2H, d, $J = 5.1$ Hz, C$_5$H$_4$N), 7.75 (2H, d, $J = 6.9$ Hz, C$_5$H$_4$N), 7.20 (2H, t, $J = 6.6$ Hz, C$_5$H$_4$N), 4.73 (4H, br s, C$_5$H$_4$), 4.46 (2H, br s, C$_5$H$_4$), 4.18 (10H, s, C$_5$H$_5$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.13 (C$_5$H$_4$N), 149.76 (C$_5$H$_4$N), 138.31 (C$_5$H$_4$N), 135.05 (C$_5$H$_4$N), 124.20 (C$_5$H$_4$N), 70.37 (C$_5$H$_4$), 70.28 (C$_5$H$_5$) and 67.16 (C$_5$H$_4$); MS (FAB) m/z 706 (55), 704 (M$^+$, 74%), 702 (30), 669 (M $-$ Cl, 15), 633 (M $-$ Cl, 8), 581 (7), 511 (13), 371 (30), 369 (M $-$ ligand, 39), 263 (ligand, 100), 198 (29), 154 (38), 136 (37), 89 (11).

4.4.5. Dichlorobis(2-ferrocenylpyridine)palladium 14

Dichlorobis(2-ferrocenylpyridine)palladium was prepared according to the procedure described in Section 4.4.2. A brown two-layer solution was observed on addition of a solution of 2-ferrocenylpyridine (0.50 g, 1.9 mmol) in dichloromethane (5 ml) to a solution of sodium tetrachloropalladate(II) (0.28 g, 0.95 mmol) in (1:2) ethanol–water (6 ml). The reaction mixture was further stirred at room temperature for 7.5 h. The two-layer reaction mixture was separated and the organic layer was concentrated. The product was precipitated on addition of pentane and collected as dark red microcrystals by vacuum filtration (0.52 g, 78%), m.p. 108–110 °C; Anal. Calc. for $C_{30}H_{26}Cl_2Fe_2N_2Pd$: C, 51.2; H, 3.7; N, 4.0%; M^+ 703.65268. Found: C, 51.56; H, 3.78; N, 4.07%; M^+ 703.92108; IR (KBr cm^{-1}) 3626, 1760, 1703, 1634, 1605, 1495, 1435, 1106, 815, 667 and 408; ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.25 (2H, d, $J = 12.8$ Hz, C$_5$H$_4$N), 8.56 (2H, br s, C$_5$H$_4$N), 7.47 (2H, d, $J = 7.7$ Hz, C$_5$H$_4$N), 7.16 (2H, d, $J = 8.1$ Hz, C$_5$H$_4$N), 4.92 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.39 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.16 (10H, s, C$_5$H$_5$); ^{13}C NMR (75 MHz; CDCl$_3$): δ 157.51 (C$_5$H$_4$N), 152.22 (C$_5$H$_4$N), 139.08 (C$_5$H$_4$N), 125.67 (C$_5$H$_4$N), 119.68 (C$_5$H$_4$N), 70.94 (C$_5$H$_4$), 70.12 (C$_5$H$_4$), 67.84 (C$_5$H$_5$); MS (FAB) m/z 704 (M$^+$, 22%), 666 (M$^+$ $-$ Cl, 3), 631 (M $-$ Cl, 17), 565 (5), 510 (4), 370 (18), 368 (M $-$ ligand, 19), 279 (35), 263 (ligand, 100), 198 (25), 154 (35), 136 (27), 89 (13).

4.4.6. Dichlorobis(4-ferrocenylphenyl-4′-pyridine)palladium 12

Dichlorobis(4-ferrocenylphenyl-4′-pyridine)palladium was prepared according to the procedure described in Section 4.4.2. 4-Ferrocenylphenyl-4′-pyridine (49.5 mg, 0.15 mmol) in dichloromethane (5 ml) was added to a solution of sodium tetrachloropalladate(II) (21.5 mg, 0.07 mmol) in (1:2) ethanol/water (3 ml). The reaction mixture was further stirred at room temperature for 8 h. The product was collected as red-brown microcrystals by vacuum filtration (49.1 mg, 82%), m.p. 224–226 °C dec.; Anal. Calc. for $C_{42}H_{34}Cl_2Fe_2N_2Pd$: C, 58.9; H, 4.0; N, 3.3%; M^+ 855.8. Found: C, 59.25; H, 4.38; N, 2.85%; M^+ 856.1; IR (KBr cm^{-1}) 3585, 1750, 1699, 1634, 1615, 1495, 1456, 818, 667, 406; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.84 (4H, d, $J = 4.1$ Hz, C$_5$H$_4$N), 7.56 (8H, br s, C$_6$H$_4$), 7.54 (4H, d, $J = 6.1$ Hz, C$_5$H$_4$N), 4.72 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.41 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.08 (10H, s, C$_5$H$_5$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 153.10 (C$_5$H$_4$N), 127.04 (C$_6$H$_4$), 126.75 (C$_6$H$_4$), 122.03 (C$_5$H$_4$N), 69.72 (C$_5$H$_4$), 69.59 (C$_5$H$_4$), 66.67 (C$_5$H$_5$); MS (FAB) m/z 856 (M$^+$, 4%), 675 (13), 610 (4), 415 (24), 339 (ligand, 100), 278 (7), 149 (25), 85 (60).

4.5. Platinum complexes

4.5.1. Chloro(1,5-cyclooctadiene)(4-pyridylimine-4′-phenylferrocene)platinum chloride

4-Pyridylimine-4′-phenylferrocene (23.1 mg, 0.06 mmol) was added to a solution of dichloro(1,5-cyclooctadiene)platinum(II) (23.8 mg, 0.06 mmol) in pentane (6 ml). The reaction mixture was stirred at room temperature for 2 days after which a purple precipitate was observed. The product was collected via vacuum filtration as purple crystalline flakes (18.3 mg, 39%), m.p. 200–202 °C; Anal. Calc. for $C_{30}H_{30}Cl_2FeN_2Pt$: C, 48.6; H, 4.1; N, 3.8%; M^+ 704.97134. Found: C, 48.76; H, 3.87; N, 3.39%; M^+ 704.10948; IR (KBr cm^{-1}) 3503, 1685, 1624, 1577, 1473, 1406, 847, 668, 552, 418; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.74 (2H, d, $J = 5.9$ Hz, C$_5$H$_4$N), 8.52 (1H, s, N=CH), 7.76 (2H, dd, $J = 5.9$ Hz, C$_5$H$_4$N), 7.52 (2H, dd, $J = 8.6$ Hz, C$_6$H$_4$), 7.22 (2H, d, $J = 8.3$ Hz, C$_6$H$_4$), 5.59 (4H, br s, COD–CH), 4.66 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.34 (2H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.04 (5H, s, C$_5$H$_5$), 2.72–2.67 (4H, m, COD–CH$_2$), 2.27–2.23 (4H, d, $J = 8.3$ Hz, COD–CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 153.71 (N=C), 150.85 (C$_5$H$_4$N), 148.54 (C$_5$H$_4$N), 143.24 (C$_6$H$_4$), 139.07 (C$_5$H$_4$N), 126.72 (C$_5$H$_4$N), 122.38 (C$_5$H$_4$N), 121.49 (C$_6$H$_4$), 69.89 (C$_5$H$_5$), 69.39 (C$_5$H$_4$), 66.69 (C$_5$H$_4$); MS (FAB) m/z 704 (M$^+$, 1%), 519 (3), 460 (8), 410 (6), 366 (ligand, 68), 277 (95), 229 (20), 176 (24), 149 (25), 91 (37) and 77 (100).

4.5.2. Dichlorobis(pyridine)platinum 15

A solution of pyridine (95.0 mg, 0.10 ml, 1.20 mmol) in ethanol (5 ml) was added slowly to a solution of

potassium tetrachloroplatinate(II) (0.25 g, 0.60 mmol) in (1:2) ethanol/water (6 ml). The reaction mixture was further stirred at room temperature for at least 24 h. A precipitate was observed to form during this time. The product was collected as a white powder via vacuum filtration (0.18 g, 72%), m.p. 227–229 °C; IR (KBr cm^{-1}) 3608, 3087, 3023, 2322, 2317, 1843, 1634, 1616, 1607, 1575, 1557, 1482, 1436, 1242, 1207, 1156, 1075, 790, 767, 697, 427, 410 and 404; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.76 (2H, d, C$_5$H$_5$N), 7.33 (2H, dd, C$_5$H$_5$N), 7.84 (1H, t, C$_5$H$_5$N); ^{13}C NMR (75 MHz, CDCl$_3$): δ 152.90 (C$_5$H$_5$N), 126.31 (C$_5$H$_5$N), 138.52 (C$_5$H$_5$N).

4.5.3. Dichlorobis(4-phenylpyridine)platinum 16

Dichlorobis(4-phenylpyridine)platinum was prepared according to the general procedure described in Section 4.5.2. A solution of 4-phenylpyridine (64.7 mg, 0.42 mmol) in ethanol (2 ml) was added to a solution of potassium tetrachloroplatinate(II) (86.5 mg, 0.21 mmol) in (1:2) ethanol/water (3 ml). The reaction mixture was stirred under nitrogen at room temperature for 2 days. A precipitate was observed to form during this time. The product was collected via vacuum filtration as a cream powder (90.8 mg, 75%), m.p. 235 °C dec.; Anal. Calc. for C$_{22}$H$_{18}$Cl$_2$N$_2$Pt: C, 45.8; H, 3.1; N, 4.9%. Found: C, 46.19; H, 3.26; N, 4.87%; IR (KBr cm^{-1}) 3565, 3055, 2349, 2322, 1662, 1616, 1575, 1505, 1498, 1447, 1393, 1292, 1076, 1014, 842, 729, 693, 562, 497, 441, 435, 416, 410, 404; ^{1}H NMR (300 MHz, DMSO–d$_6$): δ 8.61 (4H, d, $J = 5.8$ Hz, C$_5$H$_4$N), 7.86 (8H, m, C$_6$H$_5$), 7.76 (2H, d, $J = 8.0$ Hz, C$_6$H$_5$), 7.66 (4H, d, $J = 5.8$ Hz, C$_5$H$_4$N); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 149.89 (C$_5$H$_4$N), 129.09 (C$_6$H$_5$), 128.84 (C$_6$H$_5$), 126.99 (C$_6$H$_5$), 126.86 (C$_5$H$_4$N).

4.5.4. Dichlorobis(4-phenylimine-4′-pyridine)platinum 17

Dichlorobis(4-phenylimine-4′-pyridine)platinum was prepared according to the procedure described in Section 4.5.2. A solution of 4-phenylimine-4′-pyridine (0.44 g, 2.4 mmol) in ethanol (10 ml) was added to a solution of potassium tetrachloroplatinate(II) (0.50 g, 1.2 mmol) in (1:2) ethanol/water (12 ml). The reaction mixture was stirred under nitrogen at room temperature for 2 days. A precipitate was observed to form during this time. The product was collected via vacuum filtration as a mustard-yellow powder (0.53 g, 70%), m.p. 145–146 °C; Anal. Calc. for C$_{24}$H$_{20}$Cl$_2$N$_4$Pt: C, 45.7; H, 3.2; N, 8.9%; M$^+$ 630.42326. Found: C, 45.69; H, 3.12; N, 8.62%; M$^+$ 630.07145; IR (KBr cm^{-1}) 3611, 3054, 2322, 1662, 1645, 1623, 1616, 1575, 1557, 1495, 1429, 1061, 832, 765, 692, 668, 552, 435, 420, 410, 403; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 9.04 (4H, d, $J = 6.6$ Hz, C$_5$H$_4$N), 8.66 (2H, s, N=CH), 8.05 (4H, d, $J = 7.3$ Hz, C$_6$H$_5$), 7.83 (4H, d, $J = 5.8$ Hz, C$_5$H$_4$N), 7.44 (2H, dd, $J = 7.6$ Hz, C$_6$H$_5$), 7.36 (2H, t, C$_6$H$_5$); ^{13}C NMR (75 MHz; DMSO-d$_6$): δ 156.95 (N=C), 153.70 (C$_5$H$_4$N), 152.12 (C$_5$H$_4$N),

150.10 (C$_5$H$_4$N), 129.02 (C$_6$H$_5$), 123.84 (C$_6$H$_5$), 121.06 (C$_6$H$_5$), 120.78 (C$_6$H$_5$); MS (FAB) m/z 630 (M$^+$, 10%), 558 (M − 2Cl, 27), 469 (30), 375 (33), 195 (4), 183 (ligand, 100) and 77 (32).

4.5.5. Dichlorobis(4-ferrocenylpyridine)platinum 18

Dichlorobis(4-ferrocenylpyridine)platinum was prepared according to the general procedure described in Section 4.5.2. A solution of 4-ferrocenylpyridine (15.4 mg, 0.06 mmol) in ethanol (2 ml) was added to a solution of potassium tetrachloroplatinate(II) (12.1 mg, 0.03 mmol) in (1:2) ethanol/water (2 ml). The reaction mixture was stirred under nitrogen at room temperature for 24 h. A precipitate was observed to form during this time. The product was collected via vacuum filtration as a pink-red powder (16.7 mg, 72%), m.p. 228–230 °C dec.; Anal. Calc. for C$_{30}$H$_{26}$Cl$_2$Fe$_2$N$_2$Pt: C, 45.5; H, 3.3; N, 3.5%; M$^+$ 792.27. Found: C, 45.42; H, 3.54; N, 3.15%; M$^+$ 793; IR (KBr cm^{-1}) 3629, 1701, 1696, 1653, 1617, 1521, 1437, 833, 501, 423, 416, 410, 406 and 403; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.56 (4H, d, $J = 5.3$ Hz, C$_5$H$_4$N), 7.25 (4H, br s, C$_5$H$_4$N), 4.69 (4H, br s, C$_5$H$_4$), 4.51 (4H, br s, C$_5$H$_4$), 4.02 (10H, s, C$_5$H$_5$); ^{13}C NMR (CDCl$_3$): δ 152.98 (C$_5$H$_4$N), 125.23 (C$_5$H$_4$N), 73.15 (C$_5$H$_5$), 70.64 (C$_5$H$_4$), 69.96 (C$_5$H$_4$); MS (FAB) m/z 793 (M$^+$, 4%), 521 (96), 398 (12), 342 (20), 279 (52), 263 (4-Fcpy, 24) and 223 (21).

4.5.6. Dichlorobis(4-ferrocenylphenyl-4′-pyridine)platinum 19

Dichlorobis(4-ferrocenylphenyl-4′-pyridine)platinum was prepared according to the general procedure described in Section 4.5.2. A solution of 4-ferrocenylphenyl-4′-pyridine (50.0 mg, 0.15 mmol) in dichloromethane (5 ml) was added to a solution of potassium tetrachloroplatinate(II) (30.6 mg, 0.07 mmol) in (1:2) ethanol/water (3 ml). The reaction mixture was stirred under nitrogen at room temperature for 6 h. A two-layer reaction mixture was obtained with a dark red organic layer and colourless aqueous layer. The layers were separated and the solvent removed in vacuo, yielding dark red crystals (43.0 mg, 65%), m.p. 239–241 °C dec.; Anal. Calc. for C$_{42}$H$_{34}$Cl$_2$Fe$_2$N$_2$Pt: C, 53.4; H, 3.6; N, 3.0%; M$^+$ 944.38395. Found: C, 53.08; H, 3.64; N, 2.85%; M$^+$ 944.04473; IR (KBr cm^{-1}) 1601, 1121, 1105, 1073, 1030, 1002, 887, 854, 815, 524, 504, 444, 425; ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.89 (4H, dd, $J = 5.9$ Hz, C$_5$H$_4$N), 7.62 (4H, dd, $J = 6.0$ Hz, C$_5$H$_4$N), 7.54 (8H, s, C$_6$H$_4$), 4.70 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.40 (4H, t, $J = 1.8$ Hz, C$_5$H$_4$), 4.07 (10H, s, C$_5$H$_5$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 152.82 (C$_5$H$_4$N), 126.96 (C$_6$H$_4$), 126.80 (C$_6$H$_4$), 122.55 (C$_5$H$_4$N), 69.82 (C$_5$H$_5$), 69.62 (C$_5$H$_4$), 66.73 (C$_5$H$_4$); MS (FAB) m/z 944 (M$^+$, 5%), 908 (M$^+$-Cl, 3), 871 (3), 675 (10), 610 (5), 533 (15), 415 (9), 340 (63), 339 (ligand, 100), 307 (14), 261 (6), 176 (12), 154 (51), 89 (34).

5. X-ray crystallography

5.1. Structural analysis of 13

X-ray diffraction data was collected at 173 K using Nonius Kappa CCD with 1.5 kW graphite monochromated Mo radiation. The strategy for data collection was evaluated using COLLECT [29]. Several sets of data were collected with both a 199° ϕ scan and ω scans to collect cusp data. The data was scaled and reduced as well as treated for absorption by a semi-empirical method using DENZO-SMN [30]. Unit cell dimensions were refined on all data. The structure was solved and refined using SHELX 97 [31]. Molecular graphics were generated using ORTEP-III [32], PLATON [33] and X-SEED [34], a graphical interface for the SHELX program. Crystal data for **13**: M_r = 703.53 g mol^{-1}, size $0.10 \times 0.10 \times 0.04$ mm, monoclinic, space group $C2/c$, $a = 34.606(7)$, $b = 5.674(1)$, $c = 13.126(3)$ Å, $V = 2572.8(9)$ Å^3, $T = 203$K, $Z = 4$, μ(Mo Kα) = 2.036 mm^{-1}, 2950 independent reflections, $R_{int} = 0.0000$, $R_{1obs} = 0.0270$, $R_{2obs} = 0.0537$, $R_{1all} = 0.0416$, $\omega R_{2all} = 0.0641$, goodness-of-fit = 0.822.

6. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 204897 for compound **13**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EC, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

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