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The regioselective asymmetric hydrophosphination of pyridine-functionalized alkenes can be achieved in the presence of stoichiometric amounts of chiral palladium complex (*R*)-**1**. The presence or absence of base affords the respective β - and α -adducts with excellent regiocontrol. Chiral gold-phosphine complexes incorporating the adducts exhibited good *in vitro* anticancer activity against breast cancer cell line MDA-MB-231. Selectivity between cancer cell line and normal cells was also observed.

Introduction

Chelating phosphine ligands containing N-donor centres possess both hard and soft features, providing unique environment to the metal centres that coordinate to them. As such, chiral P,N bidentate ligands have been successfully used in asymmetric catalytic reactions¹ and showed promising selectivity in some reactions compared to C2-symmetric P,P ligands.² However, the typical syntheses of such ligands require multiple synthetic manipulations which involve chiral starting materials or resolution of racemates.^{1e,f,i,3} To date, examples employing the direct asymmetric hydrophosphination to give pyridyl-functionalized phosphine ligands have rarely been reported.

Besides the important role of phosphines as ligands and organocatalysts,⁴ they can be further functionalized to afford gold complexes which exhibit promising anti-cancer properties. Since auranofin was first found to have anticancer activity against P388 lymphocytic leukaemia in the early 1980s,⁵ numerous gold-phosphine complexes have been investigated for potential anticancer properties.⁶ Some examples included the classic dppe-gold-chloride series^{6a} and the relatively recent GoPl.^{6c,d} An early investigation on the structure-activity relationship of auranofin analogues showed the significance of phosphine ligands, and phosphine gold

complexes exhibit better cytotoxicity than their non-phosphine counterparts.⁷ Moreover, variations in the structural backbone of the phosphine ligands could have drastic effects in both *in vivo* and *in vitro* anticancer activity.⁷

Gold adducts bearing a pyridyl ring in the phosphine backbone could influence the lipophilicity of the complex, which in turn alters its selectivity against cancer cells over normal cells.⁸ Moreover, the pyridyl ring being prone to protonation in the comparatively acidic environment of solid tumors,⁹ therefore aiding in drug accumulation at the target site. Thus we envision the syntheses of functionalized phosphine ligands based on a pyridine backbone bearing biologically active functional groups of esters and amides.¹⁰ Chirality is also an important consideration in our drug design, for it is recognized that enantiomers perform very differently in biological environments.¹¹

Over the past decade, the asymmetric addition of secondary phosphines to unsaturated bonds promoted by a chiral palladacycle has been achieved in our group.¹² The palladium center provides sufficient activation to the substrate, allowing the reaction to proceed smoothly in mild conditions with varying enantioselectivities. While there are numerous examples on the catalytic hydrophosphination of α,β -unsaturated substrates,¹³ such protocols are only limited to highly activated unsaturated esters^{13e,i} and cannot be applied when the product results in rigid chelation with the catalyst, thereby disrupting the catalytic cycle. Employing a slightly modified protocol, the palladacycle promoted preparation of (*S*)-methyl-2-(diphenylphosphino)-3-pyridin-2-ylpropanoate succeeded in the absence of any base.^{12e} Surprisingly, when we attempted to accelerate the reaction by addition of triethylamine to the reaction setup, we found that it gave a regioisomer with good enantioselectivity. Other than pyridyl acrylates, our protocol was also applicable to substrates with

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the amide functionality. To the best of our knowledge, this is the first report on the base-controlled regioselective asymmetric hydrophosphination reaction with alkenes, although our group has previously reported similar regioselective hydrophosphination pathways with alkynes.¹⁴ Liberation and coordination of the phosphine products to gold(I) affords two pairs of gold complexes, and followed by evaluation of their cytotoxicity against breast cancer cell line MDA-MB-231.

Results and Discussion

Synthesis and Characterization

Following the procedure reported by our group,^{12e} we succeeded in the hydrophosphination of pyridyl functionalized amide in the absence of any base with a regioselectivity of 18.9:1 according to $^{31}\text{P}\{^1\text{H}\}$ NMR analysis (Scheme 1). After purification by column chromatography, crystals of the major product were obtained from dichloromethane and diethyl ether. The X-ray crystallographic analysis of the complex confirmed that the newly formed ligand coordinates to palladium to give a six-membered ring with a twist-boat conformation (Fig. 1), with the phosphorus nucleophile having added to the α -position with respect to the carbonyl group. The palladium in (*R,S*)-**5** exhibits a mildly distorted square planar geometry, with a reduced bite angle of the P,N chelate at 83° . Though it was observed in previous study the coordination of the amide oxygen to palladium,¹⁵ this was not observed when **3** was employed. This can be attributed to the strong σ -donating property of the pyridyl nitrogen as compared to the amide's oxygen, thus preferentially occupying the position *trans* to the π -accepting naphthyl ring of (*R*)-**1**. In addition, this electronic donation has also led to the Pd-N(2) bond being slightly shorter (2.1267(18) Å) and stronger than the Pd-P(1) bond (2.2651(5) Å). Van der Waals interactions were observed between the amide's oxygen and dichloromethane's hydrogen with a bond distance of 2.366 Å. Analyses of obtained data revealed that absolute configuration of the newly formed stereogenic center at C21 is *S*.

Fig. 1 Molecular structure of (*R,S*)-**5**. Hydrogen atoms except those at the chiral center are omitted for clarity. The geometry at the palladium center is a distorted square planar with angles in the range of $80.73(8)$ – $101.03(6)^\circ$ and $170.81(5)$ – $174.65(7)^\circ$.

(*R,S*)-**4** and (*R,S*)-**5**. For **2**, the reaction was completed in three days in the presence of 0.4 equivalent of triethylamine and the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the crude products showed two singlets at δ 59.4 and 53.8 in a ratio of 1:6, which was different from (*R,S*)-**4** (δ 46.4). Purification by column chromatography only afforded a mixture of stereoisomers in the ratio of 1:7. In addition, the mixture could not be crystallized from all attempted solvent systems. Base controlled hydrophosphination of **3** also gave of a mixture of stereoisomers in the ratio of 1:18 with chemical shifts of δ 60.2 and 54.1 for the crude product, with the latter value corresponding to the α -adduct of (*R,R*)-**6**. In contrast to the employment of ester **2**, the reaction was slower and only went to completion in four days. However, a low yield of less than 10% was obtained after purification by column chromatography.

Treatment of the perchlorate salts generated in the above reactions with concentrated hydrochloric acid afforded dichloro complexes^{11e} which were then crystallized from dichloromethane and diethyl ether to give enantiopure (*R*)-**8** and (*R*)-**9** for the confirmation of their structures *via* X-ray analyses (Scheme 2).

Scheme 1 Hydrophosphination of pyridyl-functionalized ester and amide.

It was interesting to observe that when triethylamine was added to accelerate the reactions (Scheme 1), $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showed singlets whose chemical shifts differ from

Scheme 2 Base-controlled regioselective asymmetric hydrophosphination of **2** and **3**.

X-ray analyses revealed that the stereogenic center was formed on the β -carbon with respect to the carbonyl group (Fig. 2). Therefore, a five membered ring consisting of a P,N bidentate chelate was formed in the presence of palladium. Interestingly, the bite angle is practically identical when compared to (*R,S*)-**5** which instead contain a 6-membered chelating ring. Detailed analyses of X-ray data revealed that the Pd-N(pyridyl) and Pd-P bond lengths are reduced upon removal of the auxiliary. Strengthening of the mentioned bonds can be attributed to the absence of steric repulsions between the chelating ligand and the auxiliary. Notably, the two Pd-Cl bond lengths were significantly different, 2.2907(7) and 2.3806(7) [Å]; with the bond *trans* to the phosphorus being remarkably elongated. This is a result of the stronger *trans* influence of the phosphorus in contrast with nitrogen. While interactions between (*R*)-**8** and **9** and dichloromethane are present, there exist more interesting intermolecular interactions where the electron lone pairs of the carbonyl oxygens in (*R*)-**9** binds weakly to the protons of C7 and C9 belonging to a separate molecule of (*R*)-**9**. The newly formed chiral center adopted the *R* absolute configuration which was the configuration of the major product of the hydrophosphination step. All palladium complexes are stable in solution and in the solid state for more than 2 years with no changes or impurities detected by NMR spectroscopy.

Fig. 2 Molecular structure of (*R*)-**8**. Hydrogen atoms except those at the chiral center are omitted for clarity. The palladium center adopts a distorted square planar geometry with angles of 83.04(6)-94.76(6) $^\circ$ and 172.01(6)-177.08(2) $^\circ$.

The confirmation of the minor products was achieved by coordination of the liberated ligands to palladacycle (*S*)-**1** (Scheme 3). The purified mixture of (*R,R*)-**7** and (*R,S*)-**7** in the ratio of 7:1 was treated with aqueous potassium cyanide and then recoordination to (*S*)-**1** to give diastereomers **10** and **11** in the ratio of 1:7 with the same chemical shifts as the original mixture on the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum.

Free ligands of the complexes **4**, **5**, **6** and **7** were achieved by treating them with aqueous potassium cyanide. Subsequent coordination of the free ligands to gold (I) chloride directly

afforded corresponding phosphine gold complexes (Scheme 4). After purification, all the gold complexes were crystallized

Scheme 3 Recoordination reaction of the ester adducts.

Scheme 4 Synthesis of phosphine gold complexes.

from chloroform and hexane. In the case of base controlled hydrophosphination adducts, a mixture of stereoisomers were used for the syntheses. However, recrystallization gave enantiopure products as shown in X-ray analyses. However, phosphine gold complex **12** was racemic due to the keto-enol tautomerization of the ester functional group. The amide group was stabilized by the conjugation of the nitrogen lone pair with the carbonyl functionality therefore rendering it less prone to tautomerization, allowing **13** to retain its absolute configuration.

X-ray analyses showed that all the four gold complexes displayed a characteristic linear geometry around the gold center with angles of 175.69(8)-177.82(15) $^\circ$ with no nitrogen-gold interaction detected in all the complexes (Fig. 3). Phosphine gold complex **13** exhibited an absolute configuration of *S*, while **14** and **15** adopted the *R* configuration, which further confirmed the configuration of the stereogenic centers generated in the initial hydrophosphination step. All gold(I) complexes are stable in the solid state for more than 2 years. The NMR sample tends to turn dark after some time but no observable changes or impurities were detected by NMR spectroscopy.

Cytotoxic Activity

Anticancer activity of the above gold complexes was tested against breast cancer cell line MDA-MB-231. While cisplatin is currently the frontline drug in chemotherapeutics, its potency towards tumourigenic breast cancer cells is limited with an IC_{50} of $>100\mu\text{M}$ being reported following an incubation time of 24

hours.¹⁶ Fig. 4 shows the complexes cytotoxicity in terms of apoptosis index with cisplatin used as a reference.

Fig. 3 Molecular structure of phosphine gold complex **13**. Hydrogen atoms except those at the chiral center are omitted for clarity.

Fig. 4 Anticancer activity of gold complexes and cisplatin. Percentage of apoptotic cells was analyzed by Fluorescence-activated cell sorting after a treatment for 18 h with drug concentrations of 0.5 μM, 1.0 μM, 1.5 μM, 2.0 μM, and 2.5 μM.¹⁷

All four complexes exhibited an improved cytotoxicity when compared with cisplatin. Crude structure-activity relationships derived from the tests showed that the functional groups in the ligands have a substantial influence on their cytotoxic activity. The two gold complexes (**12** and **14**) with the ester functional group exhibited better activities than those (**13** and **15**) with the amide functional group. The position of the phosphorus group in the complexes also has some influences, but appeared to play different roles between the esters and the amides. For the esters (**12** and **14**), β-adducts **14** was more active than α-adduct **12**. However, for the amides (**13** and **15**), it was just on the contrary.

The cytotoxicity was also measured using non-tumourgenic epithelial cell line MCF-10A to investigate the selective toxicity of these gold complexes. Except for **12** and **14**, no significant

increase in apoptotic cells was observed as the drug concentration increases for MCF-10A. Importantly, all of the four drugs exhibit noticeable selectivity in the concentration range tested (Fig. 5).

Fig. 5 Selectivities of gold complexes against breast cancer cell line MDA-MB-231 versus non-tumourgenic cell line MCF-10A. Increasing concentrations of the gold complexes were incubated with either MDA-MB-231 or MCF-10A for 18h.

Recent understanding in the central role of mitochondria regulators of programmed cell death have stimulated great interest in targeting them in new approaches to cancer chemotherapy. For example, the thioredoxin (Trx)/thioredoxin reductase (TrxR) system (in both cytoplasm and mitochondria) plays a major role in the regulation of the cellular redox state. An increase in Trx/TrxR activities has been correlated with evasion of apoptosis and acceleration of tumour growth; while inhibition of TrxR can lead to apoptosis of cancer cells. Interestingly, Au(I) complexes such as auranofin are particularly potent inhibitors of mammalian TrxR,^{5b-c} their activities attributed to Au(I) binding to the C-terminal redox active -Cys-Sec- center.^{5c} Moreover, a recent study has shown that a group of gold(I) N-heterocyclic carbene complexes are selectively toxic to breast cancer cells (including MDA-MB-231) but not normal breast cells via their accumulating in the mitochondria and therein targeting protein selenols in preference to thiols.²¹ Although not tested, the gold-phosphine complexes studied is structurally similar (gold-centred). Thus, it is conceivable that the same mechanistic pathway involving the accumulation of gold complexes in the mitochondria and therein targeting of mitochondrial key proteins/enzymes might be a possible mechanism for their specific elimination of breast cancer cells.

Conclusions

Regioselective asymmetric hydrophosphination of pyridyl acrylates and amides have been achieved via the application and omission of base, affording regioisomeric P,N bidentates. The gold-phosphine gold complexes studied exhibited good cytotoxicity and selectivity against breast cancer cell line MDA-

MB-231. Structure-activity relationship was established obtained from analysis of the obtained results, which provides a good foundation for future investigation in this class of compounds.

Experimental

Materials and instrument

Reactions involving air sensitive compounds were performed under an inert atmosphere of nitrogen. Solvents were degassed prior to use when necessary. Dichloromethane (AR) and ethyl ether (AR) were purchased from Merck, hexane (AR) from Anaqua and acetone (AR) and tetrahydrofuran (AR) from TEDIA Company. Solvents and chemicals were used directly without further purification. Concentrated hydrochloric acid was purchased from Sigma-Aldrich and potassium cyanide from Schedelco and triethylamine from Fischer Scientific. Column chromatography was conducted on Merck silica gel 60 (0.040-0.063 mm).

NMR spectra were recorded on Bruker ACF 300 and 400 spectrometers. ^1H NMR spectra chemical shifts were reported in δ ppm relative to chloroform ($\delta = 7.26$ ppm). ^{13}C NMR spectra chemical shifts were recorded relative to CDCl_3 resonance ($\delta = 77.16$ ppm). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra chemical shifts are referenced to an external standard of 85% H_3PO_4 . Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. Melting points were measured using the SRS optimeit automated melting point system, SRS MPA 100.

Crystals were obtained in the specified solvent at room temperature. The crystals were mounted onto glass fibers, and the X-ray diffraction intensity data were collected at 103 K with a Bruker Kappa diffractometer equipped with a CCD detector, employing Mo K α radiation ($\lambda = 0.71073$ Å), with the APEX2 suite of programs. All data were processed and corrected for Lorentz and polarization effects with SAINT and for absorption effects with SADABS. Structural solution and refinement were carried out with the SHELXTL suite of programs. The structures were solved by direct methods or Patterson maps. All non-hydrogen atoms were refined with anisotropic thermal parameters.

Caution! Perchlorate salts of metal complexes are potentially explosive and should be handled with care.

The enantiomerically pure forms of the complexes (*R*)-**1**, (*S*)-**1**¹⁸ and (*E*)-methyl 3-(pyridin-2-yl)acrylate¹⁹ and cisplatin²⁰ were prepared as previously reported.

Synthesis of (*E*)-*N,N*-dimethyl-3-(pyridin-2-yl)acrylamide **3.** To a solution of (*E*)-methyl 3-(pyridin-2-yl)acrylate (1.96 g, 12.0 mmol) in tetrahydrofuran (10 mL) was added a solution of sodium hydroxide (0.971 g, 24.3 mmol) in water (10 mL). The reaction was stirred at room temperature for 2 h and concentrated in vacuum to remove tetrahydrofuran. The residue was neutralized with concentrated hydrochloric acid until no additional white solids were precipitated. Solid was collected by filtration, washed with water (10 mL) and dried in vacuum to afford (*E*)-3-(pyridin-2-yl)acrylic acid as a white solid (1.69 g, 94%). To a suspension of (*E*)-3-(pyridin-2-yl)acrylic acid (1.48 g, 9.92 mmol) in dichloromethane (30 mL) was added oxalyl dichloride (2.50 g, 19.7 mmol) and several drops of

N,N-dimethylformamide. The reaction was heated to reflux for 2 hrs to form a clear solution and concentrated under reduced pressure to give a black residue. The residue was dissolved in dichloromethane (30 mL) and bubbled in dimethylamine gas prepared from dropping an aqueous solution of dimethylamine hydrochloride into solid sodium hydroxide. The reaction was monitored by TLC until its completion. The reaction mixture was washed with water (30 mL), dried over sodium sulfate and concentrated to give crude product. Purification by column chromatography eluting with hexane and ethyl acetate (1:1 to ethyl acetate alone) afforded (*E*)-*N,N*-dimethyl-3-(pyridin-2-yl)acrylamide as a brown solid (1.08 g, 62%). mp 105-107 °C. ^1H NMR (300MHz, CDCl_3) δ 8.61-7.20 (m, 6H, aromatics and vinylic protons), 3.20 (s, 3H), 3.06 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 166.39 (s, 1C), 153.51 (s, 1C), 149.87 (s, 1C), 140.69 (s, 1C), 136.80 (s, 1C), 124.75 (s, 1C), 123.75 (s, 1C), 121.54 (s, 1C), 37.49 (s, 1C), 35.86 (s, 1C). LCMS (+ESI) m/z ($\text{M}+\text{H}$)⁺: calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}$ 177.10; found 177.19.

(*R,S*)-**4** was prepared in accordance to reported procedures. Characterization data was in accordance to literature therein contained.^{12e}

Hydrophosphination of (*E*)-*N,N*-dimethyl-3-(pyridin-2-yl)acrylamide. A solution of diphenylphosphine (158 mg, 0.849 mmol), (*E*)-*N,N*-dimethyl-3-(pyridin-2-yl)acrylamide (180 mg, 1.02 mmol) and (*R*)-**1** (415 mg, 0.853 mmol) in dichloromethane (4 mL) was stirred at 40 °C under nitrogen for five weeks. The reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR to determine its completion. Then the reaction mixture was concentrated and purified by column chromatography eluting with dichloromethane and acetone (20:1 to 10:3). After concentration, the residue was crystallized from dichloromethane and diethyl ether to afford product (*R,S*)-**5** (220 mg, 34%). mp 180-185 °C. $[\alpha]_{\text{D}}^{25} = -79.6^\circ$ (c 0.49, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): δ 8.32-6.52 (m, 20H), 4.73-4.66 (m, 1H), 4.47-4.42 (m, 1H), 4.35-4.27 (m, 1H), 3.78-3.65 (m, 1H), 2.79 (d, $^4J_{\text{HP}} = 1.2$ Hz, 3H), 2.63 (d, $^4J_{\text{HP}} = 3.2$ Hz, 3H), 2.55 (s, 3H), 2.43 (s, 3H), 2.39 (d, $^3J_{\text{HH}} = 6.4$ Hz, 3H). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ 42.11 (s). ^{13}C NMR (101 MHz, CDCl_3): δ 167.97 (s, 1C), 158.26 (d, $^2J_{\text{PC}} = 5.8$ Hz, 1C), 150.05-123.13 (m, 26C), 74.01 (d, $^3J_{\text{PC}} = 2.8$ Hz, 1C), 51.75 (s, 1C), 47.87 (s, 1C), 41.01 (d, $^2J_{\text{PC}} = 5.0$ Hz, 1C), 38.75 (d, $^1J_{\text{PC}} = 25.8$ Hz, 1C), 37.70 (s, 1C), 35.99 (s, 1C), 23.81 (s, 1C). LCMS (+ESI) m/z ($\text{M}-\text{ClO}_4$)⁺: calcd for $\text{C}_{36}\text{H}_{39}\text{N}_3\text{OPPd}$ 666.19; found 666.29.

Base controlled hydrophosphination of (*E*)-*N,N*-dimethyl-3-(pyridin-2-yl)acrylamide. To a solution of diphenylphosphine (307 mg, 1.65 mmol), (*E*)-*N,N*-dimethyl-3-(pyridin-2-yl)acrylamide (290 mg, 1.65 mmol) and (*R*)-**1** (808 mg, 1.66 mmol) in dichloromethane (8 mL) under nitrogen was added triethylamine (66.7 mg, 0.66 mmol). The reaction mixture was stirred at room temperature under nitrogen for four days. The reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR to determine its completion. The reaction mixture was concentrated and purified by column chromatography eluting with dichloromethane and acetone to afford a mixture of two stereoisomers (*R,R*)-**6** and (*R,S*)-**6** (57:1, 67 mg, 5%). mp 119-121 °C. $[\alpha]_{\text{D}}^{25} = -139.5^\circ$ (c 0.86, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3): δ 8.74-6.86 (m, 20H), 4.90-4.83 (m, 1H), 4.60-4.56 (m, 1H), 3.19-3.11 (m, 4H), 3.04-2.97 (m, 4H), 2.79 (s, 3H), 2.69 (s, 3H), 2.18 (d, $^3J_{\text{HH}} = 6.3$ Hz, 3H). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3): δ 54.14(s). ^{13}C NMR (101 MHz, CDCl_3): δ 168.16 (d, $^2J_{\text{PC}} = 9.8$ Hz, 1C), 162.00 (d, $^3J_{\text{PC}} = 5.5$ Hz,

1C), 150.59-123.32 (m, 26C), 74.27 (s, 1C), 52.07 (s, 1C), 48.57 (d, $^1J_{\text{PC}} = 33.2$ Hz, 1C), 47.87 (s, 1C), 37.76 (d, $^2J_{\text{PC}} = 6.5$ Hz, 1C), 37.18 (s, 1C), 35.69 (s, 1C), 24.53 (s, 1C). LCMS (+ESI) m/z (M-ClO₄)⁺: calcd for C₃₆H₃₉N₃OPPd 666.19; found 666.29.

Base controlled hydrophosphination of (E)-methyl 3-(pyridin-2-yl)acrylate. To a solution of diphenylphosphine (497 mg, 2.67 mmol), (E)-N,N-dimethyl-3-(pyridin-2-yl)acrylate (435 mg, 2.67 mmol) and (R)-**1** (1.30 g, 2.67 mmol) in dichloromethane (10 mL) under a nitrogen atmosphere was added triethylamine (107 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for three days. The reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR to determine its completion. The reaction mixture was concentrated and purified by column chromatography eluting with ethyl acetate to afford a mixture of diastereoisomers (R,R)-**7** and (R,S)-**7** (6.72:1, 1.37 g, 68%). mp 110-115°C. $[\alpha]_{\text{D}}^{25} = -103.2^\circ$ (c 0.63, CH₂Cl₂). Further purification by column chromatography afforded trace of pure major product for NMR confirmation. ^1H NMR (400 MHz, CDCl₃): δ 8.84-6.84 (m, 20H), 4.63-4.57 (m, 2H), 3.51 (s, 3H), 3.17-3.10 (m, 1H), 3.08 (d, $^4J_{\text{HP}} = 3.6$ Hz, 3H), 2.99 (d, $^4J_{\text{HP}} = 1.6$ Hz, 3H), 2.91-2.88 (m, 1H), 2.15 (d, $^3J_{\text{HH}} = 6.4$ Hz, 3H). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl₃): δ 53.18 (s). ^{13}C NMR (101 MHz, CDCl₃): δ 169.90 (d, $^2J_{\text{PC}} = 13.9$ Hz, 1C), 160.42 (d, $^3J_{\text{PC}} = 4.4$ Hz, 1C), 151.42-123.30 (m, 26C), 74.19 (d, $^3J_{\text{PC}} = 2.8$ Hz, 1C), 52.49 (s, 1C), 52.05 (s, 1C), 48.18 (d, $^1J_{\text{PC}} = 32.6$ Hz, 1C), 47.57 (s, 1C), 38.82 (d, $^2J_{\text{PC}} = 7.8$ Hz, 1C), 24.66 (s, 1C). LCMS (+ESI) m/z (M+H)⁺: calcd for C₃₅H₃₆N₂O₂PPd 653.15; found 653.18.

General procedure for preparation of phosphine gold complexes

The palladium perchlorate complexes (1.0 eq.) was dissolved in dichloromethane and treated with excess aqueous potassium cyanide for 5 min under nitrogen. $^{31}\text{P}\{^1\text{H}\}$ NMR was used to monitor the completion of the liberation. The organic phase of the reaction was transferred into another flask and chloro(dimethylsulfide) gold (I) (0.9 eq.) was added. The reaction was stirred for 1 hr, then concentrated under reduced pressure and purified by column chromatography to give phosphine gold complex. The product was recrystallized from chloroform and hexane.

Phosphine gold complex 12, yield 67%, racemic. mp 112-114 °C. ^1H NMR (400 MHz, CDCl₃): δ 8.48-7.09 (m, 14H), 4.64-4.55 (m, 1H), 3.64-3.53 (m, 1H), 3.34 (s, 3H), 3.22-3.12 (m, 1H). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl₃): δ 40.02 (s). ^{13}C NMR (101 MHz, CDCl₃): δ 169.62 (s, 1C), 156.73 (d, $^2J_{\text{PC}} = 14.1$ Hz, 1C), 149.51-122.16 (m, 16C), 52.49 (s, 1C), 44.54 (d, $^1J_{\text{PC}} = 31.3$ Hz, 1C), 37.73 (d, $^2J_{\text{PC}} = 7.1$ Hz, 1C). LCMS (+ESI) m/z (M+H)⁺: calcd for C₂₁H₂₁AuClNO₂P 582.07; found 582.44.

Phosphine gold complex 13, yield 64%. mp 159-161 °C. $[\alpha]_{\text{D}}^{25} = -122.0^\circ$ (c 0.50, CH₂Cl₂). ^1H NMR (400 Hz, CDCl₃): δ 8.46-7.06 (m, 14H), 4.93-4.87 (m, 1H), 3.65-3.56 (m, 1H), 3.21-3.17 (m, 1H), 2.62 (s, 6H). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl₃): δ 39.78 (s). ^{13}C NMR (101 MHz, CDCl₃): δ 168.81 (s, 1C), 157.30 (d, $^2J_{\text{PC}} = 14.1$ Hz, 1C), 149.27-122.10 (m, 16C), 40.23 (d, $^1J_{\text{PC}} = 34.3$ Hz, 1C), 38.26 (d, $^2J_{\text{PC}} = 4.0$ Hz, 1C), 37.71 (s, 1C), 36.02 (s, 1C). LCMS (+ESI) m/z (M+H)⁺: calcd for C₂₂H₂₄AuClN₂OP 595.10; found 594.45.

Phosphine gold complex 14, yield 74%. mp 173-175 °C. $[\alpha]_{\text{D}}^{25} = +78.9^\circ$ (c 0.71, CH₂Cl₂). ^1H NMR (400 MHz, CDCl₃): δ 8.50-7.01 (m, 14H), 4.63-4.56 (m, 1H), 3.60-3.53 (m, 1H), 3.51 (s, 3H), 2.82-2.74 (m, 1H). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl₃): δ 44.73 (s). ^{13}C NMR (101 MHz, CDCl₃): δ 171.01 (d, $^2J_{\text{PC}} = 20.2$ Hz, 1C), 155.26 (d, $^3J_{\text{PC}} = 3.0$ Hz, 1C), 149.92-122.65 (m, 16C), 52.15 (s, 1C), 42.84 (d, $^1J_{\text{PC}} = 36.4$ Hz, 1C), 35.97 (d, $^2J_{\text{PC}} = 10.1$ Hz, 1C). LCMS (+ESI) m/z (M-ClO₄)⁺: calcd for C₂₁H₂₁AuClNO₂P 582.07; found 582.56.

Phosphine gold complex 15, yield 83%. mp 172-174 °C. $[\alpha]_{\text{D}}^{25} = +130.0^\circ$ (c 0.50, CH₂Cl₂). ^1H NMR (400 MHz, CDCl₃): δ 8.54-6.77 (m, 14H), 4.86-4.80 (m, 1H), 3.82-3.74 (m, 1H), 2.92 (s, 3H), 2.79 (s, 3H), 2.64-2.56 (m, 1H). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl₃): δ 44.61 (s). ^{13}C NMR (101 MHz, CDCl₃): δ 169.35 (d, $^2J_{\text{PC}} = 18.2$ Hz, 1C), 155.66 (s, 1C), 149.83-122.39 (m, 16C), 42.45 (d, $^1J_{\text{PC}} = 38.4$ Hz, 1C), 37.36 (s, 1C), 35.72 (s, 1C), 34.72 (d, $^2J_{\text{PC}} = 11.1$ Hz, 1C). LCMS (+ESI) m/z (M+H)⁺: calcd for C₂₂H₂₄AuClN₂OP 595.10; found 594.38.

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