Mono and dinuclear oxime palladacycles bearing diphosphine ligands: An unusual coordination mode for dppe

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Abstract

Three new oxime-based palladacycles, namely $[\text{Pd}\{C,N\text{-C}_6\text{H}_4\{\text{C}(\text{Me})=\text{NOH}\}\text{-2}\}(\text{dppm})]\text{ClO}_4$ (**1**), $[\text{Pd}_2\{C,N\text{-C}_6\text{H}_4\{\text{C}(\text{Me})=\text{NOH}\}\text{-2}\}_2(\text{dppe})_2(\mu\text{-dppe})](\text{ClO}_4)_2$ (**2**) and $[\text{Pd}\{C,N\text{-C}_6\text{H}_4\{\text{C}(\text{Me})=\text{NOH}\}\text{-2}\}(\text{dppmS}_2)]\text{ClO}_4$ (**3**), were synthesized by the reaction of dinuclear oxime complex $[\text{Pd}\{C,N\text{-C}_6\text{H}_4\{\text{C}(\text{Me})=\text{NOH}\}\text{-2}\}(\mu\text{-Cl})_2]$ with different diphosphine ligands (dppm, dppe and dppmS₂). The synthesized complexes were characterized by FT-IR, ³¹P-NMR, ¹H-NMR and ¹³C-NMR spectroscopic methods and elemental analyses, and their molecular structures were elucidated by X-ray crystallography. The structure of **2** is worthy of note as it is the first oxime palladacycle where there are both bridging (P-) and chelating (P^P) dppe ligands, giving rise to a dinuclear complex. The palladium atom is in a five-coordinate, square pyramidal P₃NC environment, while in **3** the palladium atom is in a distorted square planar environment, coordinated by the oxime ligand and a chelating (S^S) dppmS₂ ligand. These complexes were employed as efficient catalysts for the Suzuki–Miyaura cross-coupling reaction of several aryl bromides with phenylboronic acid. The *in vitro* cytotoxicity of the compounds was also evaluated against human tumor cell lines (HT29, A549 and Hela) using the MTT assay method. The results indicate that the dinuclear complex **2** has more catalytic and anticancer properties in comparison with the mononuclear complexes **1** and **3**.

Keywords: Oxime palladacycle, Diphosphine, Coordination mode, Catalyst, Antitumor agent.

1. Introduction

The phosphine ligands have been extensively applied during the last three decades in organometallic chemistry at the laboratory and industrial scale mainly because of specific and interesting physical and donor–acceptor properties.^[1] These compounds have ability to act as a mono- or di coordinating ligands as well as adopting a chelating or bridging mode leading to the synthesis of di-, tri- or poly-, homo- or hetero-nuclear transition metal complexes.^[2] The success of phosphine ligands in catalysis is a function of both electronic and steric properties, and it is advantageous to be able to vary both autonomously. This allows good tuning of the coordinated species, thus enabling the diverse steps of a catalytic cycle to be optimized.^[3] In particular, mono- and bidentate phosphine ligands are used most frequently in a wide variety of homogeneous catalysts.^[4] A good deal of knowledge about the synthesis of phosphine complexes, especially with the Pd and Pt metals, has been extensively documented.^[5] Ever since phosphapalladacycles had been highlighted by Herrmann for the Heck and Suzuki reactions,^[6] various kinds of phosphorus-,^[1a] nitrogen-,^[7] sulfur-,^[8] and oxygen-derived palladacycles^[9] have emerged as promising catalysts with high turnover numbers (TONs) in numerous C–C coupling reactions.

In the precedent decades, the chemistry of cyclometallated complexes has engrossed much attention. These compounds are usually classified according to the metal, to the donor atom, or to chelate ring size; by far the well-studied examples are five-membered palladacycles containing Pd–N and Pd–C_{phenyl} bonds.^[10] Noticeable, among latter complexes, oxime

palladacycles are very efficient and versatile pre-catalysts for a wide range of carbon-carbon bond coupling reactions in air, under very low loading conditions, and employing reagent-grade chemicals.^[11] The oxime palladacycles as a source of highly active palladium nanoparticles have been used to generate high turnover numbers (TONs) in the Heck as well as other homo- and cross-coupling reactions.^[11] Noticeable, the pioneering work of Najera *et al.*, demonstrated these compounds are robust and highly active palladium catalysts for different coupling reactions, including Mizoroki– Heck, Suzuki–Miyaura, Stille, Hiyama Sonogashira, and Ullmann type reactions.^[12] These oxime palladacycles possess remarkable air, moisture, and thermal stability with excellent TONs in organic and aqueous solvent systems.^[12-13] Although the syntheses of various oxime palladacycles have been reported, their reactivity has been very scarcely studied.^[14] Our interest in the reactivity and the coordination chemistry of phosphorus ligands led us to examine the use of an oxime palladacycle (Figure 1) and three diphosphine ligands (dppm (**1**), dppe (**2**), dppmS₂(**3**)) for the synthesis of three new oxime palladacycles and exhibiting intriguing functionalities including catalytic and antitumor activities. Herein, we report for the first time an unexpected coordination mode for dppe in oxime-based palladacycles compared with dppm and dppmS₂. The crystal and molecular structures of **2** and **3** are also reported.

<please insert Figure 1>

2. Experimental

All manipulations were carried out under dry nitrogen using standard Schlenk techniques unless otherwise noted. Commercially available reagents and solvents were of reagent grade and have been used without further purification. bis(diphenylthiophosphinoyl)methane (dppmS₂),^[15] the dinuclear chloro-bridged oxime complex of ([Pd{C,N-C₆H₄{C(Me)=NOH}-2}(μ-Cl)]₂),^[16] were prepared as described in the literature. NMR spectra were recorded at ambient temperature on Bruker Avance 250 and 400 MHz instruments in CDCl₃ as solvent. Coupling constants are given in Hz. IR spectra were recorded on a Perkin-Elmer spectrophotometer and the measurements were made by the KBr disk method. Elemental analyses (C, H, N, S) were performed using a Perkin-Elmer 2400 series analyzer. Melting points were measured on a SMP3 apparatus without correction.

2.1. Synthesis of [Pd{C,N-C₆H₄{C(Me)=NOH}-2}(dppm)]ClO₄ (**1**)

To a solution of [Pd{C,N-C₆H₄{C(Me)=NOH}-2}(μ-Cl)]₂ (0.022 g, 0.04 mmol) in CH₂Cl₂ (15 mL), dppm (0.031 g, 0.08 mmol) and NaClO₄·H₂O (0.028 g, 0.20 mmol) were added, resulting in the immediate precipitation of NaCl. The reaction mixture was stirred for a further 5 h at room temperature and then filtered. The clear colorless solution was evaporated (2 mL) and residue treated with *n*-hexane (15 mL) to give precipitate **1** as a pale yellow solid: Yield: 63%; m.p.:147–150°C. *Anal.* Calc. for C₃₃H₃₀ClNO₅P₂Pd: C, 54.71; H, 4.17; N, 1.93. Found: C, 55.17; H, 4.41; N, 1.71%. Selected IR absorption in KBr (cm⁻¹): 3401 (ν_{OH}), 1602 (ν_{C=N}), 924 (ν_{P-C}), 1100, 622 (ν_{ClO₄⁻). ³¹P{¹H} NMR (101.25 MHz, CDCl₃) δ: -10.08 (br s, PPh₂ *trans* to C),}

-31.03 (br s, PPh₂ *trans* to N). ¹H NMR (250.13 MHz, CDCl₃) δ: 2.20 (s, 3H, CH₃C=N), 4.04 (br, 2H, PCH₂), 6.33–7.04 (m, 4H, C₆H₄), 7.36–8.05 (m, 20H, 2PPh₂). ¹³C{¹H} NMR (62.9 MHz, CDCl₃) δ: 13.01 (s, CH₃), 39.63 (br, PCH₂); 125.85–135.20 (m, Ph), 137.97 (s, C³), 147.03 (s, C⁴), 167.20 (s, C²).

2.2. Synthesis of [Pd₂{C,N-C₆H₄{C(Me)=NOH}-2}₂(dppe)₂(μ-dppe)](ClO₄)₂ (2)

A similar method was used for the preparation of **2** by using dppe (0.032 g, 0.08 mmol) instead of dppm as diphosphine ligand. The white solid was washed with *n*-hexane and dried. Yield: 71%; m.p. 167–169°C. *Anal.* Calc. for C₉₈H₉₄Cl₄N₂O₁₀P₆Pd₂: C, 58.84; H, 4.74; N, 1.40. Found: C, 58.17; H, 5.11; N, 1.71%. Selected IR absorption in KBr (cm⁻¹): 3404 (ν_{OH}), 1604 (ν_{C=N}), 923 (ν_{P-C}), 1100, 622 (ν_{ClO₄⁻}). ³¹P{¹H} NMR (101.25 MHz, CDCl₃) δ: 39.35 (s, bridging PPh₂ *trans* to N), 41.94 (d, ³J_{P,P} = 27.9, chelating PPh₂ *trans* to N), 58.28 (d, ³J_{P,P} = 28.5, chelating PPh₂ *trans* to C). ¹H NMR (250.13 MHz, CDCl₃) δ: 2.06 (br, 3H, CH₃C=N); 2.39 (br, 9H, CH₂), 6.60–7.12 (m, 4H, C₆H₄), 7.34–7.68 (m, 20H, 2PPh₂). ¹³C{¹H} NMR (62.9 MHz, CDCl₃) δ: 13.49 (s, CH₃), 26.24 (d, ¹J_{P,C} = 27.05 Hz, PCH₂), 126.87–138.66 (m, Ph), 145.57 (s, C³), 162.62 (s, C⁴), 179.77 (s, C²).

2.3. Synthesis of [Pd{C,N-C₆H₄{C(Me)=NOH}-2}(dppmS₂)]ClO₄ (3)

A similar method was used for the preparation of **3** by using dppmS₂ (0.036 g, 0.08mmol) instead of dppm as diphosphine ligand. The pale yellow solid was washed with *n*-hexane and

dried. Yield: 79%; m.p: 168–170°C. *Anal.* Calc. for $C_{33}H_{30}ClNO_5P_2PdS_2$: C, 50.26; H, 3.83; N, 1.78; S, 8.14. Found: C, 50.84; H, 3.92; N, 1.95; S, 7.89%. Selected IR absorption in KBr (cm^{-1}): 3390 (ν_{OH}), 1610 ($\nu_{C=N}$), 927 (ν_{P-C}), 572 ($\nu_{S=P}$), 1100, 622 ($\nu_{ClO_4^-}$). $^{31}P\{^1H\}$ NMR (101.25 MHz, $CDCl_3$) δ : 37.17 (br s, PPh_2 *trans* to N), 39.24 (br s, PPh_2 *trans* to C). 1H NMR (250.13 MHz, $CDCl_3$) δ : 2.28 (s, 3H, $CH_3C=N$), 4.80 (t, $^2J_{P,H} = 12.50$ Hz, 2H, PCH_2), 7.09–7.25 (m, 4H, C_6H_4), 7.42–8.41 (m, 20H, PPh_2). $^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$) δ : 12.60 (s, CH_3), 35.02 (t, $^1J_{P,C} = 47.18$ Hz, PCH_2), 126.94–134.58 (m, Ph), 143.54 (s, C^3), 155.83 (s, C^4), 170.02 (s, C^2).

2.4. X-ray Crystallography

Light yellow single crystals of **2** were grown by solvent diffusion of *n*-hexane into chloroform while light yellow single crystals of **3** were crystallized by solvent diffusion of *n*-hexane into dichloromethane. While crystals of **2** were good quality, many crystals of **3** were disordered, resulting in the crystal selected for data collection showing minor disorder. The selected crystals were mounted on a cryoloop on a SuperNova Dual source diffractometer, with Atlas detector. Crystal data and structure refinement details for these complexes summarized in Table S1. The crystal was kept at 130(2) K during data collection. Using Olex2,^[17] the structures were solved with the ShelXT^[18] structure solution program using Intrinsic Phasing and refined with the ShelXL^[19] refinement package using Least Squares minimization on F^2 , using all data. Gaussian absorption corrections were applied to the data. All non-hydrogen

atoms were refined with anisotropic displacement parameters, while all hydrogen atoms were placed at geometrical estimates and refined using the riding model. Crystals of **2** were found to have two molecules of solvent dichloromethane. For each structure the perchlorate anion was disordered over two different orientations; both components were restrained to ideal geometry with the anisotropic displacement parameters values of the two components of each atom being restrained to have similar values. The final difference map for **2** showed residual electron density peaks of 0.75 and -1.06 eÅ⁻³, close to the Pd and Cl atoms, while for **3** the residual electron density peaks were 2.30 and -1.63 eÅ⁻³, close to the Pd atom, attributed to the minor disorder of the crystal.

2.5. Typical procedure for the Suzuki–Miyaura reaction

A mixture of bromobenzene (0.5 mmol, 78.5 mg), K₂CO₃ (0.75 mmol, 103.6 mg), phenylboronic acid (0.6 mmol, 73.1 mg), 0.25 mol% of complex **2** as catalyst and 2 mL EtOH:H₂O (1:1) as solvent was heated at 55 °C using an oil bath and the progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature. After completion of the reaction, the mixture was diluted with n-hexane (15 mL) and water (15 mL). The combined organic layer washed with brine (15 mL) and dried over CaCl₂. The solvent was evaporated and the crude product purified by recrystallization from ethanol and water. The reaction produced 74.02 mg (0.48 mmol) of pure biphenyl, an isolated yield of 96%.

2.6. Cytotoxicity studies

2.6.1. Cell line culture

HT29, A549 and Hela cancer cell lines have been purchased from Iran Pasteur Institute, Tehran, Iran. Then they were maintained in DMEM medium supplemented with 10% fetal bovine serum (FBS), 1% Strp/Pen at 37 °C with 5% CO₂. These cell lines were cultured in a tissue culture flask (T25, SPL, Korea) in 5 ml total medium until they became confluent. The medium was changed every 3 days and the cells were passaged with trypsin.

2.6.2. Cell viability analysis

The metabolic activity of the cells was quantitatively determined with 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT, Sigma). In this assay, 0.01, 0.1 and 1 mg/mL concentrations of **1**, **2**, and **3** have been used. The control samples were kept in DMEM medium. The cells were cultured at a density of 10×10^3 cells/well in 96-well plates and incubated. After 24 h the cells were treated with the mentioned concentration of compounds for **1** to **3** days. Then these cells were treated with MTT solution (0.5 mg/mL). After 4 hours, the MTT solution was removed and the produced formazan was solubilized in DMSO and after shaking each well, the absorbance rate was measured at 570 nm with a microplate reader (Expert 96, Asys Hitch, Ec Austria).

2.6.3. Morphology observation

Giemsa staining was done to survey the cell morphology. 10×10^3 cells well were cultured into 96 well plate and after 24 h, the cells were exposed to the mentioned concentration of the compounds for another 24 h. The normal cells have been used as controls. Then these cells were washed with phosphate buffered saline (PBS) and fixed with methanol and stained with 4% Giemsa solution for 20 min, after that the cells were rinsed with distilled water and air-dried. Then stained cells were observed under an inverted fluorescent microscope (Olympus, Japan).

2.6.4. Fluorescence observation of cell death

In this study, acridine orange/ethidium bromide (AO/EB) was used as a double staining method. The cells were seeded in plates and treated with the defined concentration of compounds for 24 h. Then the cells were trypsinized and stained with dye mixture, including 25 $\mu\text{m}/\text{mL}$ AO and 25 $\mu\text{m}/\text{mL}$ EB in PBS and they were incubated for 10 min and analyzed under an inverted fluorescent microscope (Olympus, Japan). The Untreated cells have been used as control samples.

3. Results and discussion

3.1. Synthesis and Characterization

A series of oxime complexes **1–3** were prepared using a protocol starting from $[\text{Pd}\{\text{C},\text{N}-\text{C}_6\text{H}_4\{\text{C}(\text{Me})=\text{NOH}\}-2\}(\mu\text{-Cl})_2]$ and diphosphine-type ligands (dppm/dppe/dppmS₂) by means of bridge splitting reactions according to Scheme 1. To our knowledge the complex **3** is the first

example of the reaction of dppmS_2 with an oxime palladacycles. The reactions were carried out in CH_2Cl_2 and complexes **1–3** were isolated in good to excellent yields by adding n-hexane to the concentrated solutions. All three complexes are stable towards air and moisture and can be stored for several months without apparent decomposition. These compounds have good solubility in CH_2Cl_2 , CHCl_3 , and 1,2-dichlorethane and insoluble in other organic solvents including benzene, toluene, n-hexane and acetonitrile. The structures of compounds (**1–3**) were successfully characterized by FT-IR and NMR spectroscopic methods (Figure S1–S12 in the Supporting Information). Analytical data of three complexes are in accordance with the proposed formulation. The exact structure of the complexes **2** and **3** were determined by single crystal X-ray structural analyses.

<please insert Scheme 1>

3.2. Spectroscopy

The IR spectra of **1–3** were compared with that of the free ligand in order to get a clue about the coordination and mode of coordination of ligand to Pd in the first stage. A characteristic band pertinent to CN group was observed at higher frequency than the free ligand at 1602 cm^{-1} (**1**), 1604 cm^{-1} (**2**) and 1610 cm^{-1} (**3**) indicating flow of electrons from ligand to metal.^[14, 20] The presence of ClO_4^- group was designated by two bands in 1100 and 622 cm^{-1} regions. These values are consisted with the literature values.^[21] The band at $850\text{--}950\text{ cm}^{-1}$ characteristic of all complexes is assigned to P–C vibration. For complex **3**, the P=S group appeared at 572 cm^{-1} .

This bond is displaced towards lower frequencies as compared with the free dppmS₂ ligand and corresponds to the coordinated P=S group. It clearly shows that dppmS₂ is coordinating to Pd(II) metal center *via* S donor atoms.

The ³¹P{¹H} NMR signals for the PPh₂ group of all three complexes are shifted downfield compared to those of the starting diphosphine ligands, as a consequence of the inductive effect of the metal center. In addition, the phosphorus atom *trans* to metalated carbon is shifted to the lower field with respect to nitrogen atom, in accordance with the higher *trans* influence of the *ortho*-metalated carbon.^[22] Interestingly, phosphorus chemical shifts of **1** and **3** contain two broad singlets, while in the case of **2** show one sharp singlet and two doublet signals. The singlet signal at δ 39.35 ppm is due to a bridging dppe ligand, whereas the two doublets at δ 41.94 ppm (³*J*_{PP} = 27.9) and 58.28 ppm (³*J*_{PP} = 28.5) are attributed to a chelating dppe ligand. So, the presence of both bridging and chelating dppe ligands is clearly inferred from this spectrum. In case of **3**, the signals related to the PPh₂ groups appear as two broad singlets at δ 37.17 and 39.24 ppm. Noted that these values have partially shifted downfield relative to the free dppmS₂ ligand (34.5 ppm),^[23] and the range ($\Delta\delta$) is reported for similar complexes about 2–11 ppm.^[24]

The ¹H NMR spectra of complexes **1** and **2** show the signal of CH₂ protons as a broad peak at δ 4.04 ppm and 2.39 ppm, respectively, due to the coupling with neighbor phosphorus atoms. While the presence of methinic proton in complex **3** is appeared as a triplet at 4.8 ppm with ²*J*_{P,H} = 12.50 Hz. This is in good agreement with the value for with the observation for the similar

phosphine complexes.^[21, 25] The $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of all complexes shows two peaks at around 13 and 30 ppm, which are assigned to CH_3 and PCH_2 , respectively. The $\text{C}=\text{NOH}$ and the metalate C4 carbon atoms are shifted to high frequencies in comparison with the free oxime ligand,^[26] which is in agreement with the chelating coordination mode of the oxime ligand *via* the iminic N and the C4 carbon atoms. Similar values have been reported in related Pd(II) complexes with oxime ligands.^[14, 27]

3.3. X-ray Crystal Structures

The molecular structures of **2** and **3** were confirmed by single crystal X-ray structural analyses, and the perspective drawing of the complexes are depicted in Figures 2 and 3, respectively. The selected bond distances and angles are collected in Table 1. The structures definitively confirmed the breaking of the Pd–Cl bonds in the initial oxime complex resulting in the formation of dppe and dppmS₂ complexes. As the molecular structures of both complexes are very different they will be discussed in separate sections.

<please insert Table 1 >

3.3.1. Description of the structure 2

In complex **2** the Pd atom is coordinated by the oxime ligand, one chelating dppe ligand and one dppe ligand which is bridging to another Pd atom, forming a dimeric structure. The asymmetric unit comprises half of the complex in which the centroid of the aliphatic C–C segment lies on a center of inversion.

<please insert Figure 2>

The Pd atom in **2** is in a five-coordinate, distorted square pyramidal environment surrounded by the two phosphorus atoms of a chelating dppe ligand, one phosphorus atom from the bridging dppe ligand and the *ortho*-metalated carbon and nitrogen atoms of the oxime ligand; the three phosphorus atoms and the carbon atom lie in the equatorial plane while the nitrogen atom lies in the apical position. The four atoms in the basal plane are significantly non-planar, the rms deviation being 0.156 Å, with the Pd atom lying 0.1148(8) Å out of the plane. The *trans* P1–Pd1–P3 and C4–Pd1–P2 angles also deviate significantly from ideal geometry, being 165.10(2)°–170.97(7)°, respectively. This coordination geometry is supported by the structural parameter τ_5 values (0.09).^[26] To our knowledge, five coordinate square pyramidal in palladium complexes has been very scarcely reported. A search of the Cambridge Structural Database found 12 such complexes with a P₃NC environment,^[27] all of which have the nitrogen atom in the apical position, in accordance with Bent's rule and the higher electronegativity of the nitrogen atom.

A search of the Cambridge Structural Database has found 3231 metal complexes (256 Pd complexes) with chelating dppe ligands and 556 metal complexes (21 Pd complexes) with bridging dppe ligands; there were no complexes with both chelating and bridging dppe ligands. In contrast, there were 612 metal complexes (38 Pd complexes) with chelating dppm ligands and 2772 metal complexes (154 Pd complexes) with bridging dppm ligands and 2 complexes with both chelating and bridging dppm ligands.

The Pd(1)...Pd(1) distance in **2** is 8.407 (1) Å, which lies at the upper end of the range of the Pd...Pd distances found for complexes with bridging dppe ligands: 6.058 – 8.412 Å.^[25a, 30] The bridging Pd(1)–P(3) distance of 2.362(6) Å is longer than found for existing complexes

with bridging dppe ligands, 2.252 – 2.340 Å, presumably due to the present complex being five-coordinate while the other known complexes are four-coordinate. The chelating Pd–P distances of 2.295(6) and 2.337(6) Å lies between the range of 2.202 – 2.416 Å found for Pd complexes with chelating dppe ligands.^[25a, 30a] The average Pd–P bond length (2.33 Å) is slightly shorter than the sum of the covalent radii of Pd and P atoms (2.41 Å)^[27] and are comparable to the analogous distances reported in other bridged biphosphinic palladacycles.^[25a, 30d, 30e] In addition, the Pd–C_{palladate} bond length (2.06 Å) is shorter than the predicted value of 2.08 Å (based on the sum of the covalent radii for C(sp²) and Pd, 0.771 and 1.31 Å, respectively)^[30e] but lies in the range of 1.983(2)–2.068(3) Å obtained for related cyclopalladated complexes.^[30c, 30d, 31] The Pd–N bond length (2.51 Å) is also longer than the analogous distances reported in other biphosphinic palladacycles.^[30g, 30i]

As shown in Figure 2, the five-membered cyclopalladated rings are formed through the chelating oxime ligands (C^N) and the chelating dppe ligands (P^P). The requirements of these rings force the bond angles C4–Pd1–N1 and P1–Pd1–P2 to 74.74(10)° and 85.48(2)°, respectively. The acetophenone oxime ligand is non planar, with the N and O atoms lying significantly out of the plane of the other eight atoms, by 0.321(5) Å and 0.158(6) Å, respectively, while the five-membered metallocycle ring, comprising N1, Pd1, C2, C3 and C4, has an envelope conformation, with N1 lying 0.242(4) Å out of the plane of the other four atoms. There are other similar examples where this ligand is non planar,^[28] in contrast to the structures of most complexes where the acetophenone oxime ligand is planar. The other five-

membered ring Pd(P[^]P) adopts a half chair conformation, with the two carbon atoms lying above and the plane of the Pd and P atoms. The hydroxyl hydrogen is involved in an intramolecular O-H... π interaction with a carbon atom of an adjacent phenyl group [O1-H1: 0.85, H1...C33: 2.70(5), O1...C33: 3.520(4) Å; O1-H1...C33: 164(4)°]. There are only weak intra- and intermolecular contacts, mostly C-H...O hydrogen bonds, linking the molecules into 3D networks (Tables S2 in Supplementary data).

3.3.2. Description of the Structure 3

The molecular structure of **3** shows a four-coordinate oxime complex formed by one chelating dppmS₂ (S[^]S) and one chelating oxime (C[^]N) ligands. This structure, to our knowledge, represents the first report of a mononuclear oxime-based palladacycle with bis(diphenylthiophosphinyl)methane.

<please insert Figure 3>

The palladium atom is in a tetrahedrally distorted square planar coordination environment (rms deviation from the least squares plane is 0.114 Å through C4, N1, S1 and S2 atoms). This coordination geometry is supported by the structural parameter τ_4 values (0.15).^[29] The ten atoms of the oxime ligand are coplanar (rms deviation 0.007 Å, maximum deviation N1: 0.016(3) Å), with the Pd atom and both sulphur atoms lying below the ligand plane, by 0.135(3) Å, 0.232(6) Å and 0.802(5) Å, respectively; the planarity of the ligand is similar to that found in similar Pd complexes.^[14, 28b, 30] Both P-S distances (2.0043(13) Å and 1.9883(13) Å) are longer

than is found in the free dppmS₂ ligand (1.941 (1) Å).^[31] Interestingly, there are both five- and six-membered metallocyclic rings in this complex. The five-membered metallocyclic ring is essentially planar, while the six-membered metallocyclic ring adopts a chair conformation.

The Pd–S distance of 2.4095(10) Å oriented *trans* to the carbon atom of the cyclometallated ligand is slightly longer than that of 2.3068(10) Å *trans* oriented to the Pd–N bond due to the *trans* influence originating from the orthometallated phenyl ligand. Both distances are comparable to those observed in related complexes such as [Pd(μ-SP(=O)(OCH₃)₂){C,N-(C₆H₄C(CH₃)=NOH)-2}]₂ (av. Pd–S = 2.39 Å) and [Pd₂((*t*-BuNH)₂P(=O)S)₄] (av. Pd–S = 2.34 Å).^[28b] Two of the phenyl rings lies almost planar with the P–C–P angle, with dihedral angles of 31.0(3)° and 10.0(4)°, while the other two phenyl rings are almost perpendicular, the dihedral angles being 85.44(17)° and 83.01(17)°; the dihedral angle between these two latter rings is 9.5(2)°. The hydroxyl forms a H-bond with one of the coordinating sulphur atoms [O1–H1...S2: 0.98(6)Å, 2.36(6)Å, 3.191(3)Å, 142(5)°]. Weak C–H...S and C–H...O hydrogen bonds link the moieties into a 2D layer which lies in the bc-plane (Tables S3 in Supplementary data).

3.4. Catalytic Suzuki–Miyaura Couplings

It is well established that oxime-derived palladacycles are very efficient and versatile pre-catalysts for a wide range of carbon–carbon bond coupling reactions in air, under very low loading conditions, and employing reagent-grade chemicals.^[11] From this perspective, to assess

the activities of our complexes as catalysts for the Suzuki–Miyaura coupling reaction, the coupling of different aryl bromide with phenylboronic acid was investigated as a benchmark reaction.

Initially, we carried out a model reaction to optimize the reaction conditions. To investigate the effect of different solvents on the catalytic system, we have selected the reaction between bromobenzene with phenylboronic acid under aerobic conditions at 55 °C for 1 h (catalyzed with **2**) in presence of various solvents and base. Note that the solvent used as obtained commercially without further purification in all considered instances and the reactions performed in air. Among several solvents, EtOH:H₂O is found to be more efficient for the conversion of biaryl compounds to 96% (Entries 1–5, Table S4). From green chemistry viewpoint, using non-toxic organic solvent in cross coupling reaction is valuable in the catalytic systems. The lowest yield (51%) was obtained with water as the solvent.

To verify the base effect in the Suzuki reactions, we have chosen a series of reactions by taking the model reaction with different bases such as Na₂CO₃, KOH, and CH₃COONa (NaOAc). The best results were obtained with K₂CO₃ as base. The formation of cross-coupled product was not observed in the absence of the base, so the presence of the base is an essential requisite for the coupling reaction (Entry 9, Table S4). Other bases also exert but long time is necessary to bring the admirable conversions (Entries 10–12, Table S4). The optimization results indicate that increasing the catalyst concentration leads to the higher conversion of bromobenzene; but higher loads were avoided due to the price of the catalyst. Hence, it was

found that 0.25 mol% of **2** is ideal for the cross-coupling reactions (Entries 5–8, Table S4). Noted that the initial formation of desired products was detected after 40–60 minutes of the reaction; however, the best yield was obtained in 1 h. In addition, we have established the most efficient reaction conditions for compounds **1** and **3** (Entries 13 and 14, Table S4). After 1h, the coupling reaction did not occur with **1** and **3** and black particles appear in the reactions for **3** whereas palladacycle **2** was very effective catalysts under these conditions. It has already been reported on the basis of various experimental results that sulfur-containing palladacycles decompose to Pd(0), and the actual active species [Pd(0)–Pd(II)] exists during the catalytic reaction.^[32] In view of such reports and the appearance of black particles during the course of the catalytic reactions, it seems that the both complexes **1** and **3** are not gainfully employed as catalysts for Suzuki–Miyaura cross coupling reaction.^[33] Thus, the effectiveness of **2** for the Suzuki reactions was only investigated next.

With the optimized reaction conditions in hand, the complex **2** was tested as catalyst in the Suzuki reactions of aryl bromides with phenylboronic acid and the results are given in Table 2. Following optimization experiments we found that the use of 0.25 mol% of complex **2** in EtOH:H₂O as the solvent and K₂CO₃ as the base at 55 °C. Under these conditions, as shown in Table 2, the reaction of 4-bromonitrobenzene with phenylboronic acid shows excellent yield (91%)) in short time (Entry 4, Table 2). However, coupling reaction of aryl bromides bearing electron-withdrawing substituent –COCH₃ and –COOH gave the coupled product in lower yield (Entries 2 and 3, Table 2). It may be related to the low solubility of 4-bromoacetophenone and

4-bromobenzoic acid in EtOH:H₂O, which leads to decreasing the catalytic performance. Aryl bromides containing electron donating group such as 4-bromotoluene and 4-bromoanisole with phenylboronic acid were proceed smoothly and the desired coupling products were obtained in high to excellent yields (Entries 6 and 7, Table 2). In addition, the results of coupling reactions with the same reaction time (50 min) show that an electron-withdrawing substituent on the aryl bromide has an increasing effect on the yield of cross-coupling reaction (Table 2, entries 4–7).

<please insert Table 2>

To further evaluate the catalytic performance of **2**, a comparison was made with several literature-reported palladacycles catalysts.^[33-34] The reactions of bromobenzene with phenylboronic acid were taken as the standard reactions, and the results are listed in Table 3. As a result, the catalyst under investigation leads to shorter reaction time and higher reaction yield than the previously reported catalysts. It is noteworthy that the Suzuki reactions catalyzed by **2** can be performed efficiently out in water and ethanol in the absence of toxic organic solvents, which makes this catalytic capacity more impressive.

<please insert Table 3>

Following its application to the Suzuki reaction, the potential anticancer agents of all complexes was investigated in the next part.

3.5. Cytotoxicity Studies

3.5.1. The effect of compounds on morphological changes

As shown in Figure 4, some of the cell lines, which have been exposed to the synthesized compounds, were found more sensitive compared to others. Our morphological observations demonstrated that these compounds had toxic effects on three cell lines but, A549 cells were the most sensitive cells comparing with HT29 and HeLa cells. In control, the samples showed a normal characteristic cell such as uniformity nucleus and smooth and flat morphology, while the treated cells indicated an apoptotic shape including vacuolated cytoplasm, fragmentation of the nucleus, chromatin condensation and, cellular shrinkage (Figure 5).

<please insert Figure 4>

<please insert Figure 5>

3.5.2. Cell viability assay

The apoptotic effects of determined concentrations of compounds on A549, HT29, and HeLa cells have been measured by MTT assay in 3 different days. Our results indicated that the compounds acted in a time and dose-dependent manner and the cell viability has been decreased significantly compared to the control samples in three cell lines. Moreover, the cell viability results showed that A549 cells have been the most efficient ones comparing to the other cells and HT29 cells were more sensitive than HeLa cells, when exposed to the compounds. Our data of A549 cells (here as the most sensitive cells) demonstrated that the highest concentration (1 mg/mL) of compound **2** (here as the most effective compound) decreased the cell viability to 8 % ($p < 0.001$) and it was measured about 14% and 23% ($p < 0.001$) because of 0.1 mg/mL and

0.01 mg/mL doses of **2**, respectively in comparison to the control sample after 3 days (Fig. 5). Also, the IC₅₀ values of compound **2** were 10 µg/mL, 50 µg/mL, and 10 µg/mL in A549, HT29 and HeLa cells, Table 4 presents a comparison between the cytotoxic activities against the A549 cell line for compound **2** and some of the other palladium complexes reported in the literature.^[35] The results revealed that the compound **2** exhibited similar and even higher cytotoxic activity than that of the other palladium complexes. The possible mode of bioactivity of our palladium complex maybe explained by Tweedy's chelation theory.^[36] Generally, the polarity of any central metal ion is lessened considerably due to chelation. This is due to the partial sharing of metal's positive charge with the ligand and possible π -electron delocalization over the chelate ring^[37], respectively (Figure 6). As shown in Figure 6, the comparative cell viability data of the compounds for the three cell lines, demonstrated that the cytotoxicity of the compounds was as follows: **2** > **3** > **1**. Generally, our data demonstrated that the treatment of these compounds significantly decreases the cell viability of three cancer cell lines in a time and dose-dependent manner compared to the control samples.

<please insert Figure 6>

<please insert Table 4>

3.5.3. Morphological appearance and induces apoptosis in cells

The AO/EB staining was performed to survey the morphological observations including apoptotic, necrotic and viable cells after compounds treatments. In this double staining,

apoptotic cells were the cells that fluoresced orange with the nuclear condensation or nuclear distortion and damaged membrane. Alive cells were characterized by the intact cell membrane and green fluorescence (Figure. 7). Our results showed that the number of apoptotic cells increased with the IC50 concentration of compounds treatment, indicating that these compounds induced significant apoptosis in three cell lines as compared with controls. Also, enumeration cells by AO/EB staining confirmed that apoptosis is more prominent in A549 cells than in both cell lines and is prominent in HT29 cells than in HeLa cells.

<please insert Figure 7>

Conclusion

In summary the synthesis and structural characterization of new oxime palladacycles containing dppm (**1**), dppe (**2**), dppmS₂ (**3**) ligands have been described together with an evaluation of their catalytic and biological properties. This work is interesting from several viewpoints: i) we have reported the first example of mononuclear oxime palladacycle dppmS₂ complex with five- and six-membered metallocyclic rings arising from chelating-oxime (C^N) and -dppmS₂ (S^S) ligands, respectively, ii) a valuable dinuclear oxime palladacycle (**2**) was synthesized and fully characterized in which, for the first time, there are both bridging and chelating dppe ligands, iii) structural characterization by X-ray diffraction of **2** and **3** complexes confirmed the various ligand bonding modes as P-, P,P- and S,S-coordinated, iv) the structure of complex **2** shows a novel five-coordinate palladium complex with square pyramidal geometry

while complex **3** shows a four-coordinate palladium complex with square planar geometry. Thus **2** and **3** show different coordination modes of the ligands and different geometries around the metal. In continuous, two important applications of complexes **1–3** are also investigated. Catalytic activity of all complexes in Suzuki–Miyaura cross-coupling of phenyl boronic acids with aryl bromide show that a great catalytic activity was observed for complex **2** with respect to complexes **1** and **3**. Notably, there is no catalytic efficiency for **1** and **3** during the course of catalysis and black particles appear in the reactions for two latter compounds. In addition, the biological properties of complexes **1–3** were investigated by evaluation of their antitumor activity. The results suggested that the three complexes exhibit noticeable cytotoxic activity towards the HT29, A549 and Hela cancer cell lines. Our results indicated that complex **2** was more powerful than complex **1** and **3** in A549, HT-29, and HeLa cell lines. Cytotoxicity effects of these compounds were investigated for the first time that it is the novelty of this project and these results confirmed that they can be developed as a potential cancer drug candidate.

Acknowledgements

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Appendix A. Supplementary material

CCDC 1860195 and 1860196 contains the supplementary crystallographic data for **2** and **3**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. Additional experimental and

spectroscopic data are also available in Electronic supplementary information (ESI).
Supplementary data associated with this article can be found, in the online version, at
DOI.....

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Table 1. Selected bond lengths (Å) and angles (°) for **2** and **3**.

Compound 2		Compound 3	
Bond lengths			
Pd1–P1	2.295(6)	Pd1–S1	2.306(10)
Pd1–P2	2.337(6)	Pd1–S2	2.409(10)
Pd1–P3	2.362(6)	Pd1–N1	2.048(3)
Pd1–N1	2.513(3)	Pd1–C4	2.010(4)
Pd–C4	2.061(3)	S1–P1	2.004(13)
N1–C2	1.281(4)	S2–P2	1.988(13)
P3–C35	1.841(3)	P1–C9	1.797(4)
P1–C21	1.835(3)	P1–C15	1.809(4)
C21–C22	1.533(4)	P1–C21	1.825(4)
Bond angles			
P1–Pd1–P2	85.48(2)	S1–Pd1–S2	95.88(3)
P1–Pd1–P3	165.10(2)	N1–Pd1–S1	172.88(10)
P2–Pd1–P3	101.31(2)	N1–Pd1–S2	91.16(10)
P2–Pd1–N1	102.54(6)	C4–Pd1–S1	92.98(12)
P1–Pd1–N1	93.38(6)	C4–Pd1–S2	164.67(12)
P3–Pd1–N1	97.98(6)	C4–Pd1–N1	79.91(16)
C4–Pd1–P1	86.08(7)	P1–S1–Pd1	104.84(5)
C4–Pd1–P2	170.97(7)	P2–S2–Pd1	110.31(5)
C4–Pd1–P3	87.65(7)	C9–P1–S1	106.81(14)
C4–Pd1–N1	74.74(10)	C9–P1–C15	106.59(17)
C9–P1–Pd1	119.65(10)	C9–P1–C21	106.50(17)

Table 2. Scope of Suzuki-Miyaura cross coupling reactions using **2** as Catalyst.

$\text{Ph}-\text{B}(\text{OH})_2 + \text{Br}-\text{Aryl} \xrightarrow[\text{K}_2\text{CO}_3, \text{EtOH:H}_2\text{O}]{\text{Catalyst, 55 } ^\circ\text{C}} \text{Ph}-\text{Aryl}$				
Entry	Aryl bromide	Coupling Products	Time(min)	Yield (%)
1			40	81
2			60	88
3			90	80
4			35 50	91 98
5			50	96
6			50 95	65 97
7			50 120	47 96
Catalyst 2 loading (0.25 mol%); phenylboronic acid (0.6 mmol); Aryl bromide (0.5 mmol); K ₂ CO ₃ (0.75 mmol); solvent: EtOH:H ₂ O (1:1, 2 mL).				

Table 3. Comparison of the Catalytic Performances of **2** and Other Known Catalysts in the Suzuki–Miyaura Reaction of phenylboronic acid. with bromobenzene.

Entry	Catalyst, (mol%)	Conditions	Time (h)	Yield (%) ^a	Ref
1	Catalyst 2 , (0.25)	K ₂ CO ₃ , EtOH:H ₂ O, 55 °C	0.83	96	This work
2	Fe ₃ O ₄ @PUVS-Pd, (0.09)	K ₂ CO ₃ , H ₂ O, 90 °C	1	93	[34a]
3	Pd ₁₆ S ₇ NPs, (0.1)	K ₂ CO ₃ , DMF, 100 °C	5	87	[33]
4	[Pd(L–HCl)Cl ₂], (0.01) ^b	K ₂ CO ₃ , H ₂ O, 25 °C	2	93	[34b]
5	Fe ₃ O ₄ @SiO ₂ -[Pd(L–HCl)Cl ₂], (0.2) ^b	K ₂ CO ₃ , H ₂ O, 25 °C	2	92	[34b]
6	Fe ₃ O ₄ @SiO ₂ -Im-Phos supported PdNPs, (0.3)	K ₂ CO ₃ , EtOH:H ₂ O, 60 °C	18	90	[38]
7	[{PdCl(S-Phoz)} ₂], (0.02)	K ₂ CO ₃ , EtOH:H ₂ O, 90 °C	3	94	[34c]
8	[{PdI(S-Phoz)} ₂], (0.02)	K ₂ CO ₃ , H ₂ O, 90 °C	3	75	[34c]

^aIsolated yield, ^bL= 1-[N-Benzylacetamido]-3-[1-(2-phenylsulfanylethyl)]benzimidazolium Chloride.

Table 4. Comparison of cytotoxic effects against A549 cell line between the Compound **2** and other Compounds reported in the literature.

Entry	Compound	IC ₅₀ (μ M)	Ref
1	[Pd(Ambim)Cl ₂], Ambim = 2-aminomethyl benzimidazole	23	[35a]
2	[Pd(terpy)Cl] ⁺	40.3	[35b]
3	[Pd(sac) ₂ (dppm)].H ₂ O.·EtOH	>40	[35c]
4	[PdL(PPh ₃)], L=N'-(4(Diethylamino)-2-hydroxybenzylidene) furan-2-carbohydrazide	36	[35d]
5	[Pd(LH) ₂], L=N-p-chlorophenylthiosemicarbazone	36	[35e]
6	Compound 2	10	This work

Figure Captions:

Figure 1. Structure of the oxime palladacycle used.^[16]

Figure 2. Molecular structure of **2**. Hydrogen atoms, solvent (CHCl₃) and ClO₄ anion are omitted for clarity. Displacement ellipsoids are drawn at the 50% probability level.

Figure 3. Molecular structure of **3**. Hydrogen atoms (except H1) and ClO₄ anion are omitted for clarity. Displacement ellipsoids are drawn at the 50% probability level.

Figure 4. Inverted microscopic observation for a survey of cytotoxicity of the compounds with the IC₅₀ concentration in A549, HT29 and HeLa cells after 24 h.

Figure 5. Giegma staining for a survey of cytotoxicity of the most cytotoxic compound **2** with the IC₅₀ concentration in A549, HT29 and HeLa cells after 24 h.

Figure 6. The effect of compounds with concentrations of 0.01, 0.1 and 1 mg/mL on cell viability and growth of HT29 cell by MTT assay (**a**) at day 1 (**b**) at day 2 (**c**) at day 3 (*: p<0.05 and Values are mean (n=3)).

Figure 7. EB/AO staining for HT29, A549 and HeLa cells. Cells were treated with the most cytotoxic compound **2** with the IC₅₀ concentration after 24 h.

Graphical abstract-Pictogram

Mono and dinuclear oxime palladacycles bearing diphosphine ligands: An unusual coordination mode for dppe

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AOC5098_fig 1.tif

AOC5098_fig 2.tif

AOC5098_fig 3.tif

A549

HT29

HeLa

AOC5098_fig 4.tif

AOC5098_fig 5.tif

AOC5098_fig 6.tif

AOC5098_fig 7.tif

AOC5098_scheme 1.tif

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