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SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF PALLADIUM(II) COMPLEX WITH (*L*)-3-ACETYL-5-BENZYL-1-PHENYL-4,5-DIHYDRO-1,2,4-TRIAZIN-6-ONE OXIME. PART II

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Abstract- The synthesis and structural properties of the four-coordinate $Pd(L)_2$ **(4)**, where L is chiral 3-acetyl-5-benzyl-1-phenyl-4,5-dihydro-1,2,4-triazin-6-one oxime, **(2)** are described. Deep-red needles of **4** crystallize in the hexagonal space group $P6_1$. The crystallographic data reveal that the two oxime ligands are not symmetrically coordinated to Pd(II) ion, and the 4N-donor set comprises both oxime nitrogens, an amidrazone nitrogen and a hydrazone nitrogen. ^{1}H-, ^{13}C-NMR and FD-MS spectral data of **4** are consistent with its X-Ray molecular structure.

INTRODUCTION

Previously, we described the preparation of chiral 4,5-dihydro-1,2,4-triazin-6-ones (e.g. compound (L)-**1**, Scheme **1**) using α-amino esters and hydrazonoyl chlorides as an efficient one-pot synthesis.[1] Oximation of the C3-acetyl group of 4,5-dihydrotriazinones, using hydroxylamine, readily afforded the respective oximes (exemplified by (L)-**2**, Scheme **1**).[2] In an attempt to explore the coordination capacity of the oximes **(2)** with transition metals, we have reported on the reaction of **2** with nickel acetate.[2] This reaction showed that the oxime is capable of coordinating to nickel(II) ion as a bidentate ligand and the resulting bis-ligand complex has a square-planar geometry. Concomitant with this, was observed an unusual carbon-carbon coupling between the benzylic carbon of one oxime ligand and the stereogenic center (carbon-5) of the other oxime ligand (compound **(3)**, Scheme **1**).[2] In this paper, we report on the reaction of oxime **(2)** with palladium(II) acetate whereby the Pd(II) complex **(4)** was obtained. The crystallographic data, presented

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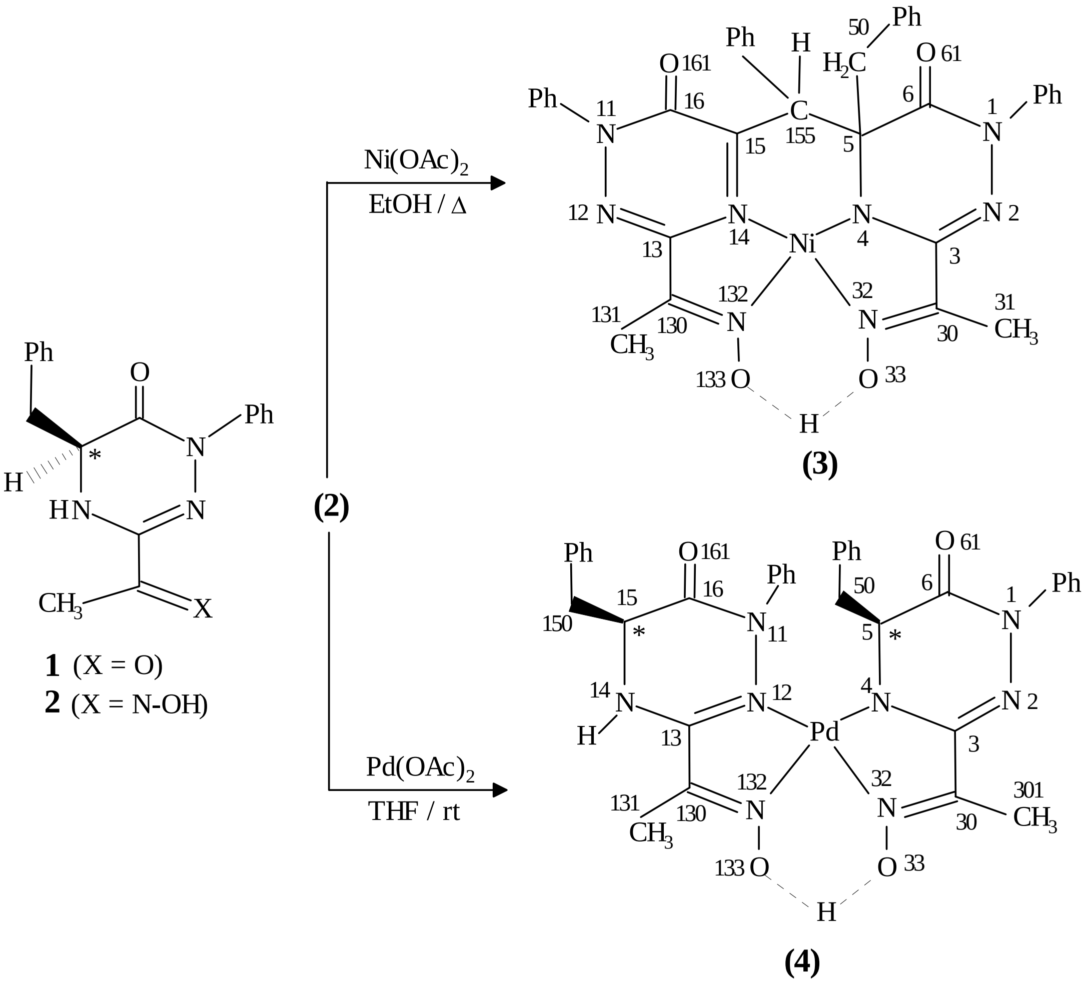
in this paper, revealed an almost square-planar geometry around the palladium ion with the two oxime ligands coordinating in an unsymmetrical fashion, *viz.*, the amidrazone nitrogen NH(4) and the oxime nitrogen of one ligand, together with the hydrazone nitrogen N(2) and the oxime nitrogen of the other ligand comprising the 4N-donor set that surrounds the palladium ion.

Scheme 1



RESULTS AND DISCUSION

As alluded to in the introduction, the reaction of nickel acetate with the oxime **(2)** in dry ethanol gave a square-planar nickel(II) complex **(3)** in which the two oxime ligands were coordinated to the metal center in a symmetrical fashion, enabling the two benzylic groups to be in close proximity to each other. Apparently, if C-C coupling between a benzylic carbon atom of one oxime ligand and the chiral center of the other oxime is to take place, the size of the cavity in the pseudo-14-membered tetraazamacrocycle would have to be suitable for the nickel(II) ion to fit in and this exactly what has happened.[2] The nickel(II) ion is evidently playing a template effect role in initiating both of σ- and π-bond forming reactions (**3**, Scheme **1**).

In an analogous manner, we sought to replace nickel(II) with palladium(II) in the framework of **3** since both are d^8 transition metals and they prefer square-planar geometry. In addition, square-planar palladium(II) complexes with nitrogen donors have been used as antitumors in cancer chemotherapy.[3] Thus several attempts were made to react palladium(II) acetate with the oxime **(2)** in dry ethanol in order to obtain a Pd(II) analogue of **3**. It was observed that ethanol is not a good solvent since it partially reduces Pd^{2+} to Pd metal, and the yield of **4** was poor ~10%. Instead, THF was found to be useful solvent and an almost quantitative yield of **4** was obtained. The palladium complex is neutral and diamagnetic and in this respect it is similar to the nickel complex as being geometrically square-planar. The MS and NMR spectral data of **4** revealed that the C-C coupling which occurred in **3** did not, however, take place in **4**. This prompted us to investigate the details of the structure of **4**.

The exact structure of the palladium complex **(4)** was determined by X-Ray diffraction and the results of crystallographic data are shown in Tables 1,2, and Figure 1. The 4N-donor set which is complexed to the palladium ion is actually composed of two oxime nitrogens, an amidrazone nitrogen and a hydrazone nitrogen. It appears that this mode of coordination places the palladium ion in an environment where the steric repulsion between the two benzylic groups on the one hand and the two *N*-phenyl groups on the other is minimum. This could be attributed to the larger size of the Pd^{2+} ion compared to Ni^{2+} ion, and this could well be the cause of the non-symmetrical coordination of the two oxime ligands around the Pd^{2+} ion, preventing the C-C coupling (which was observed in **3**) from taking place in **4**.[2]

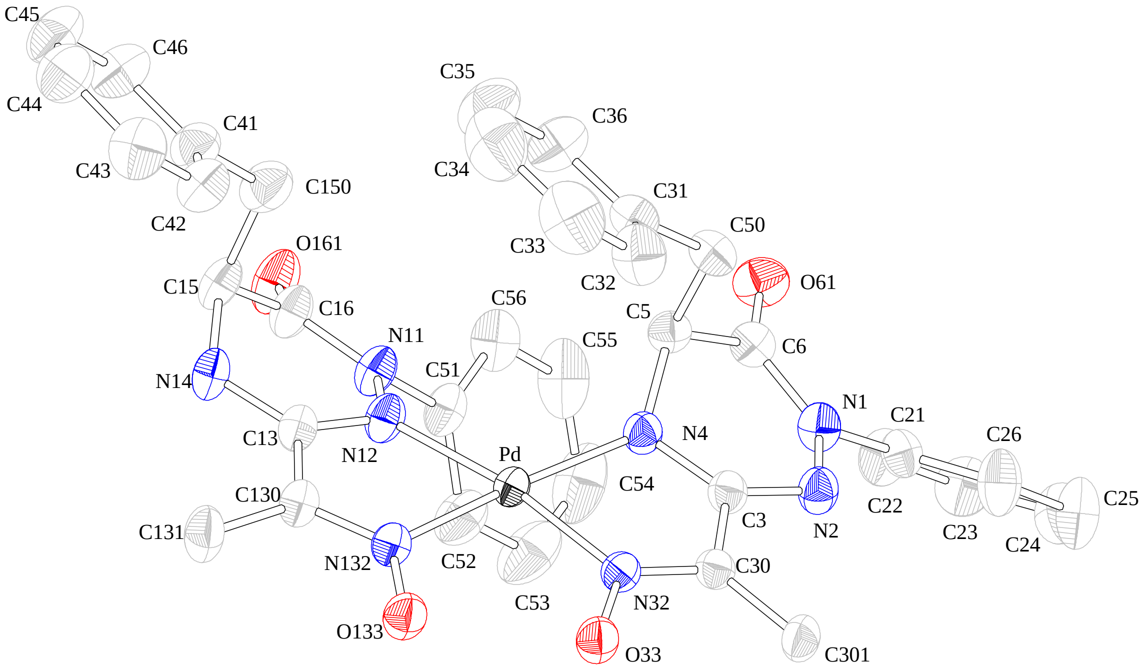


Figure 1 Molecular structure of the palladium complex **(4)** without the solvent THF. All hydrogen atoms are omitted for clarity.

The NMR spectral data for **4** are in full agreement with the X-Ray molecular structure. Thus, in DEPT experiments, and due to the dissymmetry of **4**, signal doubling is observed for all carbons of the two oxime ligands. For instance, the two methine sp^3-stereo centers (C5 and C15) resonate at δ 57.1 and 61.7 respectively, while the two benzylic methylene carbons (C150 and C50) resonate at δ 36.4 and 40.0, respectively. These data are in accord with the absence of C-C coupling reaction. In addition, the ^{1}H-NMR spectrum of **4** exhibits two exchangeable hydrogens resonating at δ 7.05 (d) and 16.65 (s) assigned to N(14)-H and the bridged (O…H…O) oxime hydrogen, respectively.

EXPERIMENTAL

Melting points (uncorrected) were determined using a Gallenkamp melting point apparatus. The magnetic moment was measured for a finely ground solid sample of **4** at ambient temperature using a Johnson Matthey Magnetic Susceptibility Balance. Optical rotations were measured on a Perkin-Elmer 141 photoelectric spectropolarimeter. NMR spectra were recorded on a Bruker WM-400 MHz spectrometer for solutions in $CDCl_3$ with TMS as internal reference. MS spectra (EI) were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV. Ion source temperature = 200 °C (for EI), and 35 °C (for FD). Elemental analysis were performed at the laboratories of Quantitative Technologies Inc., New Jersy,USA. 1-Chloro-1-phenylhydrazono-2-propanone (required for the synthesis of **1**) was prepared *via* direct coupling of 3-chloropentane-2,4-dione (Acros) with benzenediazonium chloride (Japp-Klingemann reaction[4]); mp : 141-142 °C, in agreeement with the reported values.[5]

L-3-Acetyl-5-benzyl-1-phenyl-4,5-dihydro-1,2,4-triazin-6-one (1)

This compound was prepared *via* direct interaction between 1-chloro-1-phenylhydrazono-2-propanone and L-phenylalanine methyl ester hydrochloride (Aldrich) in methanol / dichloromethane (v/v = 1/1) in the presence of triethylamine, following a general procedure.[1] The product was obtained in the form of prismatic crystals and characterized as **1** (78%). mp 114-115 °C (recrystallized from aqueous ethanol). $[\alpha]_D^{20}$ = -244.7° (c ~ 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N,13.67. Found: C, 70.41; H, 5.52; N, 13.58. MS m/z (% rel. int.): 307.13028 ($M^{+\cdot}$, 20, Calcd 307.13208), 216 ($M-CH_2Ph$, 100), 188 (12), 146 (10), 119 (8), 104 (8), 92 (22), 77 (17). ^{1}H-NMR ($CDC1_3$) δ (ppm) : 2.33 (s, 3H, CH_3), 3.09 (m, 2H, $C\underline{H}_2Ph$), 4.43 (m,1H,CH-5), 5.79 (br s, 1H, NH-4), 7.13 - 7.49 (m, 10H, CH-aromatic). ^{13}C-NMR ($CDC1_3$) δ (ppm): 23.6 (CH_3), 40.1 (CH_2), 55.0 (CH-5), 124-130 (6CH-aromatic : 124.7, 127.0, 127.4, 128.5, 128.8, 129.6), 135-141 (2C-aromatic, C-3: 135.2, 140.5, 141.0), 161.4 (C-6), 192.7 ($O=\underline{C}-CH_3$).

Table 1. Summary of crystal data and structure refinement parameters for 4.THF

Empirical formula	$C_{36}H_{34}N_8O_4Pd$. C_4H_8O
Formula weight	821.22
Temperature (K)	213 (2)
Crystal system	Hexagonal
Space group	$P6_1$
Diffractometer	STOE IPDS
Wavelength / Radiation	0.71073 Å / MoKα
Unit cell dimensions	
a (Å)	25.8354 (11)
b (Å)	25.8354 (11)
c (Å)	10.1297 (3)
α (°)	90
β (°)	90
γ (°)	120
Volume ($Å^3$)	5855.4 (4)
Z	6
Density (calculated) (mg/m^3)	1.397
Absorption coefficient (mm^{-1})	0.529
F(000)	2544
Crystal description	Red needle
Crystal size (mm)	10.00 × 0.20 × 0.10
θ range (Lattice) (°)	2.3-30.4
θ range for data collection (°)	3.14-30.43
Index ranges	$-36 \le h \le 36$, $-36 \le k$ 36, $- 13 \le l$ 13
Reflections collected	101557
Independent reflections	11618 [$R_{int} = 0.0647$]
Reflections observed	10064
Criterion for observation	$> 2\sigma(I)$
Decay	None %
MolecularGraphics	Diamond
Refinement method	Full-matrix least-squares on F^2
Weighting scheme	Calc $w = 1/[\sigma^2(F_o)^2 + (0.0561P)^2 + 0.0000P]$ where $P = [(F_o)^2 + 2\,(F_c)^2] / 3$
Data/ restraints/parameters	11618/1/598
Final R indices [$1 > 2\sigma(I)$]	$R_1 = 0.0329$, $wR_2 = 0.0812$
Goodness-of-fit on F^2	1.019
Final R indices (all) R_1/wR_2	0.0414/0.0846
Absolute structure parameter	-0.03 (2)
Largest difference peak (e.$Å^{-3}$)	0.830
Largest difference hole (e. $Å^{-3}$)	-0.310

Table 2: Selected bond lengths and angles for 4.

Bond lengths (Å)	
Pd-N(32)	1.991(2)
Pd-N(132)	2.001(2)
Pd-N(4)	2.018(2
Pd-N(12)	2.061(2)
O(33)-N(32)	1.352(3)
O(133)-N(132)	1.311(3)
O(133)-H(3)	1.590(5)
N(1)-N(2)	1.416(3)
N(2)-C(3)	1.302(3)
N(4)-C(3)	1.351(3)
N(4)-C(5)	1.455(3)
N(12)-C(13)	1.321(4)
N(11)-N(12)	1.423(3)
N(11)-C(16)	1.361(3)
N(11)-C(51)	1.433(4)
N(14)-C(13)	1.338(3)
N(14)-C(15)	1.454(4)
N(32)-C(30)	1.284(3)
N(132)-C(130)	1.303(3
C(3)-C(30)	1.473(4)
C(5)-C(6)	1.522(4)
C(13)-C(130)	1.457(4)
C(15)-C(16)	1.510(4)
C(30)-C(301)	1.485(3)
C(130)-C(131)	1.498(4)
Bond angles (°)	
N(32)-Pd-N(132)	95.17(9)
N(32)-Pd-N(4)	79.28(8)
N(132)-Pd-N(4)	173.95(9)
N(32)-Pd-N(12)	171.54(9)
N(132)-Pd-N(12)	78.16(9)
N(4)-Pd-N(12)	107.58(9)
N(132)-O(133)-H(3)	105(2)
C(6)-N(1)-N(2)	123.1(2)
C(6)-N(1)-C(21)	123.5(2)
N(2)-N(1)-C(21)	113.2(2)
C(3)-N(2)-N(1)	113.4(2)
C(3)-N(4)-C(5)	113.1(2)
C(3)-N(4)-Pd	112.2(2)
C(5)-N(4)-Pd	132.3(2)
C(13)-N(12)-N(11)	116.7(2)
C(13)-N(12)-Pd	112.2(2)
N(11)-N(12)-Pd	130.9(2)
C(13)-N(14)-C(15)	118.6(2)
C(16)-N(11)-N(12)	121.8(2)
C(16)-N(11)-C(51)	120.6(2)
N(12)-N(11)-C(51)	115.8(2)
C(30)-N(32)-O(33)	118.6(2)
C(30)-N(32)-Pd	118.5(2)
O(33)-N(32)-Pd	122.5(2)
C(130)-N(132)-O(133)	120.3(2)
C(130)-N(132)-Pd	117.8(2)
O(133)-N(132)-Pd	121.8(2)
N(2)-C(3)-N(4)	127.0(2)
N(2)-C(3)-C(30)	116.6(2)
N(4)-C(3)-C(30)	116.4(2)
N(4)-C(5)-C(6)	110.6(2)
N(4)-C(5)-C(50)	113.1(2)
N(11)-C(16)-C(15)	114.7(3)
N(12)-C(13)-N(14)	121.9(3)
N(12)-C(13)-C(130)	116.9(2)
N(14)-C(13)-C(130)	121.2(3)
N(14)-C(15)-C(16)	108.3(2)
O(161)-C(16)-N(11)	122.3(3)
O(161)-C(16)-C(15)	123.0(2)
N(32)-C(30)-C(3)	112.1(2)
N(32)-C(30)-C(301)	124.1(2)
C (3)-C(30)-C(301)	123.8(2)
C(56)-C(51)-N(11)	119.3(3)
C(52)-C(51)-N(11)	119.8(3)
N(132)-C(130)-C(13)	112.7(2)
N(132)-C(130)-C(131)	123.1(3)
C(13)-C(130)-C(131)	124.1(2)
C(31)-C(50)-C(5)	115.1(2)

L-3-Acetyl-5-benzyl-1-phenyl-4, 5-dihydro-1, 2,4-triazin-6-one Oxime (2)

To a solution of compound **(1)** (2.7 g, 8.7 mmol) in warm methanol (80 mL) were added hydroxylamine hydrochloride (1.81 g, 26.1 mmol) and sodium acetate (2.15 g, 26.1 mmol). The resulting mixture was refluxed for 4 h. The solvent was then removed in *vacuo*, the residue was digested with water (150 mL), and the insoluble solid product was collected under suction, washed with water (2 x 30 mL), dried, recrystallized from ethanol in the form of scales and characterised as **2** (2.4 g, 87%). mp 185-187 °C. $[\alpha]^{20}_{D}$ = - 106.4° (c ~ 0.4, THF). Anal. Calcd for $C_{18}H_{18}N_4O_2$: C 67.07; H, 5.63; N, 17.38. Found : C, 66.98; H, 5.61; N, 17.35. MS m/z (% rel. int.) : 322.14434 ($M^{+\cdot}$, 14, Calcd. 322.14298), 231 ($M-CH_2Ph$, 100), 215 (5), 203 (7), 186 (5), 104 (10), 91 (29), 77 (23). ^1H-NMR (DMSO-d_6) δ (ppm) : 1.81 (s, 3H, CH_3), 3.01 (d, *J* = 4.9 Hz, 2H, CH_2), 4.36 (dt, *J* = 4.9 Hz, 1.6 Hz, 1H, CH-5), 6.92 (d, *J* = 1.6 Hz, 1H, NH-4), 7.15 -7.36 (m, 10H, CH-aromatic), 11.68 (s, 1H, OH). ^{13}C-NMR (DMSO-d_6) δ (ppm) : 8.1 (CH_3), 38.0 (CH_2), 53.3 (CH-5), 123-129 (6CH-aromatic : 123.5, 125.1, 125.7, 127.0, 127.2, 128.8), 135-147 (2C-aromatic, 2C=N- : 135.1, 140.1, 142.1, 147.0), 160.5 (C-6).

L-3-Acetyl-5-benzyl-1-phenyl-4,5-dihydro-1,2,4-triazin-6-one Oxime-Palladium(II) Complex (4)

Palladium acetate (0.7 g, 3.1 mmol) and the L-oxime derivative **(2)** (2 g, 6.2 mmol) were dissolved in dry tetrahydrofuran (50 mL). The reaction mixture immediately assumes red color, and stirring was continued at rt for 15 h. At the end, the mixture was filtered off, the volume of the filtrate was reduced to about 15 mL, and petroleum ether was added dropwise until the solution was slightly turbid. After few hours, deep-red needles separated which were collected by suction filtration, dried *in vacuo* and identified as complex **(4)** (2.3 g, 90%). mp > 300 °C. $[\alpha]^{20}_{D}$ = +208° (c = 0.2, THF). Anal. Calcd for $C_{36}H_{34}N_8O_4Pd.C_4H_8O$: C, 58.50; H, 5.15; N, 13.64. Found : C, 58.17; H 4.92; N, 13.37. FD-MS m/z ~748 ($M^{+\cdot}$, calcd ~ 748). ^1H-NMR ($CDCl_3$) δ (ppm) : 1.92 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 7.05 (d, 1H, N(14)-H, *J* = 6.0 Hz), 7.15-7.70 (m, 20H, aromatic CH), 2.63-2.78 (2H, 8 lines, part of ABX system, CH_2-50, J_{AB} = 13.4 Hz, J_{AC} = 7.3 Hz, J_{BC} = 4.4 Hz), 3.36 (1H, 4 lines, X-portion, H-5), 2.80-3.16 (2H, 8 lines, part of ABX system, CH_2-150, J_{AB} = 13.0 Hz, J_{AC} = 7.2 Hz, J_{BC} = 4.6 Hz), 4.10 (1H, 6 lines, X-portion, H-15), 16.65 (s, 1H, O…H…O). ^{13}C-NMR ($CDCl_3$) δ (ppm) : 10.4 (CH_3), 12.1 (CH_3), 36.4 ($\underline{C}H_2Ph$), 40.0($\underline{C}H_2Ph$), 57.1 ($\underline{C}$H-5), 61.7 ($\underline{C}$H-15), 124.0-131.0 (12 CH-aromatic : 124.3, 125.2, 126.2, 126.3, 127.8, 127.9, 128.2, 128.3, 128.5, 129.2, 129.4, 130.2), 134.0-161.0 [10 C (4$\underline{C}$-aromatic, 4 $\underline{C}$=N, 2 $\underline{C}$=O : 134.7, 137.2, 137.7, 140.5, 140.9, 153.9 154.9, 157.6, 160.0, 160.8)].

A solution of the title complex **(4)** in THF (10^{-3} M) is non-conducting indicating that **4** is neutral. The magnetic moment measurement shows that the complex is also diamagnetic (μ ~o) which is consistent with Pd(II) metal ion (d^8) in a square geometry.[6]

Collection of X-Ray diffraction data and the structure analysis

Deep-red needle-like crystals were grown by cooling slowly a solution of **4** (~1 g) in THF/pet. ether (20/20 mL) to rt overnight. The crystals were kept solvent wet in a sealed tube. The sturcture was solved by direct method using the program SHELXS 86.[7] All non-hydrogen atoms were refined anisotropically by fullmatrix least-squares procedure based on F^2 using all unique data with SHELXL 93.[8] The hydrogen atoms have been found in the difference Fourier map and were refined isotropically. This results in an R values $R_1 = 0.0329$ and $wR_2 = 0.0812$ for the observed data and 598 parameters.

Supplimentary Material

Further information for the crystal structure determination of **4** can be ordered from Cambridge Crystallographic Data Center under the depository number CCDC 144757. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax : int. code + (1223) 336-033; e-mail : deposit @ ccdc. cam. ac. uk).

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