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# Synthesis, characterization and anticancer activity of new palladacycles derived from chiral α-diimines

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**Optically pure α-diimines quantitatively obtained in solvent-free conditions starting from 2,3-butanedione and (*S*)-(−)-1-phenylethylamine and (*S*)-(−)-1-(4-methylphenyl)ethylamine, respectively, yielded the new chiral mono-Pd complexes 2a–b, which have been partly characterized by IR, $^1$H- and $^{13}$C-NMR spectroscopies along with MS-FAB$^+$ spectrometry. The crystal and molecular structure for palladacycle 2a has been fully confirmed by single-crystal X-ray studies. Studies *in vitro* of 2a–b have displayed growth inhibition against different classes of cancer: leukemia (K-562 CML), colon cancer (HCT-15), breast cancer (MCF-7), central nervous system (U-251 Glio) and prostate cancer (PC-3) cell lines.** 

**Keywords:** anticancer activity; chiral α-diimines; Pd complexes

## Introduction

Nowadays, there is a growing interest in the synthesis, reactivity and applications of organometallic complexes with interesting ligands, and an important area of organometallic chemistry is that of cyclopalladated compounds.[1–6] Such longstanding interest in these compounds stems from their widespread utilities, ranging from potential new applications in organic chemistry, such as catalysts,[7–19] and as antitumor drugs,[20–25] and the usual efforts in understanding fundamental chemistry. Among the cyclometallated complexes described, those derived from optically pure ligands[26–41] have attracted additional interest, since they can be used for the resolution of mono- or bidentate ligands as well as in chiral discrimination processes. So far, most attention on this subject has been aimed at synthesizing novel complexes derived from a wide-ranging assortment of functionalized ligands and we are currently focusing our efforts on the synthesis of such compounds derived from optically pure *N*-donor ligands owing to their attractive features as potential catalysts and bioactive compounds. In this regard, we have synthesized new chiral Pd complexes derived from enantiopure α-ketoimines, which have shown promising anticancer activity.[42]

Along this latter line, although cisplatin and carboplatin therapy have achieved major improvements in some forms of cancer, in some cases remissions are of limited duration and the former can give rise to toxic side effects. We became interested in developing chiral α-diimines as promising carrier ligands and, by incorporation of a variety of selected functional groups into these carrier ligands, it is hoped that the clinical properties of the corresponding compounds can be modified systemically. We report herein our results concerning the preparation of the chiral mononuclear Pd complexes **2a–b**, derived from the optically pure α-diimines **1a–b**, the crystal structure of **2a** and anticancer activity of **2a–b**.

## Results and Discussion

The chiral α-diimines **1a–b** were synthesized in quantitative yield in solvent-free conditions starting from (*S*)-(−)-1-phenylethylamine and (*S*)-(−)-1-(4-methylphenyl)ethylamine with 2,3-butanedione, respectively. The reaction between $Na_2PdCl_4$ and each of the ligands **1a–b** in a MeOH solution at ambient temperature gave a precipitate leading to the formation of the corresponding complexes, **2a–b**, and their structures were partly established by spectroscopic analysis.

The complexes **2a–b**, isolated as air-stable clear brown crystalline solids in 94 and 91% yields, respectively, were given structure **2** based on their spectroscopic features. Thus, the IR spectra for **2a** exhibited absorption at 1672 as well as at 1576 cm$^{-1}$ for the CN group, with bands in the low-frequency IR region at 753 cm$^{-1}$ assigned to the Pd–C bonds and at 468 cm$^{-1}$ owing to the Pd–N bonds, and a band at 334 cm$^{-1}$ corresponding to the absorption of the Pd–Cl bond was also observed. The $^1$H NMR (400 MHz, $CDCl_3$) spectrum for complex **2a** showed at 7.7–6.7 ppm a multiple signal (9H) owing to the phenyl groups: at 5.4 and 5.1 ppm two quadruplets assigned to the protons belonging to the chiral moieties; at 2.7 and 2.2 ppm two singulets

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**Table 1.** Summary of crystallographic results for **2a**

| | |
|---|---|
| Formula | $C_{20}H_{23}ClN_2Pd$ |
| $f_w$ | 433.25 |
| Crystal size (mm) | 0.52 × 0.48 × 0.12 |
| Color, shape | Orange plate |
| $\rho$ (calc) (g cm$^{-3}$) | 1.570 |
| Space group | $P2_12_12_1$ |
| $a$ (Å) | 8.0580(4) |
| $b$ (Å) | 9.6843(5) |
| $c$ (Å) | 23.4813(10) |
| $V$ (Å$^3$) | 1832.39(15) |
| $Z$ | 4 |
| $\mu$ (mm$^{-1}$) | 1.162 |
| $2\theta$ range (deg) | 3.5–60.0 |
| Reflns coll. | 5808 |
| Unique reflns ($R_{int}$)[a] | 4918 (0.035) |
| Reflns with $F_o > 4\sigma(F_o)$ | 3983 |
| Transmission factors | 0.601–0.868 |
| Data/parameters | 4918/221 |
| GOF[a] on $F^2$ | 1.031 |
| $R$ indices[a] [$I > 2\sigma(I)$] | 0.037, 0.085 |
| $R$ indices[a] (all data) | 0.051, 0.092 |
| Max. residence density (e Å$^{-3}$) | 0.68, −0.78 |
| System used | SHELXTL-Plus[44] |

[a] $R_{int} = \frac{\sum |F_o^2 - \langle F_o^2 \rangle|}{\sum F_o^2}$, $R_1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$, $wR_2 = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2}}$, $S = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{m - n}}$

(3H) corresponding to methyl groups; and finally at 1.9 and 1.5 two doublets ascribed to the methyl groups of chiral entities. The $^{13}$C NMR spectrum (300 MHz, $CDCl_3$) displayed two signals at 174 and 171 ppm ascribed to the imine carbons; at 155–120 ppm the signals of the phenyl groups; and at 68 and 62 ppm as well as at 22 and 20 ppm the peaks assigned to the methyne and methyl carbons, respectively. By high-resolution mass spectrometry with FAB ion mode technique, the molecular weight of the complex was observed at $m/z$ 433, suggesting a mononuclear complex. This fact was unequivocally established by single-crystal X-ray diffraction studies (Table 1) and the molecular structure is given in Fig. 1. For complex **2b**, almost identical spectroscopic data were obtained (see Experimental), the only differences being the additional signals owing to the methyl groups in the *para*- position for the benzene rings of the ligand, and the distinctive features being the position of the signals in NMR for the protons of the chiral entities. Attempts to grow crystals of **2b** suitable for X-ray crystallography failed.

## Solid-state Structure

Selected geometric parameters for complex **2a** are reported in Table 2. The asymmetric unit of the orthorhombic cell contains one molecule with all atoms in general positions. The complex is mononuclear, with the Pd(II) center adopting a distorted square planar Pd[$N_2$CCl] coordination geometry, as expected for a d8 ion. The distortion from an ideal geometry mainly arises from the bite angle of the diimino moiety, N8–Pd1–N11 = 77.50(12)°.

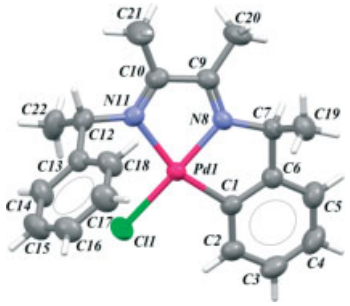


**Figure 1.** Molecular structure of complex **2a** with thermal ellipsoids for non-H atoms at the 50% probability level.[44].

**Table 2.** Selected bond lengths (Å) and angles (deg) for **2a**

| | | | |
|---|---|---|---|
| Pd1–N8 | 1.976(3) | Pd1–C1 | 1.980(4) |
| Pd1–N11 | 2.176(3) | Pd1–Cl1 | 2.3207(11) |
| C7–N8 | 1.494(5) | N8–C9 | 1.283(5) |
| C10–N11 | 1.274(5) | N11–C12 | 1.489(5) |
| C9–C10 | 1.508(6) | | |
| N8–Pd1–C1 | 83.43(14) | N8–Pd1–N11 | 77.50(12) |
| C1–Pd1–N11 | 160.93(14) | N8–Pd1–Cl1 | 172.70(12) |
| C1–Pd1–Cl1 | 94.94(12) | N11–Pd1–Cl1 | 103.93(9) |
| C9–N8–C7 | 123.1(3) | C9–N8–Pd1 | 119.0(3) |
| C7–N8–Pd1 | 117.3(2) | C10–N11–C12 | 121.4(3) |
| C10–N11–Pd1 | 111.9(3) | C12–N11–Pd1 | 126.7(3) |

In spite of the fact that the free ligand potentially belongs to the $C_2$ point group, this does not coordinate in a symmetric manner: one benzene group is bonded to the metal center, with the expected bond length Pd1–C1 = 1.980(4) Å, while the other is free of coordination. As a consequence, the diimino fragment is also asymmetrically coordinated, with significantly different Pd–N distances of 1.976(3) and 2.176(3) Å. However, the geometry of the diimino functionality is unaffected by coordination, with formal N8–C9 and N11–C10 localized double bonds and a central C9–C10 $\sigma$-bond (see Table 2). The Pd(II) atom lies almost perfectly in the plane of the two five-membered chelate rings formed by the coordination. Unexpectedly, dimerization of the mononuclear complex did not occur, although favorable conditions were available for the formation of a centrosymmetric dinuclear complex: the presence of chlorine, which commonly is bonded to Pd in a $(\mu_2\text{-Cl})_2$ bridging mode, and the use of a $C_2$ ligand containing two coordinating N atoms.[43] However, in the present case, the formation of a dinuclear complex seems to have been avoided because an entropic factor favored the formation of a Pd–C bond (five-membered ring) and because of the steric hindrance produced by the other benzene group.

## Anticancer Results

$IC_{50}$ values (μM) of complexes **2a–b** and cisplatin against U251 (CNS), PC-3 (prostate), K562 (leukemia), HCT-15 (colon) and MCF-7 (breast) human cancer cells are displayed in Table 3. The assays were performed, in the case of complex **2a**, with the crystalline solid. The data show that both complexes were cytotoxic towards the panel of cultured cell lines, mainly against U251 (CNS) and K562 (leukemia) cancer cells, with complex **2b** performing better



  

**Table 3.** $IC_{50}$ (μM)[a] values of complexes **2a–b** and cisplatin against U251 (CNS), PC-3 (prostate), K562 (leukemia), HCT-15 (colon) and MCF-7 (breast) human cancer cells

| Complex | U251 (CNS) | PC-3 (prostate) | K562 (leukemia) | HCT-15 (colon) | MCF-7 (breast) |
|---|---|---|---|---|---|
| **2a** | 23.6±1.5 | >100 | 25.4 ± 1.3 | >100 | 88.5 ± 1.3 |
| **2b** | 19.8±1.4 | 51.5±1.3 | 22.5 ± 1.1 | 54.3±1.1 | 93.3 ± 1.2 |
| Cisplatin | ND | 10.5 ± 0.05 | 3.1 ± 1.2 | 4.6 ± 1.2 | 2.52 ± 0.6 |

ND, Not determined.
[a] $IC_{50}$ corresponds to the concentration required to inhibit a 50% of the cell growth when the cells are exposed to the compounds during 48 h. Each value is the average of three independent experiments.

results in view of the relatively smaller amounts required in both cell lines ($IC_{50}$ = 19.8 and 22.5 μM for **2b** compared with 23.6 and 25.4 μM for **2a**, respectively) and, in this regard, the results of **2b** with prostate and colon cell lines ($IC_{50}$ = 51.5 and 54.3 μM, respectively) are also salient when taking into account those of complex **2a** (>100 in both cases).

## Conclusion

The synthesis of new chiral palladacycles along with their characterization are reported. Also, anticancer activity has been registered. Work is in progress with other optically pure α-diimines to increase the scope and fine-tune the cytotoxic activity by varying the functional groups. Applications of these compounds in asymmetric synthesis are also being investigated.

## Experimental Section

### General Methods

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian 400S spectrometer, using $CDCl_3$ as solvent and TMS as internal reference. IR spectra were performed on a Perkin–Elmer 283 B or 1420 spectrometer. The FAB spectra were obtained on a Jeol JMS SX 102A mass spectrometer operated at an accelerating voltage of 10 kV. Samples were desorbed from a nitrobenzyl alcohol matrix using 6 keV xenon atoms. The electronic impact (EI) ionization mass spectra were acquired on a Jeol JMS-AX505 HA mass spectrometer operated in the positive ion mode. The acquisition conditions were ion source temperature 230 °C, ionization energy 70 eV, emission current 0.14 μA and ionization current 100 μA. Mass measurements in FAB were performed at 10 000 resolution using electrical field scans, and polyethylene glycol ions were used as the reference material. Melting points were measured using a Mel-Temp II apparatus and are uncorrected. Elemental analyses were recorded on a Euro EA elemental analyzer. Reagents were obtained from commercial suppliers and used as received.

*N1,N2-di[(S)-(−)-1-phenylethyl]-2,3-butanediimine* ***1a***

A mixture of 2,3-butanedione (0.2 g, 2.3 mmol) and (*S*)-(−)-1-phenylethylamine (0.55 g, 4.6 mmol) was heated under focused-microwave irradiation in solvent-free conditions for 5 min. After cooling, the oily product was diluted with $CH_2Cl_2$, washed three times with water, and dried with sodium sulfate. Pale yellow oil (97% yield). FT-IR $\nu_{max}$ (film)/cm$^{-1}$: 1637 (C═N). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.4–7.2 (m, 10H, Ar), 4.8 (q, 2H, $J$ = 6.6 Hz, N–C*H*), 2.2 (s, 6H, $H_3$C–C═N), 1.45 (d, 6H, $J$ = 6.6 Hz, $H_3$C–CH). $^{13}$C NMR (300 MHz, $CDCl_3$): δ 166.3 (C═N), 146 (Ar*C-ipso*), 128.2, 126.7, 125.6 (Ar), 60.2 (Ar–*C*H), 24.7 ($H_3$*C*–C═N), 12.6 ($H_3$*C*–CH). EI-MS (*m/z*): 292 M$^+$. [$\alpha^{25}_D$] −80 ($c$ = 1, $HCCl_3$).

*N1,N2-di[(S)-(−)-1-(4-methylphenyl)ethyl]-2,3-butanediimine* ***1b***

A mixture of 2,3-butanedione (0.2 g, 2.3 mmol) and (*S*)-(−)-1-(4-methylphenyl)ethylamine (0.6 g, 4.6 mmol) was treated as above. Pale yellow oil (93% yield). FT-IR $\nu_{max}$ (film)/cm$^{-1}$: 1637 (C═N). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.3 (d, 4H, Ar), 7.1 (d, 4H, Ar), 4.8 (q, 2H, $J$ = 6.6, N–C*H*), 2.3 (s, 6H, C$H_3$–Ar), 2.2 (s, 6H, C$H_3$–C═N), 1.4 (d, 6H, $J$ = 6.6 Hz, $H_3$C–CH). $^{13}$C NMR (300 MHz, $CDCl_3$): δ 173.1 (C═N), 130.7 and 128.7 (Ar*C-ipso*), 129, 126 (Ar), 60.4 (CH$_3$–CH), 28.0 ($H_3$*C*–Ar), 21.1 ($H_3$*C*–C═N), 14.2 ($H_3$*C*–CH). EI-MS (*m/z*): 320 M$^+$. [$\alpha^{25}_D$] −87 ($c$ = 1, $HCCl_3$).

*Palladacycle* ***2a***

A solution of MeOH (30 ml) containing the ligand (1 mmol) and $Na_2PdCl_4$ (300 mg, 1 mmol) was stirred for 2 h at room temperature, and a brown precipitate was formed. The solid was filtered and washed with hexane. The solid was crystallized from a mixture of $CH_2Cl_2$ and EtOH (1 : 3 ratio).

Yield: 770 mg (94%), brown solid, m.p. 198–200 °C. FT-IR $\nu_{max}$ (KBr)/cm$^{-1}$: 1672 (C═NPd), 1576 (C═N), 753 (Pd–C), 468 (Pd–N), 334 (Pd–Cl). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.7–6.7 (m, 9H, *H*–Ar), 5.4 (q, 1H, *H*C–N), 5.1 (q, 1H, *H*C–N), 2.7 (s, 3H, C–C*H*$_3$), 2.2 (s, 3H, C–C*H*$_3$), 1.9 (d, 3H, NC–C*H*$_3$), 1.5 (d, 3H, NC–C*H*$_3$). $^{13}$C NMR (300 MHz, $CDCl_3$): δ 174.0, 171.5 (*C*═N–Pd), 155.0–120.1 (*C*–Ar), 68.5, 62.2 (N–*C*H), 22.0, 20.5 (HC*C*H$_3$). MS-positive FAB (*m/z*): 433 M$^+$. [$\alpha^{25}_D$] −148 ($HCCl_3$). Anal. calcd for $C_{20}H_{23}N_2PdCl$: C, 56.78; H, 6.71; N, 6.02. Found: C, 56.63; H, 6.67; N, 6.01.

*Palladacycle* ***2b***

Yield: 420 mg, (91%), brown solid, m.p. 271–273 °C. FT-IR $\nu_{max}$ (KBr)/cm$^{-1}$: 1607 (C═NPd), 1512 (C═N), 744 (Pd–C), 441 (Pd–N), 334 (Pd–Cl). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.6–6.6 (m, 7H, *H*–Ar), 5.4 (q, 1H, *H*C–N), 4.9 (c, 1H, *H*C–N), 2.3 (s, 3H, Ar–C*H*$_3$), 2.2 (s, 3H, Ar–C*H*$_3$), 2.2 (s, 3H, N═C–C*H*$_3$), 2.1 (s, 3H, N═C–C*H*$_3$), 1.9 (d, 3H, HC–C*H*$_3$), 1.48 (d, 3H, HC–C*H*$_3$). $^{13}$C NMR (300 MHz, $CDCl_3$): δ 179.0, 174.7 (*C*═N–Pd), 136.3–120.0 (*C*–Ar), 69.2, 62.3 (N–*C*H), 24.7 (Ar–*C*H$_3$), 21.1, 21.0 (N═C–*C*H$_3$), 18.3 (HC*C*H$_3$). MS-positive FAB (*m/z*): 460 M$^+$. [$\alpha^{25}_D$] −270 ($HCCl_3$). Anal. calcd for $C_{22}H_{29}N_2PdCl$: C, 58.42; H, 7.15; N, 5.68. Found: C, 58.39; H, 7.14; N, 5.64.

### Crystallographic Study

Single crystals suitable for X-ray structure determination of **2a** were obtained by slow evaporation and were handled in a non-controlled atmosphere. A summary of crystallographic results is presented in Table 1. Diffraction data were collected at 300 K on a Bruker P4 diffractometer, using graphite monochromatized Mo-$K_\alpha$ radiation (λ = 0.71073 Å), following a standard procedure.[45] Absorption effects were corrected using 12 ψ-scans. The structure was solved by direct methods and completed with difference Fourier maps.[44] Non-H atoms were refined anisotropically using full-matrix least squares, without constraints or restraints on the geometry, using an appropriate weighting scheme in the

last cycles. H atoms were placed in idealized positions and refined using a riding model with fixed isotropic displacement parameters. The configurations of the chiral centers *S*-C7 and *S*-C12 were determined from the refinement of a Flack parameter,[46] $x = 0.01(4)$, based on the measurement of 1867 Friedel pairs.

### Assay for Anticancer Activity

Colon cancer (HCT-15), breast cancer (MCF-7), leukemia (K-562 CML), central nervous system (U-251 Glio) and prostate cancer (PC-3) cell lines were supplied by the National Cancer Institute (USA). Cytotoxicity of the tumors cells with the test compounds was determined using the protein-binding dye sulforhodamine B (SRB) in microculture assay to measure cell viability and cell growth., as described in Monks *et al*.[47] The cell lines were cultured in RPMI-1640 supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 IU $ml^{-1}$ penicillin G, 100 µg $ml^{-1}$ streptomycin sulfate and 0.25 µg $ml^{-1}$ amphotericin B (Gibco). They were maintained at 37 °C in a 5% $CO_2$ atmosphere with 95% humidity. For the assay, cells were detached with 0.1% trypsin-EDTA to make single-cell suspension, and viable cells were counted using a hematocytometer and diluted with medium to give $5 \times 10^4$ cells $ml^{-1}$ (K562, MCF-7), $7.5 \times 10^4$ cells per well (U251, PC-3) and $10 \times 10^4$ cells per well (HCT-15). In 96-well microtiter plates, 100 µl per well of these cell suspensions were seeded and incubated to allow for cell attachment. After 24 h the cells were treated with logarithmic concentrations of the test products and the positive control, doxorubicin. They were initially dissolved in DMSO (40 mM) and further diluted in medium to produce five concentration test solutions (100, 31, 10, 3.1 and 1 µM). Aliquots of 100 µl of each test solution with the compound for evaluation were added to each well. After 48 h, adherent cell cultures were fixed *in situ* by adding 50 µl of cold 50% (w/v) trichloacetic acid (TCA) and incubated for 60 min at 4 °C. The supernatant was discarded and the plates were washed three times with water and air-dried. Cultured fixed with TCA were stained for 30 min with 100 µl of SRB solution (0.4% w/v in 1% acetic acid). Unbound SRB was removed by four washes with 1% acetic acid and protein-bound dye was extracted with 10 mM unbuffered tris base (tris[hydroxymetryl] aminomethane); the optical densities were read on an automated spectrophotometric plate reader at a single wavelength of 515 nm. The $IC_{50}$ (concentrations required to inhibit cell growth by 50%) was calculated according to the protocol previously established.[47] Mean and standard error (SE) of three independent experiments are reported for each selected concentration of the studied compound.

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