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Optically active endocyclic cyclopalladated derivatives of N-benzylidene-(*R*)-1-phenylethylamines

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Abstract The action of $Pd(AcO)_2$ on imines derived from (*R*)-1-phenylethylamine, R_1R_2C=NCHMePh, (R_1 = 4-ClC_6H_4, R_2 = H [**1a**]; R_1 = 3,5-$F_2C_6H_3$, R_2 = H [**1b**] and R_1 = C_6H_5, R_2 = Me [**1c**]) and subsequent treatment with LiBr gives the corresponding optically active cyclopalladated dimers **2**, $[Pd(C\text{-}N)Br]_2$. In all cases the endocyclic derivatives were formed selectively, even with the imine **1b**, which contains fluoro substituents on the carbon atom adjacent to the metallation position. The action of PPh_3 on the bromo bridged compounds **2** affords the mononuclear complexes **3**, $[PdBr(C\text{-}N)PPh_3]$.

Key words Cyclometallation · Optically active · Imines · Palladium · Chiral

Resumen La acción de acetato de paladio sobre las iminas derivadas de la *(R)*-1-feniletilamina, R_1R_2C=NCHMePh (R_1 = 4-ClC_6H_4, R_2 = H [**1a**]; R_1 = 3,5-$F_2C_6H_3$, R_2 = H [**1b**] y R_1 = C_6H_5, R_2 = Me [**1c**]) y posterior reacción con bromuro de litio da lugar a la formación de los correspondientes compuestos dímeros ciclopaladados ópticamente activos **2**, $[Pd(C\text{-}N)Br]_2$. En todos los casos se obtienen de forma selectiva los compuestos endocíclicos, incluso con la imina **1b**, que contiene sustituyentes en el átomo de carbono adyacente a la posición de metalación. La acción de la PPh_3 sobre los compuestos dímeros **2** da lugar a la formación de los compuestos monómeros **3**, $[PdBr(C\text{-}N)PPh_3]$.

Introduction

Cyclometallation reactions have been widely studied to obtain new organometallic compounds by the activation of C-H bonds [1], as well as for their applications in regiospecific organic synthesis [2]. In contrast, very few optically active cyclopalladated derivatives have been described in spite of their interesting applications. Optically active cyclopalladated derivatives have been used for optical resolution of racemic phosphines, arsines and amines [3] and for the determination by NMR spectroscopy of: a) the optical purity of chiral phosphines and amines [4], and b) the absolute configuration of chiral phosphines [5]. Furthermore, some applications of cyclopalladated compounds in asymmetric synthesis have been described [6].

Following and expanding our studies on the cyclometallation of Schiff bases, we describe here the preparation of a new series of optically active cyclopalladated compounds derived from (*R*)-1-phenylethylamine **1a-c**. Cyclopalladation of imines **1a-c** proceeds in reasonable yields (up to 70% yield), supplying a new series of optically active endocyclic cyclopalladated compounds.

Experimental

^1H NMR at 200 MHz and $^{31}P\{^1H\}$ at 101.26 MHz were recorded, respectively, on Varian Gemini 200 and Bruker DRX. Chemical shifts (in ppm) were measured relative to $SiMe_4$ for ^1H and to 85% H_3PO_4 for ^{31}P. The solvents used were $CDCl_3$ in ^1H and $CHCl_3$ in ^{31}P. Numbering refers to Chart 1. Microanalyses were performed at the Institut de Química Bio-Orgànica de Barcelona and the Serveis Científico-Tècnics de la Universitat de Barcelona.

Materials and syntheses

All solvents were dried by standard methods. (*R*)-(+)-1-phenylethylamine and aldehydes were commercial and used as received. Imine **1c** was prepared according to procedures described elsewere [7].

(R)-4-ClC$_6$H$_4$CH=NCHMeC$_6$H$_5$ [1a] and (R)-3,5-F$_2$C$_6$H$_3$CH=NCHMeC$_6$H$_5$ [1b]. Imines **1a,b** were prepared by an adaptation of one of the general methods [8]: 5 mmol of the appropriate aldehyde were treated with 5 mmols (2.424 g) of (*R*)-(+)-1-phenylethylamine in ethanol (30 ml) at reflux for 4 h and the resulting solutions concentrated *in vacuo*. The obtained residues contained the imines (>95%) and were used without further purification. Characterization data: **1a**, ^{1}H: 8.30 [s, 1H, C*H*=N], 7.70 [d, $^3J_{HH}$ = 8.0 Hz, 2H, H_3, H_5], 7.42-7.25 [m, 7H], 4.50 [q, $^3J_{HH}$ = 7.0 Hz, 1H, C*H*Me], 1.60 [d, $^3J_{HH}$ = 6.0 Hz, 3H, CH*Me*]. **1b**, ^{1}H: 8.30 [s, 1H, C*H*=N], 7.50-7.20 [m, 7H], 6.85 [m, 1H, H_4], 4.60 [q, $^3J_{HH}$ = 6.6 Hz, 1H; C*H*Me], 1.60 [d, $^3J_{HH}$ = 6.6 Hz, 3H, CH*Me*].

[Pd(2-{(R)-CH=NCHMeC$_6$H$_5$}-5-ClC$_6$H$_3$)Br]$_2$ [2a] [Pd(2-{(R)-CH=NCHMeC$_6$H$_5$}-4,6F$_2$C$_6$H$_3$)Br]$_2$ [2b] and [Pd(2-{(R)-CMe=NCHMeC$_6$H$_5$}C$_6$H$_4$)Br]$_2$ [2c]. A stirred suspension of Pd(AcO)$_2$ (2.2 mmol, 0.5 g) in acetic acid (25 ml) was treated with 2.2 mmol of the corresponding imine at 60 °C for 4 h and the resulting solution concentrated *in vacuo*. The reaction residue was treated with LiBr (3.26 mmol, 0.283 g) and the suspension stirred at room temperature for 30 min. The resulting solution was concentrated *in vacuo* to dryness and the solid obtained was eluted by SiO$_2$ column chromatography with CHCl$_3$/MeOH (100/2) as eluent. Compounds **2** were isolated as yellow powders in yields ranging from 50 to 70 %. Characterization data: **2a**, ^{1}H (major isomer): 7.65 [s, 2H, C*H*=N], 7.50-7.00 [m, 16H], 5.40 [q, $^3J_{HH}$ = 6.6 Hz, 2H, C*H*Me], 1.80 [br m, 6H, CH*Me*]. Anal. Calcd. for $C_{30}H_{26}Br_2Cl_2N_2Pd_2$: C, 41.98; H, 3.03; N, 3.27. Found: C, 41.8; H, 3.1; N, 3.2. **2b**, (major isomer) ^{1}H: 7.65 [s, 2H, C*H*=N], 7.50-7.20 [m, 10H], 6.80 [dd, 2H, $^3J_{HF}$= 7.0, $^4J_{HH}$= 2.6 Hz, H_6], 6.60 [m, 2H, $^3J_{HF}$= 7.0, $^4J_{HH}$= 2.6 Hz, H_4], 5.35 [m, 1H, C*H*Me], 1.70 [d, 6H, $^3J_{HH}$ = 6.6 Hz, CH*Me*]. Anal. Calcd. for $C_{30}H_{24}Br_2F_4N_2Pd_2$: C, 41.83; H, 2.79; N, 3.25. Found: C, 42.4; H, 2.9; N, 3.4. **2c**, ^{1}H (major isomer): 7.50-7.00 [m, 18 H], 4.60 [q, $^3J_{HH}$ = 6.6 Hz, 2H, C*H*Me], 2.05 s, 6H, *Me*C=N] 1.80 [br m, 6H, CH*Me*]. Anal. Calcd. for $C_{32}H_{32}Br_2N_2Pd_2$: C, 47.03; H, 3.95; N, 3.43. Found: C, 46.9; H, 4.1; N, 3.4.

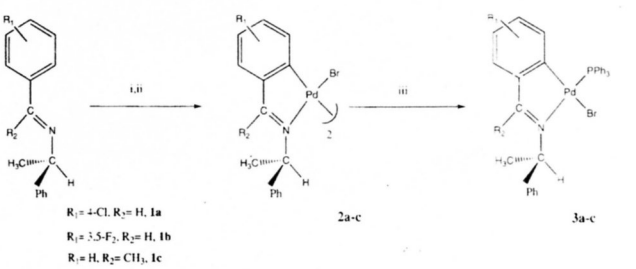
Reactions with py-d$_5$

20 mg of compound **2** were placed in an nmr tube, dissolved in 0.7 ml of CDCl$_3$ and the solution obtained was treated with an excess of py-d$_5$ (0.060 ml). Instantaneous change of colour indicated the quantitative transformation of compounds **2** in the monomers of general formula, [PdBr(C-N)py]. Characteriza-tion data: **2a+py-d$_5$**, ^{1}H: 7.75 [s, 1H, C*H*=N], 7.40-7.20 [m, 5H], 7.10-6.90 [m, 3H], 5.80 [br m, 1H, C*H*Me], 1.75 [d, $^3J_{HH}$= 7.0 Hz, 3H, CH*Me*]. **2b+py-d$_5$**, ^{1}H: 7.70 [s, 1H, C*H*=N], 7.50-7.30 [m, 5H], 6.80 [dd, 1H, $^3J_{HF}$= 7.0, $^3J_{HH}$= 2.4 Hz, H_6], 6.40 [m, 1H, $^3J_{HF}$= 7.0, $^4J_{HH}$= 2.6 Hz, H_4] 6.20 [q, $^3J_{HH}$ = 6.6 Hz, 1H, C*H*Me], 1.75 [d, 3H, $^3J_{HH}$ = 6.6 Hz, CH*Me*]. **2c+py-d$_5$**,^{1}H (major isomer): 7.50-6.70 [m, 9H], 4.70 [q, $^3J_{HH}$ = 6.6 Hz, 1H; C*H*Me], 2.00 [s, 3H, *Me*C=N] 1.80 [d, $^3J_{HH}$ = 6.6 Hz, 3H, CH*Me*].

[Pd(2-{(R)-CH=NCHMeC$_6$H$_5$}-5-ClC$_6$H$_3$)Br(PPh$_3$)] [3a] [Pd(2-{(R)-CH=NCHMeC$_6$H$_5$}-5-F$_2$C$_6$H$_3$)Br(PPh$_3$)] [3b] and [Pd(2-{(R)-CMe=NCHMeC$_6$H$_5$}C$_6$H$_4$)Br(PPh$_3$)] [3c]. A suspension formed by 0.12 mmols of **2**, 0.24 mmols of PPh$_3$ (0.062 g) and 20 ml of CHCl$_3$ was stirred at room temperature for 15 min and the resulting suspension or solution concentrated *in vacuo*. Addition of diethylether (10 ml) to the reaction residue produced the precipitation of compounds **3** as white or pale yellow solids in yields of 60 to 90%. Characterization data: **3a**, ^{1}H: 7.90-7.75 [m, 7H], 7.55-7.40 [m, 14H], 7.10 [d, $^3J_{HH}$ = 6.8Hz, 1H, H_5], 6.90 [d, $^3J_{HH}$ = 6.8Hz, 1H, H_6], 6.30 [s, 1H, H_3], 6.45 [q, $^3J_{HH}$= 7.0 Hz, 1H; C*H*Me], 1.80 [d, $^3J_{HH}$= 7.0 Hz, 3H, CH*Me*] ^{31}P: 40.7 s. Anal. Calcd. for $C_{33}H_{28}BrClNPdP$: C, 57.33; H, 4.08; N, 2.03. Found: C, 57.2; H, 4.3; N, 2.0. **3b**, ^{1}H: 7.90 [br s, 1H, *H*C=N], 7.75-7.50 [m, 6H], 7.50-7.30 [m, 14H], 6.80 [d, 1H, $^3J_{HF}$= 7.0, H_6], 6.45 [br m, 1H, H_4] 6.20 [br m 1H, C*H*Me], 1.80 [d, 3H, $^3J_{HH}$ = 6.6 Hz, CH*Me*]. ^{31}P: 35.1 br s. Anal. Calcd. for $C_{33}H_{27}BrF_2NPdP$: C, 57.21; H, 3.93; N, 2.02. Found: C, 56.9; H, 4.0; N, 1.9. **3c**, ^{1}H (major isomer): 7.85-7.60 [m, 6H], 7.50-7.25 [m, 15H], 7.15 [d, $^3J_{HH}$ = 7.5Hz, 1H, H_6], 6.90 [t, $^3J_{HH}$ = 7.5Hz, 1H, H_4], 6.60-6.50 [m, 2H, H_3, C*H*Me], 2.10 [s, 3H, *Me*C=N] 1.85 [d, $^3J_{HH}$ = 7.0 Hz, 3H, CH*Me*]. ^{31}P: 42.1 s. Anal. Calcd. for $C_{34}H_{31}BrNPdP$: C, 60.87; H, 4.65; N, 2.09. Found: C, 60.7; H, 4.5; N, 1.9.

Results and discussion

Imines **1** were treated with Pd(AcO)$_2$ in acetic acid for four hours at 60 °C. Subsequent treatment of the reaction residues with LiBr in ethanol afforded, after purification by SiO$_2$ column chromatography, the corresponding bromo bridged cyclopalladated dimers **2** (Scheme 1).



Scheme 1 i) Pd(AcO)$_2$, AcOH, 4h, 60°C; ii)LiBr, EtOH, 30 min, 20°C; iii) PPh$_3$, CHCl$_3$, 30 min, 20°C

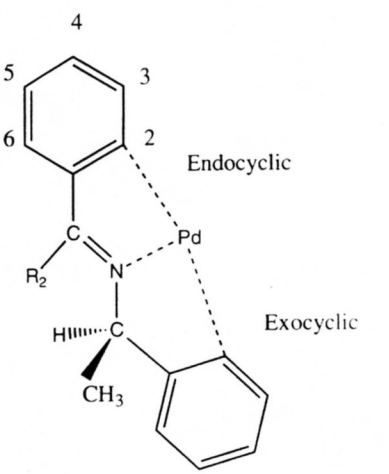


Chart 1

Schiff bases are capable of undergoing the metallation on different carbon atoms (see Chart 1) and it has been shown that there is a strong tendency to form endocyclic cyclometallated compounds (with the C=N bond contained in the metallacycle). This tendency, endo effect, is so strong that the action of $Pd(AcO)_2$ on the N-2,4,6-trimethylbenzylideneamines affords six-membered endometallacycles by activation of a C(aliphatic)-H bond in preference to the activation of a C(aromatic)-H bond with formation of a five-membered exo metallacycle [9]. Recently, it has become known that this endo effect is not restricted to cyclometallation reactions because the oxidative addition of *ortho* halogenated imines to palladium(0) or platinum(II) complexes preferentially affords the endo metallacycles [10].

Overall NMR data, chemical reactivity, and elemental analyses of compounds **2** show their endocyclic cyclopalladated nature. This fact is especially remarkable in the case of the imine **1b** because it has been shown that the presence of non-coordinating substituents in the carbon atom adjacent to the metallation position hinders the cyclometallation reaction. Thus, the action of $Pd(AcO)_2$ on N-2,5-dimethylbenzylideneaniline affords the six-membered endo-metallacycle by activation of a C(aliphatic)-H bond in preference to the formation of the five-membered endo-metallacycle by activation of the C(aromatic)-H bond adjacent to the methyl group [11], though there is a strong preference for five-membered metallacycles and also a higher tendency to activate C(aromatic)-H bonds than C(aliphatic)-H bonds. In addition, the cyclopalladation of 3,4-dimethoxybenzylideneamines occurs regioselectively at C_6, the less hindered carbon atom [12]. Recently, van Koten et al. [13] have shown that the cyclopalladation of 2-[(dimethylamino)-methyl]naphtalene occurs selectively at position 3 instead of the earlier reported metallation at position 1. These Authors propose that the sterical interference of the neighbouring substituents in the 1-metallated transition state may explain the clean palladation at carbon-3.

The ^{1}H-NMR spectra of **2a** and **2b** show two series of signals assignable to the metallated ring, as well as two methinic proton signals. When py-d_5 is added, the NMR spectra show that there is only one compound in solution, obviously the mononuclear complex [Pd(AcO)(C-N)(py-d_5)] [14]. In consequence, the two isomeric forms in solution of the bromo bridged compounds **2a** and **2b** are related to their dinuclear structure. This has previously been described for other cyclopalladated imine derivatives; the existence of two isomers in solution, one with a folded structure and the other with an unfolded structure, has been proposed to explain this [15]. The methinic proton signal appears at δ = 7.7-7.6, in good agreement with published results for endocyclic derivatives [11] and the methylenic proton signal is low-field shifted (1-1.2 ppm) in relation to the free ligand. This downfield shift can be explained by the paramagnetic anisotropy of the metal [16] and shows a close vicinity between palladium and this hydrogen atom.

When ^{1}H NMR spectrum of **2c** is recorded in the presence of deuterated pyridine two sets of signals are observed. This suggests the existence of two conformational isomers, probably due to the restricted rotation around the single nitrogen-carbon bond. It has been reported that there are analogous isomers in cyclopalladated compounds derived from ferrocenylimines [17]. The methylenic proton signal appears at δ = 4.60, very close to the shift of the free ligand, showing that this proton is far from the metal atom in this compound. Molecular models show that the presence of the methyl substituent in the methinic carbon gives place to a strong steric hindrance between this methyl and the substituents on the asymmetric carbon atom and, in consequence, the methylenic proton should be near the methinic methyl in the metallated derivatives of imine **1c**.

The action of PPh_3 on cyclopalladated dimers **2** in a 2 to 1 molar ratio gives the corresponding cyclopalladated monomers **3** (Scheme 1). The ^{1}H NMR spectrum of **3c** shows two sets of signals, confirming the existence of conformational isomers in the mononuclear derivatives of imine **1c**. The chemical shift of the phosphorus in the interval 41-42 ppm and the high-field shift of the aromatic protons of the palladated ring, due to the aromatic rings of PPh_3, show the *cis* disposition of the PPh_3 relative to the metallated carbon atom [11].

In conclusion, new optically active organometallic imine derivatives have been prepared by activation of a C(aromatic)-H bond with formation of a five-membered metallacycle. Studies on the application of these new complexes for asymmetric synthesis and the resolution of optically active amines or phosphines are currently in progress.

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