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Synthesis and characterization of orthopalladated complexes containing tridentate C,N,O-oxazolones

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ABSTRACT

The (*Z*)-4-aryliden-2-(2-acetoxyphenyl)-5(4*H*)oxazolones **1a-1c** react with H_2SO_4 to give the corresponding (*Z*)-4-aryliden-2-(2-hydroxyphenyl)-5(4*H*)oxazolones **2a-2c**.The molecular structures of **1c** and **2a** have been determined by X-ray diffraction methods, and show planar skeletons. Oxazolones **2a-2c** are potential C,N,O-tridentate ligands towards transition metals, and their molecular design obeys to the search of a rigid environment around the metal. The reaction of $Pd(OAc)_2$ with oxazolones **2a-2c** (1:1 M ratio) in CF_3CO_2H or NCMe as solvents results in the synthesis of diverse complexes (**3**–**7**). As a function of the reaction conditions, two different bonding modes have been characterized: N,O-chelate in the dinuclear complexes $[Pd(\kappa^2\text{-N,O-}\mathbf{2b,c})(\mu\text{-}O_2CCF_3)]_2$ (**3b,c**), as a result of the *N*-coordination and deprotonation of the hydroxy group; and C,N,O-tridentate in mononuclear complexes $[Pd(\kappa^3\text{-C,N,O-}\mathbf{2a,b})(L)]$ (L = CF_3CO_2H **4a,b**; dmso-d_6 **5a,b**; NCMe **6b**; pyridine **7b**), obtained after *N*-bonding, OH deprotonation and C—H bond activation. All complexes have been fully characterized by HRMS and NMR methods, showing the high stability of the C,N,O-tridentate bonding mode.

1. Introduction

(*Z*)-4-arylidene-5(4*H*)-oxazolones are versatile compounds that have been extensively studied due to their numerous applications [1]. From the point of view of the synthesis, they have been used as precursors of amino acids such as phenylalanine [2], or as key intermediates in a wide variety of organic syntheses [3]. The photophysical properties of (*Z*)-4-arylidene-5(4*H*)-oxazolones are also of high interest, because they behave as light-responsive molecular switches [4], and shows two-photon absorption and non-linear responses [5]. Beyond that, the photochemical reactivity of oxazolones, almost unknown until recently, has started to give outstanding results with the facile synthesis of 1,3-diaminotruxillic and 1,2-diaminotruxinic cyclobutane derivatives [6]. All those facts show that the significance and interest of oxazolones in different fields is undeniable.

We are interested in the study of the incorporation of transition metals to the oxazolone scaffold due to several reasons, all of them connected with the three reported applications of these substrates, and we have made contributions in all aspects previously mentioned. The C—H functionalization of oxazolones lies on the basis of the understanding of how and where the metal is incorporated to this organic skeleton. We have performed detailed studies about the selectivity of the orthopalladation through C—H activation in carboxylic acids, and the further reactivity of these complexes to give functionalized oxazolones [7]. With respect to the photophysical properties of oxazolones, their fluorescent emission has been reported, but it is significant only in solid state or when the oxazolone is embedded in a very rigid environment, in a similar way to what has been reported for structurally analogous imidazolones. In absence of a tight environment (for instance in solution) the almost complete loss of the fluorescence takes place, due to the concurrence of different non-radiative pathways related with internal rearrangements, such as *Z/E*-isomerization or hula-twist [8]. The suppression of these molecular motions by simultaneous bonding of B, Zn or Cd to the arylidene and heterocyclic rings results in a remarkable increase of the fluorescence, as it has been shown by the works of Burgess, Tolbert and Yampolski in related 5(4*H*)-imidazolones [9]. We have also contributed to this field, showing that the incorporation of the Pd atom as intramolecular lock can amplify the fluorescence of free oxazolones and imidazolones up to an order of magnitude [10]. Unfortunately, this is not a general trend, because we have also provided evidence that the presence of the Pd is necessary to amplify the fluorescence, but not sufficient by itself, and that we need to gain more information about

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these systems. Last but not least, the photochemical reactivity of orthopalladated oxazolones has allowed the stereoselective synthesis of the epsilon isomer of 1,3-diaminotruxillic derivatives in three steps [11], namely the C—H bond activation of the oxazolone, the irradiation with blue light of the resulting dinuclear derivative to give the metallated truxillic cyclobutane, and their final liberation by hydrogenation, halogenation or alkoxycarbonylation. The variety of involved processes and the improvements achieved in all fields in terms of activity and selectivity justifies clearly the studies about the metallation of oxazolones.

All examples reported up to now deal with C,*N*-bidentate oxazolones (Fig. 1, past work) and, as far as we know, there are no examples with oxazolones showing a higher denticity [7–11]. Aiming to expand the synthetic diversity of the oxazolones, we have started to explore the reactivity of multidentate oxazolones towards Pd derivatives. One interesting substrate is the oxazolone that contain an hydroxy group in ortho position of the 2-phenyl ring (Fig. 1, this work), because this ligand could, in principle, act as a C,N,O-tridentate pincer ligand and immobilize the metal in a rigid environment. The interest of non-symmetric pincer ligands in different fields has been highlighted recently [12], and pincer ligands based on oxazolones are unknown. In this contribution we report the synthesis and full characterization of three representatives of this family of oxazolones and their reactivity with $Pd(OAc)_2$, which allowed the synthesis of the orthopalladated pincer complexes.

2. Experimental

2.1. Materials and methods

All reactions were performed without special precautions against air and moisture. Solvents were obtained from commercial sources and were used without further purification. Electrospray ionization (ESI^+) mass spectra were recorded using Bruker Esquire3000 plus™ or Amazon Speed ion-trap mass spectrometers equipped with standard ESI sources. High-resolution mass spectra-ESI (HRMS-ESI) were recorded using either a Bruker MicroToF-Q™ system equipped with an API-ESI source and a Q-ToF mass analyzer, or a TIMS-TOF system, both allowing a maximum error in the measurement of 5 ppm. Acetonitrile was used as solvent. For all types of MS measurements, samples were introduced in a continuous flow of 0.2 mL/min and nitrogen served both as the nebulizer gas and the dry gas. The ^1H, $^{13}C\{^1H\}$ and ^{19}F NMR spectra were recorded on a Bruker Avance-300 spectrometer (δ in ppm; J in Hz). All experiments were recorded in solution at room temperature using $CDCl_3$, CD_2Cl_2 or DMSO-d_6 as the deuterated solvents. Other conditions are specified for each particular case. The ^1H and $^{13}C\{^1H\}$ spectra were referenced using the residual solvent signal as the internal standard, while ^{19}F spectra were referenced to $CFCl_3$. Assignment was performed, when necessary, with the help of the following 2D-NMR experiments: ^1H–^1H gCOSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC. Elemental analyses were determined on a Perkin-Elmer 2400 SeriesII CHNS/O Analyzer. Absorption spectra were measured on a Thermo Scientific Evolution 600BB spectrophotometer. All measurements were carried out at room temperature on solutions of 10^{-5} M concentration in CH_2Cl_2 using quartz cuvettes of 1 cm path length. The oxazolones **1a** and **1b** were prepared using the Erlenmeyer–Plöchl method [13].

Single crystals of **1c** and **2a** of suitable quality for X-ray diffraction measurements were grown by slow evaporation of $CDCl_3$ solutions of the respective products at room temperature. One selected single crystal of each species was mounted at the end of a quartz fiber in a random orientation, covered with perfluorinated oil (magic oil) and placed under a cold stream of N_2 gas. Crystallographic measurements were carried out at 100 K on a Bruker D8 Venture (**1c**) or at 120 K on a Bruker APEX DUO (**2a**) CCD diffractometers, using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). A hemisphere of data was collected in each case based on ω-scan or φ-scan runs. The diffraction frames were integrated using the program SAINT [14] and the integrated intensities were corrected for absorption with SADABS [15]. The structures were solved by direct methods with SHELXT-2014 [16]. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed at idealized positions and treated as riding atoms. Each hydrogen atom was assigned an isotropic displacement parameter equal to 1.2–1.5 times the equivalent isotropic displacement parameter of its parent atom. For structure solving and refinement, the SHELXL-2016 [17] program in the WINGX Package was used [18]. The structures were refined to F_o^2, and all reflections were used in the least-squares calculations.

2.2. General Synthesis and Characterization of Oxazolones *1a-1c*

The oxazolones **1a** [19] and **1b** [20] have been previously reported. The oxazolone **1c** has not been previously reported so it has been fully characterized here. The three oxazolones were prepared following the Erlenmeyer-Plöchl method, which is exemplified here with the detailed synthesis of **1a** [13].

2.2.1. Synthesis of (Z)-4-benzylidene-2-(2-acetoxyphenyl)-5(4H)-oxazolone (*1a*)

Sodium acetate (420.0 mg, 5.15 mmol) and benzaldehyde (0.53 mL, 5.20 mmol) were added to a solution of 2-hydroxyhippuric acid (1000.0 mg, 5.12 mmol) in acetic anhydride (5 mL). The suspension was heated in an oil bath to the reflux temperature (100 °C) for 3 h, and then was allowed to cool to room temperature. The solid mass formed upon cooling was treated with distilled water (30 mL) to give **1a** as a yellow solid, which was filtered off, washed with water (5 mL) and cold ethanol (10 mL), and dried under vacuum. Obtained: 882.0 mg (56% yield).

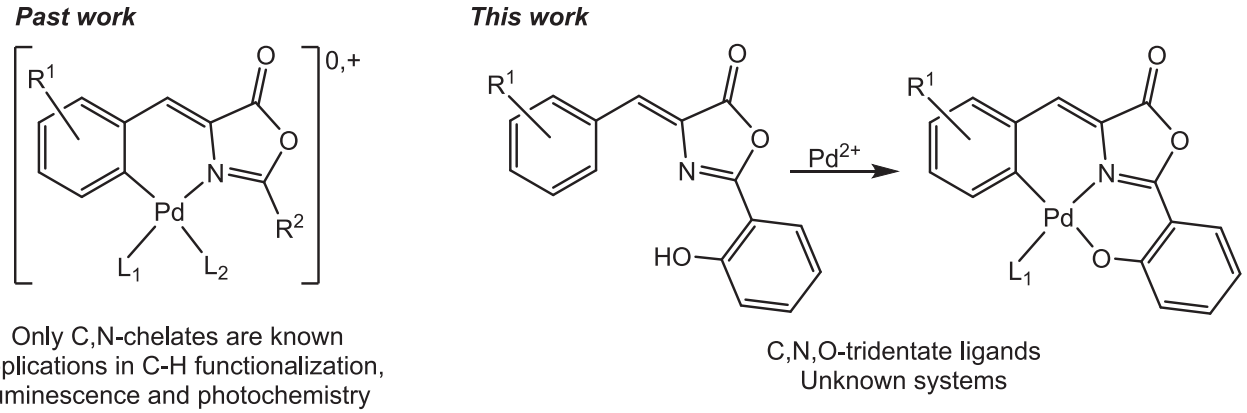


Fig. 1. Past work performed up-to-now in oxazolones, where only C,*N*-chelating systems have been reported, and new tridentate systems used in this work.

2.2.2. Synthesis of (Z)-4-(3,4-dimethoxybenzylidene)-2-(2-acetoxyphenyl)-5(4H)-oxazolone (1b)

Oxazolone **1b** was prepared following the same procedure than that reported for **1a**. Therefore, sodium acetate (420.0 mg, 5.15 mmol), 3,4-dimethoxybenzaldehyde (851.0 mg, 5.12 mmol) and 2-hydroxyhippuric acid (1000.0 mg, 5.12 mmol) reacted in acetic anhydride (5 mL) at the reflux temperature to give **1b** as an orange solid. Obtained: 670.0 mg (36% yield).

2.2.3. Synthesis of (Z)-4-(2,4-dimethoxybenzylidene)-2-(2-acetoxyphenyl)-5(4H)-oxazolone (1c)

Oxazolone **1c** was prepared following the same procedure than that reported for **1a**. Therefore, sodium acetate (420.0 mg, 5.15 mmol), 2,4-dimethoxybenzaldehyde (864.0 mg, 5.20 mmol) and 2-hydroxyhippuric acid (1000.0 mg, 5.12 mmol) reacted in acetic anhydride (5 mL) at the reflux temperature to give **1c** as a yellow solid. Obtained: 645.0 mg (34% yield). ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ: 8.73 (d, J = 8.8 Hz, 1H, H_6, C_6H_3), 8.15 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H, H_5, C_6H_4), 7.81 (s, 1H, $=CH_{vinyl}$), 7.58 (td, J = 8.1 Hz, J = 1.8 Hz, 1H, H_4, C_6H_4), 7.40 (td, J = 8.0 Hz, J = 1.2 Hz, 1H, H_6, C_6H_4), 7.19 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H, H_3, C_6H_4), 6.59 (dd, J = 8.8, J = 2.4 Hz, 1H, H_5, C_6H_3), 6.43 (d, J = 2.4 Hz, 1H, H_3, C_6H_3), 3.89 (s, 3H, OMe), 3.88 (s, 3H, OMe), 2.41 (s, 3H, Me). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.47 MHz) δ: 169.7 (OC═O), 167.7 (C═O), 164.5 ($C_{2/4}$-OMe, C_6H_3), 163.2 ($C_{2/4}$-OMe, C_6H_3), 159.4 (C═N), 149.9 (C_2-OCO, C_6H_4), 134.7 (C_6, C_6H_3), 133.7 (C_4, C_6H_4), 130.8 (C_5, C_6H_4), 129.8 (═C), 127.5 (═CH, C_{vinyl}), 126.6 (C_6, C_6H_4), 124.4 (C_3, C_6H_4), 119.6 (C_1, C_6H_4), 116.1 (C_1, C_6H_3), 106.3 (C_5, C_6H_3), 97.7 (C_3, C_6H_3), 55.8 (OMe), 55.7 (OMe), 21.5 (Me). HRMS (ESI$^+$) m/z: $[M + Na]^+$ Calc for $[C_{20}H_{17}NO_6Na]$ 390.0954; found: 390.0949. Anal. Calc. for $C_{20}H_{17}NO_6$ (%): C, 65.39; H, 4.66; N, 3.81. Found: C, 64.99; H, 4.77; N, 4.00 (%).

2.3. General Synthesis and Characterization of Oxazolones 2a-2c

The oxazolones **2a-2c** have not been previously reported, or they appear on Scifinder without a full characterization associated, so they have been prepared [21,22] and fully characterized here.

2.3.1. Synthesis of (Z)-4-benzylidene-2-(2-hydroxyphenyl)-5(4H) oxazolone (2a)

Oxazolone **1a** (682 mg, 2.223 mmol) was added during 2 min to a stirred and ice-cooled mixture of sulphuric acid (96%; 10 mL) in water (2 mL). The stirring and cooling were continued for 40 min, then the reaction mixture was poured onto ice (25 g) and dichloromethane (25 mL). On warming to room temperature, the layers separated. The organic layer was separated, washed with 10 mL of a saturated solution of aqueous $NaHCO_3$, and dried using anhydrous $MgSO_4$. The resulting solution was evaporated to give **2a** as a yellow solid. Obtained: 503.0 mg (85% yield). ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ: 11.09 (s, 1H, OH), 8.15 (m, 2H, H_o, C_6H_5), 7.81 (dd, J = 8.0 Hz, J = 1.7 Hz, 1H, H_6, C_6H_4), 7.55–7.48 (m, 4H, H_4, C_6H_4, H_m + H_p, C_6H_5), 7.29 (s, 1H, $=CH_{vinyl}$), 7.10 (dd, J = 8.5 Hz, J = 1.0 Hz, 1H, H_3, C_6H_4), 7.08 (td, J = 8.0 Hz, J = 1.1 Hz, 1H, H_5, C_6H_4). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.47 MHz) δ: 165.4 (C═O), 164.9 (C═N), 160.9 (C-OH), 135.9 (C_4, C_6H_4), 133.1 (C_i, C_6H_5), 131.9 (C_o, C_6H_5), 131.7 (C_p, C_6H_5), 131.5 (═CH, C_{vinyl}), 130.3 (═C), 129.3 (C_m, C_6H_5), 128.7 (C_6, C_6H_4), 120.2 (C_5, C_6H_4), 117.7 (C_3, C_6H_4), 108.8 (C_1, C_6H_4). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $[C_{16}H_{12}NO_3]$: 266.0819; found: 266.0813. Anal. Calc. for $C_{16}H_{11}NO_3$ (%): C, 72.45; H, 4.18; N, 5.28. Found: C, 72.43; H, 4.50; N, 5.04 (%).

2.3.2. Synthesis of (Z)-4-(3,4-dimethoxybenzylidene)-2-(2-hydroxyphenyl)-5(4H)oxazolone (2b)

Oxazolone **2b** was prepared following the same procedure than that reported for **2a**, but starting from oxazolone **1b** (650 mg, 1.77 mmol). Yellow solid. Obtained: 500.0 mg (87% yield). Compound **2b** is characterized as two rotamers by ^{1}H–^{1}H NOESY. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ: 11.11 (s, 1H, OH, N···H rotamer), 10.90 (s, 1H, OH, O···H rotamer), 8.28 (d, J = 2 Hz, 1H, H_{ar}, N···H rotamer), 7.75–7.72 (m, 2H, H_{ar}, both rotamers), 7.67 (dd, J = 8.0 Hz, J = 1.7 Hz, H_{ar}, O···H rotamer), 7.49–7.38 (m, 4H, 2H_{ar} N···H rotamer, H_{ar} O···H rotamer, $=CH_{vinyl}$, N···H rotamer), 7.33 (dd, J = 8.4 Hz, J = 2 Hz, 1H, H_{ar}, O···H rotamer), 7.16 (s, 1H, $=CH_{vinyl}$, O···H rotamer), 7.05–6.99 (m, 2H, H_{ar}, both rotamers), 6.95 (m, 2H, H_{ar}, both rotamers), 6.90–6.87 (m, 2H, H_{ar}, both rotamers), 3.97 (s, 6H, OMe, both rotamers), 3.92 (s, 6H, OMe, both rotamers). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.47 MHz, N···H rotamer) δ: 165.5 (C═O), 163.3 (C═N), 160.6 (C-OH), 152.7 (C-OMe), 149.4 (C-OMe), 140.3 (CH_{ar}), 134.7 (CH_{ar}), 128.9 (═C), 128.4 (CH_{ar}), 127.8 (CH_{ar}), 126.3 (C_1, C_6H_3), 120.1 (CH_{ar}), 117.6 (CH_{ar}), 113.4 (CH_{ar}), 111.1 (CH_{ar}), 109.0 (C_1, C_6H_4), 56.1 (OMe), 55.9 (OMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.47 MHz, O···H rotamer) δ: 163.6 (C═O), 161.0 (C═N), 160.0 (C—OH), 152.4 (C—OMe), 149.0 (C—OMe), 135.4 (CH_{ar}), 131.6 (CH_{ar}), 128.4 (CH_{ar}), 127.8 (═C), 127.7 (CH_{ar}), 126.1 (C_1, C_6H_3), 119.8 (CH_{ar}), 117.5 (CH_{ar}), 112.6 (CH_{ar}), 110.8 (CH_{ar}), 108.9 (C_1, C_6H_4), 56.1 (2C, OMe). HRMS (ESI$^+$) m/z: $[M + Na]^+$ Calcd for $[C_{18}H_{15}NO_5Na]$: 348.0842; found: 348.0837. Anal. Calc. for $C_{18}H_{15}NO_5$ (%): C, 66.46; H, 4.65; N, 4.31. Found: C, 66.35; H, 4.35; N, 3.82 (%).

2.3.3. Synthesis of (Z)-4-(2,4-dimethoxybenzylidene)-2-(2-hydroxyphenyl)-5(4H)oxazolone (2c)

Oxazolone **2c** was prepared following the same procedure than that reported for **2a**, but starting from oxazolone **1c** (645 mg, 1.76 mmol). Yellow solid. Obtained: 270.1 mg (47% yield). ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ: 11.20 (s, 1H, OH), 8.36 (d, J = 8.8 Hz, 1H, H_6, C_6H_3), 7.82 (s, 1H, $=CH_{vinyl}$), 7.80 (dd, J = 8.1 Hz, J = 1.7 Hz, 1H, H_6, C_6H_4), 7.48 (td, J = 8.7 Hz, J = 1.7 Hz, 1H, H_4, C_6H_4) 7.08 (dd, J = 8.4 Hz, J = 1.0 Hz, 1H, H_3, C_6H_4), 7.00 (td, J = 8.1 Hz, J = 1.0 Hz, 1H, H_5, C_6H_4), 6.65 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H, H_5, C_6H_3), 6.46 (d, J = 2.4 Hz, 1H, H_3, C_6H_3), 3.91 (s, 3H, OMe), 3.90 (s, 3H, OMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.47 MHz) δ: 166.0 (C═O), 164.6 ($C_{2/4}$-OMe, C_6H_3), 163.2 (C═N), 161.4 ($C_{2/4}$-OMe, C_6H_3), 160.3 (C_2-OH, C_6H_4), 135.2 (C_4, C_6H_4), 133.3 (C_6, C_6H_3), 128.4 (C_6, C_6H_4), 127.1 (═C), 126.2 (═CH, C_{vinyl}), 120.1 (C_5, C_6H_4), 117.6 (C_3, C_6H_4), 115.8 (C_1, C_6H_3), 109.3 (C_1, C_6H_4), 106.5 (C_5, C_6H_3), 98.2 (C_3, C_6H_3), 55.9 (OMe), 55.8 (OMe). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $[C_{18}H_{16}NO_5]$: 326.1028; found: 326.1023.

2.4. Synthesis and characterization of the N,O-chelates 3b and 3c

Synthesis of Trifluoroacetate-bridge complex ***3b***. $Pd(OAc)_2$ (70.1 mg, 0.308 mmol) was added to a solution of **2b** (100.0 mg, 0.308 mmol) in CF_3CO_2H (5 mL). The resulting mixture was stirred at room temperature during 4 h. After the reaction time, distilled water (10 mL) was added. The solid precipitated was filtered off, washed with more distilled water (3 × 10 mL) until the characteristic smell of trifluoroacetic acid disappeared, dried under vacuum, and identified as **3b** (orange solid). Obtained: 115.0 mg (69% yield). ^{1}H NMR (CD_2Cl_2, 300.13 MHz) δ: 7.92 (s, 1H, H_{ar}), 7.74 (s, 1H, H_{ar}), 7.58 (d, J = 8.0 Hz, 1H, H_{ar}), 7.37 (d, J = 7.6 Hz, 1H, H_{ar}), 7.20 (t, J = 7.9 Hz, 1H, H_{ar}), 6.98 (d, J = 8.7 Hz, 1H, H_{ar}), 6.83 (t, J = 7.6 Hz, 1H, H_{ar}), 6.64 (d, J = 8.7 Hz, 1H, H_{ar}), 3.95 (s, 3H, OMe), 3.93 (s, 3H, OMe). ^{19}F NMR (282.40 MHz, CD_2Cl_2) δ: −74.37 (CF_3). HRMS (ESI$^+$) m/z: [M−TFA + MeCN]$^+$ Calcd for $[C_{40}H_{33}N_3F_3O_{12}Pd_2]$: 1015.9934; found: 1015.9969. Anal. Calc. for $C_{40}H_{28}F_6N_2O_{14}Pd_2$ (%): C, 44.18; H, 2.60; N, 2.58. Found: C, 44.26; H, 2.58; N, 2.83 (%).

Synthesis of Trifluoroacetate bridge complex ***3c***. Compound **3c** was obtained following the same experimental procedure than that described for **3b**. Thus, $Pd(OAc)_2$ (35.0 mg, 0.154 mmol) was reacted with **2c** (50.0 mg, 0.154 mmol) in CF_3CO_2H (5 mL) to give **3c** as an orange solid. Obtained: 65.0 mg (78% yield). ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ: 8.37 (d, J = 9.0 Hz, 1H, H_{ar}), 7.83–7.79 (m, 2H, H_{ar}), 7.49 (t, J = 7.5 Hz, 1H, H_{ar}), 7.09 (d, J = 8.5 Hz, 1H, H_{ar}), 7.00 (t, J = 7.4 Hz, 1H, H_{ar}), 6.65 (dd, J = 8.9 Hz, J = 2.0 Hz 1H, H_{ar}), 6.47 (d, J = 2.0 Hz, 1H, H_{ar}), 3.91 (s, 3H, OMe), 3.90 (s, 3H, OMe). ^{19}F NMR (282.40 MHz,

$CDCl_3$): δ = −75.51 (CF_3). HRMS (ESI^+) *m/z*: $[M-2TFA + Na]^+$ Calcd for $[C_{26}H_{28}N_2O_{10}Pd_2Na]$: 882.9726; found: 882.9737.

2.5. General synthesis and characterization of C,N,O-tridentate orthopalladated complexes 4–7

2.5.1. Synthesis of Orthopalladated 4a

$Pd(OAc)_2$ (43.0 mg, 0.189 mmol) was added to a solution of **2a** (50.0 mg, 0.189 mmol) in CF_3CO_2H (5 mL), and the resulting mixture was stirred for 30 min at room temperature. After the reaction time, distilled water (10 mL) was added. The resulting precipitated solid was filtered, washed with more distilled water (3 × 10 mL) until the characteristic smell of trifluoroacetic acid disappeared, dried under vacuum, and identified as **4a**. Yellow solid. Obtained: 70.0 mg (77% yield). Complex **4a** showed to be soluble only in dmso-d_6, where it transforms into **5a** (see main text). Therefore, the NMR data given here correspond to complex **5a**. ^1H NMR (DMSO-d_6, 300.13 MHz) δ: 8.02 (m, 1H, PdC_6H_4), 7.80 (dd, $J = 8.5$ Hz, $J = 1.5$ Hz, 1H, H_6, C_6H_4O), 7.76 (s, 1H, $=CH_{vinyl}$), 7.65 (m, 1H, PdC_6H_4), 7.50 (t, $J = 8.0$ Hz, 1H, H_4, C_6H_4O), 7.25 (m, 2H, PdC_6H_4), 7.01 (d, $J = 8.7$ Hz, 1H, H_3, C_6H_4O), 6.72 (t, $J = 7.7$ Hz, 1H, H_5, C_6H_4O). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75.47 MHz) δ: 168.6 (C_2-O, C_6H_4O), 162.4 (C═O), 158.2 (C═N), 140.8 (═C), 135.6 (C_4, C_6H_4O), 134.5 (PdC_6H_4), 132.6 (PdC_6H_4), 130.7 (C_2, PdC_6H_4), 130.6 (═CH, C_{vinyl}), 128.6 (C_6, C_6H_4O), 128.5 (PdC_6H_4), 124.7 (PdC_6H_4), 123.3 (C_3, C_6H_4O), 119.9 (C-Pd, PdC_6H_4), 114.9 (C_5, C_6H_4O), 106.6 (C_1, C_6H_4O). ^{19}F NMR (DMSO-d_6, 282.40 MHz) δ: −75.0 (CF_3). HRMS (ESI^+) *m/z*: $[M-CF_3CO_2H + H]^+$ Calcd for $[C_{16}H_{10}NO_3Pd]$: 369.9696; found: 369.9682. For **4a**: Anal. Calc. for $C_{18}H_{10}F_3NO_5Pd$ (%): C, 44.70; H, 2.08; N, 2.90. Found: C, 44.56; H, 2.30; N, 3.15 (%).

2.5.2. Synthesis of Orthopalladated 4b

Method (a): $Pd(OAc)_2$ (70.1 mg, 0.308 mmol) was added to a solution of **2b** (100.0 mg, 0.308 mmol) in CF_3CO_2H (5 mL). The resulting mixture was heated in an oil bath to the reflux temperature during 4.5 h. After the reaction time, distilled water (10 mL) was added. The resulting precipitated solid was filtered off, washed with more distilled water (3 × 10 mL) until the characteristic smell of trifluoroacetic acid disappeared, dried under vacuum, and identified as **4b**. Orange solid. Obtained: 140.0 mg (84% yield). Method (b): Complex **3b** (50 mg, 0.046 mmol) was suspended in CF_3CO_2H (4 mL), and the resulting suspension was heated in an oil bath at the reflux temperature for 3 h. After the reaction time, the cooled solution was treated with distilled water as in method (a), giving **4b** as an orange solid. Obtained: 35 mg (70% yield). Complex **4b** dissolved only in dmso-d_6, where it transforms into **5b** (see text). Therefore, the NMR data given here correspond to complex **5b**. ^1H NMR (DMSO-d_6, 300.13 MHz) δ: 7.80 (dd, $J = 8.5$ Hz, $J = 1.8$ Hz, 1H, H_6, C_6H_4), 7.76 (s, 1H, $=CH_{vinyl}$), 7.68 (s, 1H, H_6, C_6H_2), 7.48 (ddd, $J = 8.7$ Hz, $J = 8.1$ Hz, $J = 1.8$ Hz, 1H, H_4, C_6H_4), 7.34 (s, 1H, H_3, C_6H_2), 7.02 (d, $J = 8.7$ Hz, 1H, H_3, C_6H_4), 6.72 (td, $J = 8.1$ Hz, $J = 1.0$ Hz, 1H, H_5, C_6H_4), 3.86 (s, 3H, OMe), 3.78 (s, 3H, OMe). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75.47 MHz) δ: 167.9 (C_2-O, C_6H_4O), 163.8 (C═O), 157.2 (C═N), 149.1 ($C_{4/5}$-OMe, C_6H_2), 146.5 ($C_{4/5}$-OMe, C_6H_2), 135.3 (═C), 135.1 (C_4, C_6H_4O), 131.2 (═CH, C_{vinyl}), 128.3 (C_6, C_6H_4O), 123.8 (C_2, C_6H_2), 123.2 (C_3, C_6H_4O), 117.3 (C_1-Pd, C_6H_2), 116.4 (C_6 C_6H_2), 114.9 (2C overlapped,C_3, C_6H_2 + C_5, C_6H_4O), 106.8 (C_1, C_6H_4O), 55.4 (s, OMe), 55.3 (s, OMe). ^{19}F NMR (282.40 MHz, DMSO-d_6) δ: −74.99 (CF_3). HRMS (ESI^+) *m/z*: $[M-CF_3CO_2H + H]^+$ Calcd for $[C_{18}H_{14}NO_5Pd]$: 429.9907; found: 429.9902. For **4b** Anal. Calc. for $C_{20}H_{14}F_3NO_7Pd$ (%): C, 44.18; H, 2.60; N, 2.58. Found: C, 43.82; H, 2.43; N, 2.76 (%).

2.5.3. Synthesis of Orthopalladated 6b

$Pd(OAc)_2$ (35.0 mg, 0.154 mmol) was added to a solution of **2b** (50.0 mg, 0.154 mmol) in MeCN (5 mL). The resulting mixture was heated in an oil bath for 4 h to the reflux temperature of the solvent (82 °C). After the reaction time, distilled water (10 mL) was added to the cooled suspension. The resulting precipitated solid was filtered off, dried under vacuum, and identified as **6b**. Red solid. Obtained: 59.0 mg (82% yield). Complex **6b** was also totally insoluble in common deuterated solvents, except in dmso-d_6. The ^1H NMR spectrum of **6b** in dmso-d_6 is identical to that observed for **4b** in dmso-d_6 (an additional peak at 2.07 ppm due to free NCMe was observed), suggesting the formation of **5b**.

2.5.4. Synthesis of Orthopalladated 7b

Pyridine (7.5 μL, 0.095 mmol) was added to a stirred suspension of **4b** (50.0 mg, 0.092 mmol) in CH_2Cl_2 (10 mL) at room temperature. The color of the starting suspension quickly changed from red to orange. The mixture was further stirred for 30 min at room temperature, but no additional changes were observed. The orange suspension was filtered, and the obtained orange solid of **7b** was dried under vacuum. Obtained: 25.1 mg (54% yield). ^1H NMR (CD_2Cl_2, 300.13 MHz) δ: 9.10 (m, 2H, H_o, C_5H_5N), 8.05 (t, $J = 8.0$ Hz, 1H, H_p, C_5H_5N), 7.92 (d, $J = 8.6$ Hz, 1H, C_6H_4), 7.62–7.57 (m, 3H, H_m, C_5H_5N + $=CH_{vinyl}$), 7.42 (t, $J = 8.1$ Hz, 1H, C_6H_4), 7.01 (s, 1H, H_3, C_6H_2), 6.95 (d, $J = 8.8$ Hz, 1H, C_6H_4), 6.75 (t, $J = 7.5$ Hz, 1H, C_6H_4), 6.12 (s, 1H, H_6, C_6H_2), 3.85 (s, 3H, OMe), 3.38 (s, 3H, OMe). HRMS (ESI^+) *m/z*: $[M-NC_5H_5 + Na]^+$ Calcd for $[C_{18}H_{13}NNaO_5Pd]$: 451.9726; found: 451.9716.

3. Results and discussion

The oxazolones **1a-1c** have been prepared following the Erlenmeyer-Plöchl method, by reaction of the 2-hydroxyhippuric acid with the corresponding benzaldehyde, in presence of NaOAc and using acetic anhydride as solvent [13]. We have selected oxazolones with strong electrodonating groups at the 4-arylidene ring, aiming to favor the C—H bond activation. Due to the use of acetic anhydride as solvent, the acetylation of the hydroxy group in the starting 2-hydroxyhippuric acid is unavoidable, and oxazolones **1a-1c** appear protected at this position, as it is evident from the NMR data and from the X-ray crystal structure of **1c**, which is shown in Fig. 2.

The removal of the acetyl group has been achieved by treatment with H_2SO_4, following known procedures [21,22]. The synthesis of 2-(*ortho*-hydroxyphenyl)-oxazolones has been a controversial issue [21], but the method followed here affords the expected deprotected species in moderate to good yields (47–85%). The process is shown in Scheme 1.

The characterization of oxazolones **2a-2c** has been carried out following their HRMS and NMR data (see Experimental and Supplementary Material). The ^1H NMR spectra of **2a-2c,** which do not change at low T (258 K), show the presence of a peak strongly shifted downfield, appearing at about 11 ppm, showing a very thin lineshape. This peak is assigned to the OH proton, due to its deshielded position, while the thin lineshape suggest a rigid environment, probably due to the involvement of this group in an intramolecular H-bond with the heterocyclic N atom. This fact will be confirmed by the determination of the X-ray crystal structure of **2a** (see below). Intramolecular H-bonds between the heterocyclic nitrogen and OH moieties have been reported for oxazolones and imidazolones [23,24], although all of them have the OH group in the arylidene ring, so none of them are of the type here reported. In the case of **2b** two sets of signals are observed in $CDCl_3$, suggesting the formation of two isomers. This fact is observed only in **2b**, and we are unaware for the reasons of this particular behaviour. The lineshape of the two peaks at low field, assigned to the OH protons, is quite different (see Supplementary Material), suggesting different environments. The ^1H–^1H NOESY spectrum of **2b** in $CDCl_3$ shows cross-peaks between the signals due to the two OH protons, meaning that these protons exchange their positions between the two isomeric forms in the scale of time of the technique. Different types of isomers can be invoked to explain this observation, such as rotamers, *Z/E*-conformational isomers or even tautomers. The presence of *Z/E*-isomers can be discarded because the dynamic exchange of the H positions is produced in solution at room temperature in absence of light or heating. Direct evidences suggesting the presence of rotamers, as shown in Fig. 3, are obtained from the ^1H-^{15}N HMQC 2D correlation spectrum of **2b** (Suppl. Material).

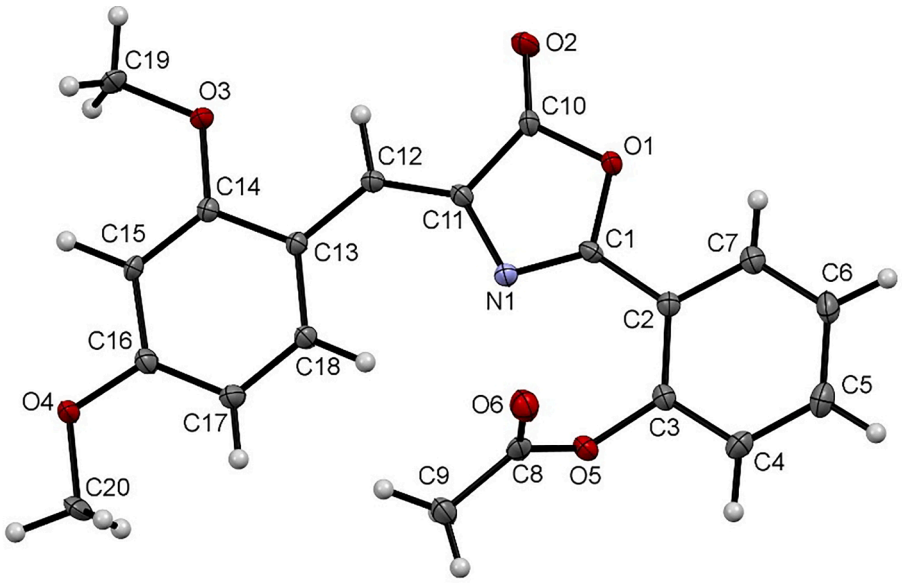
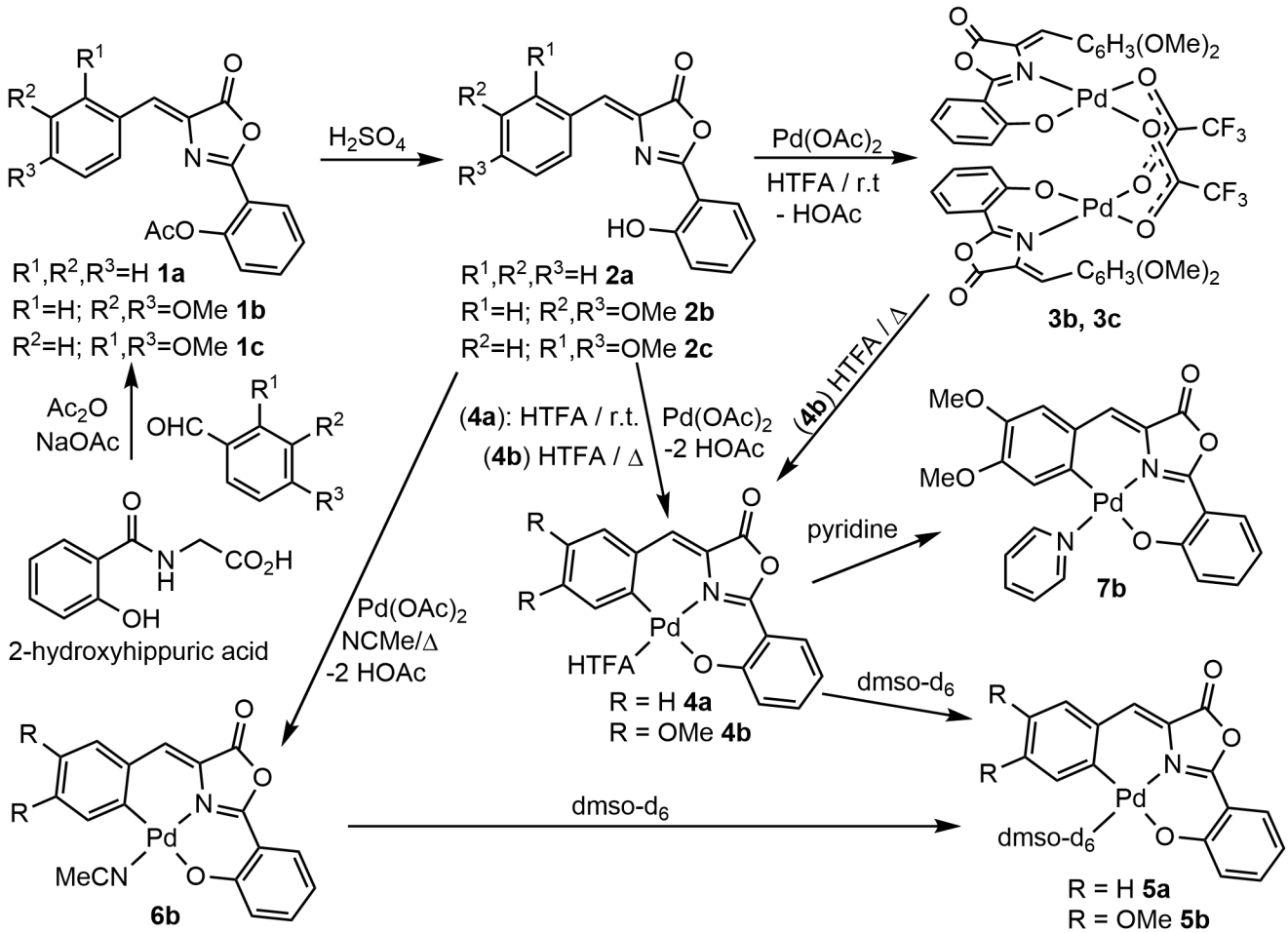


Fig. 2. Molecular plot of oxazolone **1c**. Ellipsoids are drawn at 50% probability level.



Scheme 1. Synthesis of the oxazolones **2** used in this work and further reactivity with Pd(II) to give the corresponding orthopalladated derivatives **4**–**7**.

This spectrum shows correlation peaks between one ^{15}N nucleus appearing at δ = 224.01 ppm and protons appearing at 11.1 ppm (assigned to OH) and 7.16 ppm (attributed to the vinyl CH). A second correlation peak is observed between a ^{15}N appearing at δ = 239.7 ppm and a proton at 7.38 ppm, which is assigned to the vinyl CH of the other isomer. The simultaneous observation of correlation peaks between one N and the OH and CH_{vinyl} protons strongly suggest the presence of an intramolecular H-bond (Fig. 3 left). In addition, the small difference of δ

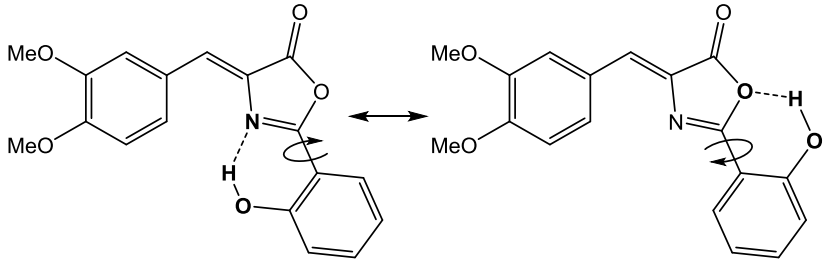


Fig. 3. Rotamers found in solution for oxazolone **2b**.

(N) between the two isomers means that the environment of the N atom is nearly the same in the two species. This fact allows to discard the formation of tautomers, because the chemical shift of the N nuclei in the *N*-protonated zwitterionic form and in the neutral form should be very different [23]. Due to these reasons, we propose the formation of the rotamers shown in Fig. 3. One additional argument in favor of this proposal is the fact that the ^{13}C NMR spectrum of **2b** shows that the two peaks assigned to each carbon in the two rotamers appear with quite similar chemical shifts, even overlapped in some cases. The C═N and C═O carbons of the heterocycle, that is, those directly bonded to the atom involved in the H-bond, are the exception to this observation. The X-ray crystal structure of **2a** has been determined (Fig. 4).

As a whole, the oxazolone **2a** is disordered over two different positions, with partial occupancies of 71.7% and 28.3%. The structure shows clearly the presence of an intramolecular H-bond between the N of the heterocycle and the *ortho*-OH group at the 2-phenyl ring. The parameters of such H-bond are D[N(1A)-O(3A) = 2.662(5) Å], d[N(1A)-H(30A) = 1.913(5) Å], angle N(1A)-H(30A)-O(3A) = 147.8(4)°. Following these data, this hydrogen bond is mostly of electrostatic nature, and can be defined as moderate following the classification of Jeffrey, with a bonding energy in the range 4–15 kcal/mol [25]. Concerning internal bond distances (Å) and angles (°), the values found in **2a** are identical, within experimental error, to those found in **1c** and in related examples found in the literature [26]. The only exception are the values of the bond angles N1A-C7A-C1A [126.2(3)°] and C7A-C1A-C2A [120.0(4)°] in **2a**, which are smaller that the respective values in **1c** N1-C1-C2 [130.3(2)°] and C1-C2-C3 [123.3(2)°], probably due to the presence of the intramolecular H-bond in the former.

Once oxazolones **2a-2c** have been prepared and characterized, the next step is the incorporation of the Pd to their skeleton. The reactivity of **2a-2c** with $Pd(OAc)_2$ affords different products as a function of the reaction conditions. Treatment of **2a** with $Pd(OAc)_2$ (1:1 molar ratio) in CF_3CO_2H (TFAH) at room temperature takes place with both OH and CH bond activations, affording palladated complex **4a**, as shown in Scheme 1. Surprisingly, the treatment of the more electron-rich substrates **2b** and **2c** with $Pd(OAc)_2$ (1:1 molar ratio) at room temperature takes place with selective activation of the OH bond and formation of the dinuclear N,O-chelates **3b** and **3c**. In the case of oxazolone **2b** the activation of the C—H bond of the arylidene ring requires stronger conditions and, either by treatment of **2b** with $Pd(OAc)_2$ (1:1 molar ratio) at the reflux temperature of the solvent (TFAH) or by heating of **3b**, the formation of the C,N,O-orthopalladated **4b** is achieved. For oxazolone **2c**, its heating with $Pd(OAc)_2$ in a variety of conditions only promoted the decomposition of the product and formation of black Pd^0.

The dinuclear nature of **3b** was inferred from the observation of a peak at 1016 a.m.u. in the HRMS spectrum, with the correct isotopic distribution for the stoichiometry $[M-TFA + NCMe]^+$ (see Experimental). The absence of C—H activation is clear in **3b** from the presence in the ^{1}H NMR spectrum of 8H, assigned to the C_6H_4, C_6H_3 and ═CH groups. In addition, the observation of a single peak in the ^{19}F NMR spectrum of **3b** suggests that the relative orientation of the two N,O-chelates is *transoid*. The low solubility of **3b** precludes the obtention of reliable ^{13}C NMR spectra. Similar conclusions can be derived from the data of **3c**. The NMR characterization of **4a** and **4b** in solution has been possible only using dmso-d_6 as solvent. The presence of the ortho-palladated [Pd(C,N,O-oxazolone)] fragment in **4a** and **4b** is evident from the analysis of their ^{1}H and ^{13}C NMR spectra, which show spin systems assigned to the C_6H_4Pd, C_6H_4O and ═CH fragments in (**4a**) and C_6H_2Pd, C_6H_4O and ═CH units in (**4b**), as well as peaks characteristics of the oxazolone ring (C═O, C═N, ═C). The ^{19}F NMR spectra of **4a** and **4b** in dmso-d_6 show the presence of a single peak at exactly the same chemical shift (−75.0 ppm) in the two cases, which is assigned to free trifluoroacetic acid (TFAH). The measurement of the ^{1}H and ^{19}F NMR spectra of **4b** in dmso-d_6 in the presence of *p*-$CF_3C_6H_4CHO$ as internal

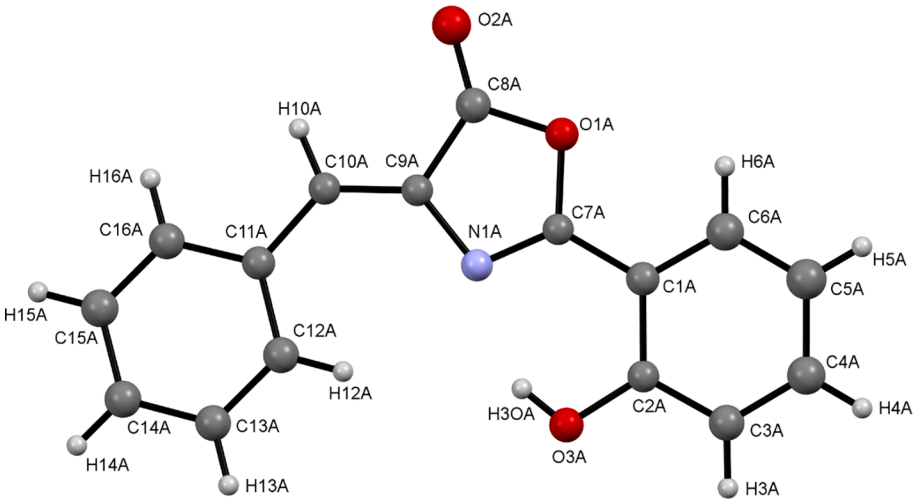


Fig. 4. Molecular plot of oxazolone **2a**. Isotropic spheres are drawn at 50% probability level.

reference allows the quantification of the amount of CF_3CO_2H per each orthopalladated unit [Pd(C,N,O-oxazolone)]. The obtained molar ratio is 1:1, meaning that the molecular formula of **4a** and **4b** is in fact [Pd(C,N,O-oxazolone)(TFAH)]. When **4a** or **4b** are dissolved in dmso-d_6 the weakly bonded TFAH is most likely displaced by the dmso-d_6, a good coordinating solvent, generating the species [Pd(C,N,O-oxazolone)(dmso-d_6)] **5a** and **5b**, which are actually the species characterized in solution. All those facts are presented in Scheme 1.

The bonding abilities of the tridentate oxazolones **2a** and **2b** seem to be higher than those shown by other bidentate oxazolones. In all cases studied up to now, the orthopalladation of 4-arylidene-5(4*H*)-oxazolones through C—H bond activation must to take place in carboxylic acids as solvent. Among them, trifluoroacetic acid showed the best performance, while attempts to use other solvents were not successful, regardless their nature [7]. In this work we have attempted the orthopalladation of **4b** in NCMe, a solvent with a boiling point (82 °C) higher than that of TFAH (72.4 °C), and with known bonding properties. The treatment of $Pd(OAc)_2$ with **2b** (1:1 M ratio) in NCMe at the reflux temperature results in the formation of an insoluble red solid **6b**. Complex **6b** is soluble only in dmso-d_6, and the ^{1}H NMR spectrum of **6b** in dmso-d_6 is identical to that of **5b**, with the exception of the NCMe peak. Therefore, we propose for **6b** a structure like that depicted in Scheme 1. As far as we know, this is the first case of orthopalladation of one oxazolone in a solvent different of a carboxylic acid, this fact expanding the scope of possibilities to incorporate the Pd center to the oxazolone scaffold. In addition, the TFAH ligand in insoluble **4b** can also be displaced by other neutral ligands, such as pyridine, producing more soluble orthopalladated complexes (Scheme 1). Therefore, **4b** reacts with pyridine (1:1 molar ratio) in CH_2Cl_2 to give **7b** in moderate yield. The presence of *N*-bonded pyridine in **7b** is clear from the observation in the ^{1}H NMR spectrum of **7b** of peaks at 9.1 ($2H_{ortho}$), 8.0 ($1H_{para}$) and 7.6 ($2H_{meta}$) ppm, assigned to this ligand, and from the anisotropic shielding undergone by the H_6 proton from 7.68 ppm (**5b**) to 6.12 ppm (**7b**), suggesting the *cis*-arrangement of the orthopalladated ring and the pyridine ligand [27].

The characterization of oxazolones **2** and complexes **4** by UV–Vis absorption spectroscopy follows the expected trends. Absorption spectra were acquired for **2a-2c** and **4a**, **4b** in CH_2Cl_2 solution (10^{-5} M) at 25 °C. Oxazolone **2a** showed a structured band with a maximum in the UV region (377 nm), while **2b** and **2c** showed bands in the visible region (431 and 422 nm, respectively), as shown in Fig. 5. In all cases the band is assigned to a π–π* charge transfer [28–30]. The incorporation of methoxide groups in the benzylidene ring promotes a redshift of the absorption maxima. In the orthopalladated derivatives **4a** and **4b** the maxima were redshifted (404 nm, **4a**; 490 nm, **4b**) with respect to the free oxazolones **2a** and **2b**, in good agreement with previous observations [10].

Oxazolones **2a-2c** and complexes **4a, 4b** are not fluorescent. These results are in line with recent reports [10], which showed that the coordination of the Pd to the oxazolone skeleton, being necessary, is not sufficient by itself. The precise role of the donor atoms and the ancillary ligands in the luminescence, as well as that of the Pd atom beyond to act as an intramolecular lock, needs to be determined more accurately. Further development of this area is currently in progess in our laboratory.

4. Conclusion

(*Z*)-4-aryliden-2-(*ortho*-hydroxyphenyl)-5(4*H*)-oxazolones with potential C,N,O-tridentate ability towards transition metals have been synthesized by the classical Erlenmeyer-Plöchl method followed by deprotection in acid medium. These ligands can encapsulate a palladium center through simultaneous bonding to the *ortho*-carbon of the arylidene ring, the heterocyclic nitrogen and the oxygen of the phenoxy group. The C,N,O-tridentate bonding mode provides a rigid environment, very stable and for which different ligands can be accommodated at the fourth bonding site.

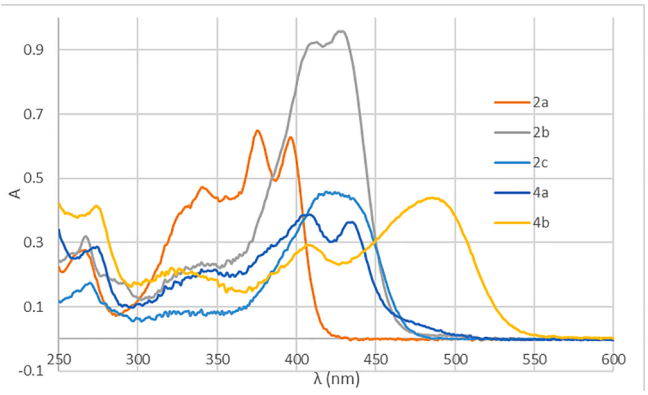


Fig. 5. UV–vis absorption spectra of **2a-2c**, **4a** and **4b** in CH_2Cl_2 solution.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.poly.2022.115904.

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