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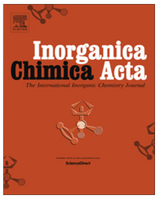

Research paper

Microwave assisted Suzuki-Miyaura and Mizoroki-Heck cross-couplings catalyzed by non-symmetric Pd(II) CNS pincers supported by iminophosphorane ligands

Sandra Ramírez-Rave [a], David Morales-Morales [b], Jean-Michel Grévy [c,*]

[a] Departamento de Química, Área de Catálisis, Grupo ECOCATAL, Universidad Autónoma Metropolitana-Iztapalapa, Avenida San Rafael Atlixco # 189, 09340 Ciudad de México, Mexico
[b] Instituto de Química, Universidad Nacional Autónoma de México, Cd. Universitaria, Circuito Exterior, Coyoacán, 04510 Ciudad de México, Mexico
[c] Centro de Investigaciones Químicas, Instituto de Investigación en Ciencias Básicas y Aplicadas, Universidad Autónoma del Estado de Morelos, Avenida Universidad # 1001, Chamilpa, CP 62209 Cuernavaca, Morelos, Mexico

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ABSTRACT

Two new Pd^{II} non-symmetrical CNS pincer type complexes $[PdCl\{C_6H_4(Ph_2P=NC_6H_4SR\text{-}\kappa^3\text{-}C,N,S)\}]$ [R = Bn (**3**) and 4-$C_6H_5NO_2$ (**4**)], supported by iminophosphorane ligands functionalized with a thioether moiety, were prepared and fully characterized. These compounds and the already known complexes **1** (R = Me) and **2** (R = Ph) were evaluated as catalysts in microwave assisted Suzuki-Miyaura and Mizoroki-Heck coupling reactions. Whereas compound **1** instantaneously decomposed under MW irradiation, as visible black Pd^0 precipitated in both processes, compounds **2**–**4** showed good conversions without apparent decomposition. The coupling reactions were dramatically accelerated under MW radiation when compared to conventional heating, with **3** (R = 4-$C_6H_4NO_2$) showing the highest catalytic efficiency of all in both processes. The catalytic activity of complex **2** was further examined in the two cross-couplings with a series of *para*-substituted bromo-benzenes. Both catalyses proceeded under normal aerobic conditions and were not affected by an excess of elemental Hg. The Mizoroki-Heck reaction operated with high regioselectivity, yielding only the linear 1,2-products.

1. Introduction

Transition metal catalysts have played a very important part in chemistry since the beginning of the 20th Century. Nevertheless, their role became invaluable for synthetic chemists with the apparition of cross-coupling reactions catalyzed by palladium, which allowed the design of new organic compounds with a wide spectrum of different applications (new materials, optical devises, drugs, etc.) [1]. They were developed in the 70′s independently by Mizoroki [2] and Heck [3], Stille [4], Negishi [5], Sonogashira [6] and Suzuki [7], with some differences in their starting reagents and the nature of the newly formed compound during the catalytic process. These reactions have in common that two organic molecules bond to Pd in different steps of the catalytic cycle through the formation of a carbon–metal σ bond and subsequently these carbon atoms migrate to form a new C—C bond, which would be difficult to obtain otherwise [8].

Actually, the Suzuki-Miyaura coupling between organic halides and phenylboronic acids is one of the most powerful methods for the synthesis of biaryl compounds. These are intermediates in the organic synthesis of performance materials and pharmaceuticals under mild reaction conditions [9]. The Mizoroki-Heck coupling between organic halides or pseudohalides (diazonium salts and triflates) and alkenes is also really attractive, as it allows the substitution of alkenes with high stereoselectivity for *trans* coupling [10]. Finding efficient and selective catalytic systems for these specific transformations using transition metal complexes is still an active subject in organic synthesis. For instance, as a result of their high thermal and oxidative stabilities, palladium-pincer complexes have been widely studied to promote very efficiently different C—C cross-couplings [11–14]. During the past two decades, the vast majority of the studies reported on this subject referred to pincer complexes of typical XYX structure with C_{2v} symmetry, were the central atom in the ligand is commonly a N or a C atom usually carrying a negative charge, and the side arms donor atoms are identical and usually a heteroatom from the non-exhaustive list: N, P, O, S, Se or a carbene (Fig. 1A). Nonetheless, it has been shown lately that non-symmetrical pincer com-

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* Corresponding author.
E-mail address: jeanmichelg@gmail.com (J.-M. Grévy).

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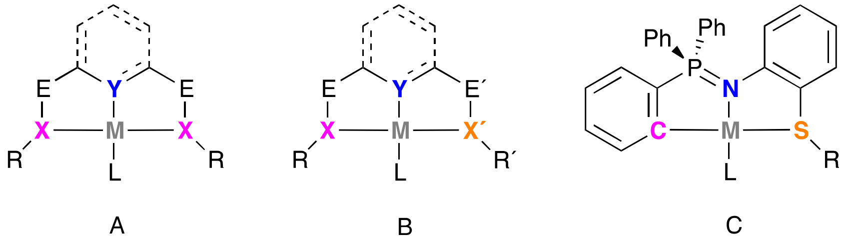


Fig. 1. General formula of pincer complexes: symmetrical (A), non-symmetrical (B) and non-symmetrical CNS (C), based on mixed iminophosphorane-thioether ligands (this work).

plexes (XYX′), were the side arm donor atoms are different (X ≠ X′), can bring some benefits to catalytic applications (Fig. 1B) [15]. In particular this ligand family provide an easiest access to hemilabile coordination with potentially increased catalyst activity, and facilitate the introduction of chirality.

In an earlier paper we have reported a rare model of non-symmetrical CNS Pd^{II} pincer complexes derived from iminophosphorane [PdCl{$C_6H_4(Ph_2P = NC_6H_4SR$-κ^3-C,N,S)} (R = Me, Ph)] were the anionic C atom occupies a lateral position instead of the typical central position in common pincer complexes (Fig. 1C) [16]. Preliminary experiments showed that the methyl substituted complex (R = Me) was an efficient catalyst in the Suzuki-Miyaura C—C cross-coupling reactions of a series of *para*-substituted bromobenzenes under conventional heating (110 °C).

In the search for more eco-friendly, economical and sustainable protocols than conventional laboratory heating techniques, it has been established that microwave (MW) assisted methods have undeniable advantages and benefit a wide range of metal-catalyzed processes and cross-coupling reactions, exhibiting faster reaction kinetics, shorter reaction times and cleaner products [17]. For instance, Larhed first reported the use of this energy source to promote C—C cross-coupling reactions in both homogenous and solid phase processes [18] obtaining high yields of conversions within 5 min of irradiation at low potencies. Since then, many reports have shown that microwave assisted methodology can be used to improve C—C cross-coupling protocols in different solvents for a wide variety of Pd compounds [19–21], including few palladacycles [22] and pincer complexes [23]. In this context, a review on the subject of MW assisted synthesis in aqueous media has recently been published and is dedicated in part to C—C cross-couplings [24]. We report here the catalytic behavior of non-symmetrical CNS pincer Pd complexes **1**, **2**, **3**, and **4** (Scheme 1) as catalysts in the Suzuki-Miyaura and Mizoroki-Heck cross-coupling reactions under MW activation.

2. Experimental

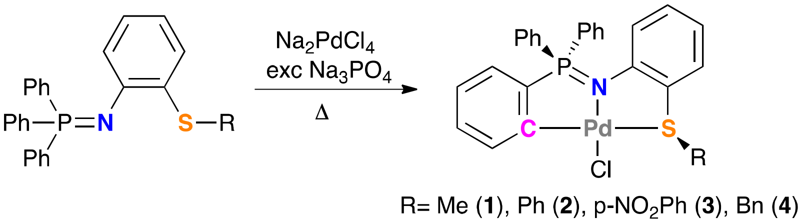
The ligands used in this work, as well as catalysts **1** and **2**, were previously reported by our laboratory [16,25]. The synthesis of complexes **3** and **4** was carried out under nitrogen atmosphere using conventional Schlenk techniques, and solvents were dried using standard procedures [26]. Infrared spectra were acquired in KBr using a Bruker Vector 22 instrument. NMR spectra were recorded on a Varian Gemini 200 MHz and a Varian Unity Inova 400 MHz instruments in $CDCl_3$, which was used as internal reference. $^{31}P\{^1H\}$ NMR spectra were acquired with complete proton decoupling and are reported in ppm using 85% H_3PO_4 as external standard. Mass measurements (FAB+) were obtained at a resolution of 3000 using magnetic field scans and the matrix ions as the reference material or, alternatively, by electric field scans with the sample peak bracketed by two (polyethylene glycol or cesium iodide) reference ions. Melting points were measured in a Mel Temp II device using sealed capillaries and are reported without correction.

2.1. Synthesis of [PdCl{$C_6H_4(Ph_2P = NC_6H_4SPhNO_2$-$\kappa^3$-C,N,S)}](3)

[Na_2PdCl_4] (0.013 g, 4.38 × 10^{-5} mol) was added to a mixture of iminophosphorane ligand [$Ph_3P = NC_6H_4SPhNO_2$] (0.022 g, 4.38 × 10^{-5} mol) and excess of Na_3PO_4 (0.0123 g, 7.5 × 10^{-5} mol) in toluene (20 ml), under N_2 atmosphere. The resulting solution was refluxed for 1.5 h. After this time, the solution was filtered on silica gel and the solvent was removed under vacuum leading to the isolation of an orange powder. Yield (0.002 g, 20%). Mp.: 155 °C. Anal. Calc. for $C_{30}H_{22}ClN_2O_2P_1Pd_1S_1$ (647.42): C, 55.66; H, 3.43; N, 4.33. Found: C, 55.93; H, 3.58; N, 4.03. MS FAB+: 468 (60%). IR (ν, cm^{-1}): 1255 (νPN). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.83$ (s, 3H, -SCH_3), 6.87 (dd, 1H, SC_6H_4N), 7.02 (t, 1H, SC_6H_4N), 8.17 (d, 1H, SC_6H_4N), 7.25 (dd, 1H, SC_6H_4N), 8.17 (m, $4H_o$ PPh_3), 7.61 (m, $4H_m$ PPh_3), 7.66 (m, $4H_p$ PPh_3). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 15.31 (-SCH_3), 156.93 (d, $^3J_{PC} = 31.9$, C_i-S, SC_6H_4N), 152.86 (C_i-N, SC_6H_4N), 129.13 (C_3, SC_6H_4N), 128.82 (C_4, SC_6H_4N), 126.74 (C_5, SC_6H_4N), 135.92 (C_6, SC_6H_4N), 125.82 (d, $^1J_{PC} = 113.02$, C_i PPh_3), 132.80 (d, $^2J_{P,C} = 10.0$ Hz, C_o PPh_3), 129.56 (d, $^3J_{P,C} = 11.0$ Hz, C_m PPh_3), 133.77 (d, $^4J_{P,C} = 2.0$ Hz, C_p PPh_3), 141.00 (d, $^1J_{P,C} = 142.1$ Hz, C_i-P, PC_6H_4Pd), 155.62 (d, $^2J_{P,C} = 19.1$ Hz, C_i-Pd, PC_6H_4Pd). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 161 MHz): $\delta = 47.3$.

2.2. Synthesis of [PdCl{$C_6H_4(Ph_2P = NC_6H_4SCH_2C_6H_5$-$\kappa^3$-C,N,S)}] (4)

Under N_2 atmosphere, [Na_2PdCl_4] (0.013 g, 4.38 × 10^{-5} mol) was added to a mixture of iminophosphorane ligand [$Ph_2P = NC_6$-



Scheme 1. Synthesis of non-symmetric CNS pincer complexes **1**–**4**.

$H_4SCH_2C_6H_5$] (0.021 g, 4.38×10^{-5} mol) and an excess of Na_3PO_4 (0.0123 g, 7.5×10^{-5} mol) in 20 ml of 1,2-dichloroethane. The resulting solution was refluxed for 1.5 h. After this time, the solution was filtered on silica gel and the solvent was removed under vacuum leading to the isolation of a yellow powder. Yield (0.022 g, 81%). Mp.: 157 °C. Anal. Calc. for $C_{31}H_{25}Cl_1N_1P_1Pd_1S_1$ (616.45): C, 60.40; H, 4.09; N, 2.27. Found: C, 60.19; H, 4.44; N, 2.55. IR (ν, cm^{-1}): 1257 (νPN). MS FAB+: 616 (40%). NMR ($CDCl_3$, 400 MHz):$\delta = 2.83$ (s, 3H, $-SCH_3$), 6.87 (dd, 1H, SC_6H_4N), 7.02 (t, 1H, SC_6H_4N), 8.17 (d, 1H, SC_6H_4N), 7.25 (dd, 1H, SC_6H_4N), 7.60 (m, $4H_o$, PPh_3), 7.48 (m, $4H_m$, PPh_3), 7.39 (m, $4H_p$, PPh_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ: 15.31 ($-SCH_2$), 156.93 (d, $^4J_{PC} = 31.90$, C_i-S, SC_6H_4N), 152.85 (C_i-N, SC_6H_4N), 129.13 (C_3, SC_6H_4N), 128.82 (C_4, SC_6H_4N), 126.74 (C_5, SC_6H_4N), 135.92 (C_6, SC_6H_4N), 128.45 (d, $^1J_{P,C} = 106.0$ Hz, C_i PPh_3), 132.86 (d, $^2J_{P,C} = 10.0$ Hz, C_o PPh_3), 129.26 (d, $^3J_{P,C} = 13.2$ Hz, C_m PPh_3), 133.25 (d, $^4J_{P,C} = 1.1$ Hz, C_p PPh_3), 140.59 (d, $J_{P,C} = 150.2$ Hz, C_i-P, PC_6H_4Pd), 154.01 (d, $^2J_{P,C} = 16.1$ Hz, C_i-Pd, PC_6H_4Pd). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 161 MHz): $\delta = 47.9$.

2.3. General procedure for the suzuki–miyaura cross-coupling

Suzuki–Miyaura couplings were done in glass tubes suitable for use in a microwave apparatus. 5 mL of a DMF solution containing an halobenzene (4.3×10^{-4} mol), phenyl boronic acid (4.7×10^{-4} mol), Na_3PO_4 (9.5×10^{-4} mol) and Pd catalyst (4.31×10^{-3} mmol, 0.1 mol%) were stirred and heated at 110 °C under microwave irradiation during 5 min in a CEM Discover reactor. Then, the reaction mixture was cooled at room temperature and extracted with CH_2Cl_2. The organic phase was collected and dried with anhydrous Na_2SO_4, filtered through Celite and analyzed by Gas Chromatography (GC–MS) on an Agilent 6890 N GC with a 30.0 m DB-1MS capillary column coupled to an Agilent 5973 Inert Mass Selective detector.

2.4. General procedure for the Mizoroki-Heck cross-coupling reactions

Mizoroki-Heck couplings were carried out in glass tubes appropriate for use in a microwave reactor. Different *p*-substituted bromobenzenes (4.317×10^{-4} mol), styrene (4.749×10^{-4} mol), Na_3PO_4 (9.498×10^{-4} mol) and Pd catalyst (4.31×10^{-3} mmol, 0.1 mol%) were mixed in 5 mL of DMF under vigorous stirring and also heated at 110 °C under microwave irradiation during 15 min in a CEM Discover apparatus. Subsequently, the reaction mixture was cooled at RT and treated with CH_2Cl_2, the organic phase was collected, dried with anhydrous Na_2SO_4 and filtered through Celite. Finally, extracted samples were analyzed by Gas Chromatography (GC–MS) on an Agilent 6890 N GC with a 30.0 m DB-1MS capillary column coupled to an Agilent 5973 Inert Mass Selective detector.

Complementary catalytic experiments were done under the same reaction conditions using different bases [Na_2CO_3, K_2CO_3, Rb_2CO_3, Cs_2CO_3, NaOH].

2.5. Mercury drop experiments

Following the catalytic procedures 1.3 and 1.4, two drops of elemental Hg were added to the reaction media before microwave irradiation. The CH_2Cl_2 extract samples were obtained and analyzed by GC-MS in the same way. No significant difference in the conversion was observed between these experiments and those in the absence of mercury, indicating that heterogeneous Pd(0) is not involved in the reaction.

3. Results and discussion

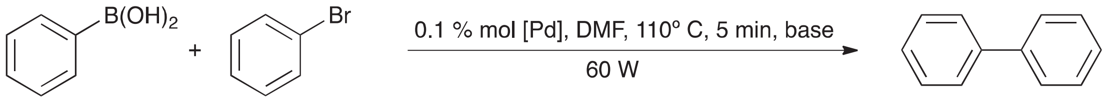
The iminophosphorane ligands were synthesized following a procedure previously reported by our group [1,2] (Scheme 1).

Following the method reported for the synthesis of complexes **1** and **2**, [Na_2PdCl_4] and an excess of base (Na_3PO_4 in this case) were reacted with the corresponding iminophosphorane ligand under reflux in toluene or 1,2-dichloroethane, yielding the new non-symmetric CNS pincer complexes **3** and **4**, respectively (Scheme 1). The formation of **3** was very slow as compared to that of **4**, and only 20% yield of **3** was obtained during the time required to obtained 80% yield of the other complexes (**1** 82%, **2** 81%, **4** 81%). Some efforts have been made to improve the yield of formation of pincer **3**, but longer reaction times and higher temperatures just lead to the formation of complex mixtures difficult to purify. Both complexes were obtained as air- and moisture-stable orange to yellow solids, soluble in organic chlorinated and polar solvents. Spectroscopic and analytical data were consistent with the proposed structures.

IR spectroscopy shows that iminophosphorane ligands coordinate the metal center through the iminic N, since the ν (P = N) absorption (**3**: 1251 cm^{-1}; **4**: 1249 cm^{-1}) has been shifted to lower frequencies when compared to the corresponding free ligand ($Ph_3P = NC_6H_4SPhNO_2$: 1330 cm^{-1}; $Ph_2P = NC_6H_4SCH_2C_6H_5$: 1332 cm^{-1}), as observed for similar compounds before [1,2,27]. Multinuclear NMR experiments, $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$, also confirm the suggested structures for complexes **3** and **4**. For instance, the $^{31}P\{^1H\}$ NMR spectra shows only one single signal and when compared with the respective free ligand this signal shows the expected 50 ppm shift due to the *endo* orthometallation (**3**, δ 47.3 ppm; **4**, δ 47.9 ppm). The similarity of chemical shift between **3** and **4** suggests that the nature of S substituents in Pd complexes has no significant electronic effect on the P atom. In ^1H NMR spectra, the new orthometallated ring gives place to four signals in the aromatic region between δ 7 and 8 ppm for both non-symmetric CNS pincer compounds. The $^{13}C\{^1H\}$ NMR spectra also validates the formation of pincer complexes **3** and **4** through orthometallation due to the presence of a new quaternary ^{13}C coupled to P, corresponding to the metallocycled C*ipso*, at δ 155.62 ppm (d, $^2JP,C = 19.1$ Hz) for **3** and 154.01 ppm (d, $^2JP,C = 16.1$ Hz) for **4**. Comparable chemical shifts and spin systems were already described for related iminophosphorane pincer compounds [1,2,28].

3.1. MW assisted Suzuki-Miyaura cross-coupling

The Suzuki-Miyaura reaction is an efficient Pd catalyzed C—C coupling reaction between organohalides and phenylboronic acids that is widely used to synthesize poly-olefins, styrene and biphenyl compounds both in laboratory and industrial scales. Thus, we chose to evaluate the activity of compounds **1**–**4** in the Suzuki-Miyaura reaction between an aryl-halide and phenylboronic acid. It is well known that C—C cross-couplings are influenced by a series of parameters, so in order to evaluate the effect of the reaction temperature, solvent, base and catalyst loading we performed experiments to define the optimal conditions. Preliminary runs of Suzuki-Miyaura coupling were carried out reacting phenylboronic acid and bromobenzene in the presence of different catalyst charges and 2.2 equivalents of base. In a previous evaluation of the catalyst activity of **1** in the same cross-coupling under conventional heating we observed better results using the base Na_3PO_4, so we selected that same base in those preliminary runs. The results showed that a 0.1% molar catalyst load was optimal, and allowed a comparison of the catalytic efficiency of **1**, **2**, **3** and **4** (Scheme 2) (Table 1).



Scheme 2. Evaluation of the catalytic activity of complexes **1**–**4** in Suzuki-Miyaura reaction.

Table 1
MW assisted Suzuki Miyaura coupling between phenyl bromide and phenylboronic acid using catalysts **1**–**4** in the presence of Na_3PO_4 as base.

L	Conversion (%)
1	0*
2	72
3	90
4	66

Reaction conditions: DMF (5 mL), phenyl bromide (0.43 mmol), Na_3PO_4 (0.95 mmol), [Pd] 0.1% mol (4.31×10^{-3} mmol), and phenylboronic acid (0.47 mmol). Temperature 110 °C (60 W), reaction time 5 min, *__1__ decomposes instantaneously under microwave irradiation.

In the reaction between bromobenzene and phenylboronic acid catalyzed by compound **1**, the formation of visible black Pd^0 indicated the decomposition of the complex. Consequently the conversion of the expected biphenyl product was not detected, suggesting that the palladacycle in this pincer compound suffers some kind of destruction under microwave irradiation. On the other hand, compounds **2**, **3** and **4** showed high yields of the expected coupled product, 72%, 90% and 66% respectively. This was quite unexpected for us, knowing that in our previous study of **1** and **2** as potential catalysts in the same cross-coupling process but under conventional heating, **1** was found to perform better than **2** who showed almost no catalytic activity (5% conversion). In the present case, it appeared that a phenyl or benzyl substituent on the S atom provided some stability to the CNS pincer under microwave irradiation without hampering the catalytic performance, because no decomposition was observed for **2**, **3** and **4**. A comparison of the activity of **2** (-SPh) and **3** ($-SC_6H_4pNO_2$), two compounds of similar steric bulk, indicated that the electron-withdrawing group NO_2 in *para* position has a positive outcome on the catalytic activity that can be related to electronic factors. This notable effect is probably not related to an expected decrease of electron density on the Pd^{II} center due to the strong electron withdrawing property of NO_2, because that would work against the oxidative addition step of the catalytic cycle. We rather believe that it is related to an improved hemilability of the coordination between S and Pd, related to a decrease of the σ donor character of S. However, even if the highest yield of conversion was obtained with **3** (90%), we chose to complete the catalytic study with complex **2** (72%), which is significantly easier to synthesize than **3** (yield of synthesis for **2** 80% vs. 20% for **3**) but still displays a satisfactory catalytic performance when compared to that of **3** (yield of conversion: 72% for **2** vs. 90% for **3**).

Due to the essential role played by the base in the Suzuki-Miyaura coupling, we kept on studying the effect of different bases using **2** as catalyst under the aforementioned conditions, but with a limited reaction time of 2.5 min of MW irradiation. As expected from our previous report, the best results were obtained when Na_2CO_3 or Na_3PO_4 were used, giving conversions of 40% and 50% respectively. Any other base tested appeared to reduce the yield of coupling product (Table 2).

Under optimized conditions (Na_3PO_4, DMF, 110 °C, 5 min), **2** was evaluated as catalyst toward different *para*-substituted bromobenzenes. The results showed a clear correlation between the yield of transformation and the nature of the aromatic substituent *para* to Br, or its Hammett substituent constant [29]. Thus, in only 5 min, fair to good conversions were observed with electron donating (EDG) *para* substituents (entries 1–4 Table 3) and excellent yields were obtained with electron-withdrawing groups (EWG) (entries 5–9 Table 3). Comparing these results with our preliminary evaluation of **1** and **2** as catalysts for the same cross-coupling process but under conventional heating, the benefits of microwave irradiation are evident. While **2** was almost inactive under conventional heating, now, under microwave assistance, **2** became a better catalyst than **1** which decomposed promptly, *i.e.* with 10 times lower catalyst charge (0.1% vs. 1%) **2** performed the coupling with better (entries 1–5, *para*-EDG) or equal (entries 6–9, *para*-EWG) conversions in shorter times (5 min vs. 5 h) and at the same temperature. The high yield of 4-chlorobiphenyl (93%) in the coupling of 1-bromo-4-chloro benzene (entry 5) indicated that **2** selectively reacted with the more activated C-Br bond and that the C-Cl bond was almost unreactive in those conditions.

Apart from the Suzuki-Miyaura coupling reaction with complex **1**, under these conditions no decomposition of the catalyst was observed during catalysis and the performance of catalysts **2**, **3**, and **4** were not affected by the presence of excess elemental Mercury. These results suggest that the reaction may not proceed through the formation of soluble palladium nanoparticles. This is worth mentioning because there is still some discussion in the literature concerning the oxidation states of the metal center involved in the catalytic cycle with palladacycles. Depending on the structure of the complex and the conditions used, two principal mechanistic schemes are possible: a Pd(0)/Pd(II) redox cycle with destruction of the palladacycle and a Pd(II)/Pd(IV) cycle maintaining the palladacycle intact. In the present study the Pd(II)/Pd(IV) scheme is more preferred because of the stabilizing effect present in the electron-donating ligand, also elemental Hg makes no difference in the isolated yields of coupling products and the catalysis operate under normal aerobic conditions. However, an earlier report from Urriolabeltia et al. [30] unveiled the hemilabile character of the thioether coordination to Pd^{II} in a related CNS complex, so that we cannot rule out here the other possibility that the S atom would be displaced from the metal during the catalysis without forming high valent Pd species [1,31].

3.2. MW assisted Mizoroki-Heck cross-coupling

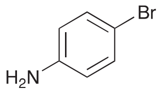
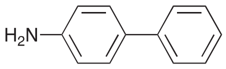
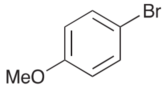
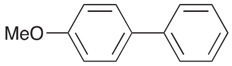
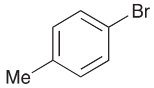
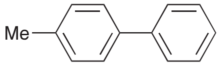
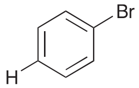
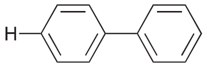
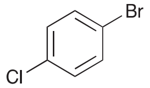
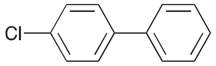
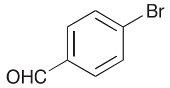
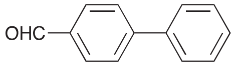
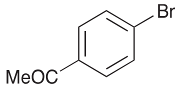
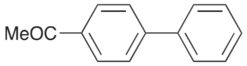
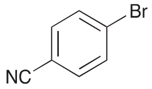
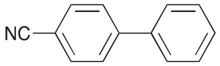
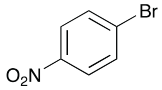
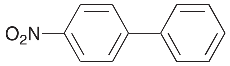
The Pd catalyzed arylation of olefins is a powerful tool for the construction of C—C bonds and it is widely used in the synthesis of polymers, pharmaceuticals and natural products. So, the

Table 2
MW assisted Suzuki-Miyaura coupling between bromobenzene and phenylboronic acid using **2** as catalyst and different bases.

Base	Conversion (%)
Na_2CO_3	40
K_2CO_3	30
Rb_2CO_3	20
Cs_2CO_3	38
NaOH	15
Na_3PO_4	50

Reaction conditions: DMF (5 mL), phenyl bromide (0.43 mmol), base (0.95 mmol), **2** 0.1 mol% (4.31×10^{-3} mmol), and phenylboronic acid (0.47 mmol). Temperature 110 °C (60 W), reaction time 2.5 min.

Table 3
MW assisted Suzuki-Miyaura coupling between phenylboronic acid and different *para* substituted phenyl bromide using **2** as catalyst.

Entry	Bromobenzene	Product	% Conversion
1			63
2			74
3			64
4			72
5			93
6			>99
7			92
8			96
9			>99

Yields obtained by GC are based on remaining bromobenzene and are the average of two runs. Reaction conditions: DMF (5 mL), phenyl bromide (0.43 mmol), Na_3PO_4 (0.95 mmol), **2** 0.1 mol% (4.31×10^{-3} mmol), and phenylboronic acid (0.47 mmol). Temperature 110 °C (60 W), reaction time 5 min.

catalytic activity of complexes **1**, **2**, **3** and **4** was also estimated in a model Mizoroki-Heck cross-coupling reaction between bromobenzene and styrene, using the generic conditions displayed in Scheme 3, with the base Na_3PO_4 and a 0.1% mol. catalyst load (Table 4). As predictable from its aforementioned behavior in the Suzuki-Miyaura coupling, complex **1** decomposed before any coupled product could be formed and detected. The instantaneous formation of visible Pd^0 black precipitate indicated that the palladacycle was quickly destroyed under microwave irradiation. However, in the same conditions complexes **2**, **3** and **4** proved again to be efficient catalysts with fairly good conversions [(**2**) 52%; (**3**) 51%; and (**4**) 43%] with the usual, although remarkable, *trans*-selectivity of the Mizoroki-Heck coupling. Compounds **2** and **3** performed as roughly equally efficient catalysts, thus, for practical reasons we preferred the easiest to synthesize pincer **2** to continue with the catalytic study.

Under optimized conditions (Na_3PO_4, DMF, 110 °C, 15 min, 0.1% mol. catalyst load), the catalytic activity of **2** was assessed in the Mizoroki-Heck cross-coupling process between styrene and different *para*-substituted bromobenzenes.

Table 4
MW assisted Mizoroki-Heck coupling between phenyl bromide and styrene using catalysts **1–4** in the presence of Na_3PO_4 as base.

L	*cis*-Stilbene	*trans*-Stilbene	Conversion (%)
1*	0	0	0
2	6	46	52
3	6	45	51
4	5	38	43

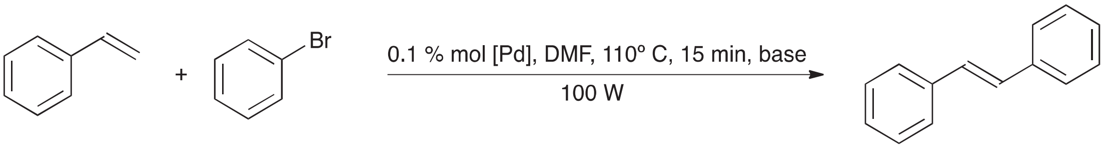
Reaction conditions: DMF (5 mL), phenyl bromide (0.43 mmol), Na_3PO_4 (0.95 mmol), [Pd] (4.31×10^{-3} mmol), and styrene (0.47 mmol). Temperature 110 °C (100 W), reaction time 15 min, ***1** decomposes instantaneously under microwave irradiation.

First, it is worth mentioning here that this catalysis occurs with high regioselectivity and only the linear, or 1,2-products, are obtained. In a study regarding the regiochemistry of the Heck reaction with Pd complexes supported by diphosphine ligands, Cabri et al. [32] proposed that differences in regioselectivity depend on the alkene substituent and the reaction pathway taken for the alkene coordination-insertion event, *i.e.* a neutral pathway vs. a cationic pathway. With styrene, the *neutral* pathway would lead to a 100% conversion in 1,2-product as in our case, while the *cationic* pathway would give rise to a mixture of 1,2- and 1,1-product in a 60%/40% proportion. Even when our non-symmetrical CNS pincer complexes are structurally radically different from the diphosphine complexes studied by Cabri and so we cannot formally refer to a *neutral* pathway, it is clear that these non-symmetrical pincers influence the carbopalladation step in such a way that a high 1,2-regioselectivity is observed here.

As observed in the Suzuki Miyaura cross-coupling study, the results collected in Table 5 show a net correlation between the yield of transformation and the nature of the aromatic substituent *para* to Br, or its Hammett substituent constant [29]. We observed a complete conversion with 1-bromo-4-nitrobenzene (99%, entry 9) and high yield conversions with other electron-withdrawing group (64 to 95%, entries 6–8). Lower conversions and yields were achieved with aryl bromides substituted with electron-donating groups (10–50%, entries 1–5). Altogether, there is a good correlation between the Hammett constant of the *para*-substituent and the conversion yield. This electronic effect is not surprising, since electron-withdrawing substituents on the aromatic ring are expected to facilitate the coupling reaction considering that an essential oxidative addition step of the aryl bromide to the metal center occurs during the catalytic cycle.

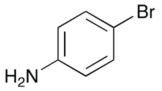
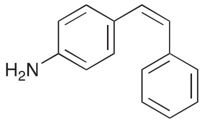
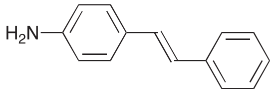
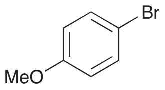
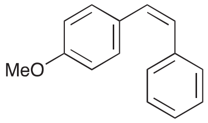
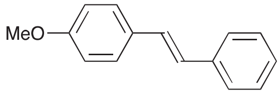
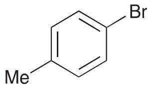
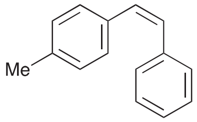
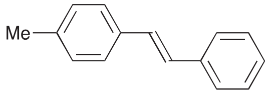
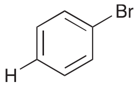
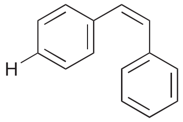
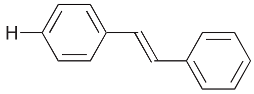
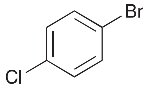
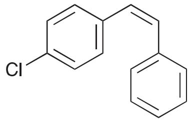
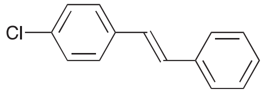
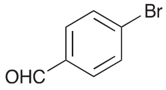
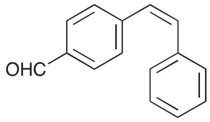
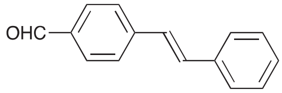
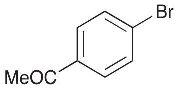
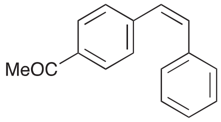
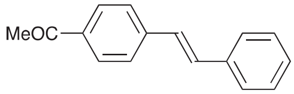
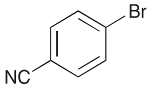
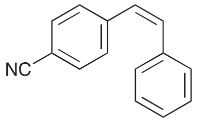
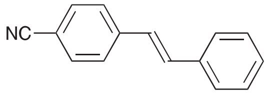
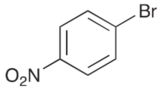
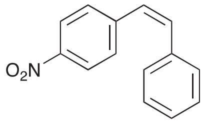
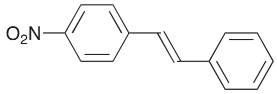
The exact mechanism of the Heck reaction is not completely understood, with the exact mechanistic pathways depending on reaction conditions and substrates employed. However, for the same reasons exposed in the Suzuki-Miyaura study, *i.e* high thermal and aerobic stability of the catalytic system and no effect of the Mercury drop on the yields of conversion, a Pd(0)/Pd(II) redox cycle with destruction of the palladacycle is not likely in this catalysis.

In summary, the microwave assisted catalytic activity of non-symmetrical pincer Pd^{II} complexes $[PdCl\{C_6H_4(Ph_2P=NC_6H_4SR-\kappa\text{-}C,N,S)\}$, **1** ($R=CH_3$), **2** ($R=Ph$), **3** ($R=p\text{-}NO_2PhNO_2$) and **4** ($R=CH_2Ph$)] was evaluated in the Suzuki-Miyaura and Mizoroki-Heck cross-coupling reactions. Apart from compound **1** which



Scheme 3. Evaluation of the catalytic activity of complexes **1–4** in Mizoroki-Heck reaction.

Table 5
MW assisted Mizoroki-Heck coupling between styrene and different *para* substituted phenyl bromide using **2** as catalyst.

Entry	Bromobenzene	Cis	%	Trans	%	Conv. Total %
1			>1		10	11
2			>1		18	19
3			>1		25	26
4			6		46	52
5			>1		50	51
6			4		95	99
7			7		64	73
8			3		85	88
9			<1		>99	>99

Yields obtained by GC are based on remaining bromobenzene and are the average of two runs. Reaction conditions: DMF (5 mL), phenyl bromide (0.43 mmol), Na_3PO_4 (0.95 mmol), **2** 0.1 mol% (4.31×10^{-3} mmol), and styrene (0.47 mmol). Temperature 110 °C (100 W), reaction time 15 min.

decomposes under the reaction conditions, they all prove efficient catalysts for these reactions, with complexes **2** and **3** displaying the highest yields of transformation in both reactions. The use of MW heating lead to a considerable diminution in reaction times when compared to conventional heating. Neither coupling reaction may involve the formation of soluble palladium nanoparticles because the new catalytic system is very thermally and air stable, and is not affected by elemental mercury. The highest activity of **3** in the Suzuki-Miyaura reaction may be an indication that hemilability of S coordination is involved during the catalytic process. Compound **2** catalyzes the Mizoroki-Heck reaction with high regioselectivity and only the linear 1,2-products are obtained. Further investigations intended to clarify the mechanism and extend the scope of these novel catalysts are in progress.

Acknowledgments

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