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Selective Cyclopalladation of $R_3P{=}NCH_2Aryl$ Iminophosphoranes. Experimental and Computational Study

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The orientation of the orthopalladation of iminophosphoranes $R_3P{=}NCH_2Aryl$ (R = Ph, Aryl = Ph (**1a**), C_6H_4–2-Br (**1b**), C_6H_4–Me-2 (**1e**), C_6H_3–$(Me)_2$-2,5 (**1f**); R = *p*-tolyl, Aryl = Ph (**1c**); R = *m*-tolyl, Aryl = Ph (**1d**); R_3P = $MePh_2P$, and Aryl = Ph (**1g**)) has been studied. **1a** reacts with $Pd(OAc)_2$ (OAc = acetate) giving *endo*-[Pd(μ-Cl){*C,N*-$C_6H_4(PPh_2{=}NCH_2Ph)$-2}]$_2$ (**3a**), while *exo*-[Pd(μ-Br){*C,N*-$C_6H_4(CH_2N{=}PPh_3)$-2}]$_2$ (**3b**) could only be obtained by the oxidative addition of **1b** to $Pd_2(dba)_3$. The endo form of the metalated ligand is favored kinetically and thermodynamically, as shown by the conversion of *exo*-[Pd(μ-OAc){*C,N*-$C_6H_4(CH_2N{=}PPh_3)$-2}]$_2$ (**2b**) into *endo*-[Pd(μ-OAc){*C,N*-$C_6H_4(PPh_2{=}NCH_2Ph)$-2}]$_2$ (**2a**) in refluxing toluene. The orientation of the reaction is not affected by the introduction of electron-releasing substituents at the Ph rings of the PR_3 (**1c** and **1d**) or the benzyl units (**1e** and **1f**), and endo complexes (**3c**–**3f**) were obtained in all cases. The palladation of $MePh_2P{=}NCH_2Ph$ (**1g**) can be regioselectively oriented as a function of the solvent. The exo isomer [Pd(μ-Cl){$C_6H_4(CH_2N{=}PPh_2Me)$-2}]$_2$ (*exo*-**3g**) is obtained in refluxing CH_2Cl_2, while *endo*-[Pd(μ-Cl){*C,N*-$C_6H_4(PPh(Me){=}NCH_2Ph)$-2}]$_2$ (*endo*-**3g**) can be isolated as a single isomer in refluxing toluene. In this case, the exo metalation is kinetically favored while an endo process occurs under thermodynamic control, as shown through the rearrangement of [Pd(μ-OAc)-{$C_6H_4(CH_2N{=}PPh_2Me)$-2}]$_2$ (*exo*-**2g**) into [Pd(μ-OAc){*C,N*-$C_6H_4(P(Ph)Me{=}NCH_2Ph)$-2}]$_2$ (*endo*-**2g**) in refluxing toluene. The preference for the endo palladation of **1a** and the kinetic versus thermodynamic control in **1g** has been explained through DFT studies of the reaction mechanism.

Introduction

The metal-mediated activation of C−H bonds is one of the most important research topics nowadays due to its central role in the functionalization of organic substrates,[1] mainly hydrocarbons.[2] If there are two or more C−H bonds on a given molecule, then several possibilities of metalation exist, and the subsequent functionalization should result in a mixture of isomers. One of the most efficient methods to direct the metalation to a given position, for instance, in aryl rings, is the introduction of one ancillary coordinating group in the starting substrate, since the functionalization is produced at the ortho position of the ancillary group.[3] These reactions occur through the formation of orthometalated derivatives, and these kind of compounds are now considered as useful tools in metal-mediated synthesis[1,4] and catalysis.[1a−c,e,5] However, most substrates show two or more aryl groups

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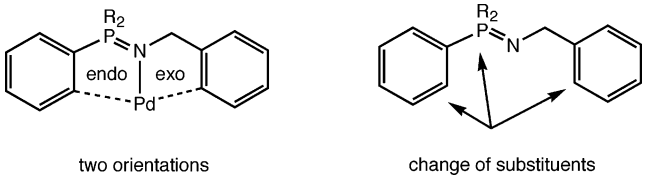

Figure 1. Orientations of the palladation and substituents changed through this work.

prone to be activated in similar structural environments. A typical case is the palladation of benzyl−benzylidene−amines [$C_6H_4C(H)$═$NCH_2C_6H_5$]. These substrates react with Pd(II) giving endo metallacycles—with an endocyclic C═N double bond—while exo metalation is obtained only if the endo form is disfavored by steric or electronic reasons.[6] This fact limits further reactivity of the starting substrate since only endo functionalization could be obtained.

Following our research work on C−H bond activations promoted by Pd(II) on iminophosphoranes,[7] a subject currently attracting the interest of chemists,[8] we present here a study of the palladation of several benzyl derivatives (Figures 1 and 2) in which a tailored change of substituents has been performed (Figure 1). These substrates display two almost equivalent metalation positions, one of them at one Ph ring of the $PPhR_2$ unit and another one at the aryl ring of the benzyl unit, which can behave as competitive activation sites, one of our main purposes being the study of the orientation of the reaction. We can speak of "almost" equivalent positions, since in the two cases the activation of a $C(sp^2)$ − H bond is involved and the formation of a five-membered palladacycle is achieved. The difference between the two activations lies, obviously, in the nature of the substituents, since the Ph ring at the phosphonium group is strongly deactivated with respect to that of the benzyl unit due to the presence of a formal positive charge at the P atom. In addition, the location of the P═N double bond with respect to the metallacycle is also determinant, since the endo arrangement seems to be more stable than that of the exo arrangement (Figure 1).[9] We have observed for most systems that the endo arrangement is kinetically and thermodynamically favored, except for Ph_2MeP═NCH_2Ph (**1g**), in which a regioselective exo- or endo-metalation is obtained as a function of the reaction temperature. All these facts have been adequately explained through molecular modeling of the complete systems, without simplifications, and study of the reaction mechanism using theoretical methods.

Results and Discussion

1. Orientation of the Palladation Position on Benzyl Iminophosphoranes. Compound **1a** has been prepared from the corresponding azide[10a] using the Staudinger method.[11] The reaction of **1a** with $Pd(OAc)_2$ (OAc = acetate, 1:1 molar ratio, Scheme 1) in refluxing toluene for 30 min, followed by solvent evaporation, dissolution of the residue in MeOH, and treatment of the solution with excess LiCl, gives the dimer [Pd(μ-Cl){*C*,*N*-$C_6H_4(PPh_2$═$NCH_2Ph)$-2}]$_2$ (**3a**). Compound **3a** is obtained as a mixture of the cis and trans geometric isomers (1:1.5 molar ratio), although an unambiguous assignment of each structure could not be done. Compound **3a** can also be obtained in less drastic reaction conditions (CH_2Cl_2, reflux, 1 h; CH_2Cl_2, room temperature (r.t.), 5 h), although in these cases the yields are substantially lower. The preparation of the acetate dimer [Pd(μ-OAc)-{*C*,*N*-$C_6H_4(PPh_2$═$NCH_2Ph)$-2}]$_2$ (**2a**) can be done by direct reaction of $Pd(OAc)_2$ with **1a**, as we have just described, but treating the residue with Et_2O after toluene evaporation. However, the product **2a** thus obtained contains many impurities, which were very difficult to remove. The reaction of **3a** with AgOAc (1:2 molar ratio) in CH_2Cl_2 affords pure **2a**, the latter method being the best synthetic alternative (see the Supporting Information (SI)).

The IR spectra of **2a** and **3a** clearly show that the iminophosphorane is N-bonded, since the ν_{PN} stretch appears at lower energies (1257 cm^{-1}, **3a**; 1278 cm^{-1}, **2a**) than those in the free ligand **1a** (1303 cm^{-1}). This shift to low energies, compared with the corresponding free ligands, is a general feature of all complexes reported here. The $^{31}P\{^1H\}$ NMR spectrum of **3a** shows two peaks at 52.29 and 53.73 ppm.

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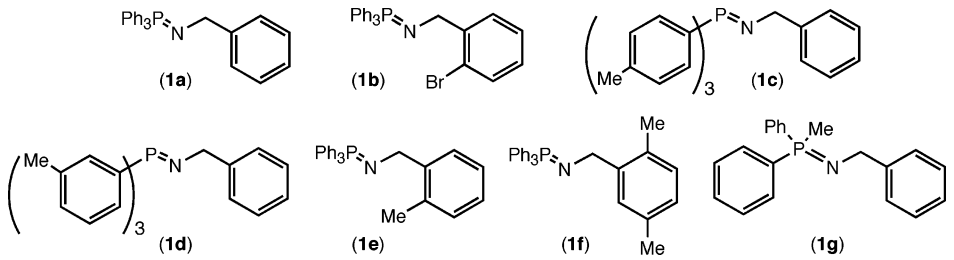
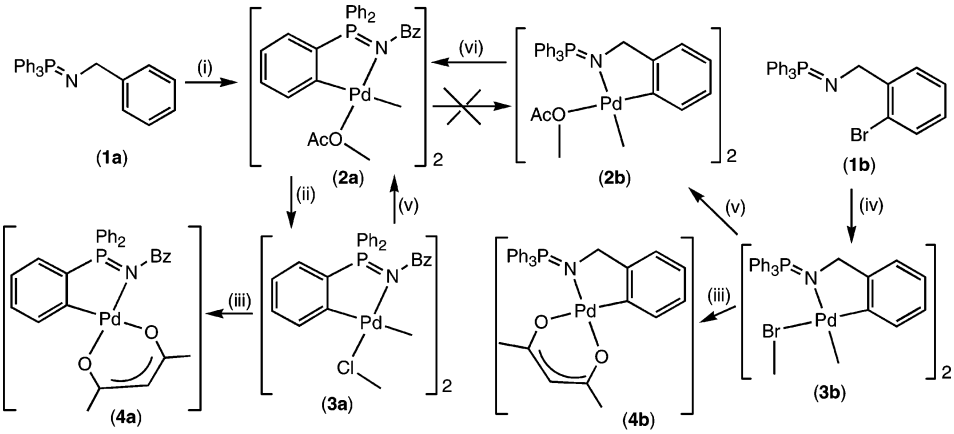


Figure 2. Iminophosphoranes employed throughout this work.

Scheme 1



Scheme 1

The position of these two peaks suggest that an endo palladation has taken place,[7a] since they are strongly deshielded, not only with respect to the free ligand **1a** (13.54 ppm) but also with respect to the usual range found in N-bonded coordination compounds (about 30 ppm).[12] The presence of the orthopalladated unit Pd(C_6H_4) is also evident from the $^{13}C\{^1H\}$ NMR spectrum, due to the observation of two peaks at 150.13 and 150.40 ppm, assigned to the metalated carbon atoms. Thus, the presence of two peaks is attributed to the fact that **3a** is obtained as a 1:1.5 mixture of two geometric isomers, cis and trans, depending of the relative arrangement of the two cyclopalladated groups. Similar conclusions can be derived form the analysis of the IR and NMR spectra of **2a**, although in this case only one isomer is present. The ^1H NMR spectrum of **2a** suggests that this complex displays the usual "open-book" structure for dinuclear acetate-bridging complexes,[6g] since the signals assigned to the diastereotopic protons of the $PNCH_2$ group appear as the AB part of an ABX spin system. These facts suggest that **2a** is obtained as the trans isomer, probably to minimize intramolecular interactions. The complete characterization of the palladated group [Pd{*C*,*N*-C_6H_4(PPh_2=NCH_2Ph)-2] has been carried out in the most soluble complexes with acac ligands **4a** (see Scheme 1 and SI) and with phosphine ligands [Pd{*C*,*N*-C_6H_4(PPh_2=NCH_2Ph)-2}Cl(PPh_2Me)] (**5a**).

The selective metalation observed in **1a** is not a complete surprise. This ligand shows a notable asymmetry on the electron density; then it could be expected a selective response of the system. What is more surprising is where the metalation has been finally produced. In principle, one could expect that the most favorable ring for the palladation reaction should be that of the benzylic phenyl, since it seems to be more electron rich than the Ph rings belonging to the deactivating phosphonium atom and since the palladation reaction occurs through an electrophilic substitution on an aromatic ring.[13] Thus, an exo metalation should be expected. From the preceding paragraphs, it is clear that **1a** has a strong preference for the endo palladation. This apparently opposite behavior could have a plausible explanation based on additional electronic grounds, mainly on a factor called metalloaromaticity.[14] This concept, defined as the presence of a partial aromatic character in metallacycles, can be reflected in endo compounds due to the presence in the palladacycle of two conjugated double bonds, the C=C double bond of the metalated aryl and the iminic P=N bond and the appropriate filled d orbitals of the Pd atom. It is clear that this conjugation is not available in exo compounds. The partial aromaticity is accompanied by a given amount of resonance energy stabilization, and thus the endo complexes are energetically more stable than the exo complexes. Thus, it seems that two counterbalancing factors could be operative in the metalation of **1a**−**1g**, the amount of electron density available on each aryl ring and the possible endo effect in the resulting palladacycle.

We have attempted the synthesis of the exo complex **2b** from **1a** and $Pd(OAc)_2$, but with a change in the reaction conditions. The reactions performed at higher temperatures

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or in toluene at longer reaction times proceed with complete decomposition. When the reactions were carried out at lower temperatures (CH_2Cl_2, 0 °C), endo **2a** was obtained. When the reaction of $Pd(OAc)_2$ with **1a** in CD_2Cl_2 was monitorized by NMR, the only detected species at any stage of the reaction were the reactants and **2a**.

The synthesis of the exo derivative **3b** has been successfully achieved only by oxidative addtion of the bromine derivative **1b** to $Pd_2(dba)_3 \cdot CHCl_3$[10b] (2:1 molar ratio, Scheme 1) in CH_2Cl_2 at r.t. The initial deep violet suspension slowly transforms into a yellow solution with Pd^0 in suspension, which can be removed by filtration. Pure **3b** can be isolated in good yield after solvent evaporation and Et_2O addition. The NMR spectra of **3b** clearly suggest the exo metalation of **1b** and also show that **3b** is obtained as a mixture of cis and trans isomers, with a different molar ratio (1:3.25) than that observed for **3a** (1:1.5). The $^{31}P\{^1H\}$ NMR spectrum of **3b** shows two peaks at 31.11 and 31.35 ppm, deshielded with respect to **1b** (13.17 ppm) and in the typical region of the N-bonded iminophosphoranes.[12] This fact means that the chemical environment of the P atom is very different from that observed in **3a**, while it is similar to those found in simple N-bonded derivatives, and that the P═N bond is not involved on any palladacycle.

Following a similar scheme of reactivity for that described for **3a**, we have prepared the dinuclear μ-acetate complex **2b** and the acetylacetonate **4b**. The purpose of the synthesis of **2b** is the study of the interconversion of the exo and endo forms of the metalated ligand[6e,f] (see below), and **4b** has been prepared to fully characterize the palladated [$Pd(C_6H_4$-$(CH_2N{=}PPh_3)$-2)] unit. Complex **2b** is obtained by the reaction of **3b** with AgOAc (1:2 molar ratio), and **4b** is prepared by the reaction of **3b** with Tl(acac) (acac = acetylacetonate; 1:2 molar ratio) as shown in Scheme 1. The reported reactivity of **1a** toward $Pd(OAc)_2$ clearly shows that one CH bond of the PPh_3 unit is selectively activated, giving the endo isomer, and that the problems found in the synthesis of the exo isomer were overcome using the functionalized **1b** and a different synthetic pathway. The relative stability of the two bonding modes (endo **a** and exo **b**) has been determined through the study of their mutual interconversion. Previous reports on the synthesis of exo and endo palladated complexes from imines have shown that, in most cases, the μ-acetate exo complex can rearrange into the μ-acetate endo isomer by heating in acetic acid.[6a,e,f] Other reports have established the exchange of palladation positions on amine derivatives, also in acetic acid,[15] while very few reports have been described in other solvents.[16] In our case, the reaction proceeds in aprotic solvents. The heating of isolated **2b** in CD_2Cl_2 at 35 °C shows a slow transformation into **2a**. No other compounds were identified by ^1H and ^{31}P NMR monitoring of the reaction. The reaction rate can be accelerated by heating in toluene at 90 °C, which produces a clean transformation of **2b** into **2a** in few minutes. The heating of **2a** does not produce any rearrangement. These experiments show that **2a** is thermodynamically more stable than **2b**, since **2a** is formed from **2b**. They also show that **2a** is kinetically more accessible than **2b**, since from the early stages of the reaction only **2a** is formed and **2b** is not observed, even when CH_2Cl_2 is used as the reaction solvent. However, the synthesis of **2b** should show a reachable energy barrier, since **2b** can rearrange to **2a**. Obviously, in the reaction conditions the exo metalation is not competitive, due to the kinetic and thermodynamic preferences for the endo activation. All these facts have been confirmed through DFT analysis of the reaction profiles—thermodynamic stabilities and energy barriers of the transition states—for the exo and the endo palladation of **1a**.

The transformation of **2b** into **2a** in nonprotic solvents seems to suggest an intramolecular transfer of the proton, although the participation of the solvent in the proton transfer (mainly in the case of toluene) could not be discarded.[17] Interestingly, the presence of a ligand able to act as an intramolecular base seems to be important. The heating of complex **3b**, under the reaction conditions described for **2b**, does not produce appreciable changes. Under harsh conditions, the decomposition of **3b** occurs. However, the heating of the acetylacetonate **4b** in toluene results in its slow and clean rearrangement into **4a**. This transformation is slower than that observed for **2b**, since after 1 h of heating of **4b** in toluene at 90 °C, the ^{31}P NMR spectrum shows the presence of a mixture of **4b**/**4a** (1:2). These facts could be related with a plausible role of the basic ligand assisting the H transfer from one ring to another. As we will see later, the acetate ligand plays a critical role on capturing the proton resulting of the C−H bond activation, stabilizing the orthopalladated product. In this context, the acetate and acetylacetonate ligands could behave similarly, differing markedly from the acid−base behavior of the halide ligand.

2. Effects of the Substituents at the R_3P and CH_2Aryl Rings. We have introduced electro-donating substituents on the phenyl rings of the phosphonium group and the benzyl unit to check if the orientation of the reaction can be modulated as a function of the presence of these substituents. If the orthopalladation occurs through an electrophilic substitution on an aromatic ring, the reactivity of the tolyl-functionalized iminophosphoranes **1c** and **1d** should again give endo metalations. In the case of the benzyl compounds **1e** and **1f**, a more competitive situation is expected.

According to this, the reaction of $Pd(OAc)_2$ with **1c** or **1d** in refluxing CH_2Cl_2 and subsequent metathesis of the bridging ligand by treatment with LiCl in methanol gives the chloride-bridging complexes [$Pd(\mu$-Cl)$\{C,N$-C_6H_3(Me-5)$(P(p$-tol$)_2{=}NCH_2Ph)$-2$\}]_2$ (tol = tolyl) (**3c**) and [$Pd(\mu$-Cl)-$\{C,N$-C_6H_3(Me-4)$(P(m$-tol$)_2{=}NCH_2Ph)$-2$\}]_2$ (**3d**) (Scheme 2)

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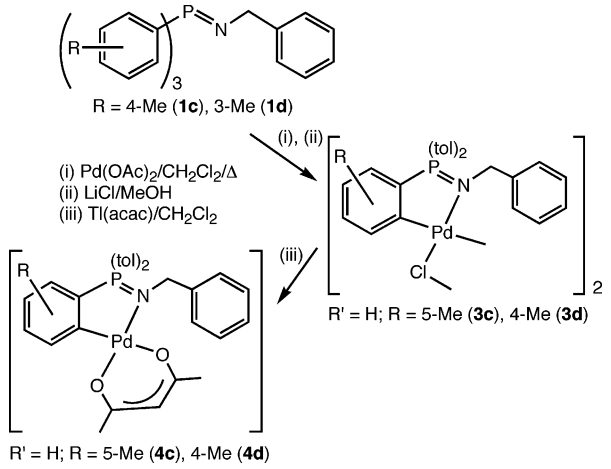
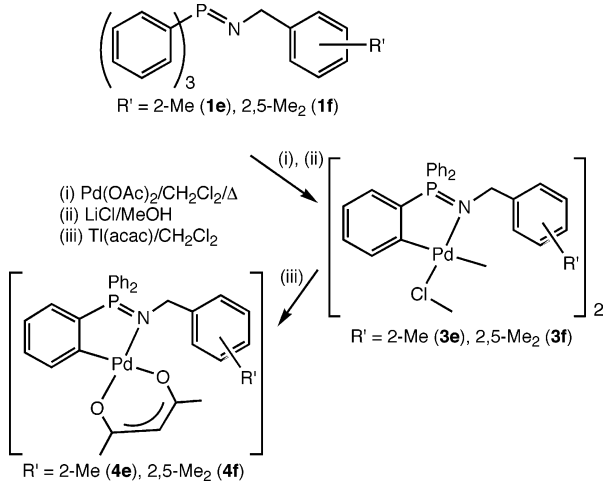
Scheme 2



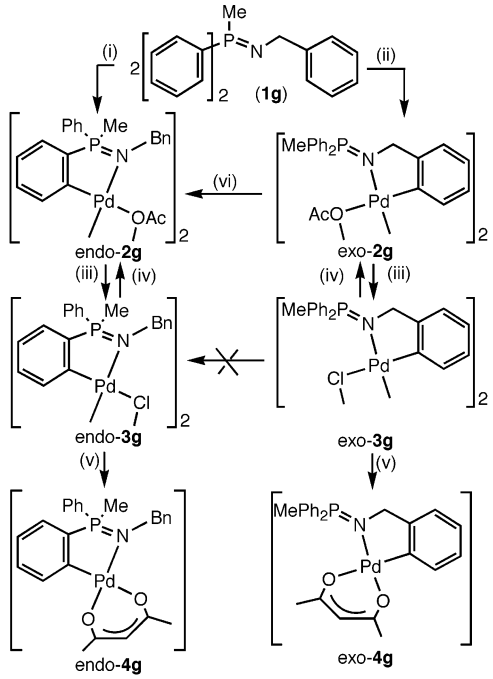
Scheme 3



As expected, the endo metalation has been obtained, as inferred from their $^{31}P\{^1H\}$ NMR spectra (signals around 53−55 ppm). Further characterization has been carried out on the acetylacetonate **4c** and **4d**, obtained by the reaction of **3c** and **3d** with Tl(acac) in a 1:2 molar ratio (Scheme 2). The ^1H NMR spectrum of **4c** shows, among others, signals assigned to the presence of a PdC_6H_3 group (multiplets at 6.80 and 6.98 ppm) and four different methyl groups, both facts confirming the endo metalation. The NMR spectra of **4d** show similar features and also that the palladation has been produced selectively at the 6 position of the P(C_6H_4-Me-*m*) ring, that is, at the least hindered position.

The reaction of the methyl substituted iminophosphoranes **1e** and **1f** (see Scheme 3) with $Pd(OAc)_2$ gives the ortho-metalated [Pd(μ-Cl){*C*,*N*-C_6H_4(PPh_2═$NCH_2C_6H_4$−Me-2′)-2}]$_2$ (**3e**) and [Pd(μ-Cl){*C*,*N*-C_6H_3(PPh_2═$NCH_2C_6H_4$-$(Me)_2$-2′,5′)-2}]$_2$ (**3f**). These complexes have also been characterized as the endo isomers, since the $^{31}P\{^1H\}$ NMR spectra show on each case two signals in the 52−53 ppm region. The synthesis of the corresponding acac complexes **4e** and **4f** (Scheme 3) by reaction of **3e** or **3f** with Tl(acac) (1:2 molar ratio) and their characterization confirm the C−H bond activation at the Ph rings of the PPh_3 unit, that is, the endo metalation, despite the presence of one or even two activating methyl groups at the benzyl unit.

Scheme 4



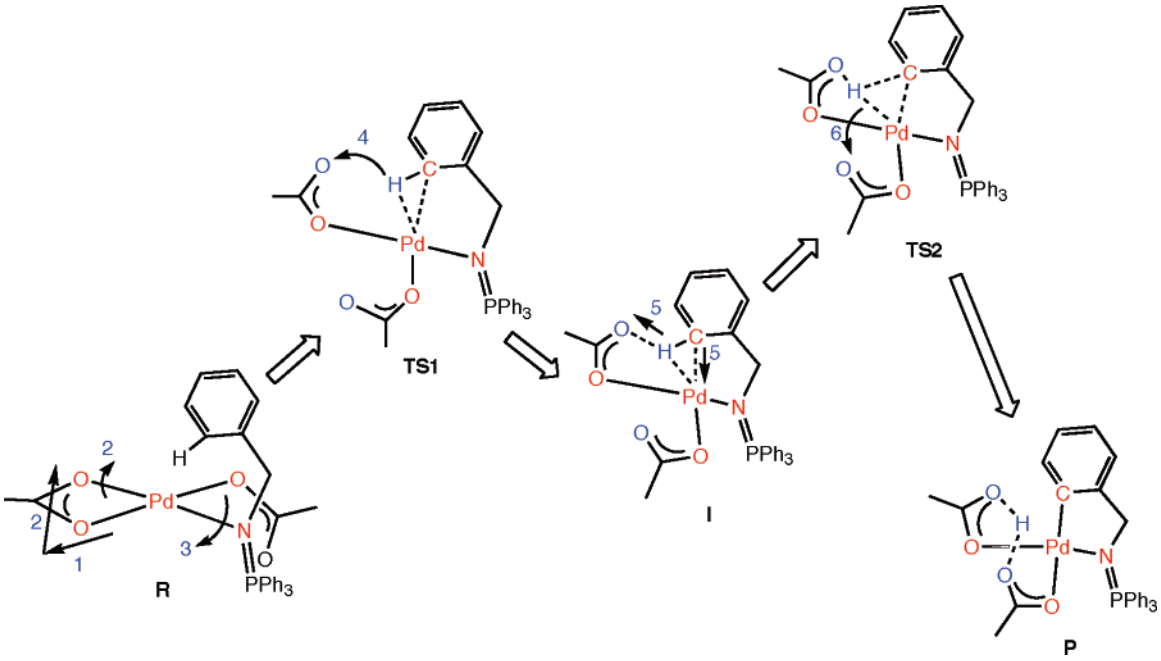
In conclusion, the endo effect dominates the orientation of the palladation reaction of these substrates over other electronic or steric parameters, such as the presence of activating (Me) or deactivating (P^+) substituents at the phenyl rings.

3. Effects of the Substituents at the Phosphorus Atom. The replacement of a phenyl by a methyl group directly on the P atom of the starting iminophosphoranes exerts a stronger influence over the orientation of the palladation than that in preceding cases. In fact, the reactivity of Ph_2MeP═NCH_2Ph (**1g**) toward $Pd(OAc)_2$ and the orientation of the reaction is strongly dependent on the reaction temperature.

1g reacts with $Pd(OAc)_2$ (1:1 molar ratio) in refluxing CH_2Cl_2 to give the exo complex [Pd(μ-OAc){*C*,*N*-C_6H_4(CH_2N═PPh_2-Me)-2}]$_2$ (*exo*-**2g**), which after acetate−chloride metathesis in methanol gives [Pd(μ-Cl){*C*,*N*-C_6H_4(CH_2N═PPh_2Me)-2}]$_2$ (*exo*-**3g**) (Scheme 4). As described for **2a**,**b**, the synthesis of the μ-acetate *exo*-**2g** is best accomplished by reaction of *exo*-**3g** with AgOAc (1:2 molar ratio), and the full characterization of the metalated ligand has been carried out on the acetylacetonate *exo*-**4g**, prepared by reaction of *exo*-**3g** with Tl(acac) in a 1:2 molar ratio. The palladation of **1g** is clear from the presence, in the ^1H NMR spectrum of **3g**, of four peaks assigned to the PdC_6H_4 unit. Moreover, the exo arrangement of the metalated ligand, that is, the palladation of the benzyl group, is easily inferred from its $^{31}P\{^1H\}$ NMR spectrum (two peaks around 35 ppm). Similar conclusions can be derived from the NMR spectra of *exo*-**2g**, except that in this case only one isomer (probably the trans isomer) is observed.

However, the reaction of **1g** with $Pd(OAc)_2$ (1:1 molar ratio) in refluxing toluene affords *endo*-**2g**, which can be

Scheme 5



transformed into *endo*-**3g** after the usual acetate−chloride metathesis in methanol. Obviously, *endo*-**2g** can be obtained by the reaction of *endo*-**3g** with AgOAc (1:2 molar ratio), and the acetylacetonate *endo*-**4g** is obtained by the reaction of *endo*-**3g** with Tl(acac) (1:2 molar ratio, Scheme 4). The NMR spectra of dinuclear complexes *endo*-**2g** and *endo*-**3g** show more signals than those observed for *exo*-**2g** and *exo*-**3g**, since four sets of signals are observed on each spectrum. This is due to the fact that endo complexes are obtained as mixtures of cis and trans isomers and that each isomer is obtained as a mixture of two diastereoisomers (RR/SS and RS/SR pairs). The presence of diastereoisomers arises from the fact that the endo C,N-metalation of the $Ph_2MeP{=}N$ fragment transforms the P atom on a chiral center, and each dinuclear complex possess two chiral centers. Thus, we have two diastereoisomers with cis arrangements and another two with trans arrangements. This give a total of four isomers, corresponding to the four sets of signals observed. Moreover, the chemical shifts of the four peaks observed in the $^{31}P\{^1H\}$ NMR spectrum of *endo*-**3g** (ranging from 57 to 59 ppm) and *endo*-**2g** (ranging from 53 to 58 ppm) confirm the endo metalation.

The opposite orientation found for the metalation in refluxing CH_2Cl_2 (exo regioselective) and in refluxing toluene (endo regioselective) drives an additional question: Is the nature of the solvent or the reaction temperature—or both—the true parameter governing the selectivity of the reaction? To gain more insight on this process we have performed the same reaction, in the same solvent (toluene), but at different temperatures. The treatment of **1g** with $Pd(OAc)_2$ in 1:1 molar ratio in toluene at 45 °C results in the selective formation of *exo*-**2g**, and the same result was obtained in toluene at 60 °C. However, when the reaction is carried out at 85 °C, an equimolecular mixture of *exo*-**2g** and *endo*-**2g** is obtained, and we have already stated that the reaction performed at the reflux temperature (111 °C) gives the isomer *endo*-**2g** regioselectively.

Thus, it seems that the true parameter governing the selectivity of the reaction is the reaction temperature, since the same result has been observed with two different solvents at almost the same temperature. Once the temperature increases and the threshold for *endo*-**2g** is reached, the relative amount of *exo*-**2g** decreases and that of *endo*-**2g** increases, until at the reflux temperature of toluene, *endo*-**2g** is obtained regioselectively. All these facts strongly suggest that the isomer obtained at the lowest temperature (*exo*-**2g**) is the kinetic isomer of the reaction, since the reaction is under kinetic control, while the product obtained at the highest temperature (*endo*-**2g**) is the thermodynamic isomer. The easy and clean conversion of *exo*-**2g** into *endo*-**2g** (Scheme 4) by simple reflux in toluene gives additional proof. This reaction was monitorized by ^{31}P NMR, and during the heating of a sample of *exo*-**2g** in toluene-d_8, the only observed species were *exo*-**2g** and *endo*-**2g**.

Intramolecular ligand exchanges similar to that here described have been reported in the literature,[6a,e,f,13,15,16] but in most cases the reason of the observed selectivity is probably related to the different nature of the solvents (for instance, $CHCl_3$ versus acetic acid), this fact being related with the different behavior of $Pd(OAc)_2$ in different solvents.[15b,f] Moreover, we have already mentioned that on isomerization of *exo*-**2b** into *endo*-**2a** that the ligand exchanges usually need acetic acid, but that in our cases—also in the isomerization of *exo*-**2g** into *endo*-**2g**—this process occurs in toluene. More interesting is the fact that the synthesis of *exo*-**2g** occurs using the same starting compounds and the same solvent as that of *endo*-**2g**, with the only difference being the reaction temperature. In these conditions, the regioslective synthesis of *exo*-**2g** is worthy of note, since this case seems to be the only reported example

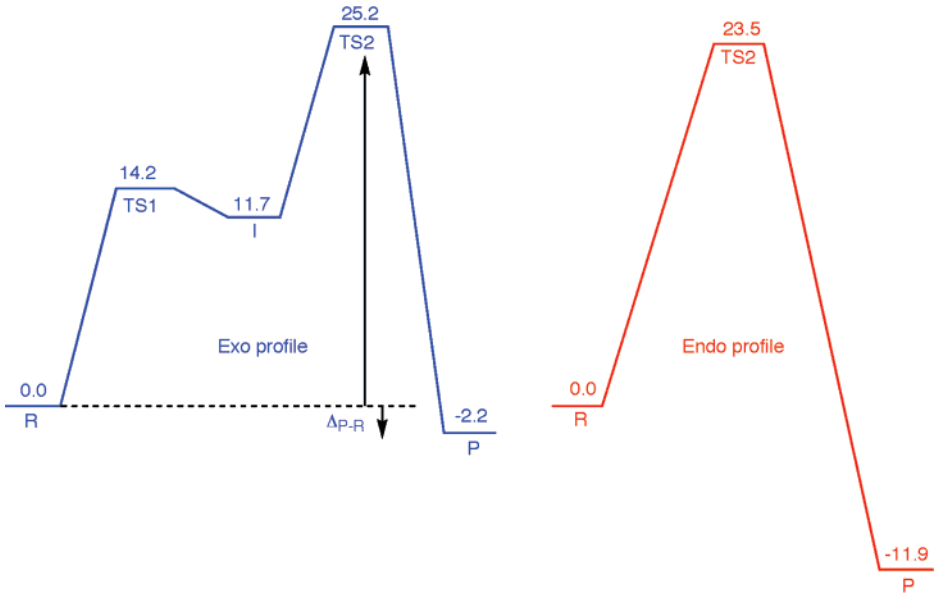


Figure 3. Computed reaction profiles (kcal/mol) for the exo and endo C−H bond activation of **1a** in toluene as solvent. The zero energy point has been taken at the [Pd(κ^2-OAc)(κ^1-OAc)(κ^1-*N*-**1a**)] species.

in which a palladation induced by $Pd(OAc)_2$ neglects the endo effect and, under controlled conditions, metalates in exo position despite (i) the presence of the same type of bonds to be activated on the two sides of the molecule (Csp^2−H), (ii) the nature of the solvent (CH_2Cl_2 or toluene), and (iii) the fact that a five-membered ring can be formed on either the exo and endo metalations.

In fact, assuming that the reaction occurs through electrophilic substitution, the exo palladation of **1g** under kinetic control can be easily explained by taking into account that the phenyl ring of the benzyl unit must be more electron rich than any phenyl ring attached to the positively charged phosphorus atom and that the former should most likely be the point of attack of the Pd center. Further evolution of *exo*-**2g** to *endo*-**2g** occurs under thermodynamic control in toluene, so it is not possible to invoke a nucleophilic behavior of the palladium salt[15b,f] to explain the shift of the Pd center from the electron-rich ring in *exo*-**2g** to the electron-deficient phenyl in *endo*-**2g**. In that case, the endo effect could provide a reasonable argument, on the grounds of the stabilization provided by the metalloaromaticity. Unfortunately, this easy explanation is not a general answer for the behavior observed on systems **1a** or **1c**−**1f**, for which only the consideration of the endo effect provides sensible and efficient arguments. In conclusion, the result of the reaction seems to reside in a delicate counterbalance between two factors orienting the metalation at opposite sites. On one hand, the electrophilic behavior of $Pd(OAc)_2$ in CH_2Cl_2 or toluene orientates the metalation to the more electron-rich benzyl ring. On the other hand, the endo effect orientates the palladation to the electron-deficient Ph ring at the P(+) atom.

4. Theoretical Study of the Reaction Mechanism. In order to shed light on the different selectivities shown during the metalation of iminophosphoranes **1a**/**1b** and **1g**, we have performed theoretical calculations of the mechanism of the orthopalladation reaction. The studies have been performed using the real complexes without any simplification in the ligands. In the case of the $Pd(OAc)_2$/**1a** system, the size of the system prevents a complete exploration of the potential energy surface at a quantum mechanical (QM) level. This exploration was carried out using a quantum mechanics/molecular mechanics (QM/MM) methodology. Thus, endo and exo profiles were built using the ONIOM[18] (B3LYP[19]/UFF[20]) method, describing two phenyl rings of the PPh_3 unit at a MM level. To take into account the electronic effects of these phenyls, the energy of each QM/MM-optimized structure was computed using full QM calculations (DFT at the B3LYP level).[19] For the system $Pd(OAc)_2$/**1g**, the endo and exo profiles were also built over the whole model using DFT (B3LYP level) calculations.[19] Although different levels of theory have been used on each system, there are not inconsistencies, since it has been shown that both methodologies are in very good agreement.[21h] Finally, solvent effects were taken into account in all calculations by means of a

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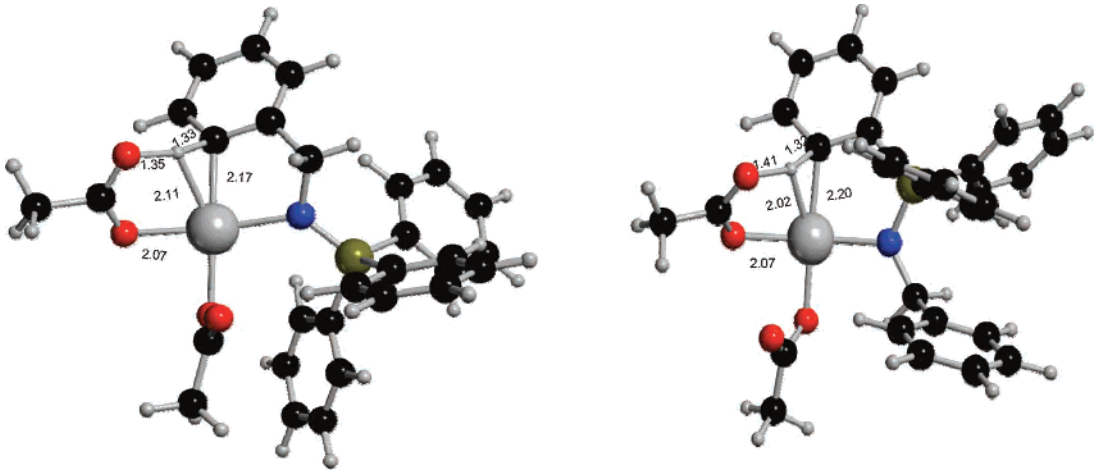

Figure 4. Computed structures for the **TS2** of *exo*-**1a** (left) and *endo*-**1a** (right); distances in Å.

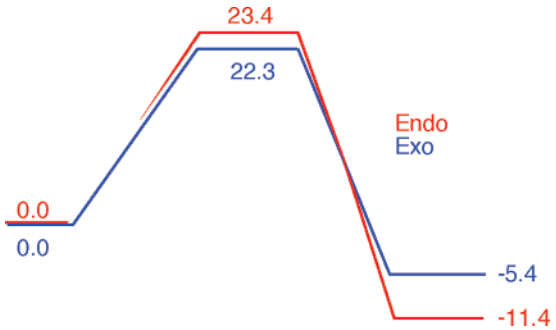

Figure 5. Computed reaction profiles (kcal/mol) for the exo and endo C−H bond activation of **1g** in toluene as solvent. The zero energy point has been taken at the [Pd(κ^2-OAc)(κ^1-OAc)(κ^1-*N*-**1g**)] species.

continuum description of the solvent with the CPCM[22] method using standard options.

The mechanism of the cyclopalladation of amines has been recently studied by DFT methods,[21a−c] and we have assumed an identical pathway for our system (Scheme 5). This mechanism implies the N-bonding of the ligand to be metalated in the reactants (R), the formation of a six-membered transition state (**TS1**, **I**, **TS2**), and the transfer of the H atom to a coordinated acetate to give the orthometalated final products (P) (see SI for computed structures). This general scheme and the proposal of a six-membered ring in the TS is similar to those proposed in the literature from experimental results,[15b,f] and fits with previous data. Similar TSs have been described for other systems.[21d−f]

The energy profile found for the exo metalation of **1a** shows the same steps reported by Mcgregor (Figure 3 and Scheme 5),[21a] with an agostic intermediate **I** 2.7 kcal/mol more stable than the transition state **TS1** (Figure S2, SI). The activation barrier of the reaction is defined by the **TS2** transition state (Table 1 and Figure 4). In the case of the endo palladation of **1a**, the reaction profile (Figure 3) is simpler than that reported,[21a] since only one TS (**TS2**, Figure 4) is found, despite intensive research on the region where the agostic intermediate is supposed to be found. The structures of the reactants (**R-1a**) and products (**P-1a**) are shown in the SI (Figures S1 and S3).

As evident from the values collected in Table 1, the endo orthopalladation is thermodynamically preferred in the gas phase and also in the two studied solvents. A small energy gain Δ_{P-R} is obtained through the exo process (0.8−2.2 kcal/mol), while the computed stabilization through the endo pathway amounts for more than 9 kcal/mol (9.3−13.2 kcal/mol). The introduction of the solvent[22] in these systems promotes non-negligible changes in the Δ_{P-R} values, and a small stabilization is observed for the exo metalation, while a small destabilization is produced for the endo process. The tendencies are the same, irrespective of the solvent considered, and the endo metalation of **1a** is thermodynamically preferred over the exo one. The analysis of the activation barriers of **TS2** shows also a kinetically favored endo process, both in gas phase and in the two solvents. In this case, the introduction of solvent produces a small stabilization of similar extension in both the endo and exo pathways. The computed energy barriers and reaction energies perfectly match the experimental facts and account for the regioselective endo metalation of ligand **1a**, since it is kinetically (lower value of **TS2** barrier in all solvents) and thermodynamically favored (higher release of energy in all solvents),

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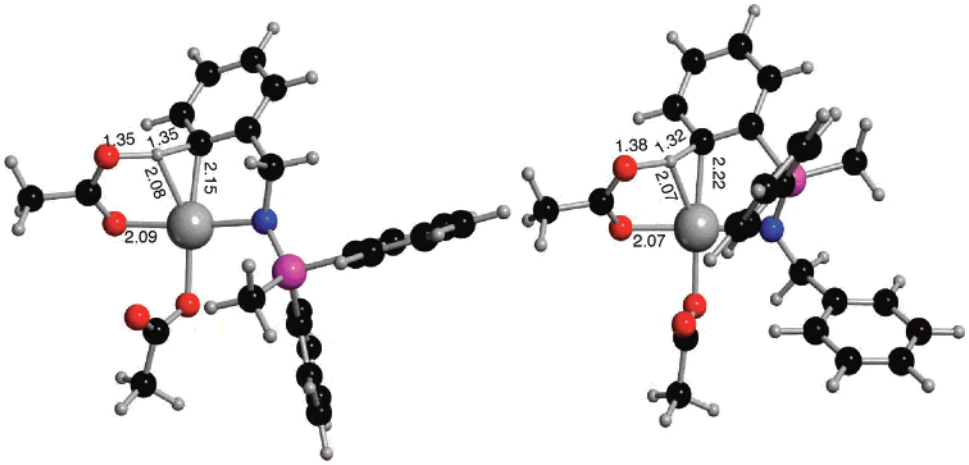


Figure 6. Computed structures for the TSs of *exo*-**1g** (left) and *endo*-**1g** (right); distances in Å.

Table 1. Activation Barriers (**TS2**) and Stabilization Energies (Δ_{P-R}) for the exo and endo Reaction Pathways in Gas Phase and in Different Solvents (Energies in kcal/mol)

	EXO_{gas}	$ENDO_{gas}$	EXO_{tol}	$ENDO_{tol}$	EXO_{dcm}	$ENDO_{dcm}$
1a−**TS2**	27.4	24.7	25.2	23.5	25.7	23.3
1a−Δ_{P-R}	−0.8	−14.0	−2.2	−11.9	−1.5	−10.8
1g−**TS2**	26.3	24.8	23.3	23.9	22.3	23.4
1g−Δ_{P-R}	−1.8	−11.8	−5.3	−12.3	−5.4	−11.4

Table 2. Decomposition of the Gas-Phase Energy Barriers Calculated Following Scheme 6 (Energies in kcal/mol)

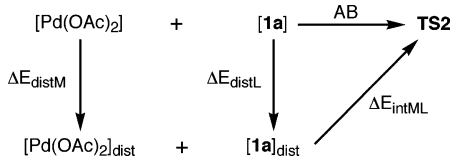
	ΔE_{distL}	ΔE_{distM}	ΔE_{intML}
endo-**1a**	31.0	24.7	−31.0
exo-**1a**	36.2	28.6	−37.4
endo-**1g**	33.6	25.6	−34.4
exo-**1g**	37.4	26.8	−37.9

and both facts militate against the existence of the exo pathway. The values given in Table 1 also agree with the easy transformation of *exo*-**2a** (or *exo*-**P-1a**) into *endo*-**2a** (or *endo*-**P-1a**) in refluxing toluene. The energy barrier of this reverse process amounts to 27.4 kcal/mol, that is, only 2.2 kcal/mol more than that of the direct process (Figure 3). This barrier is reachable in refluxing toluene, affording the most stable endo isomer. Although there is a clear kinetic preference for the endo metalation in **1a**, the difference between the endo and exo barriers is small (2−3 kcal/mol), suggesting that this preference could be reversed by small changes in the system or in the reaction conditions.

While the differences in the stabilization energies (Δ_{P-R}) between the exo and the endo palladations could be intuitively assigned to the endo effect, a thermodynamic factor, the reasons for the energy differences at the transition states of **TS2** are far from clear, and we have attempted an analysis of the activation barrier energy and its different components. We can consider the formation of the transition states (*exo*-**TS2** and *endo*-**TS**) from the $Pd(OAc)_2$ and **1a** fragments when infinitely apart (Scheme 6). The energy of this reaction is the activation barrier of the process (AB) and can be decomposed in three terms: two of them account for the distortions of the ligand **1a** and the metallic fragment $Pd(OAc)_2$ from their isolated optimized geometries to the final geometries in the complex (ΔE_{distL} for the ligand **1a** and ΔE_{distM} for the palladium fragment) and the other one accounts for the interaction energy of the distorted fragments to give the complex (ΔE_{intML}). The data presented in Table 2 show that the distortions needed to build the transition state in the exo pathway (64.8 kcal/mol) are larger than those needed in the endo process (55.7 kcal/mol). Although some of this energy is compensated for by a higher release after coordination of the distorted ligand to the distorted metal in the exo than in the endo process (37.4 kcal/mol versus 31.0 kcal/mol), its amount is not enough to favor the exo process, and the energy balance drives an easier endo metalation. In fact, the ΔE_{distL} and ΔE_{intML} terms almost compensate, and the barriers follow the trend of the ΔE_{distM} term. Thus, the endo metalation of **1a** is favored due to two concomitant facts. The first one is the own endo effect, which seems to be responsible for the higher thermodynamic stabilization of the endo metalation. The second one is the distortion needed on the ligands and metallic fragments to reach the transition state, since the endo pathway requires lower distortion energies and follows a lower energy path.

The computed profiles of the palladation of iminophosphorane **1g**, endo and exo, are shown in Figure 5, the structures of the respective transition states (**TS2**) are shown in Figure 6, and the structures of the reactants (**R-1g**) and the orthopalladated products (**P-1g**) are shown in Figures S4 and S5 (SI), respectively. The thermodynamic preference for the endo compound is doubtless, since the stabilization Δ_{P-R} for the endo compound is almost 11.8 kcal/mol while that found for the exo is only 1.8 kcal/mol, both values in gas phase. However, the computed barriers in gas phase give a slightly higher value for the exo process (26.3 kcal/mol) than for the endo process (24.8 kcal/mol), meaning that the endo metalation is favored, at least in the gas phase. A similar conclusion is obtained from computed $\Delta G(298)$ values (Figure S6, SI), meaning that the entropic contribution does not modify the energy profile. As discussed above, the small difference in the energy barriers of the endo and exo pathways suggests that the process could be tuned as a function of the reaction medium. The simulation of the reaction solvent by means of Tomasi polarized continuum model reaction−field calculations[22] induces remarkable

Scheme 6



changes, mainly at the TSs, and reverses the tendencies. When CH_2Cl_2 is considered, the TS for the exo pathway is stabilized almost 4 kcal/mol (22.3 kcal/mol) and the energy of the metalated final product drops 3.7 kcal/mol, reflecting a thermodynamic stabilization of 5.4 kcal/mol. More interestingly, although the endo derivative is still thermodynamically preferred (−11.4 kcal/mol) in CH_2Cl_2, it shows a higher TS barrier (23.4 kcal/mol). When toluene is considered as solvent, we still found a lower barrier for the exo pathway (Table 1), although the difference is very small. This higher stabilization for the exo structure as the polarity of the solvent increases is probably related with the higher dipole moment at the *exo*-TS (7.7 D) than at the *endo*-TS (6.9 D). All these facts allow the elaboration of a sensible explanation of the experimental facts. At low *T* values, the process is under kinetic control, since the reaction occurs only through the lowest energy barrier (*exo*-TS). At high *T* values, the process is under thermodynamic control, since both barriers can be reached, but only the most stable product is formed (endo ΔG).

The analysis of the activation barrier energy (**TS2**) for the metalation of **1g** does not give clear-cut processes, as those seen for **1a**. The distortion energies amount to 59.2 kcal/mol for the endo process and 64.2 kcal/mol for the exo process ($\Delta = 5$ kcal/mol), while the energy released by coordination is 34.8 kcal/mol for the endo pathway and 38.9 kcal/mol for the exo one ($\Delta = 4.1$ kcal/mol). That is, the energy balance is almost compensated, since a higher energetic cost in the distortion of the ligands is also accompanied with a higher energy release by coordination. Very small changes (such as a change in the polarity of the reaction medium) could be definitive factors to drive the reaction to one specific pathway.

Conclusions

The C−H bond activation on iminophosphoranes $R_3P{=}NCH_2Aryl$ induced by $Pd(OAc)_2$ gives two types of orthopalladated complexes, those resulting from the activation of a Ph group of the phosphonium PR_3 unit, called endo complexes, and those resulting from the activation of the aryl ring of the benzyl group, or exo derivatives. The endo palladation is observed in all derivatives of PPh_3 and $P(tol)_3$, regardless of the substituents at the benzyl group, showing that the endo effect dominates the orientation of the metalation over other electronic or steric parameters. DFT calculations on these systems show that the endo metalation is favored both kinetically and thermodynamically, since a lower activation barrier (**TS2**) is computed for the endo metalation and a higher stabilization energy (probably related with the endo effect) is also found for endo complexes. However, there is not a large difference between the energy barriers of the endo and exo pathways. For iminophosphoranes derived from PPh_2Me, the orientation of the palladation can be tuned as a function of the reaction temperature. The exo-palladated complex is obtained under kinetic control, when the reaction is performed at low *T* values (refluxing CH_2Cl_2), while the endo metalation is obtained under thermodynamic control at high *T* values (refluxing toluene). In this case, DFT studies show lower activation barriers for the exo processes and higher stabilization energies for the endo metalations, all facts perfectly matching the experimental results. These facts open new possibilities for the regioselective control of the C−H bond activations and, hence, for the functionalization of the molecules containing these bonds. The endo/exo discrimination could allow a precise functionalization at a precise part of the molecule, difficult to achieve by conventional methods. These functionalizations, as well as those other systems such as stabilized iminophosphoranes, are currently under study.

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Supporting Information Available: Complete Experimental Section with all preparative details, spectroscopic data, and references for the synthesis previously described; tables giving Cartesian coordinates of reagents (R), transition states (TS), and orthometalated products (P) for the endo and exo palladation of **1a** and **1g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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