Chemodivergent Palladium-Catalyzed Processes: Role of Versatile Ligands

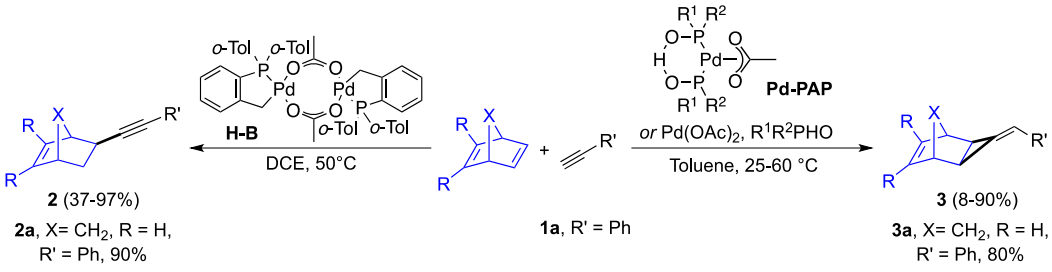
Paola Nava, Hervé Clavier, Yves Gimbert, Laurent Giordano, Gérard Buono, Stéphane Humbel

Chemodivergent palladium-catalyzed processes: role of versatile ligands

Paola Nava,[a] Hervé Clavier,[a] Yves Gimbert,[b] Laurent Giordano,[a] Gérard Buono,[a] Stéphane Humbel*[a]

Abstract: Whereas the reaction of norbornadiene with terminal alkynes in presence of a phosphapalladacycle catalyst yields to the formation of hydroalkynation products, the use of phosphinous acid-phosphinito-containing palladium complexes gave rise to formal [2+1] cycloadducts. An experimental and computational approach was employed to study the mechanisms of the palladium-promoted hydroalkynation and [2+1] cycloaddition. On the one hand, experiences highlighted the crucial role of acidolysis steps on the catalytic activities. On the other hand, DFT calculations demonstrated the specificity of the phosphinito-phosphinous acid ligands, that is the non-equivalence of the two phosphorus atoms but the interchangeability of their properties. These results may have important implications for the mechanism of other palladium-catalyzed transformations especially those involving phosphapalladacycles and phosphinous acid-phosphinito-containing palladium complexes.

Introduction



Scheme 1. Hydroalkynation versus [2+1] cycloaddition: chemodivergent palladium-promoted transformations.

Nowadays, transition-metal catalysis represents a powerful tool to achieve a wide array of selective and atom-economical transformations.[1] Among the various basic aspects and concepts regarding the use of transition metals, the elucidation of key insights into the mechanism is of primary importance as it generally helps in the design of new catalysts and leads to further synthetic developments. In this context, having insights from both experimental and computational approaches represent a growing trend and display clear advantages.[2] In the case of chemodivergent reactions, the good understanding of mechanistic pathways is difficult to apprehend, but has a particular importance for the elaboration of practical and efficient methodologies. For example, our group reported few years ago,[3] the hydroalkynation of norbornadiene derivatives with alkyl- and aryl-substituted alkynes to afford coupling products **2** in overall good yields using the Herrmann-Beller phosphapalladacycle (**H-B**)[4] as catalyst (Scheme 1). On the other hand, it has been established that with the same reactants, phosphinous acid-phosphinito-containing palladium(II) complexes (**Pd-PAP)** led to the formation of methylenecyclopropane (MCP) products **3** through a formal [2+1] cycloaddition.[5,CHL]

Of note, the well-defined **Pd-PAP** can be used to achieve this reaction, but also the *in situ* generated complex, obtained from $Pd(OAc)_2$ and two equivalents of secondary phosphine oxides (SPO)[6] by a simple heating at 60 °C for 20 min, prior to add reactants. Alternatively, platinum-based analogue of **Pd-PAP** can be fruitfully employed.[7]

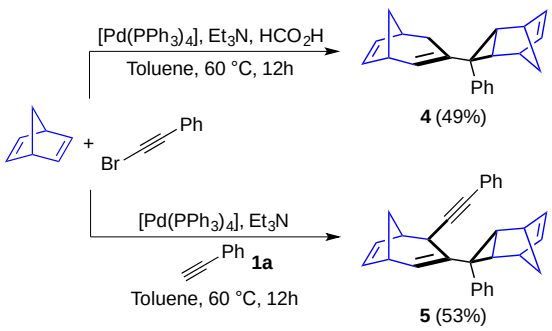
Surprisingly, when ynamides were tested as partners, [2+1] cycloadducts **3** were also isolated with **H-B**.[8] This seems to result from the strong polarization of C-C triple bond since the same reactivity was observed with ynones and propiolates using various phosphapalladacycles including **H-B**.[9]

The chemodivergence between hydroalkynation and [2+1] cycloaddition is even more intriguing when these reactivities are compared to those reported by Cheng and Peng in 1994 (Scheme 2).[10] The treatment of norbornadiene (NBD) with BrC≡CPh in presence of $[Pd(PPh_3)_4]$ and triethylamine gave rise to polycyclic compounds **4** and **5** resulting from the reaction of

[a] Dr. P. Nava, Dr. H. Clavier, Dr. L. Giordano, Prof. G. Buono, Prof. S. Humbel
Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, 13397, Marseille, France.
E-mail: stephane.humbel@univ-amu.fr
[b] Dr. Y. Gimbert
Univ Grenoble Alpes and CNRS, DCM UMR 5250, F-38000 Grenoble, France

Supporting information for this article is given via a link at the end of the document.

two NBD units with one BrC≡CPh. Whereas in presence of formic acid only **4** is observed, with phenylacetylene **1a**, this latest is incorporated in the structure of **5**. This highlighted that not only ligands,[RFR] but also additives influence the reactivity.



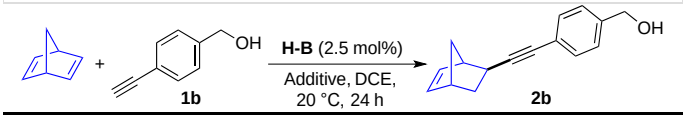
Scheme 2. Palladium-catalyzed ring formation and expansion reaction starting from norbornene and 1-bromo-2-phenylacetylene.

After investigations on the coordination mode of alkyne to the metal in the case of **Pd-PAP**, mainly by mass spectroscopies,[11] we tackled the full mechanism in order to propose a rational explanation for the reactivity difference between **H-B** and **Pd-PAP,** which are yet seemingly structurally close. We reported therein, first an experimental approach, and then Density Functional Theory (DFT) calculations, which led to establish plausible mechanisms.

Results and Discussion

We started to study again the **H-B**-mediated hydroalkynation using the benchmark substrates NBD and (4-ethynylphenyl)methanol **1b**, which facilitated the purification step. Results are depicted in Table 1. At 20 and 60 °C, only the coupling product **2b** was obtained in good yields (entries 1 and 2). Whereas the addition of acetic acid does not influence the hydroalkynation (entry 3), bases such as triethylamine and *N*,*N*-diisopropylethylamine (DIPEA) completely quenched the catalytic activity of **H-B** (entries 4 and 5). The presence of base shut down the acidolysis step but this leads only to degradation without formation of [2+1] cycloadduct.

Table 1. Influence of additives in the palladium-catalyzed hydroalkynation.[a]

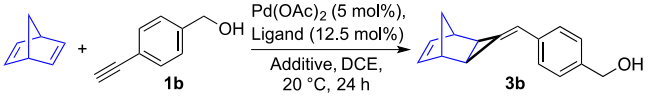


Entry	Additive	Yield (%)[b]
1	None	75
2[b]	None	80
3	AcOH (1 equiv.)	77
4	Et_3N (1 equiv.)	7
5	DIPEA (1 equiv.)	7

[a] Reaction conditions: **H-B** (0.0125 mmol, 2.5 mol%, 5 mol% [Pd]), alkyne **1b** (0.5 mmol), NBD (1 mmol, 2 equiv.) DCE (2.5 mL, 0.2 M), 20 °C, 24 h. [b] Reaction carried out at 60 °C. DIPEA = *N*,*N*-Diisopropylethylamine.

Next, NBD and alkyne **1b** were treated with 5 mol% of *in situ* generated **Pd-PAP** in DCE (Table 2). The reactions were performed at 20 °C in order to achieve a thorough comparison between the various SPO's we tested. Whereas $Cy_2P(O)H$ led to the formation of a very efficient catalyst (78%, entry 2), other SPO's are much less competent (entries 1, 3-5). Noteworthy, the replacement of DCE by toluene enhanced the quantity of [2+1] cycloadduct **2b** formed (entries 5 and 6). When the reaction was conducted in presence acetic acid, a significant improvement of the yield was noticed (entry 5 and 7). At 60 °C, the trend between the various SPO's was confirmed (entries 8-12). At this temperature due to an almost quantitative yield, it was not possible to observe a beneficial effect of acid addition (entries 12 and 13). On the other hand, DIPEA led to reduce the performances of **Pd-PAP** complex but does not totally quench its activity like for **H-B** catalyst. Several other phosphous-based ligands were investigated, including phosphite or phosphinic acid (entries 15-20), but only with ethyl phosphinate it was possible to obtain product **3b** albeit in trace amounts. With dppp, we expected to mimic the phosphinous acid-phosphinito ligands, but it failed as all other attempts to achieve the [2+1] cycloadduct in absence of SPO's preligands.

Table 2. Influence of additives in the palladium-catalyzed hydroalkynation.[a]

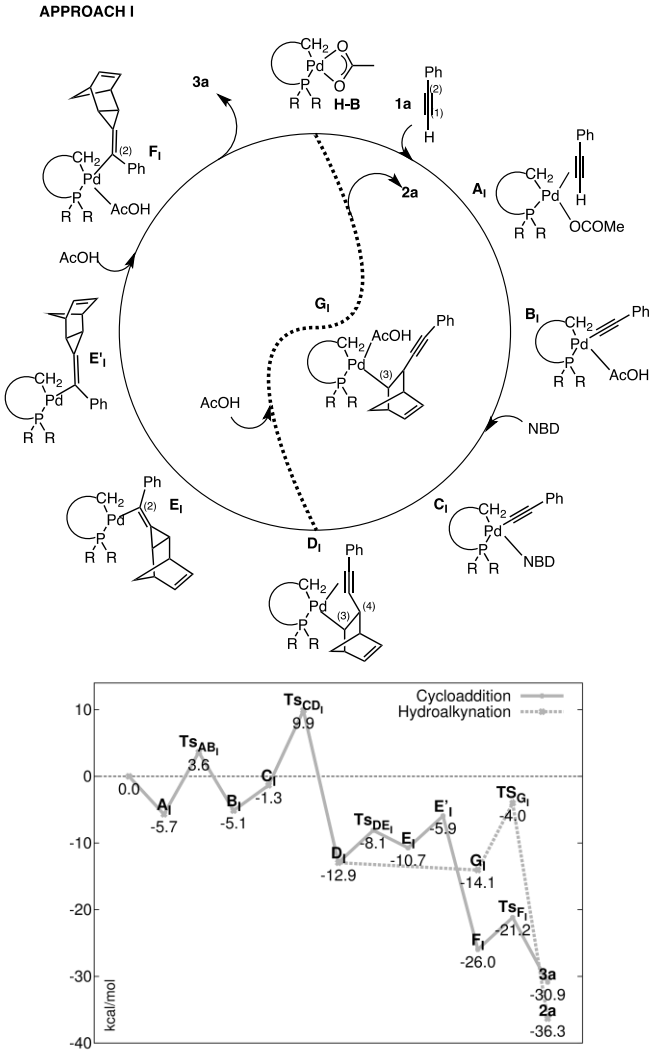


Entry	Ligand	Additive	T(°C)	Yield (%)[b]
1	$Ph_2P(O)H$	None	20	8
2	$Cy_2P(O)H$	None	20	78
3	PhBnP(O)H	None	20	9
4	Ph*t*BuP(O)H	None	20	-
5	PhCyP(O)H	None	20	25
6	PhCyP(O)H	None	20	65[b]
7	PhCyP(O)H	AcOH (1 equiv.)	20	53
8	$Ph_2P(O)H$	None	60	15
9	$Cy_2P(O)H$	None	60	91
10	PhBnP(O)H	None	60	50
11	Ph*t*BuP(O)H	None	60	33
12	PhCyP(O)H	None	60	88
13	PhCyP(O)H	AcOH (1 equiv.)	60	77
14	PhCyP(O)H	DIPEA (1 equiv.)	60	43
15	None	None	60	NR
16	PPh_3	None	60	NR
17	Ph_2POMe	None	60	NR
18	Ph_2PO_2H	None	60	NR
19	Ph(OEt)P(O)H	None	60	5
20	dppp[c]	None	60	NR

[a] Reaction conditions: $Pd(OAc)_2$ (0.025 mmol, 5 mol%), Ligand (0.0625 mmol, 12.5 mol%), alkyne **1b** (0.5 mmol), NBD (1 mmol, 2 equiv.) DCE (2.5 mL, 0.2 M), 24 h. [b] Reaction carried out in Toluene. [c] dppp (0.0323 mmol, 6.25 mol%). DIPEA = *N*,*N*-Diisopropylethylamine. dppp = 1,3-bis(diphenylphosphino)propane. NR = No reaction.

From these experimental results, we conclude that acidolyses are major steps in catalytic cycles of palladium-promoted hydroalkynation and [2+1] cycloaddition. But, whereas additions of acid or base affect significantly their rates, the selectivities of the two catalytic systems remain intact and certainly come from the complexes themselves. This led us to carried out a computational study.

For calculations convenience, phenylacetylene **1a** and **Pd-PAP** bearing phenyl and *tert*-butyl groups on phosphorus atoms were selected. The catalysts were considered in their monomeric forms. The computed structures built for **Pd-PAP** catalysts were obtained from enantiopure secondary phosphine oxides (P atoms possess a *R* configuration). DFT calculations were performed with the Gaussian09 package,[12] employing the M06 functional, and reported values are single point energy calculations with the def2-TZVP basis set on optimized structures with the def2-SVP basis set.[13] Zero Point Energies (ZPE) are added as computed at the optimizing level.

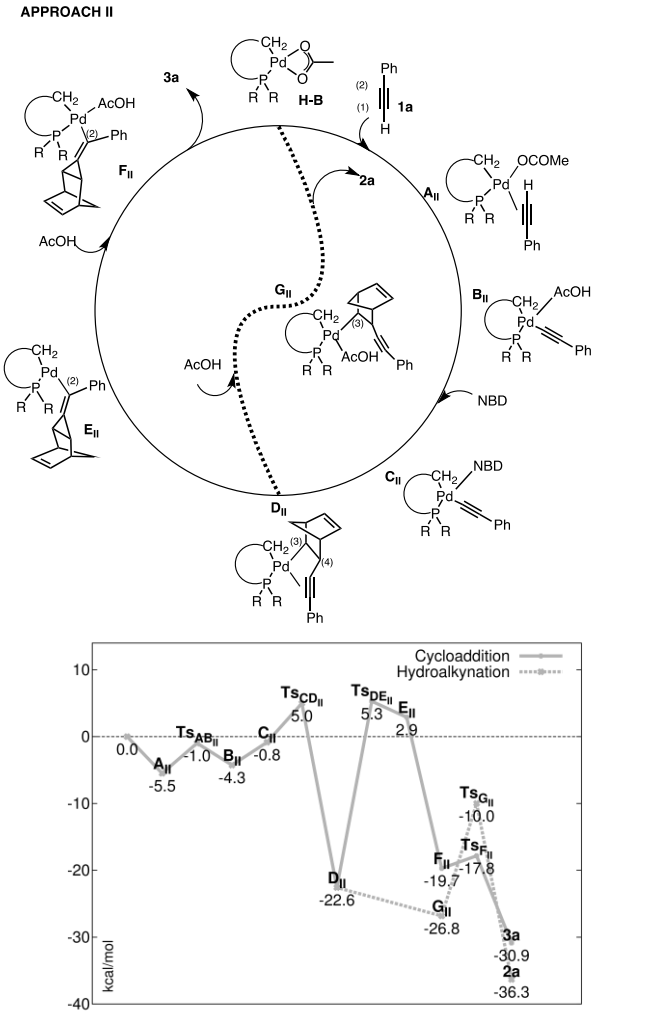


Scheme 3. Catalytic cycles for either the hydroalkynation or the formal [2+1] cycloaddition of NBD and **1a** (**2a** and **3a**, Scheme 1) with the **H-B** catalyst, according to approach I (**1a** coordinates the Pd *trans* to the phosphine). The catalyst is schematically sketched. The R substituent is *o*-Tol. The computed energetic profiles (M06/def2-SVP//M06/def2-TZVP, ZPE at the optimizing level) are reported below. Energies are relative to the separated species (catalyst + reactant).

The complete selectivity of one process over the other might suggest that reactive species could be totally different and we imagine that, in the case of **Pd-PAP**, a vinylidene-palladium[14] could be formed similarly to what we proposed for platinum.[11b] Nevertheless our calculations showed that this pathway is high in energy and therefore not likely.[15]

The **H-B** catalyst presents two different sites to coordinate reactants NBD and alkyne **1a**. Two approaches of **1a** are then possible: either as in $\mathbf{A_I}$ *trans* to the Pd-P (approach I, Scheme 2) or as in $\mathbf{A_{II}}$ *trans* to the Pd-C(sp^3) (approach II, Scheme 4). Both have been considered to compute the mechanisms leading either to the hydroalkynation product **2a** or the formal [2+1] cycloadduct **3a**. The resulting four pathways are depicted in Schemes 3 and 4, together with the corresponding energetic profiles.

The initial steps of the hydroalkynation and the [2+1] cycloaddition are the same: alkyne **1a** coordinates the metal center, forming either $\mathbf{A_I}$ or $\mathbf{A_{II}}$. Those intermediates are almost isoenergetic and an equilibrium between them is accessible.



Scheme 4. Catalytic cycles for either the hydroalkynation or the formal [2+1] cycloaddition of NBD and **1a** (**2a** and **3a**, Scheme 1) with the **H-B** catalyst, according to approach II (**1a** coordinates the Pd *cis* to the phosphine). The catalyst is schematically sketched. The R substituent is *o*-Tol. The computed energetic profiles (M06/def2-SVP//M06/def2-TZVP, ZPE at the optimizing level) are reported below. Energies are relative to the separated species (catalyst + reactant).

They are then deprotonated by the acetate ($\mathbf{B_{I\text{-}II}}$), forming acetic acid, which is displaced by the NBD ($\mathbf{C_{I\text{-}II}}$). Next, the first C-C insertion leads to the crucial intermediate $\mathbf{D_{I\text{-}II}}$, whose evolution determines which product is observed. In the hydroalkynation mechanism, the acetic acid approaches the metal center forming

intermediates $\mathbf{G_{I\text{-}II}}$ and an acidolysis on the sp^3 carbon atom C(3) occurs to release product **2a**.
In order to obtain **3a**, a second carbon-carbon bond needs to be formed, C(1)-C(3). In approach I, the cyclization, resulting in $\mathbf{E_I}$, is followed by rotation about the Pd-C(2) connection. This rotation leads to $\mathbf{E'_I}$, which has a free coordination site for an incoming acetic acid ($\mathbf{F_I}$).[16] In approach II, we have found that the formation of the second carbon-carbon bond is concerted with the rotation. The hydrolysis of the Pd-Csp^2(2) bond by the acetic acid gives rise to the product.

Noteworthy, the first discrimination between the two approaches takes place at the first C-C insertion transition state ($\mathbf{TS_{CDI}}$ vs. $\mathbf{TS_{CDII}}$), leading to the formation of the C(1)-C(4) bond. This step is more favorable both kinetically and thermodynamically for approach II, leading to intermediate $\mathbf{D_{II}}$, 10 kcal/mol more stable than the corresponding intermediate $\mathbf{D_I}$ (Schemes 3 and 4 and Figure 1). This significant difference in energy could be explained by the inconvenient *trans* position of the two alkylic strong σ-donor ligands in $\mathbf{D_I}$.[17] Here, the Pd-C distances are about 10 pm longer than in $\mathbf{D_{II}}$ (Figure 1, 217 and 218 pm in $\mathbf{D_I}$ vs. 208 and 209 pm in $\mathbf{D_{II}}$). Furthermore the steric hindrance between the bulky phosphine site of **H-B** and the former NBD moiety cannot be avoided in $\mathbf{D_I}$.
From $\mathbf{D_{II}}$, the cyclopropanation is an unlikely process compared to the hydroalkynation, Scheme 4, and we also attribute this to the positions of alkylic strong σ-donor ligands. Indeed, the cyclopropanation would lead to $\mathbf{E_{II}}$ (Figure 2). As the C(1)-C(3) bond is created, the cyclopropylidene is disconnected from the metal and the whole structure is tilted. In $\mathbf{E_{II}}$ the newly formed Pd-C(2) bond (207 pm) is thus inconveniently *trans* to a strong Pd-C σ-donor ligand (213 pm). This process would result in a late transition state ($\mathbf{TS_{DEII}}$), which is high in energy (28 kcal/mol above $\mathbf{D_{II}}$, Scheme 4).
The hydroalkynation is much easier. The coordination of an acetic acid on $\mathbf{D_{II}}$ leads to $\mathbf{G_{II}}$, which is more stable than $\mathbf{E_{II}}$ and $\mathbf{F_{II}}$ of the cyclopropanation path.

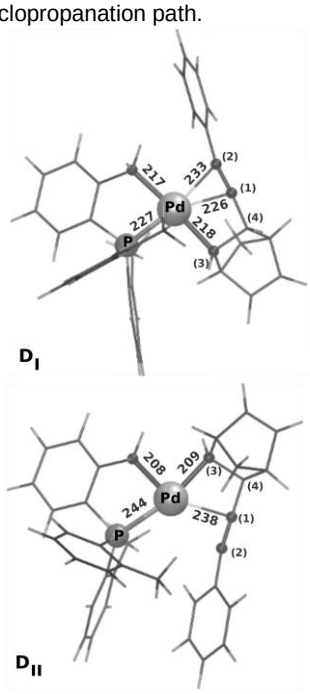


Figure 1. Computed structures (M06/def2-SVP) of intermediates $\mathbf{D_I}$ and $\mathbf{D_{II}}$, as in Schemes 3 and 4. Reported distances are in pm.

Finally, the acidolysis of the Pd-Csp^3(3) bond in $\mathbf{G_{II}}$ ($\mathbf{TS_{GII}}$) is quite demanding, with a barrier of 16 kcal/mol, whereas the acidolysis of the Pd-Csp^2(2) bond is an easy-going process (with very low energetic barriers, less than 4 kcal/mol, $\mathbf{TS_{FI\text{-}II}}$). Thus, the computed energetic profiles reveal that the preferred mechanistic path proceeds towards the hydroalkynation through approach II, but the hydrolysis in the hydroalkynation has not a negligible barrier.

In this paragraph we have invalidated the mechanistic pathway through approach I (Scheme 3). Nevertheless, it is interesting to notice that the second insertion barrier for the cyclopropanation (energy of $\mathbf{TS_{DEI}}$ with respect to $\mathbf{D_I}$) is small (less than 5 kcal/mol vs. 28 kcal/mol for approach II). In $\mathbf{D_I}$, the Pd-C(3) bond is already elongated compared to $\mathbf{D_{II}}$ (218 pm vs 209) and the interaction between the metal center and the alkyne is already established. Moreover, the *cis* position between the two Pd-alkylic strong σ bonds in $\mathbf{E'_I}$ (206 pm and 202 pm, Figure 2) makes the cyclopropanation a relatively easy process: $\mathbf{E'_I}$ is even 7 kcal/mol more stable than $\mathbf{E_{II}}$ (Schemes 3 and 4, Figure 2). Thus, if the hypothetical intermediate $\mathbf{D_I}$ were formed, the cyclopropanation would have been possible.

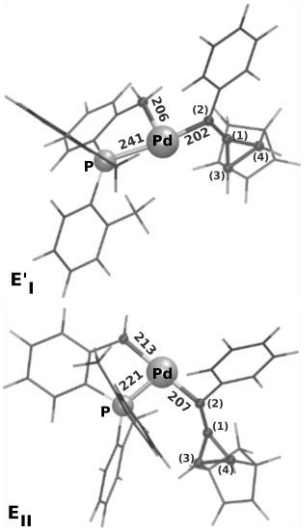
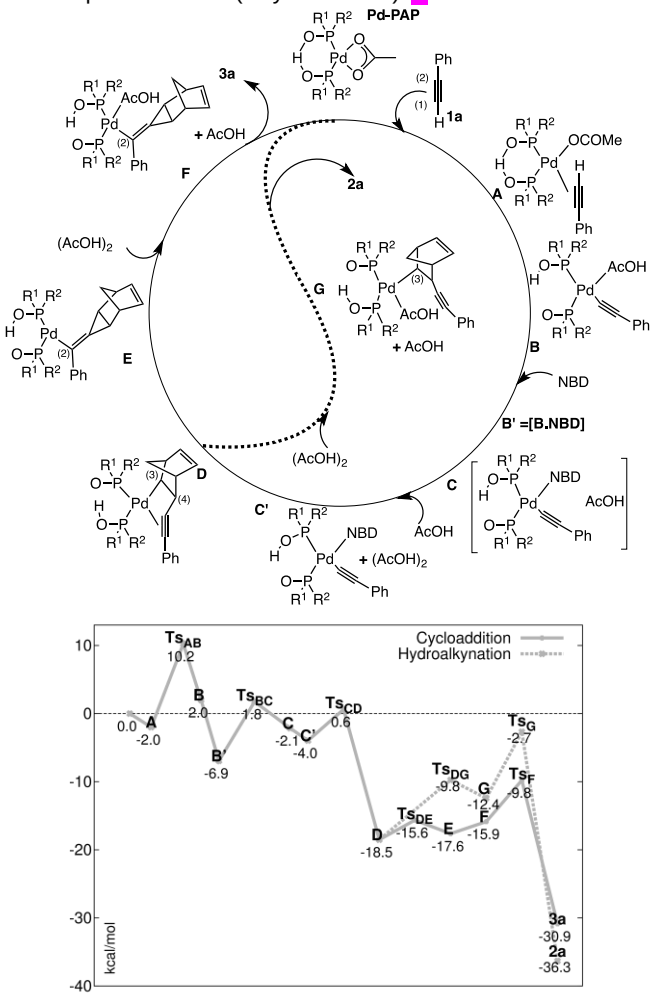


Figure 2. Computed structures (M06/def2-SVP) of intermediates $\mathbf{E'_I}$ and $\mathbf{E_{II}}$, as in Schemes 3 and 4. Reported distances are in pm.

From an experimental point of view, **Pd-PAP** complex leads only to the formal [2+1] product **3a**. For the sake of comparison with **H-B** catalyst, both pathways were computed for either the hydroalkynation or the [2+1] cycloaddition. They are reported in Scheme 5, together with their energetic profiles. We shall briefly recall the mechanistic steps: after the coordination of **1a**, its deprotonation occurs, leading to intermediate **B**. The barrier is of 12 kcal/mol, the largest in this reaction. We computed then the AcOH substitution by NBD, leading to **C**, where the AcOH is still in the coordination sphere of the complex. This substitution is an easy-going process where an NBD molecule adds to the intermediate **B**, and complexes **B'** and **C** thereby obtained have both the NBD and the AcOH moieties in the first coordination sphere of the metal (see supplementary material). In the calculations that we present here, we have chosen to mimic the usual experimental conditions, where some AcOH is available in the reactive medium. We have therefore considered that a second molecule of AcOH would catch the first molecule from

the catalyst, forming a dimer $(AcOH)_2$. The gain in energy from **C** to **C'** is quite moderate (only 2 kcal/mol).[18]



Scheme 5. Catalytic cycles for either the hydroalkynation or the formal [2+1] cycloaddition of NBD and **1a** (**2a** and **3a**, Scheme 1) with **Pd-PAP** catalyst (R^1 = Ph, R^2 = *t*Bu). The computed energetic profiles (M06/def2-SVP//M06/def2-TZVP, ZPE at the optimizing level) are reported below. Energies are relative to the separated species (catalyst + reactant).

The first insertion step follows, leading to the crucial intermediate **D**. The barrier is of about 5 kcal/mol, as it was found for **H-B** catalyst (approach II, Scheme 4). However, here the cycloaddition is kinetically preferred over the hydroalkynation. Indeed, the intermediates **D** and **E**, resulting from the second insertion, are almost isoenergetic and their interconversion is easy (barrier of less than 3 kcal/mol). This suggests that a fast equilibrium is possible between the two isomers as for **H-B** catalyst (approach I, Scheme 3). Furthermore, the second insertion step is concerted with the rotation around the Pd-C(2). Thus, the resulting intermediate **E** has a free coordination site to host the AcOH molecule and gives intermediate **F**, which undergoes the acidolysis. This acidolysis (**TS_F**) is kinetically preferred over that of the hydroalkynation process (through intermediate **G**, **TS_G**). Hence the thermodynamic product **2a** cannot be obtained.

In structure **C'** (Figure 3), **L^1** is *trans* to the acetylide, a strong σ-donating ligand, while **L^2** is *trans* to the NBD in η^2. The bridging H atom is closer to **L^1**. This allows **L^2** to process the phosphinito properties, thus a stronger σ-donor than **L^1**. The Pd-P distances provide a concrete proof of the different behavior of **L^1** and **L^2**: Pd-P(2) (237 pm) is significantly shorter than Pd-P(1) (245 pm), indicating a stronger Pd-P(2) interaction.

In the following transition state, the proton moves, while the C(4)-C(1) bond is forming. In the resulting intermediate **D**, the proton is now closer to **L^2**, which is *trans* to the direct Pd-C(sp^3) bond. We find here a similar pattern of distances as in **D_{II}**: the Pd-P distances are reversed (Pd-P(1)=232 pm, Pd-P(2)=246 pm) and the **L^1** becomes the stronger σ-donating ligand. This is desirable since **L^1** is now *trans* to the acetylide ligand, in loose π-interaction with the metal center.

When the second insertion step occurs, the proton moves again, getting closer to **L^1** and the Pd-P distances changes (Figure 3): in **E** the Pd-P(2) (230 pm) becomes shorter than Pd-P(1) (240 pm). By the proton displacement, **L^2** adapts easily and increases its donating character in an optimal fashion, since *trans* to an empty coordination site. It shall be noticed that for **H-B** in approach I, the second insertion step has also a small barrier and, as already mentioned, the resulting **E_I** is stabilized (with respect to **E_{II}**), with C(2) *trans* to the phosphine and *cis* to the other alkyl group.

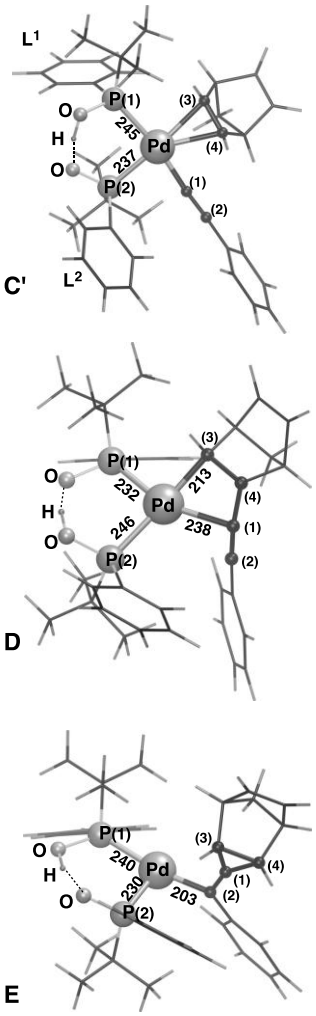


Figure 3. Computed structures (M06/def2-SVP) of intermediates **C'**, **D** and **E**, as in Scheme 5. Reported distances are in pm. **L^1** and **L^2** are the phosphorus-based ligands that contain P(1) and P(2) atoms, respectively.

We conclude that the specificity of the phosphinito-phosphinous acid ligand lies in the adapting capability of the interaction strength with the metal center,[19] thanks to the shared proton. When the proton is closer to a ligand, the σ-donating character of the other is enhanced. The complex adapts its electronic

structure by avoiding strong σ-donating ligands being in *trans* and providing that the more σ-donating ligand is *trans* to the electronically poorer coordination site. This behavior is similar to that proposed for Platinum or Rhodium in some hydroformylations.[20] Our mechanistic study shows that the SPO preligands allow the complex to have a small first insertion barrier as for **H-B** catalyst in Approach II, together with a second small insertion barrier as for Approach I.

Conclusions

In summary, we have investigated the mechanisms of chemodivergent palladium-catalyzed processes: hydroalkynation *versus* [2+1] cycloaddition in order to propose a rational explanation for the reactivity difference between **H-B** and **Pd-PAP,** which are yet seemingly structurally close. The experiments that were conducted showed the complete selectivity of both palladium catalysts and notably the specificity of **Pd-PAP** complex. It was also demonstrated the crucial role of acidolysis on the catalytic activities. From DFT calculations, we found that all the computed pathways go through a first insertion intermediate, common to the hydroalkynation and to the cycloaddition reactions, both for **H-B** and **Pd-PAP** catalysts. The last mechanistic step is always an acidolysis, which is computed to be easier (lower barriers) for the [2+1] cycloaddition than for the hydroalkynation product (this concerns C(sp^2) vs. C(sp^3), respectively). This means that something happens before the acidolysis that discriminates between the two pathways.
When the cyclopropanation occurs, a second insertion step is needed, a strong Pd-C bond breaks on one coordination site and the other Pd-C bond in *cis* is reinforced, thus triggering a large electronic rearrangement. This is possible only with the SPO catalyst, since it is able to compensate the electronic change about the metal by adapting the ligand behavior though a proton shift, meanwhile **H-B** has not the same flexibility. The peculiarity of **Pd-PAP** is that the position of the proton in the phosphinito-phosphinous acid ligands helps to adapt the strength of the Pd-P bonds, in such a way that a stronger σ-donor (with a stronger phosphinito nature) is always *trans* to the coordination site with the electronically poorer partner.
These results may have important implications for the mechanism of other palladium-catalyzed transformations, especially those involving phosphapalladacycles and phosphinous aicd-phosphinito-containing palladium complexes. Their reactivities are still under investigations in our laboratories.

Experimental Section

General considerations. All reagents were obtained from commercial sources and used as received. SPO ligands were obtained from a chemical supplier or by following literature procedures.[21] (4-Ethynylphenyl)methanol **1b** was prepared according to the procedure described by Saito and coworkers.[22] Dichloromethane and toluene were purified over Braun MB-SPS-800 solvent purification system. DCE was obtained after distillation over CaH_2 under argon atmosphere. Thin layer chromatography was carried out on Merck silica gel F254. Technical grade petroleum ether (40-60 °C b.p.) and ethyl acetate were used for chromatography column. Flash chromatography was performed with combiflash companion. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on Bruker Avance III 300 spectrometer. Solvent residual signals[23] were used as internal standard for ^{1}H (7.27 ppm) and ^{13}C (77.16 ppm) spectra. ^{13}C was observed with ^{1}H decoupling. Chemical shift (δ) and coupling constant (*J*) are given in ppm and Hz respectively. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet and br. for broad signal. High-resolution mass spectra (HRMS) were recorded on Waters SYNAPT G2 HDMS equipped with an Atmospheric Pressure Ionization (API).

(4-((-Bicyclo[2.2.1]hept-5-en-2-yl)ethynyl)phenyl)methanol 2b. In a10 mL flame-dried Schlenk, **H-B cat** (12 mg, 0.025 mmol, 5 mol% [Pd]), (4-ethynylphenyl)methanol **1b** (66 mg, 0.5 mmol), norbornadiene (100 μL, 1 mmol, 2 equiv.) and dry and degassed DCE (2.5 mL) were introduced under argon. The reaction mixture was stirred 24 h at 20 °C, then, volatiles were removed under reduced pressure. The crude mixture was purified by flash chromatography on silica gel to obtain the desired product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J*(H,H) = 8.2 Hz, *2*H, C*H*^{Ar}), 7.29 (d, *J*(H,H) = 8.2 Hz, *2*H, C*H*^{Ar}), 6.14-6.07 (m, 2H, C*H*=C*H*), 4.68 (d, *J*(H,H) = 5.2 Hz, 2H, CH_2-OH), 3.02 (br s, 1H, C*H*-CH_2-CH), 2.96 (br s, 1H, C*H*-CH_2-CH), 2.38-2.33 (m, 1H, CH-CH_2-CH), 1.79 (dt, *J*(H,H) = 11.5 and 3.8 Hz, C*H*-C≡C), 1.69-1.64 (m, 2H, CH-CH_2-CH and O*H*), 1.60-1.53 (m, 1H, CH-CH_2-CH), 1.50-1.46 (m, 1H, CH-CH_2-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.1 (*C*), 137.4 (*C*H), 135.3 (*C*H), 131.7 (*C*H), 126.7 (*C*H), 123.4 (*C*), 95.1 (*C*), 80.1 (*C*), 65.0 (CH_2), 49.3 (*C*H), 46.9 (CH_2), 41.9 (*C*H), 34.8 (CH_2), 29.6 (*C*H). HRMS (ESI): *m/z*: calcd for $C_{16}H_{16}ONa$: 247.1093 $[M+Na]^+$; found 247.1092.

(4-((Tricyclo[3.2.1.02,4]oct-6-en-3-ylidene)methyl)phenyl)methanol 3b. In a10 mL flame-dried Schlenk, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%) and CyPhP(O)H (13.0 mg, 0.0625 mmol, 12.5 mol%) were introduced under argon and dissolved in dry and degassed DCM (1 mL). The reaction was heated at 60 °C for 20 min until the yellow color disappeared. (4-Ethynylphenyl)methanol **1b** (66 mg, 0.5 mmol), norbornadiene (100 μL, 1 mmol, 2 equiv.) and dry and degassed DCE (1.5 mL) were added and the reaction mixture was stirred 24 h at 20 °C or 60 °C. Then, volatiles were removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel to obtain the desired product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, *J*(H,H) = 8.1 Hz, *2*H, C*H*^{Ar}), 7.33 (d, *J*(H,H) = 8.1 Hz, *2*H, C*H*^{Ar}), 6.55 (s, 1H, C*H*=C), 6.44 (br s, 2H, C*H*=C*H*), 4.66 (s, 2H, CH_2-OH), 3.23 (br s, 1H, C*H*-CH_2-CH), 3.11 (br s, 1H, C*H*-CH_2-CH), 1.87 (dd, *J*(H,H) = 7.9 and 1.6 Hz, C*H*-CH), 1.83 (br s, 1H, O*H*), 1.65 (dd, *J*(H,H) = 7.9 and 1.6 Hz, C*H*-CH), 1.13 (d, *J*(H,H) = 8.5 Hz, CH-CH_2-CH), 0.97 (d, *J*(H,H) = 8.5 Hz, CH-CH_2-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5 (*C*), 139.8 (*C*H), 139.3 (*C*H), 139.2 (*C*), 137.4 (*C*), 127.3 (*C*H), 126.7 (*C*H), 116.8 (*C*H), 65.2 (CH_2), 45.1 (*C*H), 44.5 (*C*H), 42.6 (CH_2), 28.5 (*C*H), 25.1 (*C*H). HRMS (ESI): *m/z*: calcd for $C_{16}H_{16}ONa$: 247.1093 $[M+Na]^+$; found 247.1092.

Acknowledgements

This work was supported by ANR (project BLAN07-1_190839 SPOs Preligands), the Ministère de l'Enseignement Supérieur et de la Recherche, CNRS, ECM and AMU. We thank Christophe Chendo and Dr. Valérie Monnier for mass spectrometry analyses (Spectropole, Fédération des Sciences Chimiques de Marseille), Dr A. Tenaglia is gratefully acknowledged for helpful discussions.

Keywords: C-C coupling; Computational chemistry; Homogeneous catalysis; P ligands; Palladium; Proton-shift; Trans-effect; Secondary Phosphine Oxydes.

[1] a) *Comprehensive Organic Synthesis*, 2nd edition, (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**; b) *Applications of Transition Metal Catalysis in Drug Discovery and Development An Industrial Perspective*, (Eds.: M. L. Crawley, B. M. Trost), John Wiley & Sons, Hoboken, **2012**; c) Transition Metals for Organic Synthesis, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**.

[2] G.-J. Cheng, X. Zhang, L. W. Chung, L. Xu, Y.-D. Wu, *J. Am. Chem. Soc.* **2015**, *137*, 1706−1725.

[3] A. Tenaglia, L. Giordano, G. Buono, *Org. Lett.* **2006**, *8*, 4315-4318; see also: b) A. Tenaglia, K. Le Jeune, L. Giordano, G. Buono, *Org. Lett.* **2011**, *13*, 636-639.

[4] W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T. H. Riermeier, K. Öfele, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357-1364.

[5] a) J. Bigeault, L. Giordano, G. Buono, *Angew. Chem.* **2005**, *117*, 4831-4835; *Angew. Chem. Int. Ed.* **2005**, *44*, 4753-4757; b) J. Bigeault, I. De Riggi, Y. Gimbert, L. Giordano, G. Buono, *Synlett* **2008**, 1071-1075.

[CHIL] J. Yin, J.D. Chisholm *Chem. Commun.*, **2006**, 632–634.

[6] For reviews on secondary phosphine oxides, see: a) L. Ackermann, *Synthesis* **2006**, 1557-1571; b) L. Ackermann, R. Born, J. H. Spatz, A. Althammer, C. J. Gschrei, *Pure Appl. Chem.* **2006**, *78*, 209-214; c) L. Ackermann, *Synlett* **2007**, 507-526; d) L. Ackermann In *Phosphorus Ligands in Asymmetric Catalysis*, *Vol. 2* (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**, pp. 831-847; e) T. M. Shaikh, C.-M. Weng, F.-E. Hong, *Coord. Chem. Rev.* **2012**, *256*, 771-803.

[7] J. Bigeault, L. Giordano, I. De Riggi, Y. Gimbert, G. Buono, *Org. Lett.* **2007**, *9*, 3567-3570.

[8] H. Clavier, A. Lepronier, N. Bengobesse-Mintsa, D. Gatineau, H. Pellissier, L. Giordano, A. Tenaglia, G. Buono, *Adv. Synth. Catal.* **2013**, *355*, 403-408.

[9] a) G.-C. Ge, D.-L. Mo, C.-H. Ding, L.-X. Dai, X.-L. Hou, *Org. Lett.* **2012**, *14*, 5756-5759; b) D.-L. Mo, T. Yuan, C.-H. Ding, L.-X. Dai, X.-L. Hou, *J. Org. Chem.* **2013**, *78*, 11470-11476.

[10] C.-H. Liu, C.-H. Cheng, M.-C. Cheng, S.-M. Peng, *Organometallics* **1994**, *13*, 1832-1839.

[RFRI] a) L. Zhou, L. Chen, R. Skouta, H.-F. Jiang, C.-J. Li *Org. Biomol. Chem.* **2008**, *6*, 2969–2977; b) L. Villarino, F. Lopez, L. Castedo, J. L. Mascareñas *Chem. Eur. J.* **2009**, *15*, 13308 – 13312.

[11] a) R. Thota, D. Lesage, Y. Gimbert, L. Giordano, S. Humbel, A. Milet, G. Buono, J.-C. Tabet, *Organometallics* **2009**, *28*, 2735-2743; b) M. Karanik, D. Lesage, Y. Gimbert, P. Nava, S. Humbel, L. Giordano, G. Buono, J.-C. Tabet, *Organometallics* **2011**, *30*, 4814-4821.

[12] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Peters-son, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gom- perts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. S. S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian 09 Revision A.1, Gaussian Inc. Wallingford CT **2009**.

[13] a) Y. Zhao and D. G. Truhlar, Theor. Chem. Acc., **2008**, *120*, 215–241; b) D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss, Theor. Chim. Acta **1990**, *77*, 123–141; c) F. Weigend, R. Ahlrichs, Phys. Chem. Chem. Phys. **2005**, *7*, 3297–3305.

[14] Whereas, to the best of our knowledge no vinylidene-palladium intermediate is described in the literature, several papers reported methylene –palladium complexes, for selected references, see: a) Z. Zhang, Y. Liu, L. Ling, Y. Li, Y. Dong, M. Gong, X. Zhao, Y. Zhang, J; Wang, *J. Am. Chem. Soc.* **2011**, *133*, 4330-4341; b) Y. Xia, S. Qu, Q. Xiao, Z.-X. Wang, P. Qu, L. Chen, Z. Liu, L. Tian, Z. Huang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 13502-13511; c) Y. Horino, Y. Takahashi, K. Koketsu, H. Abe, K. Tsuge, *Org. Lett.* **2014**, *16*, 3184−3187; d) Y. Yang, J. Li, B. Du, C. Yuan, B. Liu, S. Qin, *Chem. Commun.* **2015**, *51*, 6179-6182; e) B. M. Trost, A. S. K. Hashmi, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1085-1087 ; f) B. M. Trost, A. S. K. Hashmi, *J. Am. Chem. Soc.* **1994**, *116*, 2183-2184.

[15] For details, see supporting information.

[16] The rotation corresponds to a low energy process of large amplitude, and the corresponding transition state was not located. The acetic acid approach onto the free site of coordination is considered as a barrier less process.

[17] B. Pinter, V. Van Speybroeck, M. Waroquier, P. Gerlings, F. De Proft *Phys. Chem. Chem. Phys.*, **2013**, *15*, 17354 -17365.

[18] Otherwise, AcOH could stay at proximity of the catalyst. The formation of a dimeric $(AcOH)_2$ is somewhat overestimating the stabilizing action of an AcOH on the Pd-complex, through, for instance, a hydrogen-bond of the AcOH with the phosphinito-phosphinous acid ligands.

[19] D. Martin, D. Moraleda, T. Achard, L. Giordano, G. Buono *Chem. Eur. J.* **2011**, *17*, 12729 - 12740.

[20] a) Y.A. Ustynyuk, Y.V. Babin, V.G. Savchenko, E.M. Myshakin, A.V. Gavrikov, *Russ. Chem. Bull.*, **2010**, *59*, 686-694; b) P. M. Castro, H. Gulyàs, J. Benet-Buchholz, C. Bo, Z. Freixa , P. W. N. M. van Leeuwen *Catal. Sci. Technol.*, **2011**, *1*, 401-407.

[21] T. Achard, L. Giordano, A. Tenaglia, Y. Gimbert, G. Buono, *Organometallics* **2010**, *29*, 3936-3950 and references therein.

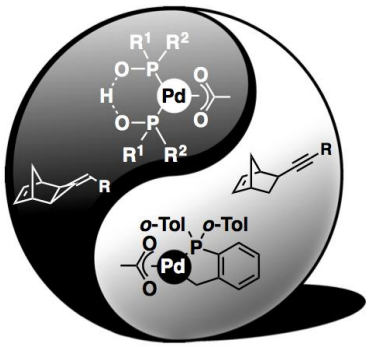
[22] Z. Liu, J. Caner, A. Kudo, H. Naka, S. Saito, *Chem. Eur. J.* **2013**, *19*, 9452-9456.

[23] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K, I. Goldberg, *Organometallics* **2010**, *29*, 2176-2179.

Entry for the Table of Contents

FULL PAPER

An experimental and computational approach was employed to study the mechanisms of the palladium-promoted hydroalkynation and [2+1] cycloaddition between norbornadiene and terminal alkynes. This study highlighted in particular, the specificity of the phosphinito-phosphinous acid ligands.



*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title