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# Of the Ortho Effect in Palladium/Norbornene-Catalyzed Reactions: A Theoretical Investigation

Giovanni Maestri,[†,‡] Elena Motti,[†] Nicola Della Ca',[†] Max Malacria,[‡] Etienne Derat,*[‡] and Marta Catellani*[†]

[†]Dipartimento di Chimica Organica e Industriale, Università degli Studi di Parma, Parco Area delle Scienze, 17/A, 43124 Parma, Italy
[‡]Institut Parisien de Chimie Moléculaire (UMR CNRS 7201), UPMC Univ Paris 06, 4 place Jussieu, C. 229, 75005 Paris, France

Ⓢ Supporting Information

ABSTRACT: Mechanistic questions concerning palladium and norbornene catalyzed aryl—aryl coupling reactions are treated in this paper: how aryl halides react with the intermediate palladacycles, formed by interaction of the two catalysts with an aryl halide, and what is the rational explanation of the "ortho effect" (caused by an ortho substituent in the starting aryl halide), which leads to aryl—aryl coupling with a second molecule of aryl halide rather than to aryl—norbornyl coupling. Two possible pathways have been proposed, one involving aryl halide oxidative addition to the palladacycle, the other passing through a palladium(II) transmetalation, also involving the palladacycle, as previously proposed by Cardenas and Echavarren. Our DFT calculations using M06 show that, in palladium-catalyzed reaction of aryl halides, not containing ortho substituents, and norbornene, the intermediate palladacycle formed has a good probability to undergo transmetalation, energetically favored over the oxidative addition leading to Pd(IV). The unselective sp^2–sp^2 and sp^2–sp^3 coupling, experimentally observed in this case, can be explained in the framework of the transmetalation pathway since the energetic difference between aryl attack onto the aryl or norbornyl carbon of the palladacycle intermediate is quite small. On the other hand, according to the experimentally observed "ortho effect", selective aryl—aryl coupling only occurs in the reactions of ortho-substituted metallacycles. The present work offers the first possible rationalization of this finding. These *in situ* formed palladacycles containing an ortho substituent could more easily undergo oxidative addition of an aryl halide rather than reductive elimination from the transmetalation intermediate as a result of a steric clash in the transition state of the latter. The now energetically accessible Pd(IV) intermediate, featuring a Y-distorted trigonal bipyramidal structure, can account for the reported selective aryl—aryl coupling through a reductive elimination which is easier than aryl—norbornyl coupling. Thus, the steric effect represents the main factor that dictates the energetic convenience of the system to follow the Pd(IV) or the transmetalation pathway. Ortho substituents cause a higher energy transition state for reductive elimination from the transmetalation intermediate than for oxidative addition to the metallacycle palladium(II) and the pathway based on the latter predominates.
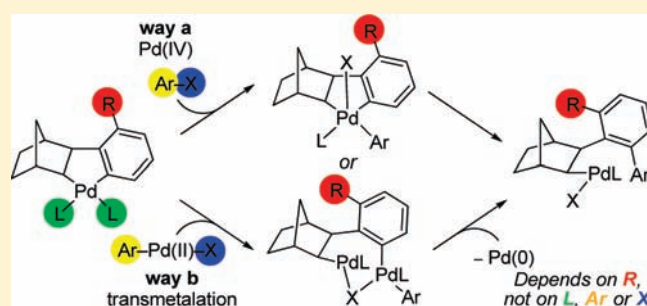
■ INTRODUCTION

Many C—C bond forming reactions of synthetic interest are palladium-catalyzed and usually involve Pd(0) and Pd(II) complexes.[1] Working in this area Heck, Negishi and Sukuzi have just been awarded the Nobel prize.[2] The intermediacy of Pd(IV) complexes in catalysis of C—C coupling reactions was initially proposed by Stille.[3] Since then, an increasing number of C—C bond forming reactions claiming Pd(II)/Pd(IV) catalysis have also been reported.[4] Stable Pd(IV) complexes resulting from oxidative addition of alkyl halides to Pd(II) have been isolated.[5] No unambiguous evidence for a similar reaction with aryl halides has been reported so far, although Pd(IV) species have been obtained by reacting aryliodonium salts and Pd(II) complexes.[6] C—C bond formation through palladium chemistry has been the topic of several reviews[7] highlighting advantages over conventional chemistry, which include high yields and selectivities, one-pot multistep reactions, mild and environmentally friendly conditions.

Some years ago, selectively alkyl-substituted aromatics have been obtained catalytically by reaction of alkyl halides R—X with a palladium complex, formed in situ from an aryl halide, a palladium salt and norbornene. This complex was shown to be metallacycle **I** (Scheme 1). Reactions of metallacycles **I** with C(sp³)—X electrophiles yield indeed the corresponding Pd(IV) octahedral complexes via oxidative addition.[8] With the use of rigid ligands, such as 1,10-phenanthroline, some structures have been characterized.[5e,8c,9]

Reductive elimination from them, although potentially involving C(sp³) attack on both the aromatic and the aliphatic sites of the planar metallacycle, only occurs with selective formation of sp²–sp³ C—C bond.[10] This circumstance has led to many synthetic applications.[11] On replacing alkyl- with aryl halides in

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Scheme 1. Palladacycle I (L = ancillary ligand) and Its Selective Reactivity with C(sp³)−X Electrophiles (R−X)

Scheme 2. Unselective Aryl−Alkyl (1, blue) and Aryl−Aryl (2, black) and Coupling by Catalytic Reaction of a 4-Substituted Bromobenzene Derivative and Norbornene

Scheme 3. Proposed Pathways for Reaction of I with C(sp²)−X Electrophiles; Ancillary Ligands Omitted for Clarity

Scheme 4. Simplified Scheme of the Pd/Norbornene Catalytic System in the Presence of an Ortho Substituent (R ≠ H)

the same reaction, however, the outcome has been quite different. A mixture of two products is obtained, which derive from aryl attack on the norbornyl or the aryl sites of the metallacycle followed by ring closure. In the presence of a para substituent, two positional isomers of hexahydromethanotriphenylene are formed. For example, 4-bromofluorobenzene gives a mixture of 45 and 15% of the two products (Scheme 2, X = F). Compound **1** comes from initial C(sp²)−C(sp³) bond formation while compound **2** results from an initial C(sp²)−C(sp²) coupling.[12]

For the aryl−aryl coupling, two mechanisms have been so far suggested. One postulates the generation of a Pd(IV) species in analogy to the known reactivity observed with alkyl halides (Scheme 3, way a),[11] while an alternative mechanism, put forward by Cardenas and Echavarren, involves a transmetalation[13] between two Pd(II) centers (Scheme 3, way b, hereinafter simply called TM in tables).[14] Their DFT calculations on simplified systems, where the norbornene unit is replaced by an ethylene bridge, suggest the latter being favored over the former.[15] The concentration of palladium salts experimentally adopted for these sequences is generally low (between 0.002 and 0.005 M)[11,17] and this should in principle disfavor the formation of bimetallic intermediates; the cascade presented in Scheme 2, on the contrary, has been achieved using a catalyst concentration of 1 order of magnitude higher (0.025 M).[12] While in Pd/norbornene-catalyzed sequences no clear-cut experiment allowed so far to discriminate between these two reaction pathways, many studies are reported in the literature showing that also dinuclear and polynuclear palladium species could be the active catalysts in cross coupling reactions.[16]

As shown in Scheme 2, the arylation reaction was found to be nonselective. This picture changed dramatically with the discovery of the "ortho effect": a substituent ortho to the aryl−norbornyl

bond of **I** (hereinafter simply called ortho substituent) was found able to direct the selective transfer of the incoming aryl unit to the aromatic site of the palladacycle. At this point, norbornene is expelled likely for steric reasons (Scheme 4).[17]

However, although the ortho effect has been referred to as "a key finding in the development of ortho arylation chemistry",[11e] so far no rational explanation has been proposed for it.

We thus decided to investigate the reactivity of **I** by means of DFT calculations trying to enlighten the still unclear aspects of the palladium and norbornene catalytic system, regarding both the mechanism involved in the reaction with aryl halides and the key role exerted by the ortho (R) substituent. To this end, we examined the energy profile of the reactions of unsubstituted (R = H) or ortho-substituted (R = Me) complexes of type **I**, involving either oxidative addition to Pd(IV) or transmetalation (TM).

■ COMPUTATIONAL METHODS

Calculations were performed with Gaussian 09 at DFT level.[18] The geometries of all complexes here reported were optimized at the generalized

Scheme 5. Summary of Examined Reaction Pathways and Simplified Presentation of the Observed Energetic Convenience between the Two Reaction Mechanisms
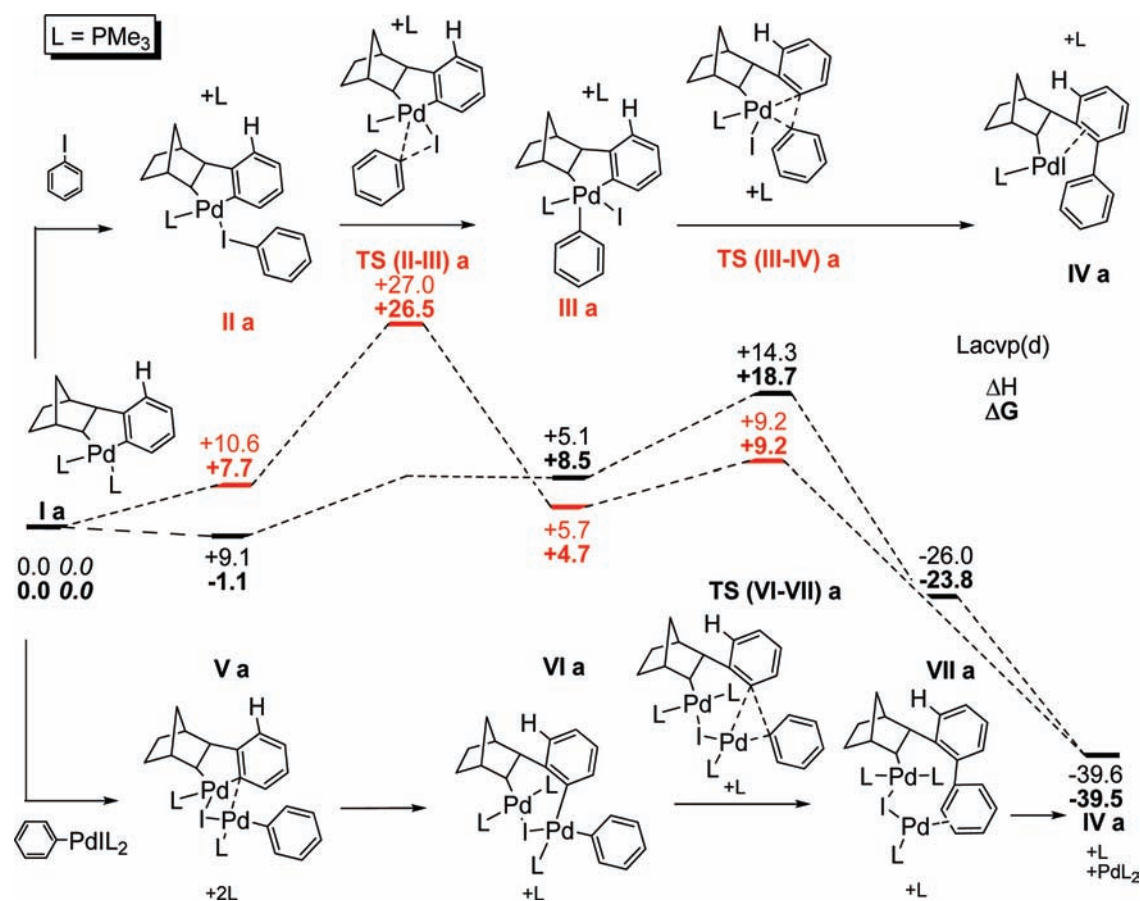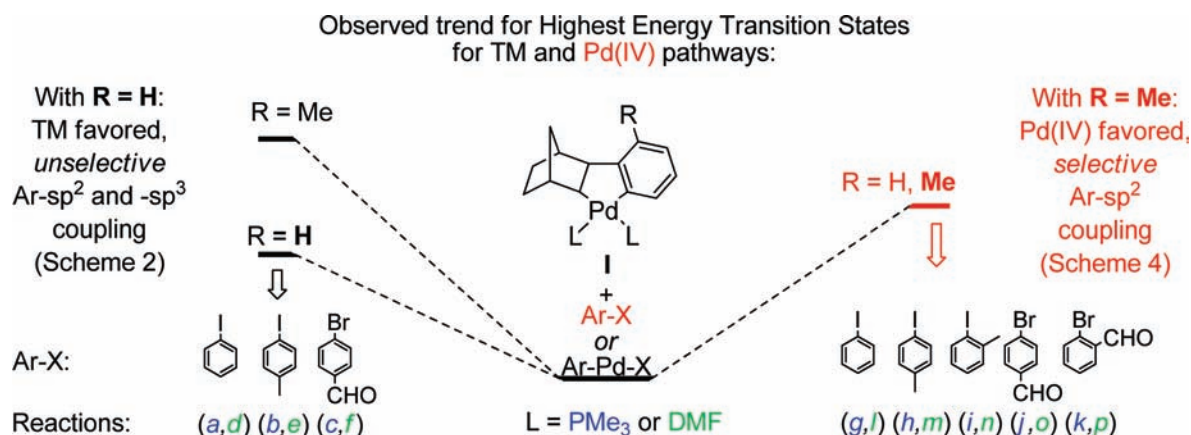

Figure 1. Reaction pathways and energies in kcal/mol at 298 K for the reaction of **Ia**.

gradient approximation using the M06 hybrid functional of Zhao and Truhlar.[19] This functional has been shown to accurately describe Pd complexes.[20] Moreover, description of high-oxidation-state metal centers (Scheme 3, *way a*) and of a possible metal–metal bond (together with its coupling to electronegative halide ligands, *way b*) demands for exchange-correlation hybrid DFT functionals rather than orthodox hybrid ones.[21]

Optimizations were carried out using LACVP(d) basis set.[22] For more accurate energy values, single-point calculations were performed on the optimized geometries using a larger basis set, def2-TZVP defined by Weigend and Ahlrichs, essentially a valence triple-ζ one,[23] and the results show no significant differences with the trends obtained with the double-ζ basis set. Harmonic frequencies were calculated at the same level of theory with LACVP(d) basis set to characterize stationary points (minima and TSs) and to determine zero-point energies corrections (ZPC) and entropies. Single-point solvent calculations were performed at the optimized gas-phase geometries for all the intermediates and
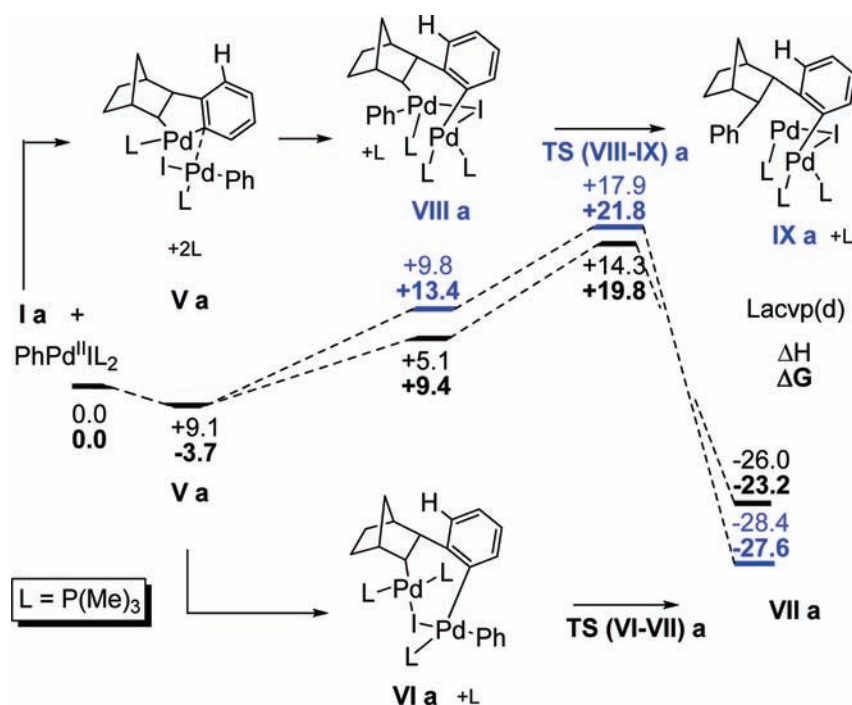
Figure 2. Reaction pathways and energies in kcal/mol at 373 K comparing the formation of sp^2–sp^3 (*blue*) and the sp^2–sp^2 (*black*) C–C bond from **Ia**.

Table 1. Relevant Free Gibbs Energies for the Reaction of Ia with Different Aryl Halides[a]

System	Aryl halide	ΔG TS (II-III) [Pd(IV)]	ΔG TS (VI-VII) [TM]
a	Iodobenzene	+ 26.5	+ 18.7
b	4-Iodotoluene	+ 26.4	+ 17.5
c	4-Bromobenzaldehyde	+ 26.2	+ 15.8

[a] Values in kcal/mol at 298 K at the M06/LACVP(d) level.

Table 2. Relevant Activation Barrier Comparing sp^2–sp^2 and sp^2–sp^3 C–C Bond Formation in the Transmetalation Pathway[a]

System	Aryl halide in Ar-Pd^{II}XL$_2$	ΔG TS (VI-VII)	ΔG TS (VIII-IX)
a	Iodobenzene	+ 19.8	+ 21.8
b	4-Iodotoluene	+ 20.0	+ 21.5
c	4-Bromobenzaldehyde	+ 16.8	+ 18.7

[a] Values in kcal/mol at 373 K, calculated at the M06/LACVP(d) level.

Table 3. Relevant Free Gibbs Energies for the Reaction of Id with Aryl Halides[a]

System	Aryl halide	ΔG TS (II-III) [Pd(IV)]	ΔG TS (VI-VII) [TM]
d	Iodobenzene	+ 17.5	+ 14.8
e	4-Iodotoluene	+ 17.6	+ 14.8
f	4-Bromobenzaldehyde	+ 17.4	+ 11.3

[a] Values in kcal/mol at 298 K at the M06/LACVP(d) level.

Table 4. Relevant Activation Barriers Comparing Pd(IV) and Transmetalation Pathways on Ig Calculated at the M06/LACVP(d) Level[a]

System	Aryl halide	ΔG TS (II-III) [Pd(IV)]	ΔG TS (VI-VII) [TM]
g	Iodobenzene	+ 26.2	+ 29.3
h	4-Iodotoluene	+ 25.9	+ 28.1
i	2-Iodotoluene	+ 28.7	+ 35.9
j	4-Bromobenzaldehyde	+ 25.4	+ 26.5
k	2-Bromobenzaldehyde	+ 28.8	+ 33.9

[a] Values in kcal/mol at 373 K, the average reported reaction temperature in the presence of phosphinic ligands.

transition states, using the CPCM[24] approach, which is an implementation of the conductor-like screening solvation model (COSMO)[25] in Gaussian09 employing DMF as a solvent. Through the same approach, full optimization was carried out only for the four most representative reactions (systems a, d, g and l of Scheme 5). In both cases, results and geometries confirm the trend observed with gas-phase calculations.[26] The temperature used to evaluate entropic contribution is 298.15 K, except for Figure 2, Tables 2 and 4 in which Gibbs free energies are presented at 373 K to refer more closely to experimental conditions. All energy diagrams are plotted relative to ΔG values, labeled in bold in Figures. The starting approximate geometries for transition states (TS)

were obtained through scans of the relative reaction coordinate starting from the corresponding reagents.

In the following discussion, computed structures will be designated by latin numbers, with letters referring to the various systems analyzed by varying ligands, aryl rings and halides. Scheme 5 anticipates the main observation we propose in the present study, encountered among all the reactions we modeled by changing substrates and ligands, and which will be demonstrated throughout the rest of this paper. The reactions of

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unsubstituted metallacycles **I** will be considered first, and then the results will be compared to the ones observed employing Me substituted palladacycles.

■ RESULTS AND DISCUSSION

1. Reaction of Palladacycle I without an Ortho Substituent (R = H). Palladacycles of type **I** were chosen as the starting complexes for our investigations, being the proposed key intermediates in the above-mentioned catalytic domino reactions (Scheme 4). In these complexes, the Pd atom and the aromatic are bonded to the norbornyl unit with a cis, exo arrangement. The square planar environment around the metal comprises two ancillary ligands, in agreement with what is observed in isolated complexes of **I**.[27] Two palladacycles were modeled, one containing PMe$_3$ and the other DMF as ligand. The phosphine PMe$_3$ was chosen to represent the tertiary phosphines employed in the reported catalytic sequences, mainly triphenylphospine and trifurylphosphine, without a severe increase of computational cost. The role of the steric effect presented hereafter for the transmetalation pathway switching from unsubstituted to methyl substituted metallacycle **I** was confirmed as well employing PPh$_3$ as ligand on the most representative reactions (for details, see section 5 in the Supporting Information), although the size of the relative TM complexes together with resulting conformational issues sets the accurate modeling of this system at the edge of possibilities offered by our computational approach.[28] DMF was tested as ligand to exemplify the catalytic processes performed under phosphine-free conditions.[29] Three aryl halides were examined: iodobenzene, 4-iodotoluene, and 4-bromobenzaldehyde, as reactions of **I** were usually reported to take place with aryl iodides and electron poor aryl bromides. Although these systems were quite costly from a computational point of view, we deemed it necessary not to simplify too much as from experimental evidence the "ortho effect" seems mainly due to steric factors rather than electronic ones and computation of the former is more laborious. We investigated the two possible reaction profiles for the reaction of **I** with aryl halides: an oxidative addition to yield a Pd(IV) species versus a transmetalation reaction between two Pd(II) centers as proposed by Cardenas and Echavarren.[14] The calculated free-energy profiles for these two pathways in the presence of PMe$_3$ as ligand are reported in Figure 1. The figure shows the reaction of **Ia** with iodobenzene, involving the intermediacy of Pd(IV) species (*highlighted in red*), and with the Pd(II) complex[30] resulting from oxidative addition of iodobenzene to Pd(0)L$_2$ (transmetalation pathway, *highlighted in black*).

The Pd(IV) pathway will be considered first. Formation of complex **IIa** implies exchange of one ancillary ligand with iodobenzene (ΔG +7.7 kcal/mol). Replacement of the phosphorus ligand with the iodide of PhI is endotermic (ΔH +10.6 kcal/mol), but is accompanied by a positive entropic variation. Transition state **TS(II−III)a** is reached from complex **IIa**, with similar values for ΔH and ΔG. However, since ligand exchange from **Ia** is endothermic, this transition state lies far above the entry channel (ΔG +26.5 kcal/mol). The reaction leads to the pentacoordinated Pd(IV) complex **IIIa**. This complex features a Y-distorted trigonal bipyramidal geometry, in which the aromatic carbon of the metallacycle and the phosphine occupy the axial positions in respect to the Y plane.[31] The **TS(III−IV)a** for reductive elimination is easily accessible (ΔG +4.5 kcal/mol in respect to **IIIa**) and takes place between the axial C(sp^2) of the metallacycle and the planar C(sp^2) of the aryl ring. Product **IVa**, containing the biaryl

unit, lies far below the entry channel (ΔG −39.5 kcal/mol), as expected in concomitance with the formation of the C−C bond. Complex **IVa** has a square planar coordination ensured by the phosphine, the iodide, the C(sp^3) of the norbornyl unit, and a slipped η^2 bond with the aryl ring previously belonging to the palladacycle, in agreement with literature data on similar complexes.[32] We also found octahedral transition states for the Pd(IV) pathway but their activation energies are higher than those presented in Figure 1.[33] These data are in accord with those previously reported for reductive elimination from a pentacoordinated Pd(IV) complex.[31]

Examining the transmetalation pathway, reaction of **Ia** with a second Pd(II) center leads to **Va** with displacement of two molecules of ligands giving a negative ΔG of −1.1 kcal/mol. In **Va**, both palladium atoms present a slightly distorted square planar coordination and the two planes form an angle of about 60°. The bimetallic complex thus assumes a clamshell conformation in which the calculated distance between metal nuclei is lower (2.78 Å) than the sum of their van der Waals radii (3.26 Å). Several X-ray structures of complexes featuring Pd−Pd distances ranging from 2.55 to 3.05 Å have been reported.[34] The metal center of the palladacycle completes its coordination with an ancillary ligand and the bridging iodide while the second one, beside sharing the iodide, interacts with both the aryl rings and a phosphine, as reported by Cardenas and Echavarren. Transfer of the aryl ring of the metallacycle to the second metal center allows the formation of **VIa** with concomitant coordination of the PMe$_3$ ligand to the palladium center originally belonging to the metallacycle, thus, providing a positive ΔG of +9.6 kcal/mol compared to **Va**. We could not find a transition state for this process, insofar as relative scans show a very flat potential energy surface around the product **VIa**.[35] Reductive elimination from **VIa** allows the biaryl unit formation of **VIIa**, through **TS(VI−VII)a**. This step, which corresponds to the most energy demanding one of the entire transmetalation pathway (ΔG +10.2 kcal/mol from **VIa**), is nevertheless lower than the **TS(II−III)a** involving Pd(IV) by 7.8 kcal in ΔG (after optimization in solution, this $\Delta\Delta G$ favors the TM pathway by 2.3 kcal/mol).[36] Even if the entropic factor is negative in the case of transmetalation pathway, the gap between the two mechanisms is always above 5 kcal in the temperature range in which these reactions usually take place (80−130 °C).

We then modeled the reaction with other aryl halides and obtained closely related results. Relevant data for the two important transition states are summarized in Table 1 (the complete pathways are reported in the Supporting Information).

For the three modeled systems, without an ortho sustituent, the transmetalation course is always favored by 8−10 kcal/mol in ΔG over the one involving the Pd(IV) intermediacy.

Beside the previously shown transfer of the aryl ring of metallacycle **Va** onto the Ph−Pd center leading to **VIa** (Figure 1), we also considered the norbornyl transfer onto the same Ph−Pd unit (Figure 2, blue pathway). The black pathway of Figure 2, referring to the aryl transfer, is reported once more, to allow a direct comparison of the two reaction modes. Migration of the C(sp^3) atom from one to the other palladium center results in complex **VIIIa**. Although this intermediate is higher in energy compared to **VIa**, its barrier for reductive elimination (**TS(VIII-IX)a**, ΔG +8.4 kcal/mol on **VIIIa**) with formation of the sp^2−sp^3 C−C bond requires a lower activation energy. Furthermore, the entropy loss from reagents is lower than in the case of **TS(VI−VII)a**, and as a result, the $\Delta\Delta G$ between them is reduced increasing the temperature. This narrow gap could thus explain the lack of selectivity

experimentally observed in the absence of an ortho substituent in palladacycle **I** (see Scheme 2 or ref 12).

To support this hypothesis, we modeled the reaction of **Ia** shown in Figure 2 also with other in situ-formed arylpalladium-(II) complexes, and found the same trend (Table 2). In all the three modeled systems, the gap between the two reductive elimination pathways, calculated at 373 K, is quite narrow, ranging between 1.5 and 2.0 kcal/mol.

We then investigated the system containing DMF as ancillary palladium ligand (Figure 3). Energy trends and geometrical considerations are very similar to those found for the phosphine system, although energy barriers in the presence of DMF are lower for both the Pd(IV) and transmetalation pathways (Table 3).

Replacing a DMF molecule of **Id** with iodobenzene affords **IId** intermediate. As expected, the process is less enthalpy demanding compared to the phosphine case (ΔH +1.6 kcal/mol); however, the DMF molecule being smaller, the resulting ΔG is similar (+5.4 kcal/mol). The oxidative addition leading to Pd(IV) complex **IIId** proceeds trough **TS(II−III)d** (ΔG +12.1 kcal/mol relative to **IId**). Reductive elimination, as in the case of **IIIa**, has a very low barrier (**TS(III−IV)d**, ΔG +5.4 kcal/mol) readily leading to product **IVd**.

The transmetalation pathway begins with the association intermediate **Vd**, which is below the entry level in both ΔH (−1.0 kcal/mol) and ΔG (−10.5 kcal/mol). Contrary to what was previously observed with the phosphine ligand, transfer of the C(sp^2) of the metallacycle to the second palladium atom to obtain **VId** does not require insertion of another L molecule.[37] As in the above-mentioned case (L = PMe$_3$, Figure 1), reductive elimination

from the bimetallic intermediate **VId** is more energetically demanding than from the Pd(IV) species (ΔG +7.1 kcal/mol relative to **VId**). **TS(VI−VII)d**, however, remains substantially lower than **TS(II−III)d** (ΔG = −2.7 kcal/mol; after optimization in solution, this $\Delta\Delta G$ favors the TM pathway by 8.3 kcal/mol).[38]

Considering other coupling partners for **Id**, results are very similar and the transmetalation pathway between two Pd atoms is always favored over the mechanism involving oxidative addition leading to Pd(IV). Differences are in the range of 3−6 kcal/mol in these representative systems (Table 3). We have thus shown that with metallacycles **I** the transmetalation pathway is favored, both in the presence of PMe$_3$ as ligand (**Ia**) and with DMF bound to Pd (**Id**) to mimic "ligand-free" conditions. The mechanism initially proposed by Cardenas and Echavarren is probably at work in the palladium catalyzed sequences (in which norbornene acts as reagent) leading to the unselective aryl−aryl and aryl−alkyl coupling (Scheme 2).

2. Reaction of Palladacycle I Containing an Ortho Substituent (R = Me). As mentioned in the Introduction, to achieve selective aryl−aryl coupling and thus develop new catalytic methodologies in which both palladium and norbornene act as catalysts,[11,16,29] an ortho substituent in **I** is required. Since the smallest group possible is the Me one, we modeled the reactions with complex **Ig** containing the methyl group in the ortho position to the C(sp^2)−C(sp^3) bond of the palladacycle (**I**, R = Me).

The Pd(IV) pathway closely resembles that obtained with metallacycle **Ia**, not containing any substituents in the aryl ring (see Figure 1, red pathway). Coordination of iodobenzene is slightly less energy demanding (**IIg**, ΔG +7.8 kcal/mol) and the following
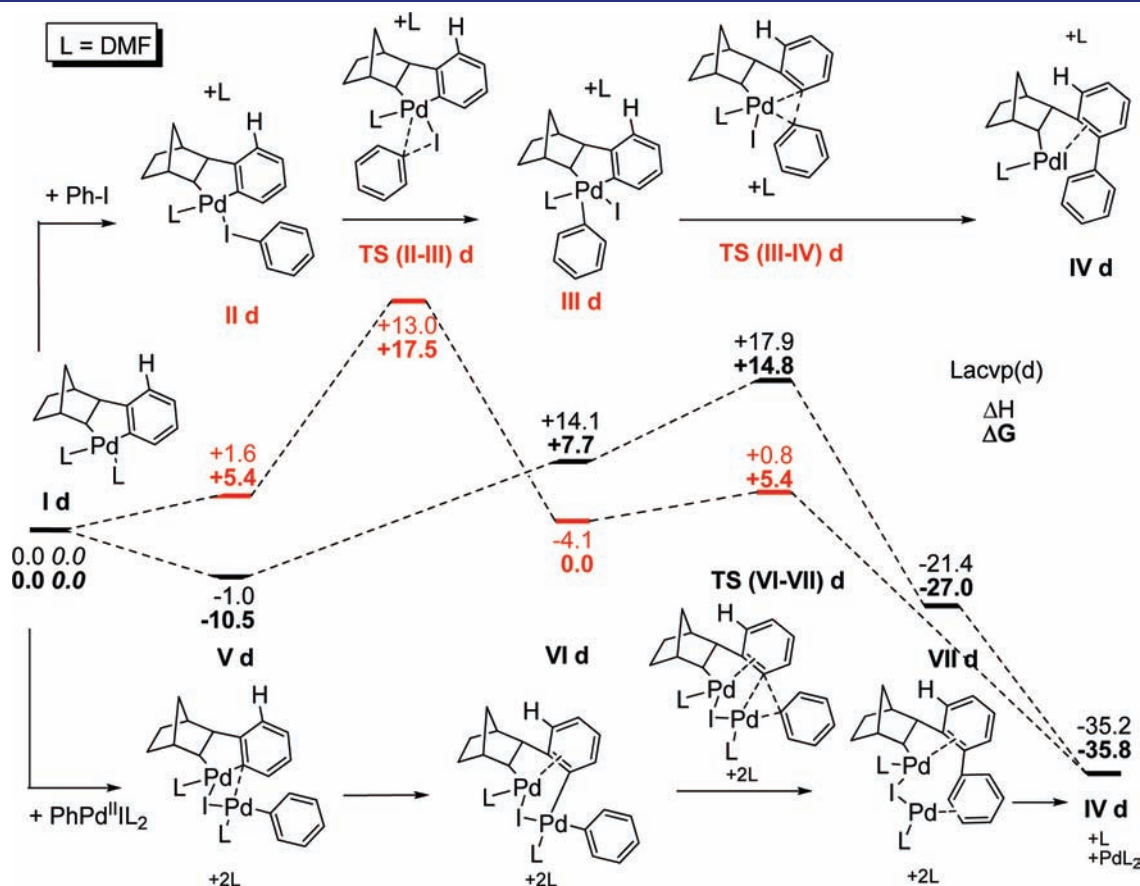

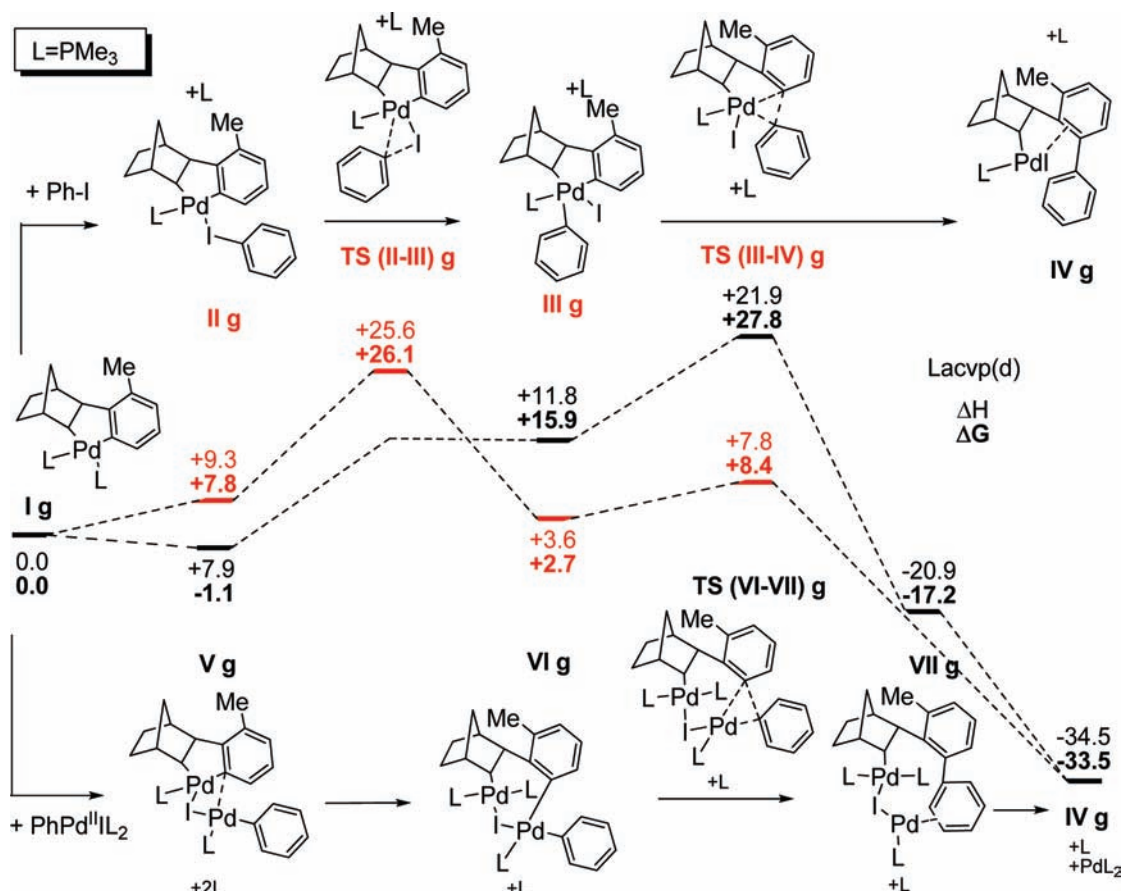**Figure 3.** Reaction pathways and energies in kcal/mol at 298 K for the reaction of **Id**.

Figure 4. Reaction pathways and energies in kcal/mol at 298 K for the reaction of **Ig**.

TS(II−III)g is 26.1 kcal/mol above the entry channel (only 0.4 kcal/mol less than the **TS(II−III)a** of Figure 1). Pd(IV) intermediate **IIIg** has the same Y-distorted trigonal bipyramidal geometry of **IIIa**, and could allow the formation of the biaryl unit present in **IVg** through **TS(III−IV)g** (ΔG +5.7 kcal/mol relative to **IIIg**).

In contrast to the Pd(IV) pathway, the values obtained analyzing the transmetalation one are very different. Formation of the association complex **Vg** accounts for a negative ΔG of −1.1 kcal/mol (exactly the same value obtained for **Va**, Figure 1). However, transfer of the aryl ring from the palladacycle to the second Pd atom to obtain **VIg** is much more energy demanding (ΔG of +17 kcal/mol relative to **Vg**). As in the case previously shown in Figure 1, it was not possible to find a transition state and scans revealed a very flat energy surface around complex **VIg**.[39] Reductive elimination from **VIg** proceeds through **TS(VI−VII)g**, which lies 27.8 kcal/mol above the entry channel, and thus 1.7 kcal/mol above **TS(II−III)g**, the highest energy transition state of the Pd(IV) pathway (after optimization in solution, this $\Delta\Delta G$ favors the Pd(IV) pathway by 9.4 kcal/mol).[40] Analyzing the reaction course in the presence of a substituent in complex **I** resulted in a significant increase in the energy of the transmetalation pathway ($\Delta\Delta G$ between **VIa−g** and **TS(VI−VII)a−g** being +7.4 and +9.1 kcal/mol, respectively). Moreover, since the entropy variation from reagents is negative for this pathway while almost negligible for the Pd(IV) one, the gap between the two mechanisms increases with the temperature, as shown in Table 4 which presents relevant activation barriers calculated at 373 K for the different aryl halides considered here (as an example for the g system, the gap between relevant TSs

increases from 1.7 kcal/mol at 298 K, Figure 4, to 3.1 kcal/mol at 373 K, Table 4).

In sharp contrast to the data reported in Table 1, the obtained values clearly show that, starting from a metallacycle of type **I** containing an ortho substituent in the aromatic ring, the Pd(IV) pathway lies below the transmetalation one (1−7 kcal/mol in the five representative systems analyzed). Although it was previously reported that the presence of an ortho substituent in the aryl halide reacting with **Ig** was not required, we also tested these reagents.[41] As expected, the barriers were found to be higher than those of the corresponding unsubstituted or para substituted halides (systems h and j), both in the Pd(IV) and in the transmetalation pathways, but much higher in the latter case.

Analysis of the geometry of relevant reaction species (Figure 5) clearly shows the reason why the Pd(IV) course reveals similar values for the reactions of **Ia** and **Ig** while the transmetalation pathway suffers a severe penalty in the presence of a methyl substituent in the starting metallacycle. Figure 5 shows the modeled structures of the relevant species involved in the Pd(IV) pathway, namely, the starting metallacycle **Ig** and the **TS(II−III)g**, the latter reaching the highest energy of the entire profile. In complex **Ig**, the norbornyl moiety, the aromatic ring and the palladium atom are coplanar and the methyl group points to a direction of the space not occupied by the bulky norbornyl ring. The geometry of **Ig** does not change significantly in the **TS(II−III)g**, as shown by the shortest H−H distances between the methyl group and the norbornyl unit observed in **Ig** and **TS(II−III)g**. A difference of 0.03 Å between the shortest H−H distances in the two modeled

structures clearly indicates that no significant change takes place on going from **Ig** to the highest energy TS of the Pd(IV) pathway.[42]
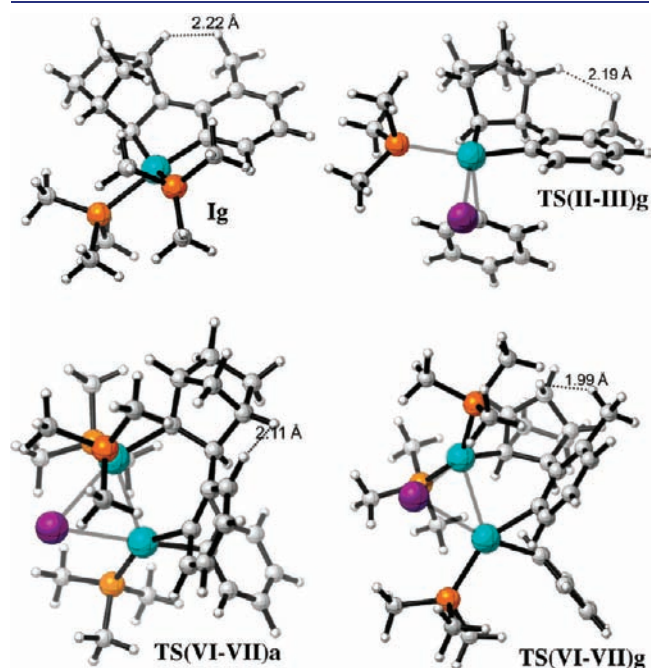

Figure 5. Modeled structures of **Ig** and **TS(II–III)g** for the Pd(IV) pathway and of **TS(VI–VII)a** and **TS(VI–VII)g** for the transmetalation one highlighting the shortest H–H distances.

Thus, in catalytic reactions where metallacycle **I**, containing an ortho substituent, is formed in situ, an oxidative addition transition state would not suffer from steric clashes related to the bulkiness of the substituent *more* than the starting metallacycle itself.[43] By contrast, the geometry of transmetalation **TS(VI–VII)a** and **-g**, depicted in Figure 5, turns out to be quite different. Transfer of the metallacycle aromatic ring to the second Pd atom occurs with a formal rotation of the aryl–norbornyl C–C bond in respect to the plane of palladacycle **I** (while the dihedral angle formed by its 4 carbon atoms in both **I** and **V** is lower than 5°, in **VI** it goes up to 65°). When a substituent is present (as in **TS(VI–VII)g** shown in the right side), it points to the region of the space occupied by the bridging CH_2 group of the norbornyl unit. A steric clash appears already in intermediate **VIg** (where the shortest H–H distance is 2.07 Å) but is more severe in the transition state (the shortest H–H distance is lower in **TS(VI–VII)g** by 0.12 Å compared to **TS(VI–VII)a**) and the trend is expected to be even more severe when more sterically demanding groups are at work. The presence of an ortho substituent also in the reacting aryl halide, as in the case of 2-iodotoluene and 2-bromobenzaldehyde (Table 4, systems i and k) enhances this steric effect in the transmetalation pathway, due to a closer proximity of their 6-hydrogens with the endo protons of the metallacycle.[44]

Analysis of the system containing DMF as palladium ancillary ligand (Figure 6) confirms the effect found in the presence of PMe_3 and reveals similar trends.

The Pd(IV) reaction course of **Il**, containing an ortho methyl group, has slightly lower energy values compared to those found for the unsubstituted **Id** system of Figure 3. Replacing a DMF
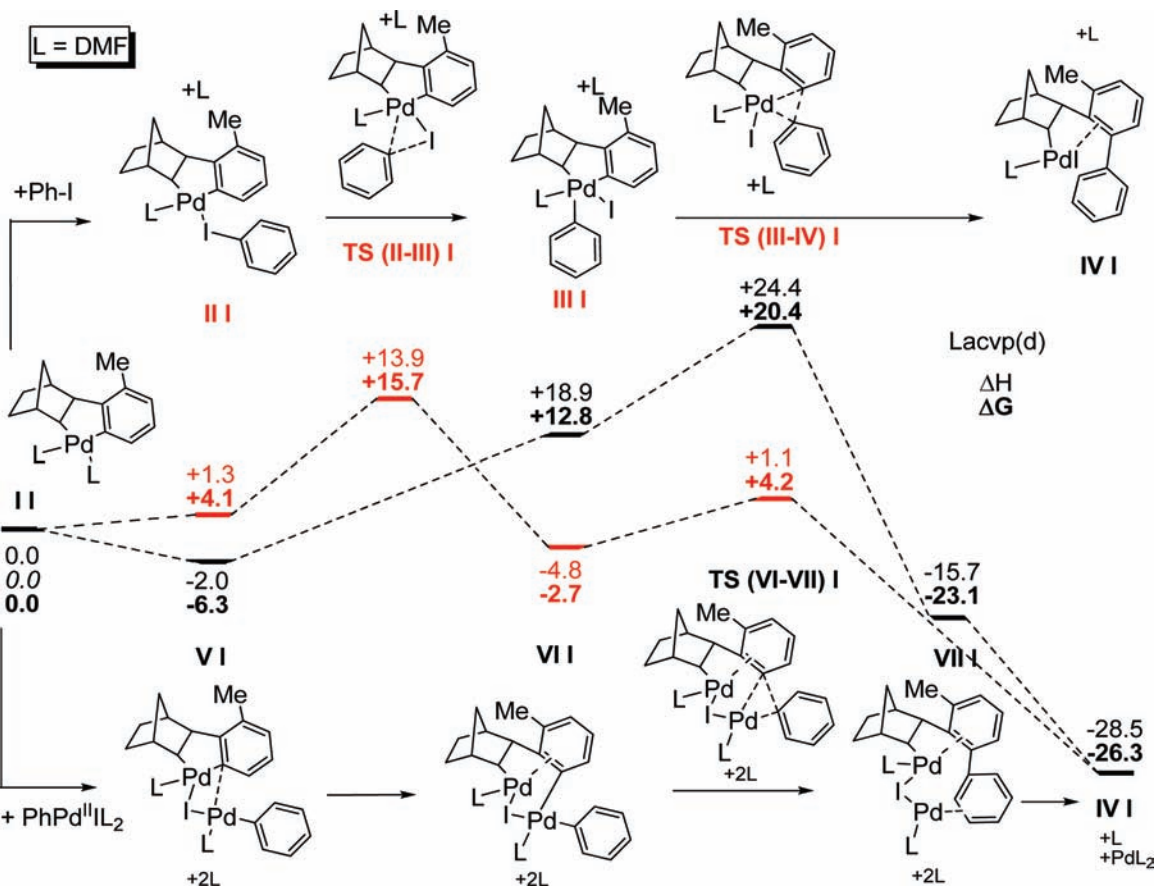
Figure 6. Reaction pathways and energies in kcal/mol at 298 K for the reaction of **Il**.

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Table 5. Relevant Free Gibbs Energies Comparing Pd(IV) and Transmetalation Pathways of Il^a

System	Aryl halide	ΔG TS (II-III) [Pd(IV)]	ΔG TS (VI-VII) [TM]
l	Iodobenzene	+ 15.7	+ 20.4
m	4-Iodotoluene	+ 15.4	+ 22.4
n	2-Iodotoluene	+ 19.2	+ 27.4
o	4-Bromobenzaldehyde	+ 14.6	+ 16.6
p	2-Bromobenzaldehyde	+ 15.2	+ 23.1

^{a} Values in kcal/mol at 298 K, calculated at the M06/LACVP(d) level.

molecule with iodobenzene is slightly less energy demanding (**III**, ΔG +4.1 kcal/mol compared to **IId**, +5.4 kcal/mol), and the oxidative addition **TS(II−III)l** is 15.7 kcal/mol above the entry channel (thus, 1.8 kcal/mol less than the **TS(II−III)d**, see Figure 3). Pd(IV) intermediate **IIIl** is now even below (ΔG −2.7 kcal/mol) the entry channel of the Pd(II) complex **Il**. It features the same Y-distorted trigonal bipyramidal geometry discussed above, and could allow the formation of the C−C bond present in **IVl** through the easily accessible **TS(III−IV)l** (ΔG +4.2 kcal/mol).

As in the case of the phosphine, values obtained analyzing the transmetalation pathway are very different from those observed in the case of the **Id** system (not containing an ortho substituent in the reagent) of Figure 3. Formation of the association complex **Vl** accounts for a negative ΔG of −6.3 kcal/mol (thus, 4.2 kcal/mol above the value obtained for **Vd**, Figure 3). Transfer of the tolyl ring from the palladacycle to the second metal atom to obtain **VIl** is costly energetically even in this case (ΔG of +19.1 kcal/mol relative to **Vl**). The reductive elimination from **VIl** proceeds through **TS(VI−VII)l**, which lies 20.4 kcal/mol above the entry channel, and, moreover, 4.7 kcal/mol above **TS(II−III)l** (after optimization in solution, this $\Delta\Delta G$ favors the Pd(IV) pathway by 0.6 kcal/mol).[45] As in the phosphine case, transition state (**TS(VI−VII)l**) of the transmetalation pathway shows a significant increase in energy over **TS(VI−VII)d** ($\Delta\Delta G$ is +5.6 kcal/mol). Even if now the entropy term favors the transmetalation pathway, the gap between the oxidative addition to Pd(IV) and the reductive elimination of transmetalation still let the former being favored over the latter, even at high temperature. Table 5 summarizes the data of the relevant activation barriers for the different aryl halides considered in this paper.

In sharp contrast to the data shown in Table 3, the values obtained reacting **Il** metallacycle with several aryl halides show that the pathway involving the Pd(IV) intermediacy invariably passes through transition states which are lower in energy than reductive elimination from transmetalation intermediates (2−8 kcal/mol less in these five representative examples).

Analysis of the geometry of relevant reaction species (Figure 7) confirms the observed feature described above in the case of the phosphine ligand: while the Pd(IV) course reveals similar values between **Id** and **Il**, the transmetalation pathway suffers a penalty due to the steric clash between the ortho substituent and the bridging CH$_2$ group of norbornyl ring. In fact, in agreement with the above-mentioned trend, in **Il**, the shortest H−H distance is 2.24 Å and, in the related **TS(II−III)l**, there is even a slight increase to 2.26 Å (similarly for the hydrogen substituent in Id the increment in the transition state is 0.04 Å). As a result, oxidative addition to Pd(II) is not affected by the presence of a (bulky) substituent in the starting metallacycle, as the steric
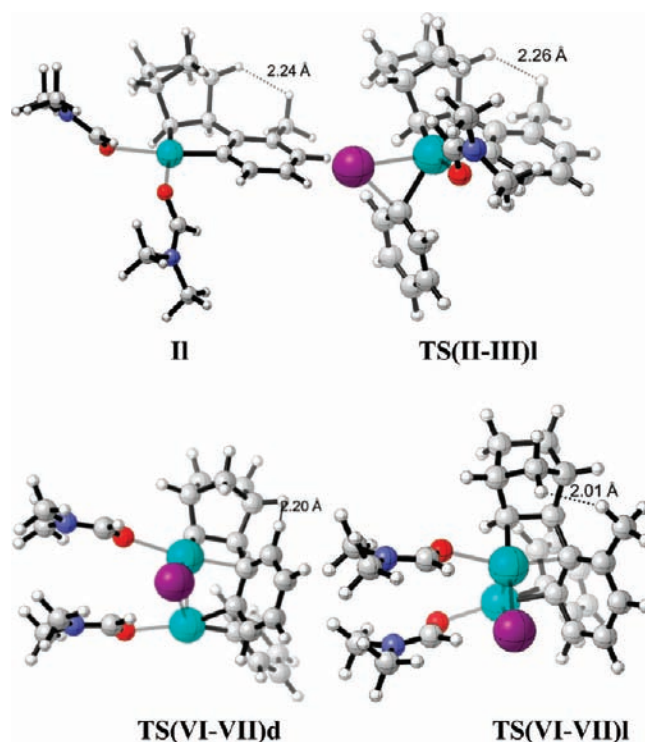

Figure 7. Modeled structures of **Il** and **TS(II−III)l** for the Pd(IV) pathway and of **TS(VI−VII)d** and **TS(VI−VII)l** for the transmetalation one highlighting the shortest H−H distance.

environment in the resulting transition state closely resembles the situation of the reagent itself.

Figure 7 shows on the other hand how the shortest H−H distance in **TS(VI−VII)d** (H substituent in the initial palladacycle) of 2.20 Å, sinks low to 2.01 Å when a (relatively) small methyl group is placed in the reagent (**TS(VI−VII)l**). In other words, the rotation of the aryl ring of the starting palladacycle, required for the reductive elimination in the transmetalation mechanism, generates a steric clash when an ortho substituent is present in **I**, between the CH$_2$ bridge of the norbornyl ring and the substituent itself. This steric clash, by increasing the energy required for the transmetalation reaction pathway, allows the Pd(IV) mechanism to become a more feasible reaction route for the aryl−aryl coupling also with DMF as ligand for metal. As mentioned in the Introduction, the presence of a substituent in the starting palladacycle is necessary to achieve the selective formation of the sp^2−sp^2 C−C bond. Analysis of the reductive eliminations from Pd(IV) complexes **III** could properly explain this experimental observation. Table 6 compares the barriers of reductive elimination from **III** to form either the sp^2−sp^2 or the sp^2−sp^3 C−C bond.

Among these representative systems, formation of the sp^2−sp^2 C−C bond is always favored over the sp^2−sp^3 one (by 4−12 kcal/mol in ΔG; after optimization in solution, $\Delta\Delta G$ favors the formation of the sp^2−sp^2 bond by 15.1 and 8.7 kcal/mol for g and l systems, respectively).[46] Reductive elimination from **III** takes place between the electrophilic sp^2 carbon atom previously belonging to the aryl halide and the aryl site of the metallacycle which, according to both APT and Mulliken formal charges, is more nucleophilic than its aliphatic counterpart.[47] Moreover, the *endo* hydrogen atom of the latter is responsible of a steric clash in each **TS(III-X)** with the incoming electrophilic carbon of the aryl ring (C−H distances are around 2.1 Å in these analyzed systems,

Table 6. Comparison of Activation Barriers for the Two Possible Reductive Eliminations from Pd(IV) Complexes IIIg−p[a]
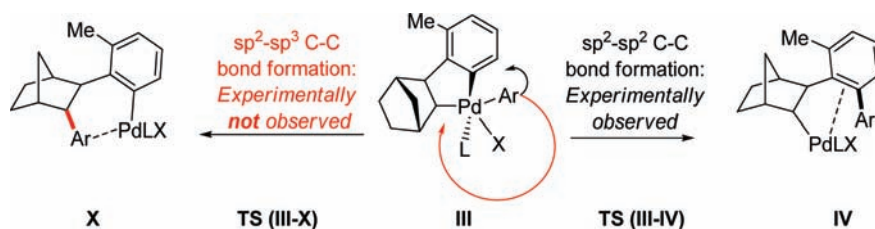
System	Ligand	Aryl halide	ΔG TS(III-IV)	ΔG TS(III-X)
g	PMe₃	Iodobenzene	+5.7	+17.5
g*	PPh₃	Iodobenzene	+4.9	+16.7
h	PMe₃	4-Iodotoluene	+6.2	+17.4
i	PMe₃	2-Iodotoluene	+10.4	+22.4
j	PMe₃	4-Bromobenzaldehyde	+4.8	+15.1
k	PMe₃	2-Bromobenzaldehyde	+9.2	+22.5
l	DMF	Iodobenzene	+6.9	+11.0
m	DMF	4-Iodotoluene	+7.6	+11.0
n	DMF	2-Iodotoluene	+4.7	+9.8
o	DMF	4-Bromobenzaldehyde	+4.6	+10.7
p	DMF	2-Bromobenzaldehyde	+3.0	+9.9

[a] Values in kcal/mol at 298 K calculated at the M06/LACVP(d) level.

thus, 0.1 Å less than the distance between the reacting carbon atoms). The proposed Pd(IV) model is thus in agreement with experimental evidence: aryl—alkyl coupling is not observed when an ortho substituent is present in the starting metallacycle as this pathway is always more energy demanding than sp^2—sp^2 bond formation.

■ CONCLUSIONS

We have attempted to answer the mechanistic questions concerning palladium and norbornene catalyzed reactions: how aryl halides react with palladacycles and what is the rational explanation of the "ortho effect". We have considered two possible pathways, one involving oxidative addition of an aryl halide to a palladacycle, the other passing through a formal palladium(II) transmetalation, also involving a palladacycle between two palladium(II) complexes.

We have shown that the palladium catalyzed reaction of ortho unsubstituted aryl halides and norbornene has a good probability to occur through a transmetalation mechanism, energetically favored over the Pd(IV) one. The reported unselective sp^2—sp^2 and sp^2—sp^3 coupling can be explained in the framework of the transmetalation pathway since the energetic difference between aryl attack onto the aryl or norbornyl carbon of the reacting palladacycle is quite small (Figure 2 and Scheme 2). On the other hand, the experimentally observed "ortho effect" stipulates that in palladium and norbornene catalyzed domino reactions involving ortho-substituted aryl halides, selective aryl—aryl coupling only occurs. The present work offers the first possible rationalization of this fact. When *in situ* formed metallacycles, containing an ortho substituent, undergo oxidative addition of an aryl halide, the process becomes less energetically costly than the one involving reductive elimination from the transmetalation intermediate, which would be subject to steric clash in the transition state. The now accessible Pd(IV) intermediate features a Y-distorted trigonal bipyramidal structure from which an easy reductive elimination can account for the reported selective aryl—aryl coupling. Thus, the steric effect represents the main factor that dictates the energetic convenience of the system to follow the Pd(IV) or the transmetalation pathway. Ortho substituents cause a higher energy transition state for reductive elimination from the transmetalation intermediate than for oxidative addition from the metallacyclic palladium(II) and the pathway based on the latter predominates. Further support of these DFT conclusions will come in due course from experimental work in progress, regarding the effect of palladium concentration through kinetics analysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Detailed computational methods, detailed reaction figures and tables, XYZ coordinates and comprehensive energetic tables in atomic units. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
etienne.derat@upmc.fr; marta.catellani@unipr.it

■ ACKNOWLEDGMENT

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(33) See Section 6 of the Supporting Inforamtion. **TS(II-III)a** and **TS(III-IV)a** lie 5.5 and 4.5 kcal/mol in ΔG below their octahedrical counterparts, respectively.

(34) Our theoretical approach has been successfully adopted to describe dipalladium complexes: Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092–14103. Recently, investigations establishing an attractive d^8–d^8 interaction in certain Pd(II) dimers have been carried out:Bercaw, J. E.; Durrell, A. C.; Gray, H. B.; Green, J. C.; Hazari, N.; Labinger, J. A.; Winkler, J. R. *Inorg. Chem.* **2010**, *49*, 1801–1810.

(35) **TS(V−VI)a** could be found employing B3LYP and PBE0 functionals. They lie only +0.3 and +0.8 kcal/mol above **VIa**, respectively.

(36) See Supporting Information Section 2. Single-points calculations on these relevant TSs for reactions a−c favor the TM pathway by 0.5−2 kcal/mol.

(37) We modeled also this system, as proposed by Cardenas and Echavarren in their model, but the resulting energies are higher than those reported in Figure 3. This is probably related to the simplified model they employed, where steric congestion was much lower.

(38) See Supporting Information Section 2. Single-points calculations on these relevant TSs for reactions d−f favor the TM pathway by 4−8 kcal/mol.

(39) Using B3LYP and PBE0 functionals did not allow to determine either the TS or intermediate **VIg**, and led to a direct connection, although very energetically disfavored, between **Vg** and **TS(VI−VII)g**.

(40) See Supporting Information Section 2. Single-points calculations on these relevant TSs for reactions g−k favor the Pd(IV) pathway by 8−17 kcal/mol.

(41) 2-Substituted aryl halides have been tested as simplified model substrates for catalytic methods featuring a final intramolecular ring closure, as those of refs 17c−17e.

(42) The distance, as reported above, is reduced by 0.03 Å only, while this contraction is greater (0.23 Å) when the Me group is replaced by a H atom, as found for **Ia** and its corresponding **TS(II−III)a**.

(43) The methyl group in our model, or even much more sterically demanding groups such as the *i*-Pr, *s*-Bu, and Ph, were experimentally employed in successful way.

(44) Modeled relevant structures evidencing these further H−H close proximity (less than 2 Å) for i,k,n and p systems could be found in the Supporting Information.

(45) See Supporting Information Section 2. Single-points calculations on these relevant TSs for reactions l−p favor the Pd(IV) pathway by 1−10 kcal.

(46) See Supporting Information Section 3. Single-points calculations on these relevant TSs for reactions g−p favor in all cases this reductive elimination pathway by 3−16 kcal/mol.

(47) Relevant data for these three reacting carbon atoms and relevant calculated charges for palladium nuclei of both formal Pd(IV) and transmetalation (TM) mechanisms are available in the Section 8 of Supporting Information.

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