Oxidative Additions of Aryl Halides to Palladium Proceed through the Monoligated Complex

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Palladium(0) complexes facilitate many catalytic transformations that begin with the oxidative addition of a halobenzene. The ligation state of the palladium during this reaction is a vexing issue, owing to the inherent difficulty of isolating reactive, coordinatively unsaturated metal complexes. By isolating them in the gas phase in an ion-trap mass spectrometer, the reactivity of mono- and bisligated palladium complexes can be directly compared, and the former proved to be several orders of magnitude more reactive towards halobenzenes. Calculations of barrier heights for the oxidative addition led to additional experiments, which demonstrated that although the reaction proceeded to completion for iodobenzene, the reaction was slower for bromobenzene and progressed only as far as an ion–molecule adduct for chloro- and fluorobenzene.

Introduction

Oxidative addition (OA) of an aryl halide to palladium(0) is the first step in the catalytic cycle of many palladium-catalyzed cross-coupling reactions that have found wide use in industrial and pharmaceutical applications.[1–3] A great deal of effort has gone into understanding the mechanistic details of the OA process, and much progress has been made. For example, it is well established that the propensity of aryl halides towards oxidative addition increases in the order ArF < ArCl < ArBr < ArI,[4] and that oxidative addition is first order in both palladium and aryl halide.[5] It is also clear that the choice of phosphine ligands (the classical type of ligand for palladium-catalyzed cross-coupling reactions) can significantly affect the energetics of the oxidative addition process.[6] As such, efforts have been focused on synthesizing "designer ligands" to enhance catalytic performance.[7,8] However, the design of effective ligands and selection of appropriate catalytic conditions can be helped by an improved understanding of the number of phosphine ligands that the active catalyst bears.

In solutions containing $Pd(PPh_3)_4$, a standard source of Pd^0 for cross-coupling reactions, the trisligated $Pd(PR_3)_3$ has long been proposed as the dominant palladium species.[9, 10] $Pd(PPh_3)_2$ is also detected in solution, and it exists in equilibrium with the more abundant $Pd(PR_3)_3$. The observation of this coordinatively unsaturated, highly reactive, 14-electron $Pd(PPh_3)_2$ complex in solution led to the hypothesis that bisphosphine palladium complexes are most likely responsible for facilitating OA of aryl halides in solution.[5, 11–14] Successful isolation and characterization of $(Ar)Pd(X)L_2$-type complexes, and the observation of a "phosphine-poisoning" effect on OA supported this hypothesis, and in the literature $Pd^0(PR_3)_2$ is widely accepted as the active catalyst for OA of aryl iodides and activated aryl bromides. More recently, less expensive aryl chlorides and unactivated aryl bromides have been successfully used as substrates for Pd-catalyzed C—C bond-forming reactions by employing electron-rich and very bulky phosphine ligands. Unlike OA of aryl iodides and aryl bromides, the OA of these difficult substrates is suggested to require a highly reactive, 12-electron, monoligated catalyst, the formation of which is favored by bulky phosphine (or N-heterocyclic carbene) ligands.[15–21] DFT calculations support this hypothesis.[22,23] Ahlquist and co-workers have gone one step further, and based on DFT calculations they suggested that mono-ligated palladium complexes of the form $Pd^0(PPh_3)(solvent)$—and not the less reactive $Pd^0(PPh_3)_2$ complexes—may also be responsible for OA of aryl iodides.[24] In addition, they propose that the commonly observed "phosphine poisoning" effect is more likely the result of driving of the equilibrium between $Pd^0(PR_3)$-(solvent) and $Pd^0(PR_3)_2$ rather than between $Pd^0(PR_3)_2$ and $Pd^0(PR_3)_3$.

Therefore, although much effort has been made to identify the palladium species, PdL_n, primarily responsible for facilitating the oxidative addition of aryl halides to palladium, there is

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still no definite answer. Theory points towards a monoligated palladium catalyst for all aryl halides but to our knowledge there is no direct experimental evidence to support the calculations. Kinetic studies suggest the identity of the halide is critical, with iodo- and bromobenzenes reacting with PdL_2 and chlorobenzenes with PdL.[25] However, it is difficult if not impossible to unambiguously isolate the highly reactive PdL complex likely responsible for OA by using traditional solution-phase methods, because their presence is likely to be fleeting and their concentration correspondingly low. Mass spectrometry is uniquely well suited to address this problem.[26–31] By using an ion-trap mass spectrometer, it is possible to isolate an individual type of metal complex and directly test its fundamental reactivity in the absence of solvents or counterions.[32] We report here a set of gas-phase ion–molecule experiments that allowed us to isolate mono- and bisligated palladium(0) complexes, PdL and PdL_2, and directly compare their reactivity, towards all of the aryl halides PhX (X = F, Cl, Br, I). The bisligated complexes are best generated in solution and transferred to the gas phase without oxidation by using electrospray ionization mass spectrometry (ESI–MS). However, charged species are required for analysis by ESI–MS; therefore, the anionic phosphine ligand $[PPh_2(m\text{-}C_6H_4SO_3)]^-$ (1) was doped into a solution of $Pd(PPh_3)_4$ to generate the anionic complexes $[Pd(1)\text{-}(PPh_3)_n]^-$ (n = 0, 1, or 2; PdL, PdL_2, PdL_3) through ligand exchange.[33] These complexes were isolated in the gas phase within an ion-trap mass spectrometer, and reacted with aryl halides to unambiguously determine which palladium species are most capable of facilitating OA. Finally, theoretical calculations provided us with key insights into the structure and bonding of the ions we observed experimentally and allowed a detailed description of the mechanism of OA in the gas phase. Oxidative addition of Ar—X bonds to Pd^0 centers has been previously used to calibrate the performance of theoretical methods to compute energy barriers,[34] and the competition with other activation processes has been shown to depend on the coordination number of the reacting complex[35,36] and on the nature of the *para*-substituent on the aryl halide.[37]

Results and Discussion

Use of an electrospray-active ligand

We have previously shown 1 to be an effective charge-tagged ligand[38–40] that allows us to probe the chemistry of Pd^0 complexes by negative-ion ESI–MS[33] without the oxidation to Pd^I that occurs during positive-ion analysis.[31] To further confirm the suitability of 1 as a substitute for triphenylphosphine in our experiments, we performed DFT calculations to compare the steric and electronic effects of 1 on OA of a halobenzene to palladium with those of the unsubstituted triphenylphosphine. We found that the presence of the sulfonate group has no steric effect on OA and only a small electronic effect that slightly favors OA (see the Supporting Information).

Reactivity of PhX with $[Pd^0(1)(PPh_3)]^-$

A fluorobenzene solution of $Pd(PPh_3)_4$ and one equivalent of [PPN][1] (PPN = bis(triphenylphosphine)iminium) was infused into an ion-trap mass spectrometer, and ions of the single isotopomer $[^{106}Pd(1)(PPh_3)]^-$ (m/z 709, PdL_2) were isolated in the gas phase within the ion trap. The neutral reagent, iodobenzene, was introduced into the trap and allowed to react with the isolated ions, which are effectively at room temperature.[41] After 0.5 s a mass spectrum was recorded. PdL_2 reacted cleanly with PhI to form $[PdL_2(Ph)(I)]^-$ (m/z 913). The same experiment was subsequently performed for the other aryl halides, PhX, with X = Br, Cl, and F. No reactivity (< 0.1 % product) was observed for the reactions between PdL_2 and PhX with X = Br, Cl, or F, even after increasing the reaction time to 3 s (Figure 1).
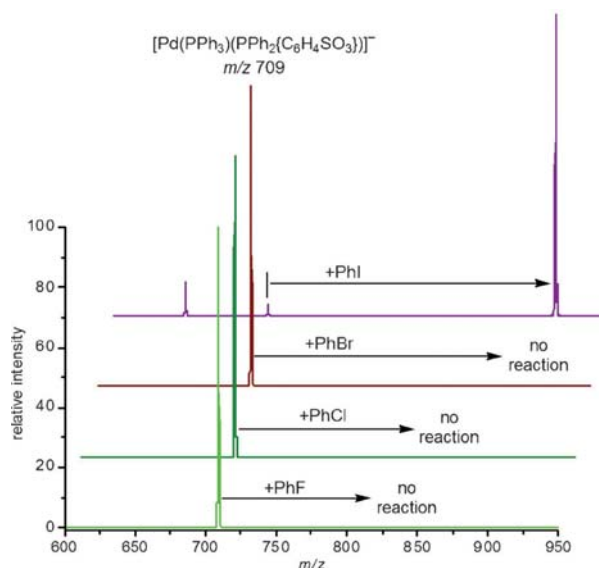
Figure 1. MS^2 mass spectra of the exposure of PhX, X = F, Cl, Br, and I to $[^{106}Pd(1)(PPh_3)]^-$ (m/z 709) for a reaction time of 0.5 s.

Reactivity of PhX with $[Pd^0(1)]$

PdL was produced in the gas phase within the ion trap by isolating PdL_2 ions and subjecting them to collision-induced dissociation (CID). CID causes fragmentation of the ions through phosphine dissociation to produce $[Pd^0(1)]^-$ (m/z 447, PdL, see the Supporting Information). The PdL product ions were isolated and allowed to react with PhI, PhBr, PhCl, or PhF for 0.5 s (MS^3, Figure 2).

The extent of reactivity varied greatly between different aryl halides. Less than 10 % of PdL reacted with PhF, but 97 %, > 99 %, and 100 % of the PdL ions reacted with PhCl, PhBr and PhI, respectively. These initial results suggested an overall reactivity order of:
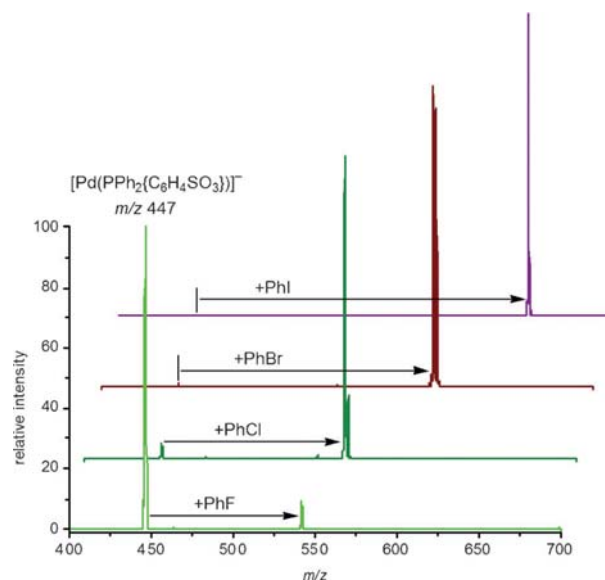
$$PhI\ (PdL) > PhBr\ (PdL) > PhI\ (PdL_2) > PhCl\ (PdL) > PhF\ (PdL)$$
$$\gg PhBr/PhCl/PhF\ (PdL_2)$$
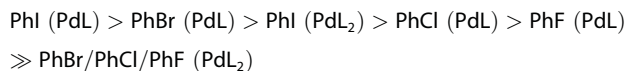
Figure 2. MS³ mass spectra of the exposure of PhX, X = F, Cl, Br, and I to [^{106}Pd(**1**)]$^-$ (m/z 447).

Figure 3. Computed free-energy profiles for the reaction between PdL and PhX and structural models. TS = transition state.

and strongly implied that PdL and not PdL$_2$ type complexes are responsible for the OA of aryl–halide bonds if X = Br, Cl, or F (as the relative ratios of reactivity are at least 10 000× higher for PdL vs. PdL$_2$). We looked to theoretical calculations to gain further insight into the experimental results.

Computational modeling of the oxidative addition

The oxidative addition process was computationally studied in the gas phase for the four different aryl halides, PhF, PhCl, PhBr, and PhI and the two metal complexes, PdL and PdL$_2$. The computational level was M06 with a double-zeta plus polarization basis set. The M06 method was found to be sufficient through comparison with B3LYP, B97D, and SCS-MP2. Only the lowest energy isomer is presented for each computed structure. Full computational details, as well as method calibration data, are provided in the Supporting Information. The choice of an energy magnitude to follow the behavior of systems under mass-spectrometry conditions is not trivial,[42, 43] as temperature and pressure are not clearly defined in such systems. We are using here free energy at a temperature of 298.15 K. Although different temperatures may be present along the reaction profile,[44] this provides a reasonable qualitative picture. Potential energy values are discussed in the Supporting Information.

For the monophosphine complex, the reactions follow the free-energy profiles presented in Figure 3, with initial formation of an adduct between the two reactants that evolves through a transition state towards the product. The structures of the adduct and the transition state for the case of PhBr are also shown in Figure 3. In the adduct there is an interaction between the palladium and the phenyl ring, with Pd–C distances of 2.185, 2.547, and 2.636 Å, the shortest distance corresponding to the atom carrying the Br substituent. This was the
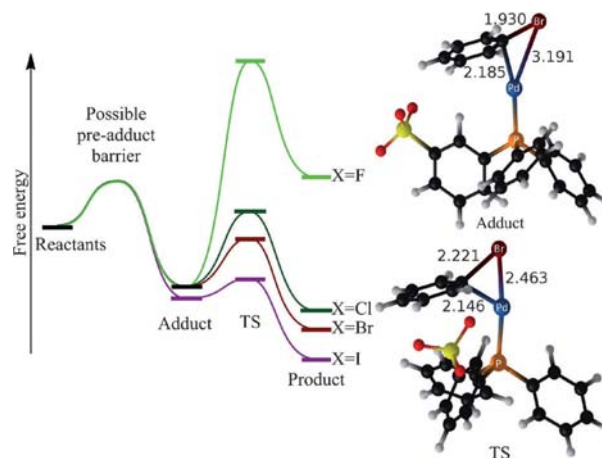
most stable arrangement we found for this adduct, but we were also able to locate other conformations (with other aryl halide carbon atoms closer to palladium) with similar energies. The transition state corresponds to a concerted oxidative addition, with simultaneous cleavage of the C–Br bond (2.221 Å) and formation of the new Pd–C (2.146 Å) and Pd–Br (2.463 Å) bonds. Alternative transition states corresponding to a stepwise process could be located in some cases, but they all had higher energies. Structures for adduct and transition state were qualitatively similar for the other monophosphine systems. Transition-state structures were also similar for the bisphosphine systems. In the bisphosphine systems, the adducts present the aryl halide further away from the metal, resulting in a weaker interaction between aryl halide and the metal complex. This has the important consequence that for the bisphosphine systems the free energy of the adduct was higher than those of the reactants, and thus should not be observed.

The computed relative free energies of adducts and transition states are collected in Table 1. The values for the barriers are also included. The barrier involves always the energy of the transition state as high energy point. In the case of the monophosphine systems the low energy point is the adduct, with free energies between −11 and −15 kcal mol^{-1} below the reactants. In the case of the bisphosphine systems, the adducts

Table 1. Computed relative free energy (in kcal mol^{-1}) of adducts and transition states (TS) with respect to the reactants.

	PhF	PhCl	PhBr	PhI
Monophosphine PdL				
adduct	−10.7	−11.1	−11.1	−14.6
TS	27.6	3.6	−1.5	−8.8
barrier (TS–adduct)	38.3	14.7	9.6	5.8
Bisphosphine PdL$_2$				
adduct	5.3	4.5	2.9	2.8
TS	42.3	22.4	16.4	7.6
barrier (TS–reactants)	42.3	22.4	16.4	7.6

were located in the potential energy surface, but they disappear as local minima if free energy corrections are introduced. Because of this, the barrier in the bisphosphine systems is directly the energy difference between transition state and reactants. As a result, the numbers in the two last rows in Table 1 are identical, but we decided to keep both rows for clarity. The ease for product formation should be ruled by the height of the free-energy barrier, and the calculations thus suggest the following order of reactivity:

PhI (PdL) > PhI (PdL$_2$) > PhBr (PdL) > PhCl (PdL) > PhBr (PdL$_2$) > PhCl (PdL$_2$) > PhF (PdL) > PhF (PdL$_2$)
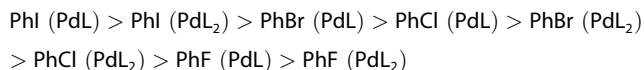
The main trends reproduce the experimental order discussed above, in particular predicting that PdL complexes are more reactive than PdL$_2$ complexes, and the heavier halides are more reactive than the lighter ones. But there are two significant differences. Firstly, our interpretation of experimental data suggest PhBr (PdL) to be more reactive than PhI (PdL$_2$), and this is not backed by calculations, which indicate free-energy barriers of 9.6 kcal mol^{-1} and 7.6 kcal mol^{-1}, respectively. An error of more than 2.0 kcal mol^{-1} in the computed value is far from satisfactory, but problems are even more serious for the PhF (PdL) system. In this case, our interpretation of the experimental results indicated it is more reactive than PhBr (PdL$_2$). However, the computed value for PhF (PdL) is 38.3 kcal mol^{-1}, whereas that for PhBr (PdL$_2$) is 16.4 kcal mol^{-1}. An error of more than 20 kcal mol^{-1} is completely unacceptable, and this prompted us to rethink our interpretation of the experimental data.

According to the calculations, the adduct for the monophosphine PhX (PdL) systems should be formed for all halides, see Figure 3. In some cases it could evolve to products and in other cases it could remain as an adduct. Both species, adduct and product, have the same molecular mass and charge, and thus should be observed in the experiment at the same m/z. Thus, computational results could be fit with the experiment if we accepted that in some cases the observed species was not the product, but instead the adduct.

Additional MS^4 experiments

Accordingly, we performed an additional MS^4 experiment to discriminate between the two possible products, in which we used CID to fragment the ion [Pd(**1**)(PhX)]$^-$ through energetic collisions with the bath gas. This type of experiment strongly favors fragmentation processes versus rearrangement alternatives. The reason is that the temperature increase mainly affects the entropic terms in the relative free energies, and these particular terms are very sensitive to fragmentation (see the Supporting Information for numeric examples). As shown in Scheme 1, if oxidative addition of PhX has occurred, the most favored fragmentation pathway should be phosphine dissociation, and the observed fragment would be [**1**]$^-$. If only an adduct is formed, it should instead fragment by loss of PhX, to provide a [Pd(**1**)]$^-$ product ion.
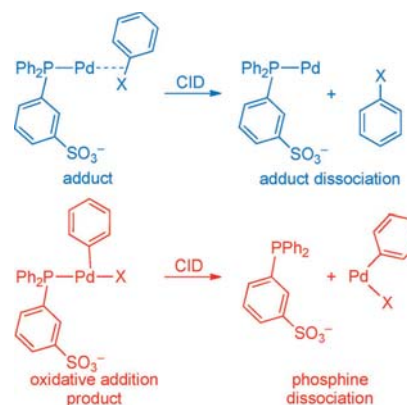
Scheme 1. Proposed dissociation pathways for the MS^4 experiment from the adduct [Pd(**1**)(PhX)]$^-$ (in blue, top) and b) from the product (in red, bottom).

Both behaviors were observed, depending on the identity of the aryl halide. Both [Pd(**1**)(PPh$_3$)$_n$(PhX)]$^-$ ($n = 0$ and 1) ions (X = I) fragmented exclusively by phosphine dissociation, indicating that oxidative addition has occurred in the case of PhI for both PdL and PdL$_2$. Conversely, the [Pd(**1**)(PhX)]$^-$ (X = Cl, F) ions fragmented exclusively through dissociation of the aryl halide (Supporting Information), indicating these ions are in fact ion–molecule adducts. [Pd(**1**)(PhBr)]$^-$ displayed both fragmenting behaviors to almost the same extent, indicating that the oxidative addition has only partially proceeded during the reaction time of 0.5 s (Figure 4).

These data, discriminating between adducts and oxidative addition products, generate a new order of reactivity entirely consistent with our computational results:
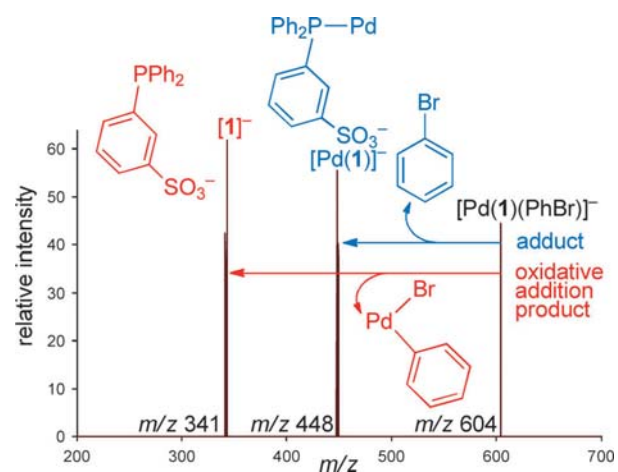
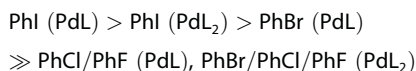PhI (PdL) > PhI (PdL$_2$) > PhBr (PdL) ≫ PhCl/PhF (PdL), PhBr/PhCl/PhF (PdL$_2$)

Figure 4. Spectrum resulting from the MS^4 experiment for PhBr. Blue color: adduct fragmentation (loss of PhBr, [Pd(**1**)]$^-$ detected m/z 448), red color: oxidative addition product fragmentation (loss of PdPhBr, [**1**]$^-$ detected m/z 341).

The joint consideration of experimental and computational results produces thus a consistent picture of the reactivity of these systems in the gas phase. We consider this indicative of their behavior in the more usual conditions in solution, although we are ready to admit that these results cannot be extrapolated to all cases. Nanoparticle formation may occur in solution, thus leading to completely different reactivity patterns. The eventual coordinating properties of solvent molecules can also play a role. Long-range solvation effects seem, however, minor. We made an estimation of the role of continuum solvation effects for the particular case of the bromobenzene system with three different solvents, THF, DMF, and water (see the Supporting Information for details) and found that the change in the relative energy of the transition state with respect to the separate reactants was in all cases smaller than 2 kcal mol^{-1}.

Conclusions

Gas-phase experiments supported the idea that bisligated PdL_2 complexes interact readily with iodobenzene and progress through a relatively low barrier to oxidative addition to form $PdL_2(Ar)(I)$ (L = PPh_3). This same reaction was not observed for the lighter halobenzenes; rather, ligand dissociation to a monoligated PdL is necessary before any interaction takes place. For fluoro- and chlorobenzene, an adduct is formed that fails to oxidatively add to the palladium, which suggests PdL is not inherently reactive enough to activate these challenging substrates without the use of elevated temperatures or rationally engineered ligands. However, for bromobenzene, oxidative addition occurred under the conditions of the experiment. The ratio of reactivity of bromobenzene with PdL versus PdL_2 was at least 10^4:1 by mass spectrometry and 10^5:1 by theory, suggesting that even if the PdL + L versus PdL_2 equilibrium is far on the side of PdL_2, oxidative addition involving PdL is important.

Experimental Section

Pd(PPh$_3$)$_4$ (0.01 g, 0.01 mmol) and [PPN][**1**] (0.009 g, 0.01 mmol) were dissolved in fluorobenzene (10 mL) in an inert-atmosphere glovebox. The solution was diluted 20-fold in fluorobenzene and injected at 5 µL min^{-1} continuously into a Finnigan LCQ quadrupole ion-trap mass spectrometer operating in negative ion mode. Sheath gas: 25 (arbitrary unit), auxillary gas: 0 (arbitrary unit), spray voltage: 4.5 kV, capillary temperature: 170 °C, capillary voltage: −13 V, tube lens offset: −15 V. ArX (X = F, Cl, Br, or I) was entrained in the heated helium damping gas and introduced into the ion trap as described by O'Hair.[45] He flow ≈ 60 Nl h^{-1}, He Pressure: 3 psi, PhX flow rate: 2 µL min^{-1}. The signals corresponding to Pd(PPh$_3$)(**1**) (m/z 709) and Pd(**1**) (m/z 447) were separately selected and stored in the ion trap by MS^2 or MS^3. Any reactivity with PhX was recorded. Pd(PPh$_3$)(**1**) trap conditions (MS^2): select 709 at collision energy = 0.0 arbitrary units, activation time = 30 ms, Q = 0.250 arbitrary units. Pd(**1**) trap conditions (MS^3): select 709 at collision energy = 10.0 arbitrary units, activation time = 30 ms, Q = 0.250 arbitrary units; select 446.3 at collision energy = 0.0 arbitrary units, activation time = 30 ms, Q = 0.250 arbitrary units. The signals corresponding to [Pd(PPh$_3$)(**1**)(PhI)]$^-$ (m/z 913) and [Pd(**1**)(PhX)]$^-$ (m/z

543, X = F; m/z 596, X = Cl, m/z 604, X = Br; m/z 651, X = I) were separately selected and stored in the ion trap by MS^3 or MS^4. Fragmentation of the signals was recorded. [Pd(PPh$_3$)(**1**)(PhI)]$^-$ trap conditions (MS^3): select m/z 708.7 at collision energy = 0.0 arbitrary units, activation time = 500/3000 ms, Q = 0.250 arbitrary units; select m/z 913 at collision energy = 5.0 arbitrary units, activation time = 30 msec, Q = 0.250 arbitrary units. [Pd(**1**)(PhF)]$^-$ trap conditions (MS^4): select m/z 708.7 at collision energy = 15.0 arbitrary units, activation time = 30 ms, Q = 0.250 arbitrary units; select m/z 447 at collision energy = 0.0 arbitrary units, activation time = 500 ms, Q = 0.250 arbitrary units; select m/z 543 at collision energy = 5.0 arbitrary units, activation time = 30 ms, Q = 0.250. [Pd(**1**)(PhCl)]$^-$ trap conditions (MS^4): select m/z 708.7 at collision energy = 15.0 arbitrary units, activation time = 30 ms, Q = 0.250 arbitrary units; select m/z 447 at collision energy = 0.0 arbitrary units, activation time = 500 ms, Q = 0.250 arbitrary units; select m/z 595.7 at collision energy = 10.0 arbitrary units, activation time = 30 ms, Q = 0.250. [Pd(**1**)(PhBr)]$^-$ trap conditions (MS^4): select m/z 708.7 at collision energy = 15.0 arbitrary units, activation time = 30 ms, Q = 0.250 arbitrary units; select m/z 447 at collision energy = 0.0 arbitrary units, activation time = 500 ms, Q = 0.250 arbitrary units; select m/z 604 at collision energy = 10.0 arbitrary units, activation time = 30 ms, Q = 0.250. [Pd(**1**)(PhI)]$^-$ trap conditions (MS^4): select m/z 708.7 at collision energy = 15.0 arbitrary units, activation time = 30 ms, Q = 0.250 arbitrary units; select m/z 447 at collision energy = 0.0 arbitrary units, activation time = 500/3000 ms, Q = 0.250 arbitrary units; select m/z 651 at collision energy = 10.0 arbitrary units, activation time = 30 ms, Q = 0.250.

Computational section

Calculations were performed by using the Gaussian 09 package.[46] Several methods were tested, the results presented correspond to the M06[47] functional, which gives similar results to SCS-MP2[48] and B97D.[49] The standard 6-31 + G(d,p) basis set was used to describe the H, C, F, Cl, Br, and P atoms, with the exception of the C and H atoms of the phenyl rings of the phosphines PPh$_3$ and PPh$_2$(m-C$_6$H$_4$SO$_3$) for which the 6-31G(d) basis set was used instead.[50] The large core scalar relativistic pseudopotentials by Dolg et al. were used for palladium coupled to a double-zeta quality basis set described by the (8s7p6d)/[6s5p3d] contraction.[51] For iodine the LANL2DZ basis sets and ECP by Hay and Wadt were used supplemented with one d function and p function.[52] Some tests presented in the Supporting Information were performed with the B3LYP[53] functional. Unless otherwise stated, all the energies presented correspond to free energies. Full geometry optimizations were performed in the gas phase. The nature of the stationary points was characterized by a vibrational analysis performed within the harmonic approximation at 298 K and 1 atm. Transition states were identified by the presence of one imaginary frequency and minima by a full set of real frequencies. Counterpoise correction was applied in all presented energies, unless otherwise stated.

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