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Published on Web 05/05/2006

Mechanism of the Palladium-Catalyzed Homocoupling of Arylboronic Acids: Key Involvement of a Palladium Peroxo Complex

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Abstract: The mechanism of the palladium-catalyzed homocoupling of arylboronic acids $ArB(OH)_2$ (Ar = 4-Z-C_6H_4 with Z = MeO, H, CN) in the presence of dioxygen, leading to symmetrical biaryls, has been fully elucidated. The peroxo complex (η^2-O_2)PdL_2 (L = PPh_3), generated in the reaction of dioxygen with the Pd(0) catalyst, was found to play a crucial role. Indeed, it reacts with the arylboronic acid to generate an adduct (coordination of one oxygen atom of the peroxo complex to the oxophilic boron atom of the arylboronic acid) characterized by ^{31}P NMR spectroscopy and ab initio calculations. This adduct reacts with a second molecule of arylboronic acid to generate *trans*-$ArPd(OH)L_2$ complexes. A transmetalation by the arylboronic acid gives *trans*-$ArPdArL_2$ complexes. The biaryl is then released in a reductive elimination. This reaction is at the origin of the formation of biaryls as byproducts in palladium-catalyzed Suzuki−Miyaura reactions when they are not conducted under oxygen-free atmosphere.

Introduction

The palladium-catalyzed cross-coupling reaction of *nucleophilic* aryl derivatives $ArB(OR)_2$ (R = H or Alkyl) with *electrophilic* aryl derivatives, Ar′X (X = I, Br, Cl, OTf) has become one of the most widely used methods for the formation of sp^2-sp^2 carbon−carbon bonds (Miyaura−Suzuki reaction, Scheme 1),[1] due to the high stability and low toxicity of arylboronic acids This reaction enables the formation of unsymmetrical biaryls, ArAr′.[1,2]

Symmetrical biaryls can be obtained by the palladium-catalyzed homocoupling of *electrophilic* aryl derivatives, Ar′X (X = I, Br, Cl, OTf) in the presence of a *reducing* agent (Red in Scheme 2).[2,3] This *reductive* coupling has been widely developed and its mechanism elucidated.[3]

Conversely, symmetrical biaryls may also be synthesized by the palladium-catalyzed homocoupling of *nucleophilic* aryl derivatives $ArB(OR)_2$ (R = H or Alkyl) in the presence of an *oxidant*[4,5] (Ox in Scheme 3, including dioxygen) in an *oxidative coupling*.

Scheme 1

$$Ar'X + ArB(OR)_2 \xrightarrow[\text{Base}]{[Pd]} Ar'Ar + "XB(OR)_2"$$

X = I, Br, Cl, OTf; R = H, Alkyl

Scheme 2

$$2Ar'X + Red \xrightarrow{[Pd]} Ar'Ar' + Ox + 2X^-$$

X = I, Br, Cl, OTf; Red = Zn, 2e, solvent

Scheme 3

$$2ArB(OR)_2 + Ox \xrightarrow{[Pd]} ArAr + Red + 2"B(OR)_2"$$

R = H, cyclic -$(CH_2)_3$-

This last *oxidative coupling* was first observed under stoichiometric conditions[6] and then as a side-reaction in Pd-catalyzed Miyaura−Suzuki cross-coupling reactions.[7] Indeed, the symmetrical biaryl ArAr generated from the arylboronic acid $ArB(OH)_2$ is often observed in Miyaura−Suzuki reactions

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(Scheme 1).[7] This side-reaction was recently developed as a main catalytic reaction in the presence of pure dioxygen or air (Scheme 3).[4,5a,e] The homocoupling of arylboronic acids was first reported by Moreno-Mañas et al. in 1996, using as catalysts Pd^0 or Pd^{II} complexes associated with monodentate phosphines.[4] This *oxidative coupling* could be accelerated by an oxidant, e.g., $Cu(NO_3)_2$.[5d] The homocoupling was later extended to arylboronic esters by Yoshida et al. in 2003, using $Pd(OAc)_2$ and dppp (1,3-bis-(diphenylphosphino)propane) as catalyst and DMSO as solvent.[5f]

However, very little is known about the reaction mechanism of this *oxidative* homocoupling. A first mechanism was proposed involving the oxidative addition of $ArB(OH)_2$ to Pd^0 complexes with the generation of $ArPd^{II}-[B(OH)_2]L_2$ (L = PPh_3) complexes.[4] However, our attempts to observe this reaction in the absence of dioxygen always failed, whereas a reaction was observed between $ArB(OH)_2$ and a peroxo complex (η^2-O_2)-PdL_2 (L = PPh_3), formed in the reaction of Pd^0L_4 with dioxygen.[8] Sheldon and Kochi have proposed the formation of the intermediate complex Ar_2PdL_2 (L = PPh_3) by a double transmetalation of $ArB(OH)_2$ with $(HO)Pd(OOH)L_2$ generated by reaction of water with the peroxo complex (η^2-O_2)PdL_2.[9] Conversely, while we were performing this work, Yoshida et al. proposed a reaction of arylboronic esters $ArB(OR)_2$ with (η^2-O_2)Pd(dppp), which would give $ArPd-[OOB(OR)_2]$(dppp) complexes.[5f] A subsequent transmetalation of the latter complex by $ArB(OR)_2$ would give Ar_2Pd(dppp) and henceforth the homocoupling product ArAr by a reductive elimination.

We report herein evidences for the mechanism of the palladium-catalyzed homocoupling of $ArB(OH)_2$ in the presence of dioxygen (Scheme 3). In this study, it is clearly mechanistically and kinetically established that a peroxo complex of palladium, (η^2-O_2)PdL_2 (L = PPh_3),[10] plays a key role in the catalytic homocoupling of arylboronic acids.

Experimental Section

General. ^{31}P NMR spectra were recorded in $CDCl_3$ or in DMF containing 10% of acetone-d_6 on a Bruker spectrometer (101 MHz) with H_3PO_4 as an external reference. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer (250 MHz) with TMS as an internal reference.

Chemicals. DMF was distilled from calcium hydride under vacuum and kept under argon. PPh_3, $PhB(OH)_2$, 4-CN-C_6H_4-$B(OH)_2$, 4-MeO-C_6H_4-$B(OH)_2$, and $PhB(O-(CH_2)_3-O)$ were commercial and used as is. The peroxo complex (η^2-O_2)$Pd(PPh_3)_2$[8a] and the dimeric complex $[PhPd(\mu\text{-}OH)(PPh_3)]_2$[11a,b] were synthesized as reported in the literature.

Typical Procedure for the Kinetics of the Reaction of (η^2-O_2)-$Pd(PPh_3)_2$ with Arylboronic Acids, As Monitored by Amperometry. All experiments were performed under argon atmosphere. Experiments were carried out in a thermostated three-electrode cell connected to a Schlenk line. The counterelectrode was a platinum wire of ca. 1 cm^2 apparent surface area; the reference was a saturated calomel electrode (Radiometer) separated from the solution by a bridge (3 mL) filled with a 0.3 M *n*-Bu_4NBF_4 solution in chloroform (or DMF). Degassed chloroform (or DMF) (15 mL) containing 0.3 M *n*-Bu_4NBF_4 was poured into a cell. (η^2-O_2)$Pd(PPh_3)_2$ (20 mg, 30 μmol, 2 mM) was then introduced into the cell. The kinetic measurements were performed at a rotating gold disk electrode (diameter = 2 mm, inserted into a Teflon holder, EDI 65109, Radiometer) with an angular velocity of 105 rad·s^{-1} (Radiometer controvit). The rotating electrode was polarized at +0.70 V (+0.48 in DMF) on the plateau of the oxidation wave of (η^2-O_2)-$Pd(PPh_3)_2$. 4-MeO-C_6H_4-$B(OH)_2$ (45 mg, 300 μmol, 20 mM) was then added into the cell, and the decrease of the oxidation current was recorded versus time up to 100% conversion.

Typical Procedure for NMR Experiments. All experiments were performed under argon atmosphere. To a solution of (η^2-O_2)$Pd(PPh_3)_2$ (5 mg, 7.5 μmol) in 0.5 mL of degassed $CDCl_3$ were added various amounts of arylboronic acids **1a**−**c** or esters **1′b** (from 0.75 to 37.5 μmol). The ^{31}P NMR and ^1H NMR were then performed.

Characterization of [$ArB(OH)_2$,(η^2-O_2)$Pd(PPh_3)_2$] 6a, 6b, 6c, and 6′b. All experiments were performed under argon atmosphere. The complexes were generated by addition of 0.5 equiv of **1a**, **1b**, **1c**, and **1′b**, respectively, to (η^2-O_2)$Pd(PPh_3)_2$ in $CDCl_3$. The ^{31}P NMR data of **6a**, **6b**, **6c**, and **6′b** are collected in Table 2.

Characterization of *trans*-$ArPd(OH)(PPh_3)_2$ 5a, 5b. All experiments were performed under argon atmosphere. The complexes were generated as above by addition of 5 equiv of **1a**, **1b**, respectively, to (η^2-O_2)$Pd(PPh_3)_2$ in $CDCl_3$. The ^1H NMR and ^{31}P NMR spectroscopies and ESI MS spectrometry of **5a**, **5b** are collected in Table 1. The characteristics of **5b** were identical to those of an authentic sample generated in situ by addition of 12 mg (46 μmol) of PPh_3 to a solution of 3.4 mg (3.24 μmol) $[PhPd(\mu\text{-}OH)(PPh_3)]_2$[11a,b] in 0.5 mL of $CDCl_3$.

Characterization of *trans*-$ArPdAr'(PPh_3)_2$ *trans*-8ac and *trans*-8bc. All experiments were performed under argon atmosphere. The complexes were generated in an NMR tube by addition of 1.1 equiv of **1c** to *trans*-$ArPd(OH)(PPh_3)_2$ **5a** or **5b** generated as above in $CDCl_3$. The spectra from ^1H NMR, NMR 2D, and ^{31}P NMR spectroscopies of *trans*-**8ac** and *trans*-**8bc** are collected in Table 6.

Typical Procedure for (η^2-O_2)$Pd(PPh_3)_2$-Catalyzed Homocoupling of Arylboronic Acids (Scheme 5). To a solution of (η^2-O_2)$Pd(PPh_3)_2$ (3 mg, 4.6 μmol) in 0.5 mL of $CDCl_3$ was added under dioxygen 500 μL (23 μmol) of the arylboronic acid **1b** (or **1a**) from a mother solution of **1b** (46 mM in $CDCl_3$). After mixing for 10 min, the yield of the homocoupling product PhPh **2b** (or 4-MeO-C_6H_4-C_6H_4-OMe-4, **2a**) was determined by ^1H NMR spectroscopy after addition of a known amount of toluene as internal standard. The ^1H NMR spectrum of PhPh (or 4-MeO-C_6H_4-C_6H_4-OMe-4) was identical to that of an authentic commercial sample. The yield of the byproduct Ph-OH (or 4-MeO-C_6H_4-OH) was determined in a similar way.

Computational Methods. All calculations were carried out using the Gaussian code.[12] A hybrid Hartree−Fock/density functional model, hereafter referred to as PBE0, was used throughout.[13] In this functional, derived from the PBE,[14] the ratio of HF/DFT exchange is fixed a priori to 1/4.[15] A double ξ quality LANL2 basis[16] and corresponding pseudopotential[17] was used for all calculations. Such level of theory was proven to provide reliable results both for thermochemical and

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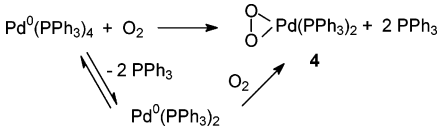
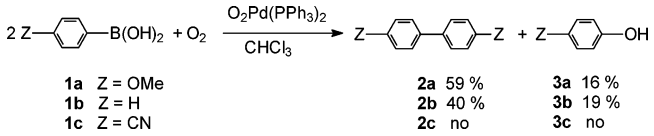
Scheme 4



Scheme 5



spectroscopic properties.[18] No symmetry constraints were imposed during structural optimizations, and the nature of the optimized structures and energy minima were defined by subsequent frequency calculations. Basis set superposition errors were evaluated using the standard Counterpoise correction, the largest being of the order of 6 kcal/mol. Additional calculations were performed using the larger 6-311G(d) basis set (hereafter **BS2** basis) on O, P, and B atoms, to test basis set dependence of energetic and structural features. The results are collected in Table 4 and in the Supporting Information. Finally, the effect of addition of a diffuse function on oxygen atoms (i.e., 6-311+G(d)) was also tested. If not differently specified, all values discussed in the following correspond to those obtained with the LANL2DZ basis.

Results and Discussion

Homocoupling of Arylboronic Acids Catalyzed by (η^2-O_2)-Pd(PPh_3)$_2$. Moreno-Mañas et al. have observed that the homocoupling of arylboronic acids catalyzed by $Pd^0(PPh_3)_4$ in toluene was more efficient in the presence of dioxygen.[4] Interestingly, the complex $Pd^0(PPh_3)_4$ is known to react with dioxygen to generate the peroxo complex (η^2-O_2)Pd(PPh_3)$_2$ **4**[8a] via $Pd^0(PPh_3)_2$ (Scheme 4).[8b] Complex **4** was isolated as a stable greenish complex.

This prompted us to investigate the homocoupling of arylboronic acids in the presence of $O_2Pd(PPh_3)_2$ (20%) as a catalyst (Scheme 5). In nonoptimized test reactions, yields of 59% and 40% were obtained for **2a** and **2b**, respectively, after 10 min in chloroform. The corresponding phenols **3a** and **3b** were also obtained as byproducts. The biaryl **2c** was not formed in chloroform due to the low solubility of **1c** in this solvent, whereas it was generated in DMF.

The peroxo complex **4** thus appears to be a true catalyst for the homocoupling reaction of arylboronic acids. This prompted us to fully investigate its reaction with arylboronic acids.

Rate and Mechanism of the Reaction of (η^2-O_2)Pd(PPh_3)$_2$ with Arylboronic Acids 1a−c. Characterization of the Aryl-Palladium(II) Complexes Formed in the Reaction of (η^2-O_2)Pd(PPh_3)$_2$ with Arylboronic Acids or Esters. As recalled in the Introduction, we could not observe any reaction between $Pd^0(PPh_3)_4$ and the arylboronic acids, **1a**,**c**, at room temperature, in chloroform or DMF under argon. However, when the same reaction was performed in the presence of dioxygen, i.e. from (η^2-O_2)Pd(PPh_3)$_2$ generated in situ, new signals for aromatic protons appeared in the ^{1}H NMR spectra, in the range 5.9−6.6 ppm, which differed from those of the arylboronic acids **1a**,**b**, the biaryls **2a**,**b** or the phenols **3a**,**b**.[19] These signals, located upfield, characterized an aryl group attached to a palladium(II) center, e.g. as observed in *trans*-ArPdX(PPh_3)$_2$ (X = I, Br, Cl) complexes.[20] This suggests the formation of aryl-palladium(II) complexes.

The reaction of the arylboronic acids **1a**,**b** with isolated (η^2-O_2)Pd(PPh_3)$_2$ **4**, synthesized as in Scheme 4,[8] was also investigated. When an excess of the arylboronic acids **1a** or **1b** was added to a solution of the peroxo complex **4** in chloroform, the aromatic ^{1}H NMR signals of the aryl-palladium complexes detected above were observed. Concomitantly, the ^{31}P NMR singlet of the peroxo complex **4** (33.2 ppm in $CDCl_3$, 33.4 in DMF) disappeared, and a new singlet was observed, characteristic of a palladium ligated to two magnetically equivalent PPh_3 sitting in a trans position (Table 1). The structure of one of the new aryl-palladium(II) complexes, *trans*-PhPd(OH)-(PPh_3)$_2$ **5b**, formed in the reaction of (η^2-O_2)Pd(PPh_3)$_2$ with **1b** (Scheme 6), was determined by comparing its ^{1}H, ^{31}P NMR, and ESI MS spectra to those of the authentic complex. The latter was generated by reacting the dimeric μ-hydroxo complexes *cis*- and *trans*-[PhPd(μ-OH)(PPh_3)]$_2$ (^{31}P NMR: δ = 33.66 and 32.96 ppm) with 10 equiv of PPh_3, as reported by Grushin and Alper (Scheme 7).[11a,b] The same complex **5b** was also formed by reacting *trans*-PhPdI(PPh_3)$_2$ with *n*-Bu_4NOH in chloroform (this work) or DMF[11c] or THF.[11d]

At this level, we have established that a fast reaction occurred between the peroxo-palladium complex **4** and arylboronic acids **1a**,**b**. Nevertheless, a crucial question arises about the mechanism of this reaction. When **1a**−**c** (0.5 equiv) were added to a solution of **4** in chloroform, i.e., under substoichiometric conditions, the ^{31}P NMR spectrum exhibited, besides the singlet of complex **4**, two doublets of equal magnitude (Table 2).[23] This suggests the formation of new complexes **6a**−**c** possessing two magnetically nonequivalent phosphines (Scheme 8).

At this stage, the ^{1}H NMR spectroscopy did not reveal the presence of complexes of type **5**, nor biaryls **2**, nor phenols **3**. The two doublets of **6a**−**c** and the singlet of the nonreacted peroxo complex **4** disappeared with time, and only the phosphine oxide (O)PPh_3 was observed at long times. Similar sets of doublets were also observed in DMF containing 10% acetone-d_6 as well as from the ester **1′b** (Table 2).

When an excess of **1b** was added to a solution in chloroform exhibiting the two doublets of **6b**, the latter disappeared, and the singlet of complex *trans*-**5b** was observed, suggesting that complex **6b** might be an intermediate complex generated on the way to complex **5b**. When an excess of peroxo complex **4** was added to the previous solution, the two doublets of complex **6b** were recovered. This establishes that complex **6b** is only observed under substoichiometric concentrations of $ArB(OH)_2$ and that an excess of $ArB(OH)_2$ is required to yield complex **5b**. Similar reactions were observed by reacting **1a** with the peroxo complex **4**. Complex *trans*-**5c** was not observed in chloroform, whereas **6c** was observed. Due to the low solubility

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(19) No reaction occurs by bubbling dioxygen in a solution of **1a**−**c**, in the absence of palladium.

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(21) Other peaks at 753 for **5a** or 723 for **5b** were also observed. MS/MS experiments on **5a** and **5b** showed that (O)PPh_3 was released, suggesting the formation of ArPd(PPh_3)((O)PPh_3)$^+$. This is due to the ESI MS technique in which the ionization also produces some triphenylphosphine oxide which coordinates the cationic Pd complex.[22]

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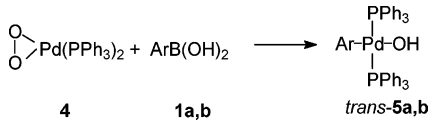
(23) Some phosphine oxide was also detected at 29.2 ppm.

Table 1. ^{1}H NMR (250 MHz, TMS), ^{31}P NMR (101.3 MHz, H_3PO_4) Shifts and ESI MS of Complexes **5a**,**b** Formed by Reacting (η^2-O_2)Pd(PPh_3)$_2$ **4** with the Arylboronic Acids **1a**,**b** in Chloroform (Scheme 6)[a]

trans-ArPd(OH)(PPh_3)$_2$ Ar	^{1}H NMR δ ppm ($CDCl_3$)	^{31}P NMR δ ppm ($CDCl_3$)	ESI MS[21]
5a MeO−C_6H_4	6.42 (d, J = 8.5 Hz, 2H, *o*-H) 5.93 (d, J = 8.5 Hz, 2H, *m*-H) 3.5 (s, 3H, Me)	23.5 (s)	737 [M-OH]$^+$ 630 [Pd(PPh_3)$_2$]$^+$
5b C_6H_5	6.62 (d, J = 7.3 Hz, 2H, *o*-H) 6.38 (t, J = 7 Hz, 1H, *p*-H) 6.30 (t, J = 7.3 Hz, 2H, *m*-H)	23.7 (s)	707 [M-OH]$^+$ 630 [Pd(PPh_3)$_2$]$^+$

[a] The aromatic protons of the PPh_3 ligand are omitted for clarity.

Scheme 6



Scheme 7

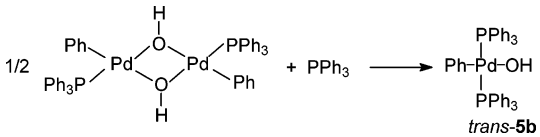
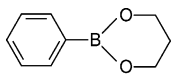


Table 2. ^{31}P NMR Shifts (101.3 MHz, H_3PO_4) of the Intermediate Complexes **6a**−**c** Formed by Reacting (η^2-O_2)Pd(PPh_3)$_2$ **4** with 0.5 equiv of Arylboronic Acids **1a**−**c** in Chloroform or DMF[a]

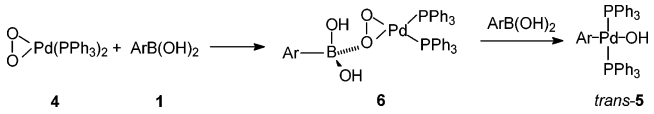


1'b

1	6 δ ppm ($CDCl_3$)	6 δ ppm (DMF + 10% acetone-d_6)
1a	31.1 (d, J_{PP} = 37 Hz, 1P) 27.3 (d, J_{PP} = 37 Hz, 1P)	31.2 (d, J_{PP} = 38 Hz, 1P) 27.3 (d, J_{PP} = 38 Hz, 1P)
1b	31.2 (d, J_{PP} = 37 Hz, 1P) 27.3 (d, J_{PP} = 37 Hz, 1P)	31.1 (d, J_{PP} = 38 Hz, 1P) 27.1 (d, J_{PP} = 38 Hz, 1P)
1c	31.6 (d, J_{PP} = 37 Hz, 1P) 27.6 (d, J_{PP} = 37 Hz, 1P)	31.3 (d, J_{PP} = 38 Hz, 1P) 27.4 (d, J_{PP} = 38 Hz, 1P)
1′b	31.2 (d, J_{PP} = 37 Hz, 1P) 27.3 (d, J_{PP} = 37 Hz, 1P)	31.2 (d, J_{PP} = 38 Hz, 1P) 27.1 (d, J_{PP} = 38 Hz, 1P)

[a] Same reaction with **1′b**. [a] The ^{11}B NMR broad signal (29 ppm) of **1b** in $CDCl_3$ disappeared after addition of **4** in excess, but any other signal was observed, suggesting the formation of **6** in equilibrium with **4**.

Scheme 8

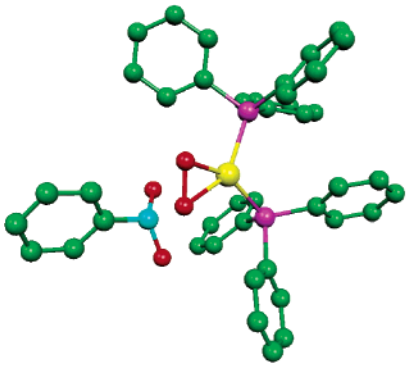


of **1c** in chloroform, it could not be added in large excess. Since the ^{31}P NMR shifts of the two doublets depend on the nature of the aryl group, the intermediate complexes **6** necessarily contain one aryl group. This rules out the formation of complexes such as *trans*-(HO)Pd(OOH)L_2 or [Pd_2(μ-OH)(μ-OO)L_4]$^+$ which might have been generated by the reaction of water with (η^2-O_2)Pd(PPh_3)$_2$ **4**, as proposed by Sheldon and Kochi.[9] Intermediate complexes **6** are proposed on the basis of kinetic data (see below), and their structures were confirmed by DFT calculations (Scheme **8**, Figure 1). Selected computed structural parameters of the optimized complexes **6** are collected in Table 3. Their computed formation energies and enthalpies are gathered in Table 4.

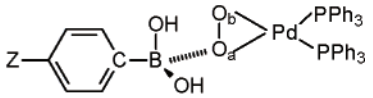
The intermediate complexes **6** are stabilized through the direct interaction between the boron atom and one of the two oxygen atoms of the peroxo complex. It is worthwhile to note that in our preliminary DFT calculations made using L = PH_3 as model ligand for O_2PdL_2 intermediates of type **6** were found to be unstable. Instead, the only adducts which were found to be stable were complexes in which the O_2PdL_2 was hydrogen bonded through one of its oxygen atoms to one proton of the arylboronic acid. The possibility of having a direct interaction between the boron atom and one oxygen atom of the peroxo was ruled out using this simplified model. This highlights the crucial electronic role of the ligand and the fact that DFT results obtained using PH_3 as model for the PPh_3 ligand cannot be always straightforwardly extrapolated to fully describe the behavior of the real systems.[24] For the sake of clarity, it should also be noted that hydrogen-bonded structures analogous to those found in the case of PH_3 were also found to be stable in the case of the systems containing PPh_3 in the gas phase. However, we expect solvent effects to be more important in this latter case, so that the two coordination modes of the arylboronic acid could become competitive in polar or protic solvents, but in favor of complexes **6**. To evaluate bulk solvent effects, single-point calculations on the gas-phase optimized structures (using the **BS2** basis) were performed using the polarizable continuum model (Table 4).[25] Inclusion of solvent, here chloroform, does not significantly affect the relative stability of the complexes that are computed to be likely to be formed also in solution. Finally, from a more technical point of view we can notice that addition of a polarization function on O, B, and P atoms does not strongly change either structure (refer to Supporting Information) or thermochemistry of the formation of complexes **6**. In particular, adding a diffuse function only on O atoms in the case of **6b** has a negligible effect on both structure (about 0.01Å) and thermochemistry (about 3 kJ/mol).

Kinetics of the Reaction of (η^2-O_2)Pd(PPh_3)$_2$ with Arylboronic Acids. The overall reaction in Scheme 8 was monitored by electrochemistry under an argon atmosphere, taking the advantage that the peroxo complex (η^2-O_2)Pd(PPh_3)$_2$ **4** (2 mM) exhibited an oxidation peak at +0.63 V vs SCE in chloroform containing *n*-Bu_4NBF_4 (0.3 M) (+0.43 V vs in DMF),[8b] at a steady gold disk electrode and a scan rate of 0.2 V s^{-1}. The oxidation peak totally disappeared when an excess of **1a**−**c** was added to the peroxo complex **4**. In the experiments performed in chloroform, **1a**−**c** were introduced as a concentrated solution on DMF due to their low solubility in chloroform. The kinetics

(24) (a) Kozuch, S.; Amatore, C.; Jutand, A.; Shaik, S. *Organometallics* **2005**, *24*, 2319−2330. (b) Goossen, L. J.; Koley, D.; Herrmann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102−11114.
(25) (a) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117−129. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669−681.



6b



6a Z = MeO
6b Z = H
6c Z = CN

Figure 1. Computed optimized structure for complex **6b** (left): B atom (blue); O atoms (red); Pd atom (yellow); P atoms (purple); C atoms (green). The H atoms are omitted for clarity.

Table 3. Selected Computed Structural Parameters of the Optimized Structures (distances *d* in Å and Angles θ in Degrees)[a]

6	d (O_a–O_b)	d (O_a–B)	d (Pd–O_a)	d (Pd–O_b)	θ (PPdP)	θ (PdO_aB)	θ (O_aO_bB)
6a	1.452	1.653	2.128	2.024	104.5	105.7	112.8
6b	1.452	1.650	2.123	2.025	104.2	106.2	113.0
6c	1.455	1.642	2.136	2.021	104.4	105.8	112.8
6′b	1.432	3.193	2.042	2.058	105.8	98.8	97.2

[a] See Figure 1 for nomenclature and labeling. See also Supporting Information for computed structural parameters of free (η^2-O_2)Pd(PPh_3)$_2$ **4**.

Table 4. Formation Energies (ΔE), Enthalpies (ΔH), BSSE Energy Correction (BSSE), and Formation Energies in Solution ($\Delta E_{Solvent}$) Computed for Different Complexes **6** and **6′** as a Function of the Substituent (Z) on the Arylboronic Acid[a]

6	ΔE	ΔH	BSSE	$\Delta E_{solvent}$
6a	−28.101 (−29.377)	−26.788 (−27.153)	29.015 (29.998)	(1.713)
6b	−33.125 (−34.195)	−31.783 (−31.993)	29.025 (32.096)	(−2.545)
6c	−51.285 (−53.107)	−49.432 (−50.834)	29.090 (30.384)	(−17.895)
ester **6′b**	−19.633 (−23.523)	−18.851 (−21.875)	14.879 (17.611)	(−9.309)

[a] Values reported in parentheses correspond to the **BS2** basis. All values are in kJ/mol.

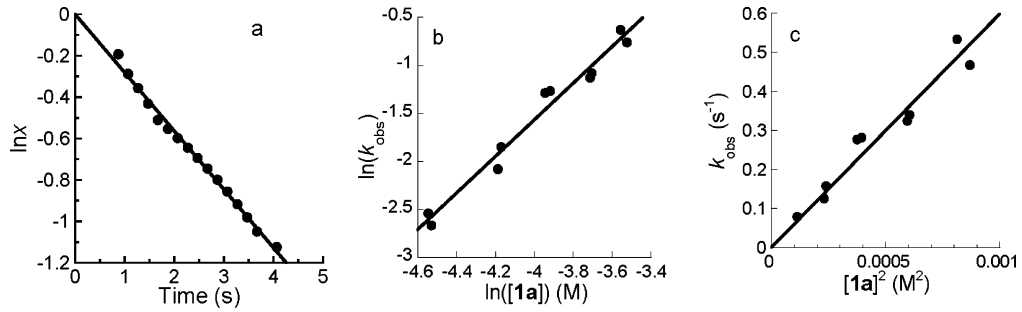


Figure 2. Kinetics of the reaction of the arylboronic acid **1a** with (η^2-O_2)Pd(PPh_3)$_2$ **4** (C_0 = 2 mM) in chloroform (containing *n*-B_4NBF_4, 0.3 M) at 25 °C, as monitored by amperometry at a rotating gold disk electrode. (a) [**1a**] = 20 mM. Variation against time of ln x ($x = [\mathbf{4}]_t/[\mathbf{4}]_0 = i_t/i_0$; i_t = oxidation current of **4** at t, i_0 = initial oxidation current of **4**). ln $x = -k_{obs} \times t$. (b) Determination of the reaction order in **1a**: plot of ln(k_{obs}) against ln([**1a**]): ln(k_{obs}) = 1.9 × ln([**1a**] + 6. (c) Determination of the reaction order in **1a**: plot of k_{obs} against [**1a**]^2. $k_{obs} = k_{app} \times [\mathbf{1a}]^2$.

of the reaction was followed by amperometry performed at a rotating gold disk electrode polarized on the plateau of the oxidation peak of **4** (+0.48 V in DMF, +0.70 V in chloroform). After addition of **1a**−**c** in excess, the decrease of the oxidation current of **4** (proportional to its concentration) was recorded with time, up to total conversion. A plot of ln x ($x = [\mathbf{4}]_t/[\mathbf{4}]_0 = i_t/i_0$; i_t = oxidation current of **4** at t, i_0 = initial oxidation current of **4**) against time was linear (Figure 2a) indicating a first-order reaction of the peroxo complex. The observed rate constant k_{obs} was determined from the slope of the straight line in Figure 2a, viz. evidencing the rate law: $\ln x = -k_{obs}t$.

The reaction order in **1a** was found to be +2, as evidenced by the observed dependence of k_{obs}: $k_{obs} = k_{app}[\mathbf{1a}]^2$ (Figure 2b,c). This suggests the occurrence of a mechanism involving sequentially two molecules of **1**, as reported in Scheme 9.

The arylboronic acid is involved both in the reversible formation of complex **6** and in the irreversible evolution of this complex to complex *cis*-**7**. The latter may evolve to complex *trans*-**5** either by route **A** or **B** (Scheme 9). The water involved in route **A** and **B** may result from the formation of a boroxine from the arylboronic acid.[26] Whatever the relative weight of route **A** or **B**, neither route affects the overall rate of disappearance of **4**. This latter assumption was confirmed by the fact that, in the reaction of **4** with **1** in excess, no sets of two doublets

(26) Lappert, M. F. *Chem. Rev.* **1956**, *56*, 959−1064.

Scheme 9

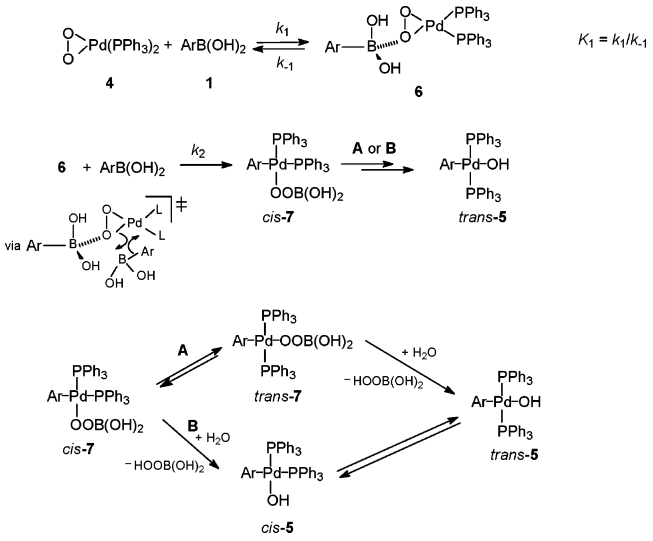


Table 5. Rate Constants K_1k_2 for the Reaction of the Peroxo Complex **4** with Arylboronic Acids **1a**−**c** in Chloroform[a] and DMF at 25 °C (Scheme 9)

	K_1k_2 ($M^{-2}s^{-1}$)		
solvent	**1a** (Z = OMe)	**1b** (Z = H)	**1c** (Z = CN)
$CDCl_3$	600	2500	n.d.
DMF	5.8	1025	46000

[a] Containing 1% DMF.

were observed which would have characterized *cis*-**7** or *cis*-**5**, whenever either of these species would accumulate.

Therefore, the peroxo complex must be activated by the arylboronic acid before it undergoes a transmetalation with another molecule of $ArB(OH)_2$ (Scheme 9). We indeed observe from the calculations that one Pd−O bond has been elongated (by ca. 10 pm, Table 3) due to the coordination of the boron atom. The kinetic law corresponding to the formation of *cis*-**7** is complex and highly dependent on the excess of **1** (see Supporting Information). However, for large excesses of **1**, the formation of **6** is fast and equilibrated and continuously displaced by the formation of *cis*-**7**. Under those conditions, the rate-determining kinetic law for Scheme 9 is given in eqs a,b under specific conditions which apply here. Our experimental results are in total agreement with eqs a,b. The value of K_1k_2 was determined from the slope of the straight line in Figure 2c (Table 5).[27]

$$\text{rate} = \frac{k_1k_2[\mathbf{4}][\mathbf{1}]^2}{k_{-1}} = K_1k_2[\mathbf{4}][\mathbf{1}]^2 \qquad \text{(a)}$$

$$\ln x = -K_1k_2[\mathbf{4}][\mathbf{1}]^2t = -k_{\text{app}}[\mathbf{1}]^2t = -k_{\text{obs}}t \qquad \text{(b)}$$

The kinetics of the reaction of the peroxo complex **4** with **1a**−**c** was similarly investigated in chloroform or DMF. The values of K_1k_2 are collected in Table 5 (Figures S2−5 in Supporting Information).

(27) In the time scale investigated here, the two doublets of the intermediate complexes **6a**−**c** were observed in chloroform and DMF (without the singlet of complex *trans*-**5a**−**c**) when less than one equiv of **1a**−**c** was added to the peroxo complex **4**. This supposes that $k_1[\mathbf{4}] \gg k_2[\mathbf{6}]$. Since [**4**] and [**6**] are then very similar at low substoichiometric conditions, one must have $k_1 \gg k_2$. with $k_{-1} \gg k_2[\mathbf{1}]$. See also Supporting Information.

Whatever the solvent, the following reactivity order was observed: $K_1^{CN}k_2^{CN} > K_1^{H}k_2^{H} > K_1^{OMe}k_2^{OMe}$. The reaction of the second molecule of **1** may be considered as a transmetalation of complexes **6** by the arylboronic acid (Scheme 9). This suggests that $k_2^{CN} < k_2^{H} < k_2^{OMe}$, viz. because the arylboronic acid is expected to be more nucleophilic when the aryl group is substituted by an electron donor group. One then deduces that $K_1^{CN} \gg K_1^{H} \gg K_1^{OMe}$ in agreement with the decreasing Lewis acidity of the arylboronic acid when going from CN to OMe (Table 4). The reaction was faster in chloroform than in DMF, suggesting a competitive solvatation of $ArB(OH)_2$ by DMF.

Transmetalation on $ArPd(OH)(PPh_3)_2$ (*trans*-5a,b) Complexes. Thus far we have identified and characterized the formation of complexes $ArPd(OH)(PPh_3)_2$ (*trans*-**5a**,**b**, Scheme 9) through the fast reaction of the peroxo complex $(\eta^2\text{-}O_2)Pd(PPh_3)_2$ with 2 equiv of **1a**,**b**, respectively. It was of interest to investigate the role of such complexes in the context of the palladium-catalyzed homocoupling of arylboronic acids. The complex *trans*-C_6H_5-$Pd(OH)(PPh_3)_2$ (*trans*-**5b**), generated by reaction of **1b** with **4**, was reacted with 1.5 equiv of 4-CN-C_6H_4-$B(OH)_2$ (**1c**) and the reaction monitored by ^1H NMR. The recorded spectrum exhibited two different aryl groups on a Pd^{II} center, in the range 6.2−6.8 ppm. The 2D NMR spectrum allowed the identification of the three different protons of the C_6H_5 group associated with the two different protons of the 4-CN-C_6H_4 group (Table 6, Figure 3). The ^{31}P NMR spectrum exhibited one sharp singlet (Table 6), attesting a trans coordination of the two phosphines. The reaction gave the new complex *trans*-**8bc** in a reaction which is a transmetalation step (Scheme 10). The same spectrum was observed when starting from *trans*-**5b** synthesized in situ as in Scheme 7.

This reaction was confirmed by reacting *trans*-**5a** with **1c** leading to *trans*-**8ac** (Scheme **10**, Table 6). The coupling products C_6H_5-C_6H_4-CN-4 and 4-MeO-C_6H_4-C_6H_4-CN-4 were also formed and characterized by ^1H NMR and mass spectrometry. They could only be formed by a reductive elimination from *cis*-**8bc** and *cis*-**8ac** (Scheme 11). The detection of complexes *trans*-**8bc** and *trans*-**8ac** indicates that they were rather stable *vis-á-vis* a reductive elimination in agreement with the fact that this must proceed from the uphill *cis*-**8bc** and *cis*-**8bc** complexes, respectively.

This confirms the observation made by Aliprantis and Canary,[28] when monitoring Pd-catalyzed Miyaura−Suzuki cross-coupling reactions by ESI MS. Indeed, complexes $ArPdAr'(PPh_3)_2$ formed in the transmetalation step were clearly observed in their work and assumed to adopt trans configuration.[28] It is worthwhile to note that the reaction of $ArPd(OH)(PPh_3)_2$ with $Ar'B(OH)_2$ observed here may also occur in the Miyaura−Suzuki cross-coupling reaction performed in the presence of hydroxyl bases which were found to react with $ArPdX(PPh_3)_2$ (X = I,[11c] Br[11d]) to form $ArPd(OH)(PPh_3)_2$.

When *trans*-**5b** $PhPd(OH)(PPh_3)_2$ was reacted with **1a** 4-MeO-C_6H_4-$B(OH)_2$ (1.3 equiv), the mixed complex *trans*-**8ba** was not observed (Scheme 10), but the coupling biaryl C_6H_5-C_4H_5-OMe-4 was produced together with 4-MeO-C_6H_4-$Pd(OH)(PPh_3)_2$. The catalytic cycle was completed via the successive transmetalation and reductive elimination to generate

(28) Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6, 6985−6986.

Table 6. ^{1}H (250 MHz, TMS) and ^{31}P NMR (101.3 MHz, H_3PO_4) Shifts (δ ppm) of Complexes **8** Formed by Reacting Complexes **5** with Arylboronic Acids **1** in $CDCl_3$ (Scheme 10)[a]

4-Y-C_6H_4-Pd-C_6H_4-Z-4(L)$_2$ L = PPh_3	^{1}H NMR 4-Y-C_6H_4-Pd	^{1}H NMR Pd-C_6H_4-Z-4	^{31}P NMR
8bc (Y = H, Z = CN)	6.61 (d, J = 7 Hz, 2H, *o*-H) 6.37 (t, J = 7.5 Hz, 1H, *p*-H) 6.22 (t, J = 7.3 Hz, 2H, *m*-H)	6.61 (d, J = 6.7 Hz, 2H, *m*-H) 6.44 (d, J = 6.7 Hz, 2H, *o*-H)	22.40
8ac (Y = OMe, Z = CN)	6.41 (d, J = 7.4 Hz, 2H, *o*-H) 6.14 (m, 2H, *m*-H) 3.56 (s, 3H, Me)	6.8 (d, 2H, *o*-H) 6.27 (d, J = 8.8 Hz, 2H, *m*-H)	n.d.

[a] The aromatic protons of the PPh_3 ligand are omitted for more clarity. The terms: *o*, *m*, and *p* are defined relative to the Pd atom.

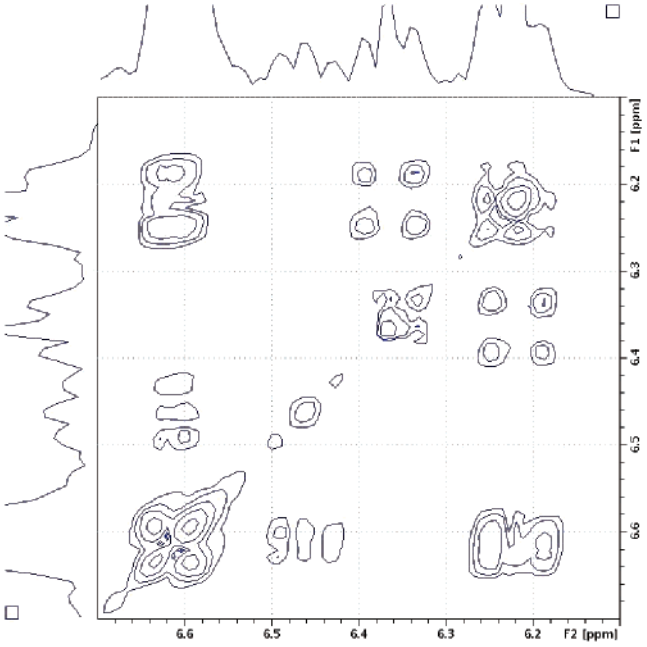
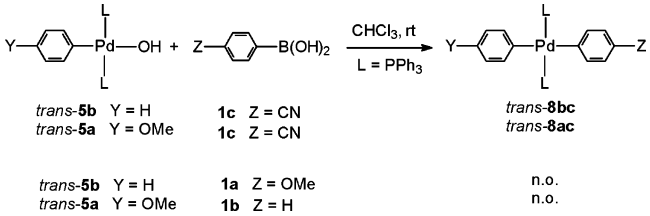
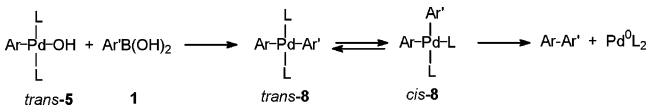


Figure 3. ^{1}H−^{1}H (250 MHz, TMS) of complex **8bc** formed by reacting complex **5b** with **1c** in $CDCl_3$ (Scheme 10).

Scheme 10

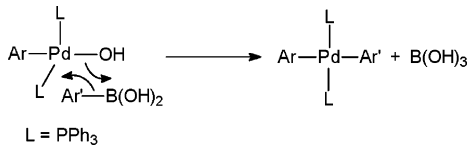


Scheme 11



the biaryl together with a Pd^0 complex (Scheme 11). The peroxo complex $O_2Pd(PPh_3)_2$, formed by reaction of $Pd^0(PPh_3)_2$ with dioxygen, reacted again with excess **1a** to generate 4-MeO-C_6H_4-Pd(OH)$(PPh_3)_2$, as established in the first part of this work. Then, the intermediate complex *trans*-**8ba** could not be observed because it was involved in a fast reductive elimination via the *cis*-**8ba** and consequently could not accumulate, as complexes *trans*-**8bc** and *trans*-**8ac** did. Similarly, when *trans*-**5a** 4-MeO-C_6H_4-Pd(OH)$(PPh_3)_2$ was reacted with **1b** $PhB(OH)_2$ (1.3 equiv), the mixed complex *trans*-**8ab** was not observed (Scheme 10) but the coupling biaryl 4-MeO-C_6H_4-C_6H_5 was produced together with *trans*-PhPd(OH)$(PPh_3)_2$. This indicates that once

Scheme 12



the catalytic cycle was closed, the excess of **1b** reacted with the peroxo complex $O_2Pd(PPh_3)_2$ to form *trans*-PhPd(OH)-$(PPh_3)_2$.

All these results suggest that the overall reductive elimination from complexes *trans*-**8** is slower when one aryl is substituted by a CN group. However, we could not establish whether this slow kinetics was due to a more endergonic *trans/cis* isomerization from *trans*-**8** (Scheme 11) or/and to intrinsic effects related to the reductive elimination from the *cis*-**8** complexes.

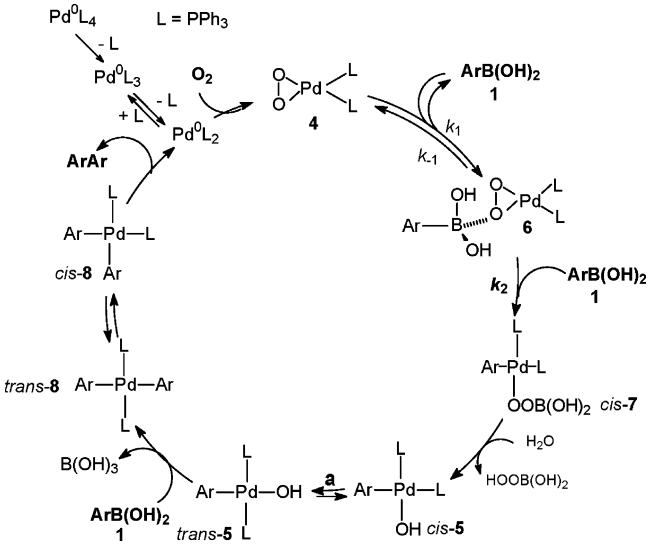
We now have experimental evidence for the formation of *trans*-ArPdAr′$(PPh_3)_2$ complexes in a transmetalation step performed from *trans*-ArPd(OH)$(PPh_3)_2$ and Ar′$B(OH)_2$. However, because the transmetalation and reductive elimination might be simultaneous steps, the rate and mechanism of the transmetalation could not be investigated in detail. A mechanism is proposed (Scheme 12) on the basis of Miyaura's proposal for the reaction of Ar′$B(OH)_2$ with ArPd(OAc)$(PPh_3)_2$.[29] In a theoretical work (DFT calculations), Ujaque, Maseras et al.[30] gave further evidence of the involvement of a transmetalation step between vinyl-$B(OH)_2$ and *trans*-vinyl-Pd(OH)$(PH_3)_2$ complexes.

Catalytic Cycle for the Pd-Catalyzed Homocoupling of Arylboronic Acids in the Presence of Dioxygen. The reaction of $ArB(OH)_2$ with the peroxo complex followed by transmetalation and reductive elimination steps is summarized in Scheme 13. However, such mechanism was established step by step, and the intermediate complexes, *trans*-**5** and *trans*-**8**, were characterized at long times, which excluded the observation of the intermediate *cis*-**5** and *cis*-**8** complexes under our experimental conditions.

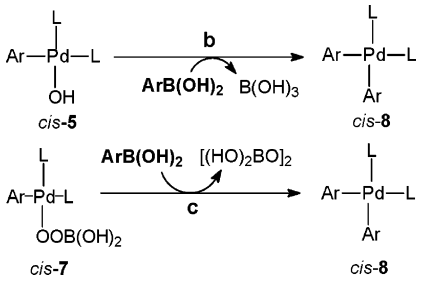
The (η^2-O_2)Pd$(PPh_3)_2$-catalyzed homocoupling of $ArB(OH)_2$ **1a**,**b** under dioxygen worked readily, and the complexes observed at the end of the reaction were *trans*-ArPd(OH)$(PPh_3)_2$ (*trans*-**5a**,**b**) which accumulated due to lack of reagent. The fact that *trans*-ArPdAr′$(PPh_3)_2$ (*trans*-**8ba**) could not be observed when the substituent on one aryl group was MeO, whereas ArAr′ was obtained, suggests that the reductive elimination from *trans*-ArPdAr′$(PPh_3)_2$ **8** via *cis*-ArPdAr′$(PPh_3)_2$ was fast in this case and that the mechanism of the catalytic cycle may thus involve

(29) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510. (b) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54−57.
(30) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298−9307.

Scheme 13. Mechanism Based on Observed **4**, **6**, *trans*-**5**, and *trans*-**8** Complexes



Scheme 14

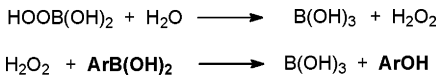


trans-**5** and *trans*-**8** complexes as intermediate complexes (Scheme 13).

However, in the real catalytic reactions, the catalytic cycle may involve only reactive cis complexes. Indeed, at high $ArB(OH)_2$ concentrations, the *cis*-**5**/*trans*-**5** isomerization (route **a** in Scheme 13) may be much slower than the transmetalation on *cis*-**5** (route **b** in Scheme 14). The latter reaction would directly generate the reactive *cis*-**8** complex, prone to undergo reductive elimination (last step in Scheme 13). An even shorter pathway to *cis*-**8** in which the intermediate complex *cis*-**7** would be trapped by $ArB(OH)_2$ cannot be excluded (route **c**, in Scheme 14).

Mechanism of the Formation of Phenol as Byproduct. ArOH is often a byproduct in the Pd-catalyzed homocoupling of arylboronic acids in the presence of dioxygen (Scheme 4).[4] We observed that (i) phenol was formed together with the biaryl, (ii) phenol was not formed from complexes **6a** or **6b** when they were observed in absence of complexes **5a** and **5b** respectively, (iii) phenol was not formed from *trans*-$PhPd(OH)(PPh_3)_2$ **5b**, (iv) phenol was not formed upon bubbling dioxygen in a solution

Scheme 15



of $ArB(OH)_2$ over 3 days. It has been suggested that phenols could be produced by reacting hydrogen peroxide with arylboronic acids.[9,5f] PhOH was indeed generated upon addition of H_2O_2 to a solution of $PhB(OH)_2$ in chloroform. This suggests that H_2O_2 is produced in the Pd-catalyzed homocoupling of arylboronic acids in the presence of dioxygen. A reasonable route for H_2O_2 production would consist in the subsequent hydrolysis of $HOOB(OH)_2$ (Schemes 9 and 15).

Conclusions

The palladium-catalyzed homocoupling of arylboronic acids (4-Z-C_6H_4-$B(OH)_2$, Z = MeO, H, CN) in the presence of dioxygen proceeds via the peroxo complex (η^2-O_2)PdL_2 (L = PPh_3), generated in the reaction of dioxygen with the Pd(0) catalyst. The peroxo complex is indeed at the origin of the formation of *trans*-Ar-$Pd(OH)L_2$ via an activation of one of its Pd−O bond by the arylboronic acid, followed by a transmetalation step by a second arylboronic acid. *trans*-Ar-$Pd(OH)L_2$ complexes react with the arylboronic acid to give *trans*-Ar-$PdArL_2$ complexes in a second transmetalation step. The biaryl is formed in a reductive elimination. Because of the common intermediate Pd^0L_2, the palladium-catalyzed homocoupling reaction may compete with the Miyaura−Suzuki cross-coupling if the work atmosphere is not inert. Work is in progress to extend this *oxidative coupling* to other nucleophiles, i.e., organostannanes derivatives. Farina et al. have indeed observed as a side reaction the homocoupling of arylstannanes in palladium-catalyzed Stille reactions performed in the presence of dioxygen.[31] The palladium-catalyzed homocoupling of organostannanes under oxygen (or air) has been reported later on.[32]

Acknowledgment. This work has been supported in part by the Centre National de la Recherche Scientifique (UMR CNRS-ENS-UPMC 8640, UMR CNRS-ENSCP-UMPC 7575) and the Ministère de la Recherche (Ecole Normale Supérieure). We thank Prof. René Thouvenot for performing ^{11}B NMR spectroscopy at the University Paris VI. Johnson Matthey is thanked for a generous loan of palladium salt.

Supporting Information Available: Detailed kinetic analysis of the reaction of $O_2Pd(PPh_3)_2$ with arylboronic acids **1a**−**c** in chloroform or DMF, complementary structural information from DFT calculations and complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0569959

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