

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-C₆H₄ with Z = MeO, H, CN) in the presence of dioxygen, leading to symmetrical biaryls, has been fully elucidated. The peroxo complex (η^2 -O₂)PdL₂ (L = PPh₃), 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 ³¹P NMR spectroscopy and ab initio calculations. This adduct reacts with a second molecule of arylboronic acid to generate *trans*-ArPd(OH)_{L2} complexes. A transmetalation by the arylboronic acid gives *trans*-ArPdArL₂ 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 palladiumcatalyzed 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

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Scheme 1

Ar'X + ArB(OR)₂ $\xrightarrow{[Pd]}$ Ar'Ar + "XB(OR)₂' X = I, Br, CI, OTf; R = H, Alkyl

Scheme 2

$$2\text{Ar'X} + \text{Red} \xrightarrow{[PQ]} \text{Ar'Ar'} + \text{Ox} + 2\text{X}^{-1}$$

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

[Dal

Scheme 3

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

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

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*.

This last *oxidative coupling* was first observed under stoichiometric conditions⁶ and then as a side-reaction in Pdcatalyzed 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 Pd⁰ or Pd^{II} complexes associated with monodentate phosphines.⁴ This oxidative coupling could be accelerated by an oxidant, e.g., Cu(NO₃)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 Pd⁰ complexes with the generation of $ArPd^{II}-[B(OH)_2]L_2$ (L = PPh₃) 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 -O₂)- PdL_2 (L = PPh₃), 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 = PPh₃) by a double transmetalation of ArB(OH)₂ with (HO)Pd(OOH)L₂ generated by reaction of water with the peroxo complex $(\eta^2-O_2)PdL_2$. Conversely, while we were performing this work, Yoshida et al. proposed a reaction of arylboronic esters ArB(OR)₂ with (η^2 -O₂)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 Ar₂Pd(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, $(\eta^2 - O_2)PdL_2$ (L = PPh₃),¹⁰ plays a key role in the catalytic homocoupling of arylboronic acids.

Experimental Section

General. ³¹P NMR spectra were recorded in CDCl₃ or in DMF containing 10% of acetone-d₆ on a Bruker spectrometer (101 MHz) with H₃PO₄ 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. PPh3, PhB(OH)2, 4-CN-C6H4-B(OH)2, 4-MeO-C₆H₄-B(OH)₂, and PhB(O-(CH₂)₃-O) were commercial and used as is. The peroxo complex $(\eta^2-O_2)Pd(PPh_3)_2^{8a}$ and the dimeric complex $[PhPd(\mu-OH)(PPh_3)]_2^{11a,b}$ were synthesized as reported in the literature.

Typical Procedure for the Kinetics of the Reaction of $(\eta^2 \cdot O_2)$ -Pd(PPh₃)₂ with Arylboronic Acids, As Monitored by Amperometry. All experiments were performed under argon atmosphere. Experiments

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were carried out in a thermostated three-electrode cell connected to a Schlenk line. The counterelectrode was a platinum wire of ca. 1 cm² 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-Bu₄NBF₄ solution in chloroform (or DMF). Degassed chloroform (or DMF) (15 mL) containing 0.3 M n-Bu₄NBF₄ was poured into a cell. $(\eta^2-O_2)Pd(PPh_3)_2$ (20 mg, 30 μ mol, 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 $(\eta^2 - O_2)$ -Pd(PPh₃)₂. 4-MeO-C₆H₄-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 $(\eta^2-O_2)Pd(PPh_3)_2$ (5 mg, 7.5 µmol) in 0.5 mL of degassed CDCl₃ were added various amounts of arylboronic acids 1a-c or esters 1'b (from 0.75 to 37.5 µmol). The ³¹P NMR and ¹H NMR were then performed.

Characterization of $[ArB(OH)_{23}(\eta^2-O_2)Pd(PPh_3)_2]$ 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 $(\eta^2$ -O₂)Pd(PPh₃)₂ in CDCl₃. The ³¹P NMR data of 6a, 6b, 6c, and 6'b are collected in Table 2.

Characterization of trans-ArPd(OH)(PPh₃)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 $(\eta^2-O_2)Pd(PPh_3)_2$ in CDCl₃. The ¹H NMR and ³¹P 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 μ mol) of PPh₃ to a solution of 3.4 mg (3.24 µmol) [PhPd(µ-OH)(PPh₃)]₂^{11a,b} in 0.5 mL of CDCl₃.

Characterization of trans-ArPdAr'(PPh₃)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)(PPh₃)₂ 5a or 5b generated as above in CDCl₃. The spectra from ¹H NMR, NMR 2D, and ³¹P NMR spectroscopies of trans-8ac and trans-8bc are collected in Table 6.

Typical Procedure for $(\eta^2 - O_2)Pd(PPh_3)_2$ -Catalyzed Homocoupling of Arylboronic Acids (Scheme 5). To a solution of $(\eta^2-O_2)Pd$ -(PPh₃)₂ (3 mg, 4.6 µmol) in 0.5 mL of CDCl₃ was added under dioxygen 500 μ L (23 μ mol) of the arylboronic acid **1b** (or **1a**) from a mother solution of 1b (46 mM in CDCl₃). After mixing for 10 min, the yield of the homocoupling product PhPh 2b (or 4-MeO-C₆H₄-C₆H₄-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-C₆H₄-C₆H₄-OMe-4) was identical to that of an authentic commercial sample. The yield of the byproduct Ph-OH (or 4-MeO-C₆H₄-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 basis¹⁶ and corresponding pseudopotential¹⁷ 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

O₂Pd(PPh₃)₂ B(OH) CHCk Z = OMe2a 59 % 3a 16 % Z = H 2b 40 % 3b 19 % 1b Z = CN 2c 3c no 1c no

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 $(\eta^2 \cdot O_2)$ -Pd(PPh₃)₂. Moreno-Mañas et al. have observed that the homocoupling of arylboronic acids catalyzed by Pd⁰(PPh₃)₄ in toluene was more efficient in the presence of dioxygen.⁴ Interestingly, the complex Pd⁰(PPh₃)₄ is known to react with dioxygen to generate the peroxo complex $(\eta^2-O_2)Pd(PPh_3)_2 4^{8a}$ via Pd⁰(PPh₃)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 O₂Pd(PPh₃)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 $(\eta^2 - O_2)Pd(PPh_3)_2$ with Arylboronic Acids 1a-c. Characterization of the Aryl-Palladium(II) Complexes Formed in the Reaction of $(\eta^2$ -O₂)Pd(PPh₃)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 $(\eta^2-O_2)Pd(PPh_3)_2$ generated in situ, new signals for aromatic protons appeared in the ¹H 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(PPh₃)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(PPh₃)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 ¹H NMR signals of the aryl-palladium complexes detected above were observed. Concomitantly, the ³¹P NMR singlet of the peroxo complex 4 (33.2 ppm in CDCl₃, 33.4 in DMF) disappeared, and a new singlet was observed, characteristic of a palladium ligated to two magnetically equivalent PPh₃ 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 $(\eta^2 - O_2)Pd(PPh_3)_2$ with **1b** (Scheme 6), was determined by comparing its ¹H, ³¹P 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)(PPh₃)]₂ (³¹P NMR: δ = 33.66 and 32.96 ppm) with 10 equiv of PPh₃, as reported by Grushin and Alper (Scheme 7).^{11a,b} The same complex **5b** was also formed by reacting trans-PhPdI(PPh₃)₂ with n-Bu₄NOH 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 ³¹P 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 ¹H 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)PPh3 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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Table 1. ¹H NMR (250 MHz, TMS), ³¹P NMR (101.3 MHz, H₃PO₄) Shifts and ESI MS of Complexes **5a,b** Formed by Reacting $(\eta^2-O_2)Pd(PPh_3)_2$ **4** with the Arylboronic Acids **1a,b** in Chloroform (Scheme 6)^{*a*}

trans-ArPd(OH)(PPh ₃) ₂	¹ H NMR	³¹ P NMR	
Ar	δ ppm (CDCl ₃)	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 ₆ H 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 PPh₃ ligand are omitted for clarity.

Scheme 6



Scheme 7



Table 2. ³¹P NMR Shifts (101.3 MHz, H₃PO₄) of the Intermediate Complexes **6a**-**c** Formed by Reacting (η^2 -O₂)Pd(PPh₃)₂ **4** with 0.5 equiv of Arylboronic Acids **1a**-**c** in Chloroform or DMF^a



^{*a*} Same reaction with **1'b**. ^{*a*} The ¹¹B NMR broad signal (29 ppm) of **1b** in CDCl₃ 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 ³¹P 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)L₂ or $[Pd_2(\mu-OH)(\mu-OO)L_4]^+$ which might have been generated by the reaction of water with $(\eta^2-O_2)Pd(PPh_3)_2$ **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 O₂PdL₂ 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 PH₃ as model for the PPh₃ 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 PH₃ were also found to be stable in the case of the systems containing PPh₃ 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 $(\eta^2-O_2)Pd(PPh_3)_2$ with Arylboronic Acids. The overall reaction in Scheme 8 was monitored by electrochemistry under an argon atmosphere, taking the advantage that the peroxo complex $(\eta^2-O_2)Pd(PPh_3)_2 4$ (2 mM) exhibited an oxidation peak at +0.63 V vs SCE in chloroform containing *n*-Bu₄NBF₄ (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

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6b

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 ₃ –B)	d (Pd–O₃)	d (Pd–O _b)	θ (PPdP)	θ (PdO ₂ B)	θ (O ₂ O _b B)
	1 452	1 653	2 128	2.024	104.5	105.7	112.8
6b	1.452	1.650	2.128	2.024	104.2	106.2	112.8
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 $(\eta^2-O_2)Pd(PPh_3)_2$ 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	$\Delta \mathcal{E}_{solvent}$
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 $(\eta^2 - 0_2)Pd(PPh_3)_2 \mathbf{4}$ ($C_0 = 2 \text{ mM}$) in chloroform (containing *n*-B₄NBF₄, 0.3 M) at 25 °C, as monitored by amperometry at a rotating gold disk electrode. (a) $[\mathbf{1a}] = 20 \text{ mM}$. Variation against time of $\ln x$ ($x = [\mathbf{4}]_{i}/[\mathbf{4}]_0 = i_i/i_0$; $i_t =$ oxidation current of $\mathbf{4}$ at t, $i_0 =$ initial oxidation current of $\mathbf{4}$). $\ln x = -k_{obs} \times t$. (b) Determination of the reaction order in $\mathbf{1a}$: plot of $\ln(k_{obs})$ against $\ln([\mathbf{1a}])$: $\ln(k_{obs}) = 1.9 \times \ln([\mathbf{1a}] + 6$. (c) Determination of the reaction order in $\mathbf{1a}$: plot of k_{obs} against $[\mathbf{1a}]^2$.

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

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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)

	$K_1 k_2 (M^{-2} s^{-1})$		
solvent	1a (Z = OMe)	1b (Z = H)	1c(Z = CN)
CDCl ₃ DMF	600 5.8	2500 1025	n.d. 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

rate =
$$\frac{k_1 k_2 [\mathbf{4}] [\mathbf{1}]^2}{k_{-1}} = K_1 k_2 [\mathbf{4}] [\mathbf{1}]^2$$
 (a)

$$\ln x = -K_1 k_2 [\mathbf{4}] [\mathbf{1}]^2 t = -k_{\text{app}} [\mathbf{1}]^2 t = -k_{\text{obs}} t \qquad (b)$$

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).

Whatever the solvent, the following reactivity order was observed: $K_1^{\text{CN}}k_2^{\text{CN}} > K_1^{\text{H}}k_2^{\text{H}} > K_1^{\text{OMe}}k_2^{\text{OMe}}$. 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 $k_2^{\text{CN}} < k_2^{\text{H}} < k_2^{\text{OMe}}$, 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 $K_1^{\text{CN}} \gg K_1^{\text{H}} \gg K_1^{\text{OMe}}$ 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)(PPh₃)₂ (trans-5a,b) Complexes. Thus far we have identified and characterized the formation of complexes ArPd(OH)(PPh₃)₂ (trans-5a,b, Scheme 9) through the fast reaction of the peroxo complex $(\eta^2-O_2)Pd$ -(PPh₃)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-C₆H₅-Pd(OH)(PPh₃)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 PdII center, in the range 6.2-6.8 ppm. The 2D NMR spectrum allowed the identification of the three different protons of the C₆H₅ group associated with the two different protons of the 4-CN-C₆H₄ group (Table 6, Figure 3). The ³¹P 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 ArPd-Ar'(PPh₃)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)-(PPh₃)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(PPh₃)₂ (X = I,^{11c} Br^{11d}) to form ArPd(OH)(PPh₃)₂.

When *trans*-**5b** PhPd(OH)(PPh₃)₂ was reacted with **1a** 4-MeO-C₆H₄-B(OH)₂ (1.3 equiv), the mixed complex *trans*-**8ba** was not observed (Scheme 10), but the coupling biaryl C₆H₅-C₄H₅-OMe-4 was produced together with 4-MeO-C₆H₄-Pd(OH)(PPh₃)₂. The catalytic cycle was completed via the successive transmetalation and reductive elimination to generate

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

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

Table 6. ¹H (250 MHz, TMS) and ³¹P NMR (101.3 MHz, H₃PO₄) Shifts (δ ppm) of Complexes **8** Formed by Reacting Complexes **5** with Arylboronic Acids **1** in CDCl₃ (Scheme 10)^a

$\begin{array}{l} \text{4-Y-C}_6\text{H}_4\text{-Pd-C}_6\text{H}_4\text{-Z-4(L)}_2\\ \text{L}=\text{PPh}_3 \end{array}$	¹ H NMR 4-Y-C ₆ H₄-Pd	¹ H NMR Pd-C ₆ H₄-Z-4	³¹ P NMR
$\mathbf{8bc} (\mathbf{Y} = \mathbf{H}, \mathbf{Z} = \mathbf{CN})$	6.61 (d, <i>J</i> = 7 Hz, 2H, <i>o</i> -H) 6.37 (t, <i>J</i> = 7.5 Hz, 1H, <i>p</i> -H) 6.22 (t, <i>J</i> = 7.3 Hz, 2H, <i>m</i> -H)	6.61 (d, $J = 6.7$ Hz, 2H, <i>m</i> -H) 6.44 (d, $J = 6.7$ Hz, 2H, <i>o</i> -H)	22.40
8ac ($Y = OMe, Z = CN$)	6.41 (d, <i>J</i> = 7.4 Hz, 2H, <i>o</i> -H) 6.14 (m, 2H, <i>m</i> -H) 3.56 (s, 3H, Me)	6.8 (d, 2H, <i>o</i> -H) 6.27 (d, <i>J</i> = 8.8 Hz, 2H, <i>m</i> -H)	n.d.

^a The aromatic protons of the PPh₃ 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 CDCl₃ (Scheme 10).





the biaryl together with a Pd⁰ complex (Scheme 11). The peroxo complex $O_2Pd(PPh_3)_2$, formed by reaction of Pd⁰(PPh_3)_2 with dioxygen, reacted again with excess **1a** to generate 4-MeO-C₆H₄-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-C₆H₄-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-C₆H₄-C₆H₅ was produced together with *trans*-PhPd(OH)(PPh_3)_2. This indicates that once



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'(PPh₃)₂ complexes in a transmetalation step performed from *trans*-ArPd(OH)(PPh₃)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)(PPh₃)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)(PH₃)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 $(\eta^2$ -O₂)Pd(PPh₃)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)(PPh₃)₂ (*trans*-**5a,b**) which accumulated due to lack of reagent. The fact that *trans*-ArPdAr'(PPh₃)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'(PPh₃)₂ **8** via *cis*-ArPdAr'(PPh₃)₂ was fast in this case and that the mechanism of the catalytic cycle may thus involve

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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)(PPh₃)₂ **5b**, (iv) phenol was not formed upon bubbling dioxygen in a solution Scheme 15 HOOB(OH)₂ + H₂O → B(OH)₃ + H₂O₂

$$H_2O_2 + ArB(OH)_2 \longrightarrow B(OH)_3 + ArOH$$

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 -O₂)PdL₂ (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)L2 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)L₂ complexes react with the arylboronic acid to give trans-Ar-PdArL₂ complexes in a second transmetalation step. The biaryl is formed in a reductive elimination. Because of the common intermediate Pd⁰L₂, 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 palladiumcatalyzed 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

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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.

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