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ACS Catal., Just Accepted Manuscript • DOI: 10.1021/acscatal.6b02527 • Publication Date (Web): 24 Jan 2017 Downloaded from http://pubs.acs.org on January 24, 2017

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#### **ACS Catalysis**

# A Remarkably Robust and Efficient Pd<sub>3</sub> Cluster Catalyst for the Suzuki Reaction and its Odd Mechanism

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### Abstract

The palladium-catalyzed Suzuki-Miyaura coupling reaction is one of the most versatile and powerful tools for constructing the synthetically useful unsymmetrical aryl-aryl bonds. In designing a robust Pd cluster as candidate for efficient catalysis and mechanistic investigations, it was envisaged to study a case intermediate between-, although very different from the "classic" Pd(0)Ln and Pd nanoparticle families of catalysts. Herein, the cluster  $[Pd_3Cl(PPh_2)_2(PPh_3)_3]^+$   $[SbF_6]^-$  (abbreviated Pd<sub>3</sub>Cl) was synthesized and fully characterized as a remarkably robust framework stable up to the  $170^{\circ}$ C and fully air stable. **Pd<sub>3</sub>Cl** was found to be an excellent catalyst for the Suzuki-Miyaura cross C-C coupling of a variety of aryl bromides and aryl boronic acid under ambient aerobic conditions. The reaction proceeds by keeping the integrity of the cluster frame all along the catalytic cycle via the intermediate  $Pd_3Ar$ evidenced by mass spectrometry, and quick X-ray absorption fine structure. In the absence of the substrate in the reaction condition the Pd<sub>3</sub>OH species was detected by mass spectrometry, which strongly favors the "oxo-Pd" pathway of the transmetallation step involving substitution of the Cl ligand by OH followed by binding of the OH ligand with the arylboronic acid. The kinetics of the Suzuki-Miyaura reaction shows the lack of induction period consistent with the lack of cluster dissociation. This study may provide new perspectives for the catalytic mechanisms of cross C-C coupling reactions catalyzed by metal clusters.

**Keywords:** metal cluster; catalysis; Suzuki-Miyaura reaction; mechanism of Pd-catalyzed reaction; cross-C-C coupling

### Introduction

The palladium-catalyzed Suzuki-Miyaura reaction<sup>1,2</sup> is among the most efficient and useful cross carbon-carbon coupling reactions in organic synthesis, because it allows the synthesis of a large variety of organic compounds from readily accessible reactants under mild conditions.<sup>3,4</sup> In particular unsymmetrical aryl-aryl coupling using the Suzuki-Miyaura reactions between aryl bromide and arylboronic acids leads to the biaryl scaffold that has received increased attention as a privileged structure by the pharmaceutical industry. This motif has shown activity across a wide range of therapeutic classes including antifungal, anti-inflammatory, antirheumatic, antitumor, and antihypertensive agents.<sup>5</sup> Here we present a new approach of this reaction using a robust cationic Pd<sub>3</sub> cluster catalyst that bridges the areas of well-defined mononuclear palladium complexes<sup>[1-7]</sup> and palladium nanoparticles<sup>[8-13]</sup> that have so far both provided efficient catalysts for this reaction. The interest of this work is the handling and use of an air stable, robust catalyst that therefore in the same time can be subjected to specific mechanistic investigations some of which are presented herein.

The catalytic cycle of the Suzuki-Miyaura reaction is well known to be mainly composed of oxidative addition, transmetallation and reductive elimination with classic molecular catalysts of the type  $Pd(0)L_2$  usually generated in situ from pre-catalysts consisting of a Pd(II) salt and a phosphine (L).<sup>1,14-27</sup> The transmetallation step of this mechanism has been much debated, however (vide infra).<sup>14-27</sup> The reaction mechanism is more elusive with palladium nanoparticles, although it has been considered that a related mechanism also proceeds at the Pd atom level subsequent to leaching rather than at the nanoparticle surface.<sup>8,13</sup> Indeed, it has been disclosed that even sub-ppm Pd nanoparticles stabilized by dendrimers were effective for the Suzuki reaction.<sup>12,13</sup> In such cases the surface structure of nanoparticles is hard to probe and reaction intermediates are not detectable. The atomically precise nanoclusters that are a recently developed field modelize nanoparticles and have therefore stimulated tremendous interest regarding their catalytic implications.<sup>24-26</sup> For instance our group, for the first time, employed  $Au_{25}^{z}$  (z = -1,0,+1) nanoclusters as electron transfer catalysts to induce an intramolecular cascade reaction in liquid phase.<sup>[27]</sup> Various Pd clusters have also been generated to investigate the correlation between their structures and chemical properties.<sup>[32-41]</sup> Corma's group found that C-C coupling reactions catalyzed by various palladium sources including a salt, a complex and nanoparticles proceeded at high rates when three- or four-atom Pd clusters were formed. Such small Pd clusters were suggested to be the active catalytic species in the C-C cross-coupling reactions.<sup>42</sup>

Here we report the very facile catalysis of the Suzuki-Miyaura reaction under ambient and aerobic condition using the robust cluster  $[Pd_3Cl(PPh_2)_2(PPh_3)_3]^+[SbF_6]^-$ 

#### **ACS Catalysis**

noted in short  $Pd_3Cl$ . The synthesis of the cationic cluster with the BF<sub>4</sub><sup>-</sup> counter anion has previously been reported by Dixon's group, but the X-ray crystal structure was not reported for this complex.<sup>43</sup> The formation of a triangular Pd<sub>3</sub> cluster containing PPh<sub>2</sub> bridges resulting from P-phenyl bond cleavage in PPh<sub>3</sub> had first been suggested earlier by Coulson. The compound had been formulated as a neutral complex [Pd<sub>3</sub>(PPh<sub>3</sub>)<sub>3</sub>(PPh<sub>2</sub>)<sub>3</sub>Cl<sub>2</sub>], and the exact molecular formula had not been disclosed.<sup>44</sup>

We have devised a new method to prepare  $Pd_3Cl$  (Scheme 1) and conducted Suzuki-Miyaura coupling with a variety of substrates using the Pd<sub>3</sub>Cl catalyst. Our finding is accompanied by studies using mass spectrometry, NMR and optical spectroscopy, quick X-ray absorption fine structure, and density functional theory calculation (DFT). The crystal structures of the catalyst before and after the reaction are disclosed and kinetic studies were also performed. Altogether these investigations show that this cluster that is unusually robust is an excellent catalyst and allow suggesting particular mechanistic features that significantly differ from those generally ascertained using the classic palladium chloride/phosphine catalysts.

### **Results**

### Crystal and electronic structure of Pd<sub>3</sub>X (X = Cl or Br)

The new standard procedure for the synthesis of Pd<sub>3</sub>Cl follows Scheme 1 (see the experimental section).



Scheme 1. Synthesis of the Pd<sub>3</sub>Cl catalyst

The structure of Pd<sub>3</sub>Cl was determined by X-ray crystallography (see the crystal data in Table S1) and is shown in Figure 1. UV-vis. absorption measurements show that the Pd<sub>3</sub>Cl cluster exhibits multiple bands centered at 485, 418 and 340 nm

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(Figure S1). Square-wave voltammetry in  $CH_2Cl_2$  shows a reversible oxidation wave at +1.13 V vs. Ag<sup>+</sup>/Ag and a reversible reduction wave at – 1.32 V vs. Ag<sup>+</sup>/Ag. This shows stability extended to the reduced and oxidized cluster states at least at the cyclovoltammetry time scale; it also highlights the existence of a very large HOMO-LUMO energy gap (*vide infra*) that is consistent with a great robustness, including in aerobic conditions.



**Figure 1.** Crystal structure of the **Pd<sub>3</sub>Cl** catalyst [Pd<sub>3</sub>Cl(PPh<sub>2</sub>)<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>]<sup>+</sup> [SbF<sub>6</sub>]<sup>-</sup>.

Pd<sub>3</sub>Cl has a single positive charge on the cluster, thus an average oxidation state of +4/3 for the three Pd atoms and an electron count of 16.67 valence e per Pd. There are 74 valence electrons in  $Pd_3Cl$  modelized here by the cluster  $[Pd_3(PH_2)_3(PH_3)_3]Cl^+$ , in which each Pd, P, H atoms contribute 10, 5 and 1 valence electrons, respectively. According to the Adaptive Natural Density Partitioning (AdNDP) analysis, as shown in Figure 2 (B, C and D) using this simplified model cluster, there are twelve lone-pair 4d orbits  $(yz, zx, x^2-y^2, z^2)$  of three Pd atoms with occupancy numbers (ON = 1.93-1.99 |e|), fifteen P-H bonds (ON = 1.99 |e|), nine P-Pd bonds (ON = 1.97-1.98 |e|), and one three-center two-electron (3c-2e) delocalized Pd-Pd-Pd bond (ON = 1.98 |e|). The P atoms are in sp<sup>3</sup> hybridization, and the symmetry of the P-Pd and Pd-Pd-Pd bonds shows that Pd is in  $dsp^2$  hybridization (4d<sub>xy</sub>, 5s and 5p<sub>xy</sub>). The square  $dsp^2$  hybridization of Pd leads to the planarity of the cluster; the 3 center-2 electron Pd-Pd-Pd bond and the bridging ligands are the reason for the stability of the Pd<sub>3</sub> triangle. The PPh<sub>3</sub> and PPh<sub>2</sub> ligands of Pd<sub>3</sub>Cl provide a bulky protection making the approach of the Pd centers by large substrates difficult.

DFT calculation was also used to calculate the HOMO-LUMO energy gap of Pd<sub>3</sub>Cl, Pd<sub>3</sub>Br and Pd<sub>3</sub>Ar. Figure 2E shows the DFT optimized structures of these three clusters at the TPSSh/6-31G\*/LANL2DZ level, where the starting

coordinates are from the single-crystal structure of  $Pd_3Cl$ . The HOMO-LUMO energy gap of  $Pd_3Cl$  is calculated to be 2.61 eV in good agreement with the experimental value (~2.49 eV, Figure S2; compare with 2.45 eV in square-wave voltammetry, *vide supra*), which indicates that the results of these calculations are reliable. The molecular structure of  $Pd_3Br$  is very similar to that of  $Pd_3Cl$  without distortion, and its HOMO-LUMO energy gap is also very large (2.55 eV), indicating the similar stability of these two clusters. However, the HOMO-LUMO energy gap of  $Pd_3Ar$  is obviously lower (2.19 eV), which indicates that  $Pd_3Ar$  is somewhat less stable than the other two structures.



**Figure 2.** Optimized geometry (A) and AdNDP chemical bonding (B, C, D) of  $[Pd_3(PH_2)_3(PH_3)_3]^+$ . E: Optimized structures of **Pd\_3Cl**, **Pd\_3Br** and **Pd\_3Ar** at TPSSh/6-31G\*/LANL2DZ level (the calculated HOMO-LUMO energy gaps are indicated in parentheses at the bottom of the figure).

#### Suzuki-Miyaura reactions catalyzed by Pd<sub>3</sub>Cl

The cluster  $Pd_3Cl$  was utilized to catalyze the Suzuki–Miyaura cross-coupling reaction between various aryl bromides and phenylboronic acid (Table 1). All the substituted substrates with either electron-donating groups or electron-withdrawing substituents gave rise to high yield products in 15-60 min reaction time (turnover frequency (TOF): 1100-5000 h<sup>-1</sup>).

Page 6 of 20





Entry	R	R'	Product	Time	Yield <sup>[b]</sup>	TON	TOF(h <sup>-1</sup> )
				(min)	(%)		
1	Н	Н		30	97.2	1220	2450
2	CH <sub>3</sub>	н		30	93.3	1200	2390
3	CH <sub>3</sub> O	н	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	30	94.1	1220	2440
4	<i>t</i> -Bu	н		60	99	1230	1230
5	CH <sub>3</sub> CO	н		60	91.1	1160	1160
6	NO <sub>2</sub>	н		60	90.0	1170	1170
7	CF <sub>3</sub>	н	CF3-CF3	60	96.2	1240	1240
8	Н	CH <sub>3</sub>		15	96.4	1240	4950
9	Н	CH <sub>3</sub> O	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	15	93.8	1200	4820
10	Н	<i>t</i> -Bu	⟨	15	95.6	1230	4920
11	Н	CF <sub>3</sub>	CF3-CF3	30	92.3	1190	2370
12	Н	Cl	С)-Сі	30	94.1	1210	2420

[a] Reaction conditions: bromobenzene (1.64 mmol), arylboronic acid (1.64 mmol), 0.08 mol% catalysts,  $K_2CO_3$  (3.28 mmol), *i*-propanol (5 mL), water (5 mL). [b] GC yields.

The UV-vis. spectra of the solution in the reaction process are represented in Figure 3A, showing that the  $Pd_3Cl$  absorption spectrum almost remains the same, indicating the absence of apparent cluster size change or decomposition.

 The <sup>31</sup>P-NMR analysis (Figure 3B) shows that the initial  $Pd_3Cl$  gives signals at 11.25, 11.75, 12.25, 18.5 and 19 ppm. During the course of the catalytic reaction, all the peaks move to lower field due to the Cl to Br exchange on the Pd<sub>3</sub> skeleton. Both ESI and X-ray analyses confirmed that Cl<sup>-</sup> in Pd<sub>3</sub>Cl was replaced by Br<sup>-</sup>, explaining why all the <sup>31</sup>P-NMR peaks moved to lower field (*vide infra*).



**Figure 3.** (A) UV-vis. spectrum and (B) <sup>31</sup>P-NMR tracking of the Suzuki-Miyaura reaction.

ESI-MS was performed in order to analyze the catalyst and gain insight into the reaction intermediates of the  $Pd_3Cl$  catalyzed Suzuki-Miyaura cross coupling reaction. Canary and co-workers observed catalytic intermediates in the "classic" Suzuki-Miyaura reaction mechanism by using ESI-MS.<sup>45</sup> Pd<sub>3</sub>Cl was mixed with the two reactants, respectively, and the reaction process was monitored by ESI-MS. As shown in Figure S3, Pd<sub>3</sub>Cl showed the absence of discernable change when only bromobenzene and K<sub>2</sub>CO<sub>3</sub> were added, but Pd<sub>3</sub>Cl reacted with phenylboronic acid and K<sub>2</sub>CO<sub>3</sub> in 2h. Pd<sub>3</sub>Cl would interact with phenylboronic acid under alkaline conditions, and a new substance at m/z1553.11 was observed (Figure 4A, profile c). Then 0.006 mL bromobenzene was added, the 1553.11 Da peak disappeared and a new peak at 1557.06 Da resulted (Figure 4A, profile d). This indicates that  $Pd_3Cl$  first reacts with phenylboronic acid to generate an intermediate of mass 1553.11 Da. The structure of this intermediate is assigned to  $[Pd_3Ar(PPh_2)_2(PPh_3)_3]^+$  (theoretical mass: 1553.13 Da, denoted Pd<sub>3</sub>Ar in short), and the 1557.06 Da species is due to  $[Pd_3Br(PPh_2)_2(PPh_3)_3]^+$  (theoretical mass: 1557.00 Da, denoted Pd\_3Br in short; see the crystal structure in Figure S4 and the crystal data in Table S2). The experimental isotope patterns are consistent with the simulations based upon the two formulas (Figure 4B). Although the mass difference is small (~4 Da only), ESI readily distinguishes  $Pd_3Ar$  from  $Pd_3Br$ . In order to further prove this evolution, iodobenzene was used to replace bromobenzene in this

process. As showed in Figure S5, when iodobenzene was added, the 1553.11 Da peak disappeared, and a new peak at 1603.03 Da resulted, which is due to  $[Pd_3I(PPh_2)_2(PPh_3)_3]^+$  (Pd\_3I, theoretical mass: 1602.99 Da). This experiment further demonstrates that Pd\_3Ar is an intermediate of the Suzuki-Miyaura reaction catalyzed by Pd\_3Cl. The reaction between Pd\_3Cl and phenylboronic acid is in a stationary state without bromobenzene, but upon adding bromobenzene the reaction system breaks the equilibrium, and the intermediate Pd\_3Ar reacts with bromobenzene to generate Pd\_3Br. Before adding bromobenzene, the only addition of phenylboronic acid and K<sub>2</sub>CO<sub>3</sub> leads to partial decomposition of Pd\_3Cl in the reaction (Figure 4A), but it does not if both reactants are introduced at the same time (Figure S6). Hence, bromobenzene plays a role of protecting the catalysis in this process.



**Figure 4.** (A)ESI-MS tracking of  $[Pd_3Cl(PPh_2)_2(PPh_3)_3]^+$ reacts with phenylboronic acid under alkaline condition: 0.0072 g (0.06 mmol) phenylboronic acid, 2 mg (1.32x10<sup>-3</sup> mmol) catalyst, 0.0164 g (0.12 mmol) K<sub>2</sub>CO<sub>3</sub> and 3 mL CH<sub>2</sub>Cl<sub>2</sub>, rt. a:0 h. b:1 h. c:2 h. d: adding 0.006 mL bromobenzene on the basis of c. (B)The evolution of  $[Pd_3Ar(PPh_2)_2(PPh_3)_3]^+$  to  $[Pd_3Br(PPh_2)_2(PPh_3)_3]^+$ . (C)EXAFS  $k^2\chi(k)$  oscillation functions, and (D) their transform spectra of  $[Pd_3Cl(PPh_2)_2(PPh_3)_3]^+$ Fourier reacting with phenylboronic acid under alkaline condition during 2 h, with or without adding corresponding bromobenzene. The spectra of the solution of  $[Pd_3Cl(PPh_2)_2(PPh_3)_3]^+$ , solution of H<sub>2</sub>PdCl<sub>4</sub> and Pd bulk are also displayed for reference.

Page 9 of 20

#### **ACS Catalysis**

Additional information on the structural evolution of the clusters during the Suzuki reaction was provided by the Pd K-edge XAFS measurements. We compare the EXAFSk<sup>2</sup> $\chi$ (k) oscillation functions (Figure 4C) and their Fourier transform spectra (Figure 4D) of Pd<sub>3</sub>Cl reacting with phenylboronic acid under alkaline conditions, with or without the addition of bromobenzene. As a reference, the spectra of Pd<sub>3</sub>Cl in CH<sub>2</sub>Cl<sub>2</sub> solution, solution of H<sub>2</sub>PdCl<sub>4</sub> and Pd bulk are also plotted. The Fourier transform curve of the starting Pd<sub>3</sub>Cl solution shows two characteristic peaks located at around 1.7 and 2.7 Å. As the Pd-Cl peak of  $H_2PdCl_4$ , the main peak at 1.7 Å is attributed to Pd-P and Pd-Cl that could not be discriminated by EXAFS. The weaker peak at 2.7 Å is ascribed to the Pd-Pd pairs, but located at higher position than the Pd-Pd peak of bulk Pd, indicating the atomic arrangements of the triangle Pd<sub>3</sub> skeleton of the cluster. For the catalysis by Pd<sub>3</sub>Cl of the Suzuki-Miyaura reaction, regardless of the addition time of bromobenzene, the overall EXAFS spectral shape remains almost unchanged. This provides strong evidence that the triangle Pd<sub>3</sub> skeleton of the Pd<sub>3</sub>Cl catalyst appears intact during the Suzuki reaction, in agreement with the UV-vis., NMR, and ESI analyses. Closer inspection of the XAFS spectra suggests that there are still some discernible differences caused by the different reaction times of the bromobenzene addition. Observed from the k-space EXAFS oscillation functions  $k^2 \chi(k)$ , the oscillation amplitude in the low k-region (k<5  $Å^{-1}$ ) is considerably reduced if no bromobenzene is added. Taking into account the different scattering amplitudes of C, Cl/P, and Br atoms to X-ray, this is due to the coordination of Pd atoms by lighter atoms than Cl/P, which could only be C and/or O atoms coming from the aromatic or hydroxyl group respectively. Combining the XAFS result with the ESI-MS analysis, the formation of  $Pd_3Ar$  intermediate in the reaction is ascertained. In contrast, in the presence of bromobenzene the oscillation amplitude in the low k-region is only slightly weakened, but the oscillations in the medium k-region ( $k \sim 8 \text{ Å}^{-1}$ ) are intensified. Moreover, the first coordination peak exhibits some notable shift to higher R-position. These changes could only come from the coordination of heavier neighbors than Cl/P to Pd atoms, consistent with the generation of Pd<sub>3</sub>Br, rather than Pd<sub>3</sub>Ar, as suggested by the ESI-MS analysis.

We investigated the fate of the catalyst under the reaction conditions in the presence of the base, but in the absence of the reagents. The MALDI-MS (Figure S8) showed the presence of  $Pd_3OH$  and other peaks that have not been identified. This reactivity contrasts with the clean behavior of the catalyst in the presence of the substrates for which only the sequence  $Pd_3Cl-Pd_3Ar-Pd_3Br$  is observed along the catalytic process.

Finally the kinetic analysis of the catalytic reaction shows the absence of induction time (Figure S9) and of linear correlation with the Hammet parameters of the substituents of the aryl bromide and arylboronic acid (Figure S10).

Nevertheless, under the same condition as with bromobenzene (Table 1,  $25^{\circ}$ C) the reaction of chlorobenzene with PhB(OH)<sub>2</sub> in 3 h yielded the SM coupling product in 25% yield, whereas during the same time the yields raised to 71.7% and 76.7% % at 60°C and 80°C respectively.

#### Discussion

The cationic clusters  $Pd_3X$  (X = Cl or Br) have been shown here to be excellent catalysts for the Suzuki-Miyaura reaction of a variety of bromoarenes and aryboronic acids in hydro-alcoholic medium in the presence of  $K_2CO_3$  under ambient aerobic conditions. This catalyst contrasts with the usual PdCl<sub>2</sub>/phosphine or N-heterocyclic carbene (NHC) systems that have been shown to generate Pd(0) catalysts in situ and for which the well-known cycle involving the succession of the three steps, oxidative addition-transmetallation-reductive elimination has been well established.<sup>1,2,14-28</sup> Indeed in these classic catalysts, the generated square planar species such as  $PdL_2S_2$ (L = phosphine or NHC ligand; S = labile solvent ligand) readily undergoes oxidative addition onto the Pd(0) center as the first step of the catalytic cycle.<sup>1</sup> On the other hand, the present catalysts are exceptionally robust. For instance they are stable up to 170°C as shown by the thermogravimetric analysis (Figure S11). Such a great robustness is rather exceptional in cluster chemistry and contrasts with the thermal lability of transition metal nanoparticules that easily give rise to Oswald ripening upon heating. Their molecular peak is easily found in the ESI mass spectrum without loss of any ligand or other impurity. Thus these features show that the integrity of the Pd<sub>3</sub> cluster frame is preserved during the catalysis process, and catalysis by mononuclear Pd species subsequent to cluster dissociation is clearly discarded. On the contrary the first catalytic step must occur on the intact Pd<sub>3</sub>X catalyst itself. This situation contrasts with that of many late transition metal triphenylphosphine complexes such as Wilkinson-Osborn catalyst<sup>46</sup> for which the large phosphine cone angle<sup>47</sup> and electronic requirement allows facile reversible phosphine dissociation from the metal center creating free coordination sites.<sup>4</sup> In  $Pd_3X$ , the robustness is insured by the great stability of the tetra-triangular framework containing the 9 coplanar  $Pd_3P_5X$  atoms and in particular three bridging ligands around the  $Pd_3$  triangle as witnessed by the theoretical calculations confirming the great stability and a very large HOMO-LUMO gap. The overall positive cluster charge brings about aerobic stability. Not surprisingly, the cationic clusters are completely unreactive with arylbromides alone in spite of their great catalytic activity, discarding the possibility

of such a primary step involving aryl bromide oxidative addition in the catalytic reaction.

On the other hand and interestingly, the cluster  $Pd_3Ar$  is formed as the only observable intermediate during the catalytic reaction before the final formation of  $Pd_3Br$  when the reaction is conducted with aryl bromides or  $Pd_3I$  in the presence of aryl iodides. This shows that transmetallation is the first step proceeding before the reaction of aryl bromide or aryl iodide.

Transmetallation as the first step of the Suzuki reaction has to our knowledge already been suggested in only one case with a  $PC_{sp3}P$  pincer Pd(II) catalyst by Olsson and Wendt in 2009, but the Suzuki-Miyaura reaction was conducted at 160°C, and the product yields were mediocre to modest.<sup>48</sup>

The transmetallation step of the Suzuki-Miyaura reaction that is the second step following the oxidative addition of the aryl halide onto Pd(0) has been the subject of considerable discussion in the literature.<sup>14-28</sup> In early works, it had been proposed that arylboronates generated from the reaction between the arylboronic acid and the nucleophile MeO<sup>-</sup>, EtO<sup>-</sup> or HO<sup>-</sup> were more active than arylboronic acid in the transmetallation step.<sup>1,14,15</sup> Two competitive mechanisms have later been computed and much been debated by the groups of Maseras and Lloyd-Jones.<sup>16-21</sup> (Scheme 2).



Scheme 2. The two possible mechanisms for the transmetallation step of the Suzuki-Miyaura reaction in Pd catalysis. With  $Pd_3Cl$  the "oxo pathway" is priviledged by the observation of the Pd-OH species in the absence of the substrates.

The first mechanism involves substitution of the halide by the boronate in the Pd(II)-X intermediate resulting from oxidative addition ("boronate" pathway), and the second mechanism involves substitution of the halide in Pd(II)-X by the nucleophilic base OH<sup>-</sup> or OR<sup>-</sup> followed by bond formation between the oxygen atom of the hydroxo or alkoxo Pd ligand and the boron atom of the neutral borane ("oxo-palladium" pathway, Scheme 2). The priviledged mechanism has been proposed

to depend on the reagents and reaction conditions.<sup>21</sup> This latter mechanism was favored, however, on the basis of kinetic and NMR studies by Carrow and Hartwig<sup>22</sup> and by Amatore and Jutand<sup>23-26</sup> for coupling of aryl boronic acids with simple aryl halides in aqueous solvents with  $[PdL_n]$  (L = PPh<sub>3</sub> and PCy<sub>3</sub>) as catalyst and M<sub>2</sub>CO<sub>3</sub> as base (producing OH<sup>-</sup> by reaction with water). An insightful review of this competition between these mechanisms has recently been published by Lennox and Lloyd-Jones.<sup>21</sup> Amatore and Jutand also showed some negative roles of OH<sup>-</sup> that are the formation of unreactive arylborate and complexation of the OH ligand by the counter cation of OH<sup>-</sup>.<sup>26</sup> In a recent article in *Science* by Thomas and Denmark, three different species containing palladium-oxygen-boron linkages were proposed, a tricoordinate boronic acid complex, and two tetracoordinate boronate complexes with 2: 1 and 1: 1 stoichiometry with respect to palladium. All of these species transfer their boron-bearing aryl groups to a coordinatively unsaturated palladium center in the critical transmetallation step.<sup>27</sup> All these investigations refer to the Pd(II) intermediate species that follows the classic oxidative addition and show the complexity of this step.

Concerning the presently reported catalysis by the  $Pd_3Cl$  species, the attack of an anion is favored by the positive charge, and this significant electrostatic effect is consistent with the priority of the transmetallation step before the reaction of ArBr. The present situation is therefore different from the classic mechanism of  $PdL_2$  species, because the transmetallation occurs here with a Pd species that has not yet reacted with the aryl halide. Note, however, that the chloro ligand is present in the catalyst, which is reminiscent of the halogeno-alkyl Pd(II) intermediate following oxidative addition of the PdL<sub>n</sub> catalysts (but the Pd oxidation states are different). The Cl-Pd bond is actually the only active site in the otherwise very bulky  $Pd_3Cl$  catalyst. The two options of the "oxo-palladium" vs. "boronate" mechanism pathway both also remained open here, however (Scheme 2).

Indeed, the bridging chloro ligand of  $Pd_3Cl$  could be substituted either by OH<sup>-</sup> resulting from the reaction of carbonate with water or with boronate resulting from the nucleophilic attack of OH<sup>-</sup> onto the B atom of RB(OH)<sub>2</sub>. The experiment conducted with the base under the reaction conditions (presence of excess water, 5 mL) in the absence of substrate showing the formation of some Pd<sub>3</sub>OH species involved in the "oxo-palladium" mechanism strongly favors this later transmetallation mechanism. Kinetic studies showed the absence of induction time, consistent with the absence of cluster dissociation, but no correlation could be established with the Hammet parameters of the different substituents to determine the rate-limiting step of the reaction (see SI, Figures S9 and S10). Computational studies are called for and should confirm the "oxo-Pd" pathway of the transmetallation step and investigate the reaction mechanism of the aryl halide with the **Pd<sub>3</sub>Ar** intermediate. *A priori*, an oxidative addition would be difficult given the steric crowding around the Pd centers and the

oxidation state of +4/3, and a  $\sigma$ -bond metathesis is more likely for this step. So far the order of the steps is now well established. Presently the overall mechanism is indicated in Scheme 3. After one cycle the species **Pd<sub>3</sub>Br** is formed and becomes the catalyst for further cycles as confirmed also using this complex as the starting catalyst.



Scheme 3. Mechanism of Suzuki coupling reaction catalyzed by the  $Pd_3Cl$  cluster  $[Pd_3Cl(PPh_2)_2(PPh_3)_3]^+ [SbF_6]^-$ .

### Conclusion

A  $Pd_3Cl$  cluster has been designed and characterized here as a very robust framework, stable up to 170°C. This cluster has been used as catalyst for the Suzuki-Miyaura reaction in air whereby short reaction times, room temperature and low Pd concentrations have been applied with excellent results. The catalytic reaction was followed in order to investigate its mechanism. The crystal structures of the catalysts before and after the reaction were also resolved, and the identity of the structures suggests that the reaction is catalyzed by the intact Pd<sub>3</sub> frame. During the reaction  $Pd_3Cl$  first reacts with phenylboronic acid to generate the intermediate  $Pd_3Ar$ . This difference is essential with the "classic" mechanism of Suzuki-Miyaura reactions under similar room temperature conditions (using alkylphosphine-Pd catalysts)<sup>49</sup> that also proceed in which oxidative addition is the first step, as summarized in Scheme 4.



Scheme 4. Comparison between the "classic" mechanism of the Suzuki-Miyaura reaction and the mechanism shown with the  $Pd_3Cl$  cluster as catalyst (see the mechanistic details in Schemes 2 and 3).

In the absence of substrate, the catalysts reacts with a base under the reaction conditions of the catalytic reaction (rt) to form  $Pd_3OH$  resulting from the substitution of the Cl ligand by OH. The formation of the species  $Pd_3OH$  at rt strongly argues in favor of its intermediacy in the catalytic reaction, i.e. in favor of the "oxo-palladium" mechanism of the transmetallation step that is the first step of the Suzuki-Miyaura reaction catalyzed by  $Pd_3Cl$ . The substrate Ar-Br attacks the intermediate  $Pd_3Ar$  to generate the final product, while Br<sup>-</sup> replaces Ar<sup>-</sup> in the intermediate  $Pd_3Ar$  to form  $Pd_3Br$  that continues the role of  $Pd_3Cl$  as catalyst in the Suzuki-Miyaura reaction. Novel insights into the catalysis of various cross C-C coupling reactions catalyzed by metal clusters or nanoparticles can further be envisaged at the light of this new catalyst type and mechanistic operation. In conclusion, the new catalyst  $Pd_3X$  (X = Cl or Br) are very different from both the mononuclear and nanoparticle families of Pd catalysts due to their exceptional robustness with only open reactive site at the Pd-X bond of the rigidly held Pd<sub>3</sub> cluster framework.

### **Experimental Section**

#### General data

All the chemicals and reagents are commercially available and were used as received. Thin plate chromatography (TLC) commercial Merck Silica Gel 60 F254 was used for analytical TLC, and Merck Kieselgel 200-300 was used in preparative column chromatography. <sup>1</sup>H NMR spectra were acquired on a Brucker AM 400 operating at 400 MHz (solvent: CDCl<sub>3</sub> or CD<sub>2</sub>Cl<sub>2</sub>). <sup>13</sup>C NMR spectra were acquired on a Bruker AM 400 operating at 100 MHz (solvent: CDCl<sub>3</sub>). <sup>31</sup>P NMR spectra were acquired on a Bruker AM 400 operating at 100 MHz (solvent: CD<sub>2</sub>Cl<sub>2</sub>). Conversion and was measured with Shimadzu GC Page 15 of 20

#### **ACS Catalysis**

2010 plus. The crystal structure was determined via a CCD X-ray diffractometry. UV-vis. spectra were recorded on a Techcomp UV1000 spectrophotometer. Mass spectrometry analyses, including electrospray ionization mass spectrometry (ESI-MS) and matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS), were performed on Agilent and Bruker instruments, respectively. Square wave voltammetry measurements (SWV) were performed on an electrochemical workstation (CHI 660D) at a scan rate of  $0.05 \text{ V} \cdot \text{s}^{-1}$  under ambient conditions. Ouick X-ray absorption fine structure (OXAFS) measurements at Pd K-edge (24 350 eV) were performed in transmission mode at BL14W1 beamline of the Shanghai Synchrotron Radiation Facility (SSRF), China. The storage ring of SSRF worked at 3.5 GeV with a maximum current of 210 mA. In the QXAFS measurements, the Si (311) monochromator moved continuously, so that quick measurement (about 15 s per scan) became possible. Electrochemical measurements were performed with an electrochemical workstation (CHI 700E) using a Pt working electrode (diameter 0.4 mm), a Pt wire counter electrode, and a Ag wire quasi-reference electrode in 0.1 M  $Bu_4NPF_6/CH_2Cl_2$ . Prior to use, the working electrode was polished with 0.05 mg mL<sup>-1</sup> Al<sub>2</sub>O<sub>3</sub> slurries and then cleaned by sonication in dilute CH3CH<sub>2</sub>OH and nanopure water successively. The electrolyte solution was deaerated with ultra-high purity nitrogen for 40 min and blanketed with a nitrogen atmosphere during the entire experimental procedure.TGA was conducted by SDTO600 (USA), ramp at 10 °C/min to 800 °C.

### Preparation of the [Pd<sub>3</sub>Cl(PPh<sub>2</sub>)<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>]<sup>+</sup> clusters.

All the procedures were conducted at room temperature (rt,  $21-24^{\circ}$ C). PdCl<sub>2</sub> (1.42 g, 8 mmol) was dissolved in an aqueous solution of HCl acid (16 mmol, 2 equiv. per palladium), then the solution was diluted to 10 mL. An aliquot of the above solution (0.6 mL, 0.48 mmol) was added into 10 mL THF, followed by addition of triphenylphosphine (0.313 g, 1.2 mmol). After vigorous stirring for 8 minutes, NaBH<sub>4</sub> (0.08 g, 2.1 mmol, dissolved in 5 ml ethanol) was added, and the reaction solution was kept under vigorous stirring for 60 minutes. Then, centrifugation was performed to remove undissolved (excess) triphenylphosphine, and the left solution was rotaevaporated to dryness in vacuo. To exclude sodium salt, the solid was redissolved in 10 mL methylene dichloride, and washed with water, then evaporated to dryness again. The remaining solid was extracted by ethanol several times, and the ethanol solution obtained was rotaevaporated to dryness. The solid was dissolved in minimum ethanol, and the solution was added dropwise to hexane. The precipitate was collected by centrifugation, and the product was Pd<sub>3</sub>Cl obtained.

For crystallization, the cluster  $Pd_3Cl$  was dissolved in ethanol (1.5-2 mL), and  $NaSbF_6$  was added to the solution, followed by centrifugation. The solid was collected and redissolved in methylene dichloride, followed by centrifugation again. Finally, the solution was crystallized via layering with hexane at rt for two days.

#### Typical procedure for the Suzuki reaction

To a round-bottom flask phenylboronic acid (0.2 g, 1.64 mmol) and halogenobenzene (1.64 mmol), 2 mg ( $1.32 \times 10^{-3}$  mmol) cluster, K<sub>2</sub>CO<sub>3</sub> (0.453 g, 3.28 mmol) and 5 mL/5 mL H<sub>2</sub>O/iso-propanol were successively added. After stirring at r.t., the reaction was tracked by TLC analysis. The mixture was rotaevaporated to dryness in vacuo and purified by silica gel column chromatography (see text and Table 1).

NMR spectra, ESI-MS and MALDI-MS tracking of the Suzuki reaction: a round-bottom flask was charged with 0.0072 g (0.06 mmol) phenylboronic acid and 0.006 ml (0.06 mmol) bromobenzene, 2 mg ( $1.32 \times 10^{-3}$  mmol) cluster, 0.0164 g (0.12 mmol) K<sub>2</sub>CO<sub>3</sub> and 3 ml CH<sub>2</sub>Cl<sub>2</sub> (NMR tracking was carried out for the reaction in CD<sub>2</sub>Cl<sub>2</sub>) or H<sub>2</sub>O/iso-propanol with stirring at rt.

#### **DFT** calculation

The structures and energies were calculated using DFT as implemented in GAUSSIAN 09.<sup>50</sup> Geometry optimization and frequency analysis were performed using the metahybrid functional of Tao, Perdew, Staroverov, and Scuseria (TPSSh).<sup>51</sup> Structural minima were verified by the absence of imaginary vibrational modes. A modest 6-31G\* basis set was used for all atoms except Pd, for which the LANL2DZ basis set was used. In order to gain insight into the nature of the bonding in Pd<sub>3</sub> cluster, we apply a tool named Adaptive Natural Density Partitioning (AdNDP)<sup>52</sup> to obtain the patterns of chemical bonding.

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications

website at DOI: xxx

Additional observations and data (PDF)

Crystallographic information (CIF)

Crystallographic information (CIF)

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## ACKNOWLEDGMENT

Financial support from NSFC 21571001, 21372006&U1532141, the Ministry of Education, and the Education Department of Anhui Province, China, 211 Project of Anhui University is gratefully acknowledged.

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