Tetrameric Aryl Palladium Bromide Intermediates Leading to Facile Transmetalation in Suzuki–Miyaura Cross-Couplings with Pd@MIL-101-NH$_2$(Cr)

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ABSTRACT: The composition and structure of catalytic intermediates in the context of the Suzuki–Miyaura cross-coupling reaction catalyzed by Pd@MIL-101-NH$_2$(Cr) has been investigated. Trimeric and tetrameric palladium species with formula [Br–Pd–Ar]$^-$ (n = 3–4) have been identified by electrospray ionization mass spectrometry (ESI-MS) and density-functional theory (DFT) calculations, and their role in the transmetalation step has been studied. The weak nature of the bonds between Pd and the bridging halides in these species enables a very easy transmetalation step, with an estimated activation free energy of only 10 kcal/mol. Further experimental support for Pd speciation was obtained using scanning transmission electron microscopy (STEM), inductively coupled plasma-optical emission spectroscopy (ICP-OES), and fluorine-19 nuclear magnetic resonance spectroscopy ($^{19}$F NMR).

The Suzuki–Miyaura cross-coupling reaction is one of the most efficient methods for the construction of C–C bonds, and it is widely used in industry for the synthesis of building blocks and pharmaceuticals.$^{1-4}$ A wide range of palladium catalysts may be used, including palladium nanoparticles (NP) and palladium complexes with or without strong donor ligands.

Catalysts with P$_2$- N$_2$- or NHC-based ligands have been very important for studying the mechanism of Suzuki-Miyaura cross-coupling reactions.$^{5-14}$ For example, complexes with ligands bearing NMR-active nuclei (i.e., $^{19}$F) have been used to monitor the reactions by NMR spectroscopy.$^{15}$ Ligandless systems, i.e., those lacking strong donor ligands, have proved to be highly active catalysts when used at very low catalyst loadings (e.g., parts per million or billion), resulting in turnover numbers (TON) of up to 10$^7$. $^{16-25}$ Often, these palladium species are stabilized by a support (e.g., carbon, polymers, dendrimers, metal-organic frameworks (MOFs),$^{26-28}$ quaternary ammonium salts (e.g., NBu$_4$X, Jeffery system),$^{29,30}$ or other additives (i.e., N,N-di-methylglycine).$^{31}$

Identifying the composition and morphology of the catalytically active species in ligandless systems, which are generated from Pd salts or from Pd NPs, is a very challenging task. To a large extent, this is due to their low concentration and their dynamic character.$^{17,32-40}$ Numerous studies indicate that a “cocktail” of Pd(0) species is involved, and when Pd NPs are used, these species are produced by Pd leaching from the NPs (Figure 1). Despite intense research in this field, very little is known about the structure of the specific intermediates that may be involved in the catalytic cycle, more specifically, in the turnover-limiting step, which for aryl bromides and iodides is usually the transmetalation step.$^{41}$ It has been proposed that the oxidative addition step in the catalytic cycle may involve atomic Pd species in solution (Figure 1).$^{42,43}$ Palladium dimers have also been identified and isolated from the reaction mixtures, but these kinetically stable species were considered to be off-cycle
intermediates that enter the catalytic cycle upon cleavage into monomers.\(^{44,45}\) Using other ligandless systems, such as Pd(OAc)\(_2\), very facile transmetallation.\(^{46}\) Importantly, it was found that these intermediates undergo a Miyaura cross-oxidative addition species.\(^{47}\) The catalyst consisted of highly functionalized arylboronic acids and aryl halides.\(^{48}\) The catalyst consisted of evenly distributed Pd NPs, with an average size of 2.6 nm.\(^{49}\) Loadings of palladium as low as 0.01 mol% could be used, under very mild conditions (20 °C) with H\(_2\)O/EtOH mixtures as the solvent, resulting inTONs of up to 10000. In contrast, similar palladium nanoparticles immobilized on other supports require very harsh reaction conditions.\(^{50-52}\) With the aim of understanding the distinctive activity in all these systems, we have now investigated the structure of the Pd species formed in the Suzuki–Miyaura cross-couplings mediated by Pd@MIL-101-NH\(_2\)(Cr) by means of electrospray ionization mass spectrometry (ESI-MS), density functional theory (DFT) calculations, and \(^{19}\)F NMR spectroscopy. In this report, we have identified trimeric and tetrameric palladium oxidative addition species as key intermediates in Suzuki-Miyaura cross-couplings catalyzed by Pd@MOF. Importantly, it was found that these intermediates undergo a very facile transmetallation. These species, which have never been proposed before, have also been identified when using other ligandless systems, such as Pd(OAc)\(_2\): \(^{53,54}\) in absence of strong donor ligands.

We began our study by investigating the coupling reactions of 1-bromo-4-(trifluoromethyl)benzene (1a) or 1-iodo-4-(trifluoromethyl)benzene (1a') with phenylboronic acid (2a). We compared the catalytic performance of Pd@MIL-101-NH\(_2\)(Cr) (2.4 nm average NP size, 7.25 wt% Pd content in the MOF, 3 mol% Pd loading in the catalytic reaction, Figure 2a and Figure S1) with that of the filtrates obtained from these same reactions. The reaction profiles (Figure 2a) show that starting from 1a, a yield of 94% of 3a was obtained after only 60 min with the MOF catalyst, which agrees with our previous results.\(^{60,61}\) Interestingly, the yield was much lower when the iodide substrate 1a' was used (35% yield of 3a after 60 min). The catalytic activity of the filtrates from both reactions was analyzed after 60 min (Figure 2b). After filtration, the filtrate was added to a new load of reagents without additional Pd@MIL-101-NH\(_2\)(Cr) (i.e., 1a or 1a', 2a, and KF) and the mixture was left to react for a further 60 min. For aryl bromide 1a (filtrate A), an accumulated yield of 90% was obtained, which is similar to the yield obtained by using only Pd@MIL-101-NH\(_2\)(Cr) (i.e., 94%, Figure 2a).

Filter A, obtained from a parallel experiment, was analyzed by inductively coupled plasma optical emission spectroscopy (ICP-OES). This revealed the concentration of palladium to be very low, only 0.1 ppm. Therefore, with this low catalyst loading, a TON of ca 5 \(\times\)10\(^4\) can be estimated. The presence of Pd in filtrate A was also confirmed by scanning transmission electron microscopy (STEM), which showed the presence of crystalline Pd NPs of 4.8 nm average size together with Pd clusters (<1 nm); MOF crystals where not observed (Figure 2c and Figure S2). In contrast, the accumulated yield of 3a when using aryl iodide 1a' (18%) indicated that filtrate B was inactive, as the second load of reactants were barely consumed. This result is in contrast with the usual reactivity of aryl iodides vs aryl bromides in cross-coupling reactions; the lower bond-dissociation energy (BDE) of C–I vs. C–Br bonds is a major factor controlling their oxidative addition to Pd(0) (BDE C–I = 67.2, C–Br = 82.6 kcal/mol).\(^{62}\) To further assess the nature of the species in filtrate A, we turned into electrospray ionization mass spectrometry (ESI-MS).\(^{63,64,65}\) Filtrate A obtained after 30 min of \(t_f\) was analyzed by ESI-MS in positive-ion mode, and palladium species were not found (Figure S3). However, a series of substrate-bound palladium adducts were observed in negative-ion mode, specifically in the m/z region between 400 and 1450 (Figure 2d). Adducts 4a–7a were identified as oxidative-addition clusters (Pd = 1–4), with anionic tetramer 4a as the base peak of the spectrum (Figure 2d). The structure of oxidative-addition tetramer 4a was calculated using density functional theory (DFT) at the B3LYP-D3 level (Figure 2d). Related tetramers, lacking the central bromide, have been computationally proposed,\(^{66}\) but not observed experimentally.

These calculations indicated that each palladium(II) center in 4a retains a geometry close to square planar, and that the central bromide is slightly outside of the plane of the four palladium atoms (27°) (Figure 2b). The Gibbs free energy was also calculated to assess the stability of the species, and we found that there is a significant driving force for each step, from monomer to tetramer, at standard state (Figure 3a). Since all intermediates (4a–7a) are negatively charged, and the reactions are run in aqueous media, [ArPdBr\(_2\)(OH\(_2\))]\(^+\) (7a) and three neutral [ArPdBr(OH\(_2\))]\(_2\) species were chosen...
as the references. As Pd–OH₂ bonds will be broken in every step and replaced by Pd–Br bridges, which are essentially half bonds, it appears that the driving force for the formation of the higher oligomers (4a, 5a) cannot be the bonding enthalpy. We therefore split the Gibbs free-energy change into the entropic contribution (–TΔS) and the enthalpic contribution (ΔH). We found that for every step there is an unfavorable enthalpic change, except from trimer 5a to tetramer 4a, which is minimally exothermic. On the other hand, the entropic contribution favors every step significantly due to the

Figure 2. (a) Model Suzuki–Miyaura reaction used in this work (left), and reaction profiles for aryl bromide 1a and aryl iodide 1a’ (right); (b) Filtration experiments with aryl bromide 1a and aryl iodide 1a’. Yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; yields after filtration are expressed as accumulated yield (based on the total amount of ArX added); (c) HAADF-STEM image of Pd NPs and clusters in filtrate A (left) and EDX elemental mapping of Pd overlaid of HAADF image (right). Some Pd clusters are indicated with white arrows; (d) Identified adducts in Filtrate A (reaction time = 30 min), indicating measured mass (monoisotopic), formula, and error. Inset shows obtained (grey) and simulated (black) isotopic patterns for each adduct. On the right, 3D structure of 4a from DFT calculations.
release of bound water molecules. The stability of the complexes therefore arises from entropy (released molecules) rather than from enthalpy (released heat). This may have a significant impact on the reactivity, as described below. The calculations showed that the most stable oxidative-addition adduct was tetramer 4a, and this same adduct was also the one found with the highest relative abundance by ESI-MS.

Analysis by ESI(−)-MS of filtrate B (t = 15 min) from the reaction of iodide 1a’ also indicated the formation of tetrameric (4a’) and trimeric (5a’) iodide adducts, but monomer 7a’ was found to be the major species (Figure 4a). Analysis of filtrate B after 120 min revealed that tetramer 4a’ and trimer 5a’ had been consumed, and a series of palladium iodide salts with formulas [Pd2I4]n− (n = 1 or 2) and [Pd2I3]n− (n = 3 or 5) were detected (Figure S4). These palladium iodide salts have been previously detected and isolated in other studies, and due to their high stability they were considered off-cycle species.44,72,73 Their formation may explain the slower kinetics in the reaction of 1b, as the concentration of active palladium species leading to product is diminished (Figure 2b). This is also in agreement with the findings by Ananikov and coworkers, who determined that in dynamic systems there are factors other than ease of oxidative addition (iodides > bromides) that can affect the efficiency of a process, e.g., the stabilization of Pd(II) and Pd(0) intermediates by halides.74 Although aryl iodides undergo a faster oxidative addition than aryl bromides, iodide anions exert a greater stabilization on Pd(II) than bromide anions, thereby “trapping” these palladium species as kinetically stable salts.

Figure 4b shows the kinetic profile of the reaction (i.e., yield of 3a over time) catalyzed by Pd@MIL-101-NH₂(Cr) and by Pd(OAc)₂ (3 mol% of Pd in both instances). The relative intensity of tetramer 4a over time is also presented for these two catalytic systems (see also Figure S5 for a representation including trimer 5a). Importantly, the similarity of the plots indicates that the catalytically active species produced from Pd@MIL-101-NH₂(Cr) are essentially the same as those formed from Pd(OAc)₂. Tetramer 4a builds up quickly at the start of the reaction, reaching a maximum concentration at t = 30 min when the yield of 3a is already close to 80%. After this time, the concentration of these oxidative-addition Pd species quickly diminishes as the concentration of bromide 1a depletes, and the yield of 3a reaches 94% (t = 55 min). From this point, the yield of 3a remains essentially constant, and the oxidative-addition intermediates reach a steady state. The fact that the yield of 3a does not progress further to >99%, and that the relative intensity of 4a remains constant, indicates a lack of boronic acid available to use in the transmetalation step. To test this hypothesis, additional boronic acid 2a (1 equiv.) and potassium fluoride (2 equiv.) were added to the reaction mixture at t = 125 min, and the reaction was monitored until t = 135 min. We observed then that oxidative-addition intermediate 4a was fully consumed, and at the same time the yield of 3a increased to >99%. Although this indicates that the oxidative-addition tetrabromides are consumed upon reaction with boronic acid 2a, at this point we could not distinguish whether a direct transmetalation from 4a occurs or, alternatively, a breakdown into an oxidative-addition monomer is promoted upon reaction with the boronic acid. We therefore turned to density functional theory (DFT) calculations to try to understand the reactivity of 4a and 7a.

![Figure 3](image-url)

**Figure 3.** (a) Oligomerization of oxidative-addition intermediates and Gibbs free-energy change for the equilibrium species involved in the formation of tetramer 4a. Optimized structures for monomeric and dimeric oxidative-addition intermediates found by MS (note that for both monomer and dimer, H₂O has been considered for coordinatively saturated Pd centers). Ar = C₆H₄CF₃.
hydroxy(phenyl)borate (vide infra).

The computational study of the transmetalation step started by studying the reaction of tetramer 4a with fluorodiarylborate 8a (Figure 6). Fluoroborates are formed under the reaction conditions when fluoride salts are used as the base.75 In the initial step of the transmetalation, borate 8a enters from below the plane of the four palladium atoms and coordinates to one of the four Pd centers, forming a Pd–O bond, with concomitant breaking of Pd–Br bond to the central bromide. Since this central bromide in 4a was coordinated to three additional Pd centers, the bond-breaking step is very easy, and has a low activation free energy of 7.9 kcal/mol, and a reaction free energy of −1.0 kcal/mol (Int1). Next, a π-phenyl interaction replaces the second Pd–Br bond, through another very easy process with an activation free energy of only 1.9 kcal/mol, and a reaction free energy of −2.0 kcal/mol (Int2). Now the tetramer is set for the actual transmetalation step, where the Pd–C σ bond is formed (Int3). The barrier is very low, only 10.0 kcal/mol relative to the reacting intermediate. The very low trans influence of the bridging bromide is probably facilitating the formation of the Pd–C bond, and the reaction is very exergonic, leading to a tetramer with one of the Pd(II) species bearing two aryl groups. In this same step, BF(OH)$_2$ spontaneously decodes from Pd, and is replaced by a Pd–Br bond. Overall, all the steps involved in the transmetalation process were found to be very easy. This might be because no strong bonds in the palladium cluster need to be broken. As the Pd–Br interaction decreases at the reacting palladium center, the remaining Pd–Br interactions are strengthened at the spectator Pd sites, leading to very low activation energies. As tetramer 4a has an unfavorable enthalpy of formation (Figure 3b), it is very susceptible to react, but it still forms in substantial amounts due to the entropic increase in its formation. The fact that it is possible for this tetramer to form relies on the coordination features of halides, and the absence of other stronger donor ligands (vide infra). Phosphines and carbenes interact strongly with palladium, and thus minimize its aggregation. However, the formation of reactive palladium intermediates from complexes bearing these ligands requires ligand-dissociation steps that in some cases can be rate determining.76,77 Reductive elimination of two aryl groups from Pd(II) is usually a straightforward process, and also here we find low activation energies of only 11.6 kcal/mol leading to a Pd(0) species with the product coordinated (Int4).

The oxidative addition of 1-bromo-4-(trifluoromethyl)benzene (1a) to Int4, regenerating tetramer 4a, was then investigated. Replacing the π-coordinated biaryl 3a by aryl bromide 1a was found to be slightly exergonic (6.5 kcal/mol). Oxidative addition then proceeds with a very low activation free energy of 0.5 kcal/mol to regenerate tetramer 4a. The very low oxidative-addition barrier is probably due to the very bare Pd atom, where the only two ligands other than 1a are the bridging bromides. This limited stabilization of the Pd(0) leads to very high reactivity towards the reactant, but could also lead to rapid aggregation and the formation of larger Pd(0) clusters. We also calculated the transmetalation from a monomeric palladium species (7a), which resulted in an activation energy of 25.8 kcal/mol. This result indicates that it is significantly more favorable for tetramer 4a to undergo transmetalation than for monomer 7a (Figure S6).
Oxidative-addition tetramer 4a was also observed by ESI(−)-MS when p-fluorophenylboronic acid (2b) was used. On the other hand, the nature of the aryl bromide 1a significantly influences the formation of tetrameric intermediates 4. Only aryl bromides with electron-withdrawing groups (EWG), such as 1a (R = CF₃), 1b (R = F), 1c (R = SF₃), 1d (R = OCF₃), 1e (R = SCF₃), and 1f (R = SO₂CF₃) led to the formation of tetramers (4a–4f), as observed by ESI(−)-MS (Figures 7 and Figure S7). With non-electron-poor aryl bromides, such as 1g (R = H), 1h (R = Me), and 1i (R = OMe), species 4 were not detected (Figure 7). The stability of tetrameric oxidative-addition intermediates containing electron-donating groups (EDGs) was assessed by DFT calculations. The results showed that the formation of these species is still thermodynamically favored, however they are less stable than those containing EWGs. Replacement of the CF₃ groups on the aryl group with CH₃ led to a change from −22.6 kcal/mol for the formation of the tetramer (as shown in Figure 3) to −15.7 kcal/mol. Note that the free-energy calculation assumes the reference state to be one [PdBr₂Ar(OH₂)]⁺ and three PdBr₂Ar(OH₂)⁻, but the reaction mixture may actually contain more species that affect the equilibria. However, the difference between the aryl groups with EWG or EDG is probably due to the difference in stability of the respective tetramers. This difference in stability may explain why the adducts containing EDGs could not be detected by ESI(−)-MS.

![Figure 6. Free energy profile for the transmetalation and reductive elimination steps from 4a.](image)

![Figure 7. Pd(II) anionic oxidative-addition tetramers from diverse aryl bromides.](image)

We carried out in situ ¹⁹F NMR spectroscopy studies with Pd(OAc)₂ as the catalyst to avoid the use of the insoluble MOF (Figures 8 and Figure S8). We used a Pd loading of 10 mol% in these experiments so that we would be able to detect palladium intermediates. Besides the expected signals for aryl halide 1a (~62.72 ppm) and product 3a (~62.36 ppm), three signals for CF₃-containing species were observed: I (singlet, −61.45 ppm), II (broad singlet, −61.11 ppm), and III (transient broad singlet, −60.41 → −60.94 ppm) (Figure 8a). The transient band III showed a rather constant intensity over time, reaching a steady state at ca. 93 min (Figure S9) when the yield of 3a was 76%. Bands I and II showed significantly higher intensities than band III, both
reaching their maximum intensities at ca. 93 min (\(I/II/III = 0.9/1/0.1\), Figure 8a and Figure S9). The intensity of band I over time is rather similar to that of band II over time (Figure S9). At \(t = 373\) min, further boronic acid 2a (1 equiv.) and base (1 equiv.) were added to the NMR tube. This resulted in a rapid fading of bands I and II, while the chemical shift of band III moved from –60.94 to –60.41 ppm (Figure 8b, black solid arrows). From the ESI(–)–MS analysis (Figure 5), we determined that tetramer 4a was consumed when boronic acid 2a and base were added. As bands I and II also faded away when these reagents were added, this indicates that these bands may correspond to oxidative-addition intermediates. To test this idea, we compared the reaction profile of tetramer 4a as determined in Figure 4b (black squares, cat. = \(\text{Pd(OAc)}_2\)) with the combined intensities of bands I and II over time, obtained from the \(^{19}\text{F}\) NMR experiments, also using \(\text{Pd(OAc)}_2\). As the conditions were different in these two experiments (i.e., reaction flask vs NMR tube, stirring rate, and catalyst loading), we have plotted the normalized intensities of 4a (ESI) and that of bands I + II (NMR) vs a normalized time-scale (\(t/t_{\text{max}}\)) for each experiment (Figure 8c). The correlation of the intensities along the reaction profile is excellent, and thus we can assign bands I and II as oxidative-addition intermediates. The correlation is also excellent when the intensities of band I and band II are considered separately (Figure S10). Note that the evolution of the yield of 3a in the NMR and ESI experiments correspond very well with each other across the normalized timescale (Figure 8a). The structures of the species responsible for bands I and II cannot be fully elucidated, but probably these bands correspond to tetramer 4a and a related oxidative-addition species. The latter might be a species where a bromide bond has been substituted by a water ligand, which may well occur under the conditions of the NMR experiment. This assignment is also supported by the rapid fading of the two bands after the addition of boronic acid (min 373, Figure 8b). When 1 equiv. of aryl bromide 1a was added (\(t = 418\) min), bands I and II reappeared (Figure 8b, blue arrows), which further reinforces the assignment. Elucidation of the identity of the species responsible for band III is more difficult, as this band is probably due to a number of interconverting palladium species.

This study provides insights into the mechanism of the Suzuki–Miyaura cross-coupling reaction catalyzed by \(\text{Pd(OAc)}_2\) to nanomaterials immobilized into MIL-101-NH\(_2\)(Cr). The excellent activity of this heterogeneous catalyst in the coupling of aryl bromides with boronic acids can be explained by the formation of tetrameric oxidative-addition palladium(II) intermediates. These species were observed by electrospray ionization high-resolution mass spectroscopy in the negative mode in the coupling of electron-poor aryl bromides with boronic acids. The weak bonding in the tetrameric oxidative-addition species allows an easy transmetalation at room temperature (activation energy 10.0 kcal/mol); in contrast, the activation energy for the corresponding reaction with an oxidative-addition monomer was significantly higher (25.8 kcal/mol). Aryl iodides also give rise to tetrameric palladium adducts. However, the formation of stable off-cycle palladium iodide salts, such as \([\text{PdI}_4]_n\), results in much lower catalytic efficiencies than those obtained with aryl bromides.

![Figure 8](image)

Figure 8. (a) Real-time \(^{19}\text{F}\) NMR spectra. Inset shows the signals for catalytic intermediates between –60.6 and –61.6 ppm, using 1,4-difluorobenzene as an internal standard (–120.00 ppm); (b) \(^{19}\text{F}\) NMR addition experiments and monitoring of catalytic intermediates; (c) Correlation between the intensity of 4a (ESI–MS) and the intensity of bands I and II, plotted against reaction progress.

The same tetrameric species have been observed in this work when using \(\text{Pd(OAc)}_2\), which leads us to conclude that \(\text{Pd@MIL-101-NH}_2\)(Cr) behaves as a reservoir of very active ligandless catalytically active species. The advantage of using \(\text{Pd@MIL-101-NH}_2\)(Cr) vs. \(\text{Pd(OAc)}_2\) is that in the former case, the catalyst can be filtered off and reused. When using \(\text{Pd(OAc)}_2\), the catalyst cannot be recycled, resulting in
a significantly higher consumption of palladium. Thus, the synthetic efforts needed to prepare Pd@MOF catalysts can be fully justified. In “cocktail”-type systems, multiple mechanistic pathways are possible, and the electronic properties of the substrates may determine which pathway is favored in any particular case. This work suggests that tetrameric oxidative-addition palladium(II) species can provide a reaction pathway that proceeds via a very facile transmetallation step, usually the rate-limiting step in Suzuki-Miyaura cross-couplings.

ASSOCIATED CONTENT
Supporting Information

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REFERENCES

(1) Miyaura, N.; Suzuki, A. Stereoselective Synthesis of Arylated (E)-Alkenes by the Reaction of Alk-1-Enylboranes with Aryl Halides in the Presence of Palladium Catalyst. J. Chem. Soc. Chem. Commun. 1979, 866.
(2) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. Chem. Rev. 1995, 95, 2457–2483.
(3) Hooshmand, S. E.; Heidari, B.; Sedghi, R.; Varma, R. S. Recent Advances in the Suzuki-Miyaura Cross-Coupling Reaction Using Efficient Catalysts in Eco-Friendly Media. Green Chem. 2019, 21, 381–405.
(4) Beletskaya, I. P.; Alonso, F.; Tyurin, V. The Suzuki-Miyaura Reaction after the Nobel Prize. Coord. Chem. Rev. 2019, 385, 137–173.
(5) Schmidt, A. F.; Kurokchina, A. A.; Larina, E. V. Role of a Base in Suzuki-Miyaura Reaction. Russ. J. Gen. Chem. 2011, 81, 1573–1574.
(6) Carrow, B. P.; Hartwig, J. F. Distinguishing between Pathways for Transmetalation in Suzuki-Miyaura Reactions. J. Am. Chem. Soc. 2011, 133, 2116–2119.
(7) Amatore, C.; Le Duc, G.; Jutand, A. Mechanism of Palladium-Catalyzed Suzuki-Miyaura Reactions: Multiple and Antagonistic Roles of Anionic “Bases” and Their Counterions. Chem. Eur. J. 2013, 19, 10082–10093.
(8) Amatore, C.; Jutand, A.; Leduc, G. The Triple Role of Fluoride Ions in Palladium-Catalyzed Suzuki-Miyaura Reactions: Unprecedented Transmetalation from [ArPdF₂] Complexes. Angew. Chem. Int. Ed. 2012, 51, 1379–1382.
(9) Amatore, C.; Jutand, A.; Le Duc, G. Kinetic Data for the Transmetalation/Reductive Elimination in Palladium-Catalyzed Suzuki-Miyaura Reactions: Unexpected Triple Role of Hydroxide Ions Used as Base. Chem. Eur. J. 2011, 17, 2492–2503.
(10) Amatore, C.; Jutand, A.; Le Duc, G. Mechanistic Origin of Antagonist Effects of Usual Anionic Bases (OH-, CO 3 2−) as Modulated by Their Countercations (Na +, Cs +, K +) in Palladium-Catalyzed Suzuki-Miyaura Reactions. Chem. Eur. J. 2012, 18, 6616–6625.
(11) Thomas, A. A.; Denmark, S. E. Pre-Transmetalation Intermediates in the Suzuki-Miyaura Reaction Revealed: The Missing Link. Science 2016, 352, 329–332.
(12) Olding, A.; Ho, C.; Canty, A.; Lucas, N.; Horne, J.; Bissember, A. C. Synthesis of Arylpalladium(II) Boronates: Confirming the Structure of Pre-transmetalation Intermediates in the Suzuki-Miyaura Reaction Crystallographically. Angew. Chem. Int. Ed. 2021, anie.202104802.
(13) Fu, F.; Xiang, J.; Cheng, H.; Cheng, L.; Chong, H.; Wang, S.; Li, P.; Wei, S.; Zhu, M.; Li, Y. A Robust and Efficient Pd₃ Cluster Catalyst for the Suzuki Reaction and Its Odd Mechanism. ACS Catal. 2017, 7, 1860–1867.
(14) Schoenebeck, F.; Houk, K. N. Ligand-Controlled Regioselectivity in Palladium-Catalyzed Cross Coupling Reactions. J. Am. Chem. Soc. 2010, 132, 2496–2497.
(15) Albéniz, A. C.; Casado, A. L.; Espinet, P. O- and m-(Bromometrafluoroaryl)palladium(II) Complexes: Atropisomerism Studies by 19F NMR and Measurement of through-Space F-F Coupling Constants. Organometallics 1997, 16, 5416–5423.
(16) Liu, C.; Zhang, Y.; Liu, N.; Qiu, J. A Simple and Efficient Approach for the Palladium-Catalyzed Ligand-Free Suzuki Reaction in Water. Green Chem. 2012, 14, 2999–3003.
(17) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. Chem. Rev. 2018, 118, 2249–2295.
(18) Alimardanov, A.; Schneider-Van De Vondervoort, L.; De Vries, A. H. M.; De Vries, J. G. Use of “Homeopathic” Ligand-Free Palladium as Catalyst for Aryl-Aryl Coupling Reactions. Adv. Synth. Catal. 2004, 346, 1812–1817.
(19) Alonso, D. A.; Nájera, C.; Pacheco, M. C. Highly Active Oxime-Derived Palladacycle Complexes for Suzuki-Miyaura and Ullmann-Type Coupling Reactions. J. Org. Chem. 2002, 67, 5588–5594.
(20) Han, W.; Liu, C.; Jin, Z. Aerobic Ligand-Free Suzuki Coupling Reaction of Aryl Chlorides Catalyzed by in Situ Generated Palladium Nanoparticles at Room Temperature. Adv. Synth. Catal. 2008, 350, 501–508.
(21) Boruah, P. R.; Ali, A. A.; Saikia, B.; Sarma, D. A Novel Green Protocol for Ligand Free Suzuki-Miyaura Cross-Coupling Reactions in WEB at Room Temperature. Green Chem. 2015, 17, 1442–1445.
(22) Xu, L.; Liu, F. Y.; Zhang, Q.; Chang, W. J.; Liu, Z. L.; Lv, Y.; Yu, H. Z.; Xu, J.; Dai, J. J.; Xu, H. J. The Amine-Catalysed Suzuki–Miyaura-Type Coupling of Aryl Halides and Arylboronic Acids. Nat. Catal. 2021, 4, 71–78.
(23) Avanthay, M.; Bedford, R.; Begg, C.; Böse, D.; Clayden, J.; Davis, S.; Eloi, J.C.; Goryunov, G.P.; Hartung, I.V.; Heeley, J.; KhaiKaın, K.A.; Kiching, M.; Krieger, J.; Kulyabin, P.S.; Lennox, A.; Nolla-Salliel, R.; Pridmore, N.E.; Rosewell, B.J.S.; Sparkes, H. J. Amine-Catalysed Suzuki-Miyaura-Type Coupling? The Identification and Isolation of the Palladium Culprits. ChemRiv 2021.
(24) Novák, Z.; Adamík, R.; Csenki, J. T.; Béke, F.; Gavaldík, R. Curse or Blessing? Influence of Impurities on Cross-Coupling — Guideline for Elucidating Catalysts. ChemRiv 2021, 1–17.
(25) Diálo, A. K.; Onelás, C.; Salomón, L. I.; Aranzales, J. R.; Astruc, D. “Homeopathic” Catalytic Activity and Atom-Leaching Mechanism in Miyaura-Suzuki Reactions under Ambient Conditions with Precise dendrimer-Stabilized Pd Nanoparticles. Angew. Chem. Int. Ed. 2007, 46, 8644–8648.
(26) Yang, Q.; Xu, Q.; Jiang, H. L. Metal-Organic Frameworks Meet Metal Nanoparticles: Synergistic Effect for Enhanced Catalysis. Chem. Soc. Rev. 2017, 46, 4774–4808.
(27) Van Velthoven, N.; Waitschat, S.; Chavan, S. M.; Liu, P.; Smolders, S.; Vercammen, J.; Bueken, B.; Bals, S.; Lillerud, K. P.; Stock, N.; De Vos, D. E. Single-Site Metal-Organic Framework Catalysts for the Oxidative Coupling of Arenes: Via
Mechanisms.

Wu, B.; Hou, K.; Wang, D.; Li, X.; Yang, Q.; Yao, F.; Zhong, Y.; Chen, F.; Shu, X.; Li, H.; Zhou, X.; Palladium Nanoparticles Confined in the Cages of MIL-101: An Efficient Catalyst for the One-Pot Indole Synthesis in Water. ACS Catal. 2011, 1, 1604–1612.

Catal. 2015, 245, 122–128.

Water-Soluble Pd@MIL-101 Nanoparticles as Recyclable Cross-Coupling Catalysts for Suzuki Coupling Reaction. Catal. Today 2012, 142, 313–318.

Sahu, D.; Sen, R.; Maity, T.; Koner, S. Anchoring of Palladium onto Surface of Porous Metal-Organic Framework through Post-Synthesis Modification and Studies on Suzuki and Stille Coupling Reactions under heterogeneous conditions. Langmuir 2013, 29, 3140–3151.

Huang, Y.; Zhang, J.; Liu, T.; Li, J.; Lin, Z.; Li, H.; Cao, R. Palladium Nanoparticles Supported on Amino Functionalized Metal-Organic Frameworks as Highly Active Catalysts for the Suzuki-Miyaura Cross-Coupling Reaction. Catal. Commun. 2011, 14, 27–31.

Yuan, B.; Pan, Y.; Li, Y.; Yin, B.; Jiang, H. A Highly Active Palladium Catalyst for the Suzuki-Miyaura and Ullmann Coupling Reactions of Aryl Chlorides in Aqueous Media. Angew. Chem. Int. Ed. 2010, 49, 4054–4058.

Pascuau, V.; Hansen, P.; Bermejo Gómez, A.; Ayats, C.; Platero-Prats, A. E.; Johansson, M. J.; Pericás, M.; Martin-Matute, B. Highly Functionalized Biaryl via Suzuki-Miyaura Cross-Coupling Catalyzed by Pd@MOF under Batch and Continuous Flow Regimes. ChemSusChem 2015, 8, 123–130.

Pascuau, V.; Yao, Q.; Bermejo Gómez, A.; Gustafsson, M.; Yun, Y.; Wan, W.; Samain, L.; Zou, X.; Martin-Matute, B. Sustainable Catalysis: Rational Pd Loading on MIL-101Cr-NH2 for More Efficient and Recyclable Suzuki-Miyaura Reactions. Chem. Eur. J. 2013, 19, 17483–17493.

Verho, O.; Nagendiran, A.; Johnston, E. V. T.; Tai, C. W.; Bäckvall, J. E. Nanopalladium on Amino-Functionalized Mesocellular Framework: An Efficient Catalyst for Suzuki Coupling Reactions and Surface Hydrogenation. ChemCatChem 2013, 5, 612–618.

Tao, B.; Hu, X.; Qu, H.; Li, B.; Jiang, R.; Xiong, Y. Anchoring Positively Charged Pd Single Atoms in Ordered Porous Ceria to Boost Catalytic Activity and Stability in Suzuki Coupling Reactions. Small 2020, 16, 1–11.

Li, Y.; Xu, L.; Xu, B.; Mao, Z.; Xu, H.; Zhong, Y.; Zhang, L.; Wang, B.; Sui, X. Cellulose Sponge Supported Palladium Nanoparticles as Recyclable Cross-Coupling Catalysts. ACS Appl. Mater. Interfaces 2017, 9, 17155–17162.

Luo, S.; Zeng, Z.; Zeng, G.; Liu, Z.; Xiao, R.; Chen, M.; Tang, L.; Tang, W.; Lai, C.; Cheng, M.; Shao, B.; Liang, Q.; Wang, H.; Jiang, D. Metal Organic Frameworks as Robust Host of Palladium Nanoparticles in Heterogeneous Catalysis: Synthesis, Application, and Prospect. ACS Appl. Mater. Interfaces 2019, 11, 32579–32598.

Song, K.; Liu, P.; Wang, J.; Tan, B.; Li, H. Highly Active Palladium Nanoparticles Immobilized on Knitting Microporous Organic Polymers as Efficient Catalysts for Suzuki-Miyaura Cross-Coupling Reaction: Controlled Release and Capture of Palladium. ACS Appl. Mater. Interfaces 2020, 12, 11419–11427.

Song, K.; Liu, P.; Wang, J.; Tan, B.; Li, H. Highly Active Palladium Nanoparticles Immobilized on Knitting Microporous Organic Polymers as Efficient Catalysts for Suzuki-Miyaura Cross-Coupling Reaction. Chem. Eur. J. 2015, 21, 10896–10902.

Galli, C.; Pau, T. The Dehalogenation Reaction of Organic Halides by Tributylphosphane: The Energy of Activation vs. the BDE of the C-X Bond. Tetrahedron 1999, 55, 2893–2904.

Belyakov, P. A.; Kad entsév, V. I.; Chizhov, A. O.; Kolotyrkina, N. G.; Shashkov, A. S.; Ananikov, V. P. Mechanistic Insight into Organic and Catalytic Reactions by Joint Studies Using Mass
Spectrometry and NMR Spectroscopy. *Mendelev Commun.* 2010, 20, 125–131.

(65) Vikse, K. L.; McIndoe, J. S. Mechanistic Insights from Mass Spectrometry: Examination of the Elementary Steps of Catalytic Reactions in the Gas Phase. *Pure Appl. Chem.* 2015, 87, 361–377.

(66) Enquist, P. A.; Nilsson, P.; Sjöberg, P.; Larhed, M. ESI-MS Detection of Proposed Reaction Intermediates in the Air-Promoted and Ligand-Modulated Oxidative Heck Reaction. *J. Org. Chem.* 2006, 71, 8779–8786.

(67) Qian, R.; Liao, Y. X.; Guo, Y. L.; Guo, H. ESI-FTICR-MS Studies on Gas Phase Fragmentation Reactions of ArPd(PPh3)2I Complexes. *J. Am. Soc. Mass Spectrom.* 2006, 17, 1582–1589.

(68) Limberger, J.; Leal, B. C.; Monteiro, A. L.; Dupont, J. Charge-Tagged Ligands: Useful Tools for Immobilising Complexes and Detecting Reaction Species during Catalysis. *Chem. Sci.* 2015, 6, 77–94.

(69) Vikse, K. L.; Henderson, M. A.; Oliver, A. G.; McIndoe, J. S. Direct Observation of Key Intermediates by Negative-Ion Electrospray Ionisation Mass Spectrometry in Palladium-Catalysed Cross-Coupling. *Chem. Commun.* 2010, 46, 7412–7414.

(70) Yunker, L. P. E.; Ahmadi, Z.; Logan, J. R.; Wu, W.; Li, T.; Martindale, A.; Oliver, A. G.; McIndoe, J. S. Real-Time Mass Spectrometric Investigations into the Mechanism of the Suzuki-Miyaura Reaction. *Organometallics* 2018, 37, 4297–4308.

(71) Kolter, M.; Koszinowski, K. Second Comes First: Switching Elementary Steps in Palladium-Catalysed Cross-Coupling Reactions. *Chem. Eur. J.* 2020, 26, 12212–12218.

(72) De Vries, J. G. A Unifying Mechanism for All High-Temperature Heck Reactions. the Role of Palladium Colloids and Anionic Species. *Dalt. Trans.* 2006, No. 3, 421–429.

(73) Kashin, A. N.; Ganina, O. G.; Cheprakov, A. V.; Beletskaya, I. P. The Direct Non-Perturbing Leaching Test in the Phosphine-Free Suzuki-Miyaura Reaction Catalyzed by Palladium Nanoparticles. *ChemCatChem* 2015, 7, 2113–2121.

(74) Galushko, A. S.; Prima, D. O.; Burykina, J. V.; Ananikov, V. P. Comparative Study of Aryl Halides in Pd-Mediated Reactions: Key Factors beyond the Oxidative Addition Step. *Inorg. Chem. Front.* 2021, 8, 620–635.

(75) Lennox, A. J. J.; Lloyd-Jones, G. C. Selection of Boron Reagents for Suzuki-Miyaura Coupling. *Chem. Soc. Rev.* 2014, 43, 412–443.

(76) McMullin, C. L.; Fey, N.; Harvey, J. N. Computed Ligand Effects on the Oxidative Addition of Phenyl Halides to Phosphine Supported Palladium(0) Catalysts. *Dalt. Trans.* 2014, 43, 13545–13556.

(77) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. Effect of Ligand Steric Properties and Halide Identity on the Mechanism for Oxidative Addition of Haloarenes to Trialkylphosphine Pd(0) Complexes. *J. Am. Chem. Soc.* 2009, 131, 8141–8154.

(78) Howe, P. W. A. Recent Developments in the Use of Fluorine NMR in Synthesis and Characterisation. *Prog. Nucl. Magn. Reson. Spectrosc.* 2020, 118–119, 1–9.

(79) Zientek, N.; Laurain, C.; Meyer, K.; Kraume, M.; Guthausen, G.; Maiwald, M. Simultaneous 19F-1H Medium Resolution NMR Spectroscopy for Online Reaction Monitoring. *J. Magn. Reson.* 2014, 249, 53–62.
Supplementary Information

Tetrameric Aryl Palladium Bromide Intermediates Leading to Facile Transmetalation in Suzuki–Miyaura Cross-Couplings with Pd@MIL-101-NH₂

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1. **General information**

Reagents and solvents were used as obtained from commercial suppliers. ICP-OES analysis was carried out by MEDAC Ltd (UK).

**General Procedure for the Suzuki–Miyaura Reaction.**
Pd@MIL-101-NH₂(Cr) (7.25 wt%; 4.4 mg, 0.009 mmol, 3 mol%), arylboronic acid (0.13 mmol, 1.4 equiv.), and KF (12 mg, 0.18 mmol, 2 equiv.) were added to a 4 mL glass vial. Then EtOH (50% aq. added together with the aryl halide (0.1 mmol), and the mixture was stirred (900 rpm) at room temperature. For kinetic profiles, the reactions were quenched at the desired times by the addition of HCl (1 M aq.; 300 µL).

**General Procedure for Filtration Tests.**
Filtration tests were carried out by filtering the whole reaction mixture (prepared as described in the general procedure above) at \( t_1 = 60 \text{ min} \) using a filter (0.22 µm pore size). The filtrate was added to a new glass vial containing a second load of boronic acid, base, and aryl halide (no MOF was added). The mixture was stirred for a further 60 min \( (t_2) \), and the reaction was quenched as described above. The product yield was determined by \(^1\)H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard, and the total amount of aryl halide added (0.2 mmol) as the limiting reagent.

**ESI Mass Spectrometry**
High-resolution mass spectra (HRMS) were recorded with a Bruker micrOTOF ESI-TOF mass spectrometer. Sample solutions were transferred into the ESI source with gastight syringes at flow rates of 180
µL/min, which was maintained by a syringe pump. The ESI source was operated with a voltage of +4000 V (HV end plate offset: −500 V) using N₂ as nebulizer (0.3 bar) and drying gas (4 L/min, temperature: 453 K). The experiments were typically carried out in negative mode ESI(−)-MS, with a scan range of m/z = 200–2000. Accuracies of <10 ppm were obtained for the measured m/z ratios after external calibration using a low concentration tuning mix solution (mixture of CF₃COOH and phosphazenes in H₂O/CH₃CN, Agilent Technologies). Theoretical exact m/z ratios and isotope patterns were calculated with the DataAnalysis software package (Bruker Daltonics).

**Computational details**

All computations were performed with the Jaguar program package by Schrödinger LLC. All geometries were optimized using the dispersion corrected B3LYP-D3 functional with the LACVP** core potential and basis set, which applies the 6-31G** basis set to all light elements. Solvation free energies were calculated using the PBF solvation model for all palladium species with standard parameters for water solvation. Solvation free energies for all organic compounds were calculated using the SM8 model with the B3LYP-D3 functional and 6-31+G* basis set, which generates CM4 charges. The solvation free energy for water was -2.05 kcal mol⁻¹ corresponding to the hydration free energy. Harmonic vibrational frequencies were calculated to assure that intermediates contained no imaginary frequencies and that transition states contained only one. Gibbs free energies for each species were calculated as the sum G = E(B3LYP-D3/LACV3P**++) + G_{solv} + ZPE + ΔH_{298} –TS, where a single point energy correction was made for each species with the larger LACV3P** basis set and core potential, and thermochemical parameters (ZPE = zero point vibrational energy, ΔH_{298} = contribution from excited vibrations at T = 298K and the pressure volume term pV, –TS = entropy at T = 298K). All solvation free energies were calculated at standard state at T = 298K.

**General Procedure for the NMR Spectroscopy Experiments**

ⁱ⁹F NMR spectra were recorded with a Bruker Avance III HD 500 MHz spectrometer equipped with a helium-cooled probe. ⁱ⁹F chemical shifts (δ) are reported in ppm using 1,4-difluorobenzene (−120.00 ppm) as an internal standard. 32 scans per spectrum were collected at a scan rate of 1 second/scan. Typically, aryl halide (0.1 mmol), NBu₄F·(H₂O)₃ (62 mg, 0.2 mmol, 2 equiv.) and the internal standard (0.1 mmol) were dissolved in the THF-d₈/D₂O mixture (10:1, v/v) in a 2 mL glass vial. The homogeneous solution was transferred into another vial containing the Pd(OAc)₂ precatalyst (2 mg, 0.01 mmol) and the boronic acid (0.14 mmol, 1.4 equiv.). As the reaction starts at room temperature, to avoid the loss in information between sample preparation and the start of the measurements, the mixture was immediately transferred into an NMR tube and cooled at −78 ºC until it was frozen. After this, the tube was placed into the NMR spectrometer, and the acquisitions were started while the sample slowly returned to 25 ºC and the reaction proceeded.

**Transmission Electron Microscopy**

Scanning Transmission Electron Microscopy (STEM) and energy dispersive x-ray spectroscopy study were performed on a Thermo Fischer aberration-corrected Themis Z microscope equipped with SuperX EDX system. The instrument was operated at 300 kV with a probe corrector (CEOS DCOR) corrected up to the fifth order. The electron probe with a convergence angle of 21.4 mrad and current of 100 pA was used. Bright-field (BF) and High-angle annular dark-field (HAADF) images and EDX spectra were acquired using Velox software (Thermo Fischer). MOF samples were placed on Cu TEM grids with holey carbon supporting films as dry powder. Reaction samples were dispersed on the TEM grids in the reaction solvent. Nanoparticle size analysis was carried out using ImageJ software. The reported values correspond to the average value of ca. 100 samples.
2. Supplementary figures

Figure S1. BF- and HAADF-STEM micrographs of Pd@MIL-101-NH$_2$
Figure S2. STEM micrographs of filtrate A: HAADF- (a – d, f); BF- (e) and EDX elemental mapping showing Pd (g).
Figure S3. ESI(+) mass spectrum of the Suzuki reaction after 15 minutes.
Figure S4. ESI(−)-MS of the Suzuki reaction with 1a' after 120 min

Figure S5. Relative abundance vs. time for tetramer 4a and trimer 5a using Pd@MOF (left) and Pd(OAc)₂ (right).
Figure S6. Free-energy profile for the transmetallation and reductive elimination steps from monomer 7a.
Figure S7. Detection of tetramers 4b-4f. In grey experimental patterns, simulated in black.
**Figure S8.** ESI(−)-MS spectrum of the Suzuki reaction using Pd(OAc)$_2$.

**Figure S9.** Intensity vs. time for bands I, II and III
Figure S10. Correlation of the relative abundance of 4a with bands I (left) and II (right).

3. References

(1) Bochevarov, A. D.; Harder, E.; Hughes, T. F.; Greenwood, J. R.; Braden, D. A.; Philipp, D. M.; Rinaldo, D.; Halls, M. D.; Zhang, J.; Friesner, R. A. *Int. J. Quantum Chem.* 2013, 113, 2110–2142.

(2) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* 2010, 132.

(3) Becke, A. D. *J. Chem. Phys.* 1993, 98, 5648–5652.

(4) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* 1988, 37, 785–789.

(5) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* 1985, 82, 299–310.

(6) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* 1996, 100, 11775–11788.

(7) Marenich, A. V.; Olson, R. M.; Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* 2007, 3, 2011–2033.