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Real-Time Mass Spectrometric Investigations into the Mechanism of the Suzuki−Miyaura Reaction

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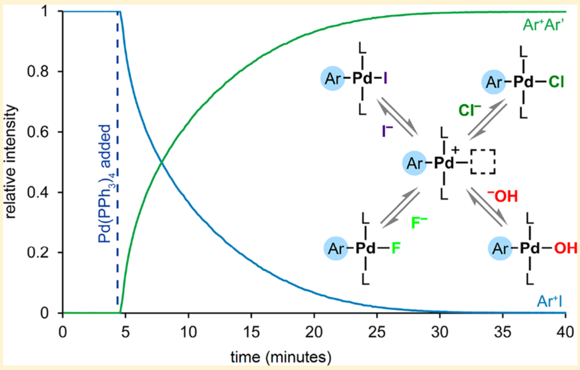
Supporting Information

ABSTRACT: Real-time monitoring of the Suzuki−Miyaura reaction using mass spectrometry during sequential addition of the various reaction components suggests that a dynamic series of equilibria exist in these solutions. Depending on conditions, the boronic acid can be dehydrated, deprotonated, hydroxylated (or alkoxylated), or fluorinated. Palladium−phosphine species present include Pd(0) (to which the aryl iodide rapidly oxidatively adds), the Pd(II) aryl iodide complex, a cationic Pd(II) species formed by dissociation of the iodide ligand, and the Pd(II) bisaryl complex that ultimately extrudes the product through reductive elimination. No fluorinated or hydr(alk-)oxylated palladium complexes were observed under catalytic conditions. Several transmetalation combinations were excluded as reactive partners, but several possibilities remain, and more than one mechanism is likely to be operative, even under similar conditions.



INTRODUCTION

The Suzuki−Miyaura (SM) reaction is the most commonly used cross-coupling protocol in organic chemistry.[1] It has been performed countless times under the influence of catalysts that are extraordinarily active, including an array of challenging substrates such as aryl chlorides and sterically encumbered boronic acids.[2−7] The mechanism is thought to proceed via three main steps: oxidative addition of the aryl halide to a Pd(0) species, transmetalation of the other coupling partner from boron to palladium, and reductive elimination of the two coupling partners from palladium while forming a new C−C bond.[8,9] The number of phosphines coordinating the palladium species undergoing oxidative addition varies according to ancillary ligand and electrophile,[10−12] but the step that generates most debate is transmetalation. There have been a variety of mechanisms mooted for this part of the Suzuki−Miyaura reaction, and many have been whittled away by a plethora of studies to leave two popular mechanisms. One involves a ligand exchange of X^- for HO^-, and the reaction of $L_2Pd(aryl)(OH)$ with the neutral boronic acid (Scheme 1A),[13−17] and the other involves the reaction between a boronate $[RB(OR)_3]^-$ and $L_2Pd(aryl)X$ (Scheme 1B).[18−22] These two possibilities are summarized nicely by Buchwald,[23] as well as Lennox and Lloyd-Jones,[20] and the weight of evidence seems to point toward involvement of an intermediate species of the type $L_nPd(aryl)(OH)$. However, recent work by Lima and co-workers has suggested that in typical Suzuki−Miyaura reaction conditions, the major mechanism proceeds through the reaction of boronate $[RB(OR)_3]^-$ and $L_2Pd(aryl)X$, but they also note that the mechanism is likely highly dependent on reaction conditions, and both or either mechanism may be active depending on the conditions.[21] Denmark and co-workers have employed low temperature nuclear magnetic resonance (NMR) to determine the structures of pretransmetalation intermediates bearing Pd−O−B−aryl linkages.[24,25] They note that the formation of this pretransmetalation species does not require formation of $L_nPd(aryl)(OH)$, and instead the intermediate may be approached by more than one mechanism (Scheme 1, both A and B). The Carrow group has recently found evidence for a palladium cation-mediated transmetalation pathway ($[LPd(aryl)]^+$ where L is PAd_3); Scheme 1D),[26] and the Braun group found evidence implying a fluoride-mediated cationic transmetalation pathway.[27]

For the most part, characterization of the $L_nPd(aryl)(OH)$ monomer species has relied on ^{31}P NMR and cyclic voltammetry,[14−17,28] and only the L = Cy_3P or $i\text{-}Pr_3P$ monomer species have been isolated.[13,16,19,20,29−32] The related bridged dimeric species, $L_2Pd_2(aryl)_2(\mu\text{-}OH)_2$, has been well-characterized by solid-state NMR and X-ray crystallography for a range of L = phosphine.[33] Electrospray ionization mass spectrometry (ESI-MS) studies have previously observed the presence of cationic $[L_2Pd(aryl)]^+$, but

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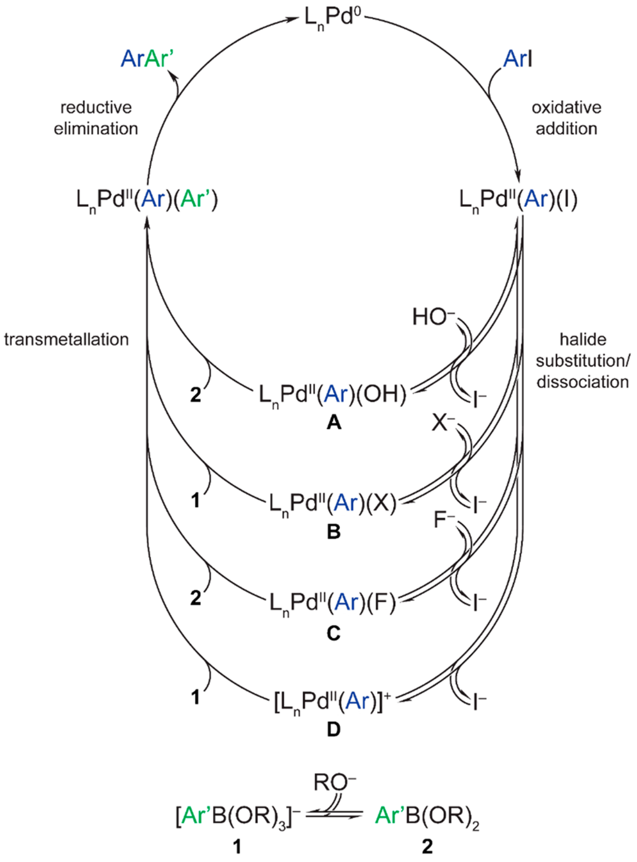
Scheme 1. Various Mechanisms for the Transmetalation Step of Suzuki Cross-Coupling of Aryl Iodides[a]



[a] Ar, Ar′ = aromatic groups, L = PPh_3, X = halide.

did not find L_nPd(aryl)(OH) species.[34−37] One of these studies suggested that the transmetalation was between cationic [LPd(aryl)]$^+$ and $RB(OR)_2$,[34] and the other suggested that the observed [L_2Pd(aryl)]$^+$ was generated via dissociation of an anionic ligand from the L_2Pd(aryl)(X) species.[35] Computational approaches have also been extensively employed to probe the various possibilities, and where mechanistic pathways were compared, these studies found that the most feasible path is the reaction between L_2Pd(aryl)(X) and the anionic $[ArB(OH)_3]^-$.[2,11,18,38]

We set out to study the Suzuki−Miyaura reaction using pressurized sample infusion electrospray ionization mass spectrometry (PSI-ESI-MS),[39] with the aim of gathering evidence for one (or more) transmetalation mechanisms. PSI is a simple method of transferring reacting solution continuously from the reaction flask directly into a mass spectrometer, akin to a cannula transfer. PSI-ESI-MS allows the straightforward measurement of the abundances of reactants, products, byproducts, intermediates, resting states, and decomposition products in a catalytic reaction, with the caveat that only the ionic species are observable by this technique.[40] Cooks has used a slightly different setup to examine a variety of catalytic reactions; however, no catalyst-containing species were observed.[41] We alter the substrate (natively neutral) by the use of charged tags,[42−47] and in this instance the aryl group was appended with a phosphonium tag in the *para* position, $[\text{-}C_6H_4{-}CH_2{-}PPh_3]^+[PF_6]^-$, denoted "Ar$^+$". The phosphonium group conveys a positive charge to all species incorporating it, and in the case of the Suzuki−Miyaura reaction, it may be included on either the boronic acid or the aryl halide (also, charged spectator ligands can be used to interrogate the catalyst directly).[46,48] In this study, we focused on the aryl iodide (Ar$^+$I), as it highlights post oxidative addition intermediate species (as oxidative addition is not turnover-limiting for aryl iodides), where the $Ar^+B(OH)_2$ only shows post-transmetalation species (additionally complicated by the zwitterionic aryl-boronate that forms in the presence of base; see Supporting Information). The phosphonium tag is sufficiently bulky and surface-active that it dominates the ESI mass spectrum to such an extent that the total ion current remains approximately constant throughout the reaction (providing good mass balance throughout), and the inclusion of a noncoordinating anion ensures aggregate ions do not complicate the spectra and that ion pairing does not diminish intensity. Additionally, the phosphonium no longer bears the lone pair of electrons necessary for involvement as an L-type ligand, avoiding the complication of mixed-ligand systems. We have previously employed this charge tag to study the Sonogashira reaction and found that PSI-ESI-MS reaction progress traces agree well with ultraviolet/visible spectroscopy and NMR data, indicating that the relative intensity of species bearing this moiety can represent the overall progress of reaction.[49]

■ RESULTS AND DISCUSSION

Experiments with a Positively Charged Aryl Iodide. As a first step in order to verify that the charge tag does not significantly affect the overall chemistry, a laboratory scale Suzuki reaction was conducted that yielded the expected coupled biaryl product (Figure 1). The reaction can also be studied using the uncharged version (to enable the detection of charged species that appear without the involvement of a charged tag) and in the negative ion mode (to detect any possible anionic catalyst species or boronate species).

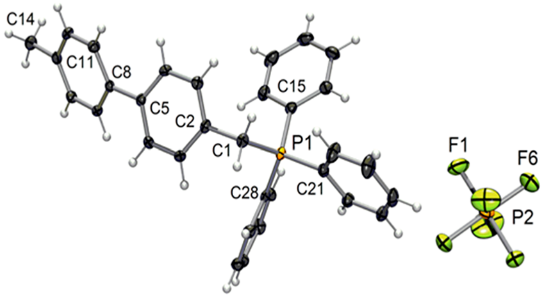


Figure 1. X-ray crystal structure of $[4,4'\text{-}MeC_6H_4C_6H_4CH_2PPh_3][PF_6]$. The new C−C bond is between C5 and C8. The angle between the benzyl and tolyl rings is 26.76(8)°, and the bond angles and lengths were similarly ordinary.

Perhaps the most informative perspective our approach (real-time analysis with mass spectrometry of a catalytic reaction using a charged tag) can provide is through direct observation of the intermediates, noting how their abundance changes over the course of the reaction, and their dynamic response to the addition of various reaction components. This information is generally difficult to obtain with other techniques, at least in a way that provides unambiguous identification of potential intermediates. Our initial results were promising: we found conditions in which the reaction proceeded quickly, under which our charged tag was stable, and where ESI-MS response factors between product and starting material were very similar (demonstrable by the consistency of the total ion current over the course of reaction). We could observe the charge-tagged aryl iodide starting material ($Ar^{+}I$), the coupled biaryl product ($Ar^{+}Ar'$), and a possible palladium-bearing intermediate (Figure 2). If the abundances of these species were tracked over time, we observed the expected pseudo-first-order kinetics of $Ar^{+}I$ and $Ar^{+}Ar'$ (Figure 3A), as well as the behavior of observed palladium intermediates (Figure 3B), and the traces showed good reproducibility across replicates (see Supporting Information). The *pseudo*-first-order behavior of the traces is demonstrated in Figure 3A, inset, where the natural logarithm of $Ar^{+}I$ intensity is linear with time to 5 half-lives (∼97% consumption), indicating that the intensity is a good representation of the relative amount of $Ar^{+}I$ in solution, thus allowing for reliable kinetic analysis. The stable ion current during these experiments is diagnostic of the homogeneity of the solution (phase separation or insolubility manifests as irregularities in the spray, and the traces become very noisy).

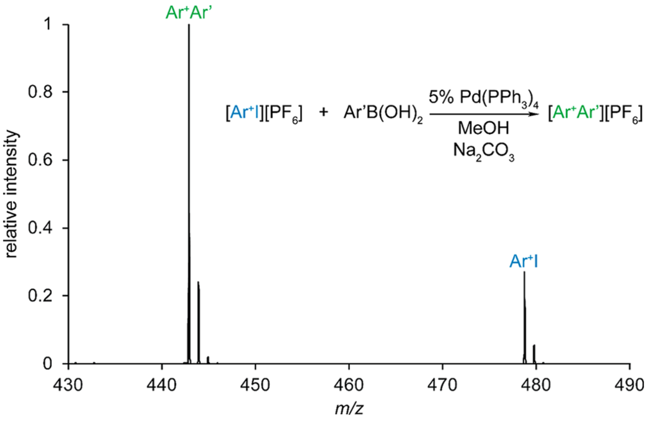


Figure 2. Summed ESI(+) mass spectrum of a Suzuki reaction run in methanol (40 °C). $Ar^{+}I = [IC_6H_4CH_2PPh_3]^{+}$, $Ar' = p\text{-}CH_3C_6H_4B(OH)_2$. $[Ar^{+}I][PF_6]$ 0.6 mM, $ArB(OH)_2$ 1.2 equiv, Cs_2CO_3 17 equiv in 10 mL of MeOH.

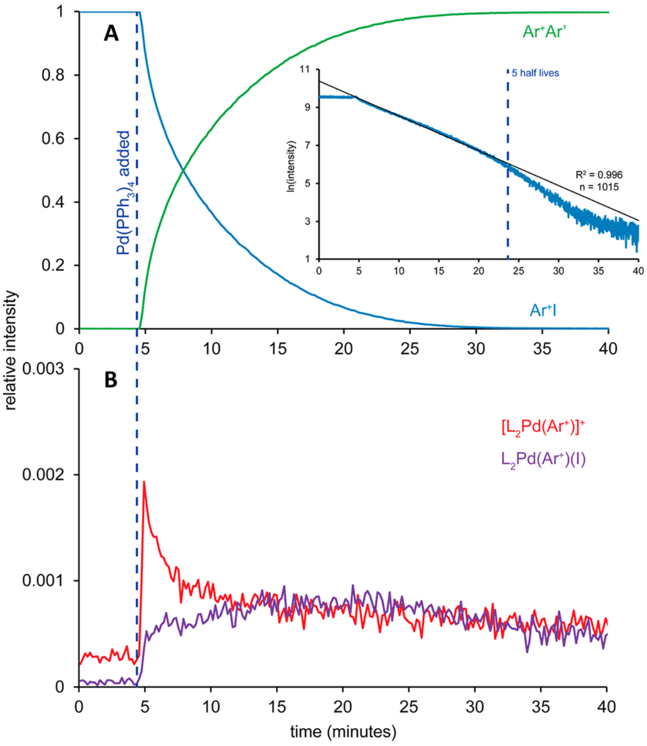
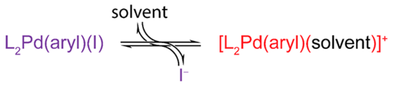


Figure 3. Relative species intensity over time for reactant and product (A) and palladium intermediates (B) using the same conditions as Figure 2. Inset: natural log of the intensity of $Ar^{+}I$ over time showing well-behaved pseudo-first-order kinetics out to 5 half-lives.

In methanol, the two intermediates visible to ESI-MS are $[L_2Pd(Ar^{+})I]$ and $[L_2Pd(Ar^{+})]^{+}$ (where $L = PPh_3$). The bis-cationic $[L_2Pd(Ar^{+})]^{+}$ is likely the product of halide dissociation (eq 1):



$[L_2Pd(Ar^{+})]^{+}$ exists in solution as the solvent stabilized adduct (see Supporting Information); it is doubly charged as it both bears the phosphonium-tagged aryl moiety and is an ML_2X species with a palladium(II) center and so is inherently cationic even without the charged tag. $[L_2Pd(aryl)]^{+}$ species have been detected before by ESI-MS, but in those cases, it was thought they appeared because halide loss was the most facile mechanism by which a charged complex could be produced for detection by ESI-MS.[35,50] In the absence of a charged tag, ionization can occur through a variety of different mechanisms including association with a cation or oxidation,[51] but the inherent efficiency of a permanent charge tends to render these processes relatively unimportant. In this case, $[L_2Pd(Ar^{+})]^{+}$ forms *despite* the fact that the electrospray ionization process would *disfavor* its appearance (separation of an anion from a dication is energetically prohibitive in the gas phase), confirming that it is indeed formed in solution. Both $[L_2Pd(Ar^{+})I]$ and $[L_2Pd(Ar^{+})]^{+}$ are pretransmetalation species, indicating that transmetalation is turnover-limiting under these conditions. Once the cation is formed, any X-type ligand available in solution may coordinate to the palladium, with the equilibria between these X-type ligands being governed by the nucleophilicity of the ligand as well as the donor ability of the solvent. We frequently observe low levels of $[L_2Pd(Ar^{+})(Cl)]$ in our reaction solutions due to the ubiquity of chloride ions and the sensitivity of the ESI-MS technique.

Under our conditions, the reaction is first order in boronic acid with constant base concentration (see Supporting Information) and is known to be first order in catalyst.[15] The reaction is complete within a few minutes in refluxing methanol, but takes hours at room temperature. The reaction was monitored at 30, 40, 50, and 65 °C, and the entropy and enthalpy of activation for the overall reaction were determined from an Eyring plot as $\Delta S^{\ddagger} = 20 \pm 20\ \text{J·mol}^{-1}$ and $\Delta H^{\ddagger} = 104 \pm 6\ \text{kJ·mol}^{-1}$, respectively (Figure 4). The variable effect of temperature on reaction rate in this plot clearly demonstrates that the reaction is taking place in solution as opposed to being an artifact of the ESI-MS process.[52,53]

A variety of boronic acids (*para*-substituted $-H$, $-CH_3$, -Cl, $-CN$, $-COOCH_3$, $-OCH_3$, and $-CF_3$) were subjected to our reaction conditions to probe the relative substituent effects. The resulting Hammett plot (Figure 5) gave $\rho = -2.1$, a trend that indicated that electron-donating groups on the boronic acid resulted in rate enhancement, which is in agreement with

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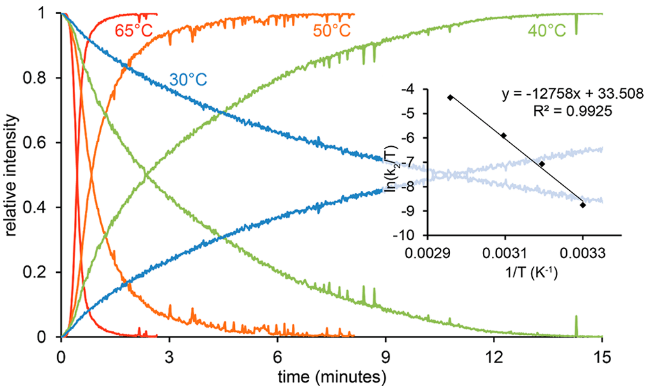

Figure 4. Relative species intensity over time of several Suzuki reactions monitored at 30, 40, 50, and 65 °C in methanol with $Ar^{+}I$ (0.5 mM), solid Na_2CO_3 (10 equiv), *p*-tolylboronic acid (1.2 equiv), and 5 mol % $Pd(PPh_3)_4$. Reactions are first-order. Inset: Eyring plot constructed from the consumption rates of $Ar^{+}I$.

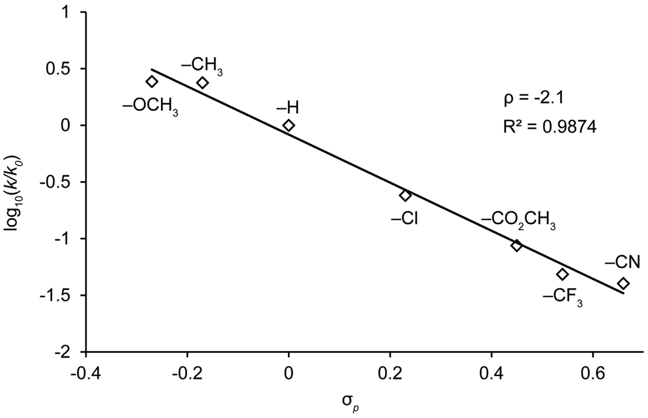

Figure 5. A Hammett plot showing the effect of the para-substituent[57] of the boronic acid on the rate of reaction. The trend indicates that electron-donating *para*-substituents enhance the reaction rate under our conditions. $Ar^{+}I$ 0.32 mM, $ArB(OH)_2$ 1.1 equiv, Cs_2CO_3 20 equiv, 8 mol % Pd for all reactions.

previous findings in other studies in methanol and dimethylformamide[21,54,55] but is in contrast with another study on aryl boronic acids, which found a small positive correlation in 1,4-dioxane.[56]

These kinetic experiments illustrate that PSI-ESI-MS can be used to obtain the expected kinetic behavior of the Suzuki—Miyaura reaction, but does not provide insight into the transmetalation mechanism. If consumption of $[L_2Pd(Ar^{+})I]$ was turnover-limiting, what was it reacting with? Based on the currently accepted mechanism, we assumed that halide dissociation and methoxide coordination was occurring to form $[L_2Pd(Ar^{+})(OMe)]$, which is rapidly consumed by boronic acid to form $[L_2Pd(Ar^{+})(Ar')]$. As such, we needed to conduct experiments in a nonprotic solvent, so we could examine directly the effect of adding methoxide. We repeated our reactions in dry acetonitrile, which is an excellent solvent for ESI-MS and one in which the coupling reactions proceeded readily (Figure 6).[34,55,58] Interestingly, $[L_2Pd(Ar^{+})]^{+}$ was the most prominent palladium species in the spectrum, with $[L_2Pd(Ar^{+})I]$ lost in the noise. Clearly, acetonitrile is a better donor for the stabilization of I^{-} displacement from palladium than methanol.

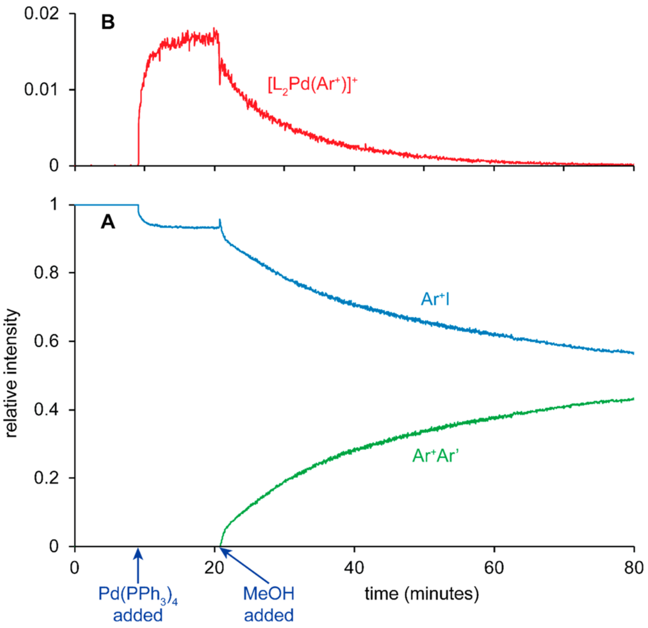

Figure 6. Relative species intensity over time for (A) abundant species and (B) palladium intermediate in a sequential addition of $Pd(PPh_3)_4$ (5 mol %, at 9 min) and MeOH (excess, at 22 min) to a MeCN solution of Ar + I (0.15 mM), p-tolylboronic acid (1.1 equiv), and solid Na_2CO_3 (10 equiv) monitored by PSI-ESI(+)-MS.

Even with all reaction components present in MeCN *except* for a protic solvent (aryl halide, boronic acid, Na_2CO_3 base, $Pd(PPh_3)_4$ catalyst), *no* reaction occurred. $[L_2Pd(Ar^{+})I]$ and $[L_2Pd(Ar^{+})]^{+}$ both formed, but they did not react to form any product *until* an aliquot of methanol was added (Figure 6). The logical roles of the MeOH could be formation of $[L_2Pd(Ar^{+})(OMe)]$, formation of the boronate $[Ar'B(OR)_3]^{-}$ (R = H or Me), or as a phase transfer catalyst for boronic acid or boronate. The latter can be can be excluded because both boronic acid and boronate are soluble in MeCN to concentrations much higher than those employed. This experiment would seem to exclude mechanisms involving direct transmetalation between $[L_2Pd(Ar)I]$ and $Ar'B(OH)_2$, and between $[L_2Pd(Ar)]^{+}$ and $Ar'B(OH)_2$, because under these conditions, all these components are present and they do *not* result in catalytic turnover.

Experiments in the Negative Ion Mode. We decided to examine the speciation in the negative ion mode, to see if the changes were consistent with what was happening in the positive ion mode. An experiment was set up where an MeCN solution containing $Ar'B(OH)_2$ ($Ar' = p\text{-}C_6H_4OMe$) and Na_2CO_3 was examined, while adding first MeOH, then $Ar^{+}I$, then the $Pd(PPh_3)_4$ catalyst (the order of addition was modified to observe the changes in boron speciation). The speciation changes were rapid (Figure 7).

The boronic acid does not appear in these traces because it is neutral, but weak signals were observed for boroxine species $[(BOAr')_n + OH]^{-}$ (n = 3 or 4).[59] These however disappeared instantly upon addition of methanol, to be replaced by the $[Ar'B(OMe)_3]^{-}$ boronate species, which achieved a stable intensity within 10 min. Addition of aryl halide ($Ar^{+}I$) did not affect the equilibrium significantly (all boronate species remained unchanged, though the signal was partially suppressed by the addition of $[PF_6]^{-}$). However, addition of catalyst caused a precipitous drop in aryl boronate concen-

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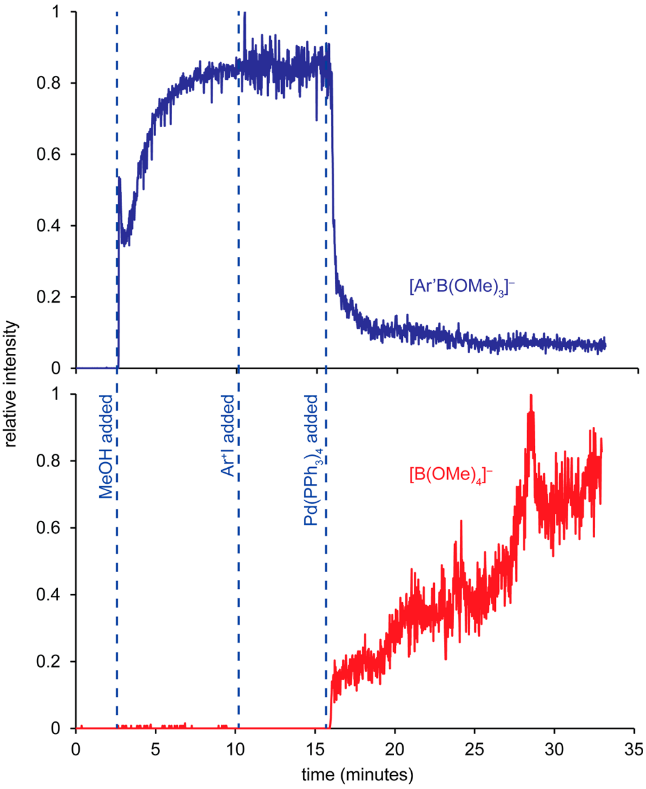


Figure 7. Relative species intensity over time in a sequential addition of MeOH (excess, at 3 min), Ar$^+$I (1 equiv., at 11 min), and Pd(PPh$_3$)$_4$ (5 mol %, at 16 min) to a MeCN solution of MeOC$_6$H$_4$B(OH)$_2$ (0.7 mM) and solid Na$_2$CO$_3$ (14 equiv). Traces are shown for all abundant anions except PF$_6$ (the counterion for Ar$^+$I which is not involved in the reaction). Due to changes in the spray conditions with each addition, each species is normalized to its maximal intensity value.

tration down to a low steady-state concentration, and [B(OMe)$_4$]$^-$ byproduct was steadily generated (significant changes in the ESI spray are likely to blame for the exaggerated drop in arylboronate intensity).

The prominence of the boronate species in the spectrum, and especially their appearance only after methanol was added, led us to consider the possibility that perhaps it was the boronate that was the coupling partner rather than the boronic acid. This observation is consistent with a mechanism involving L$_2$Pd(aryl)X and [(aryl)B(OR)$_3$]$^-$. A 1994 paper by Smith et al. pointed out that the transmetalation reactivities of aryl bromide and iodotoluene are about the same, so they assumed from this that a dissociative transmetalation involving [L$_2$Pd(Ar)]$^+$ and [ArB(OH)$_3$]$^-$ was unlikely.[58] However, it is not completely clear to us why this should be the case; the iodide ligand may be less strongly bound to palladium, but the degree of solvation of the bromide anion is likely to be higher, and exactly how these effects compare to each other deserves further investigation.

Experiments with Premade Boronates. Given that aryl boronates have been previously shown to undergo Suzuki–Miyaura couplings in the absence of added base or nucleophile,[60] an experiment was devised to determine the extent of the participation of boronates. Miyaura introduced caged triesterboronates as effective coupling partners that do not require added base,[8] and we were interested to see if these reacted directly with either [L$_2$Pd(Ar$^+$)I] or [L$_2$Pd(Ar$^+$)]$^+$ in acetonitrile. With no source of protic solvent present (water or methanol), we could determine whether boronates are important transmetalation partners. We prepared a Miyaura caged triesterboronate and characterized it fully as the tetraethylammonium salt (Figure 8).[61]

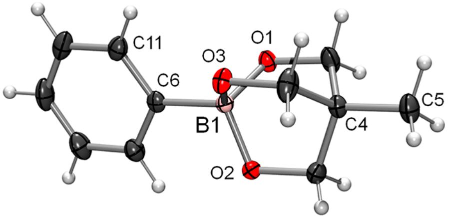


Figure 8. X-ray crystal structure of [NEt$_4$][PhB(O$_3$C$_5$H$_9$)]. The tetraethylammonium cation and solvent of crystallization have been excluded for clarity. The compound was characterized crystallographically as the dihydrate, but all samples used in the MS studies were dried until no water was observable in the ^{1}H NMR spectrum (see Supporting Information). Key bond lengths and angles: B1–C6 1.6142(16) Å; B1–O$_{\text{average}}$ 1.494 Å; C6–B1–O$_{\text{average}}$ 110.5°; B1–O–C$_{\text{average}}$ 111.2°.

The triesterboronate was soluble and stable in acetonitrile solutions, and ^{11}B studies indicated that a single boronate species exists in aprotic solvents on the NMR time scale (see Supporting Information). In the presence of stoichiometric amounts of water or methanol, only trace amounts of hydrolysis (or methanolysis) products were observed, and a large excess of water or methanol resulted in more extensive reaction (see Supporting Information). However, without additional water or methanol, no other boronate species are observed, and the intensity remains constant.

The charged aryl iodide (Ar$^+$I) and catalyst precursor were combined in acetonitrile in the absence of base, and as before, the [L$_2$Pd(Ar$^+$)]$^+$ and [L$_2$Pd(Ar$^+$)(I)] complexes appear with good intensity (indicating that the base does not significantly affect the oxidative addition reaction). A solution of the triesterboronate was injected to instant effect: the intensity of both intermediates plummeted into the baseline, and product was rapidly formed (Figure 9). An identical reaction tracked in the negative ion mode showed *pseudo*-first-order disappearance of the caged boronate (see Supporting Information).

In this case, the possibility of an [L$_2$Pd(Ar$^+$)(OR)] intermediate forming is greatly reduced, as no ROH (R = H or Me) is present, but it is possible that one of the alkoxy arms of the triesterboronate dissociates from the boron and coordinates to palladium. ESI-MS cannot distinguish to which atoms each oxygen is bonded, but the dissociation of oxygen from boron should be suppressed by the chelate effect. Despite this transformation being disfavored, L$_2$Pd(aryl)(OR) has been shown to rapidly transmetalate, so this is still a possible reaction pathway.[16] Given that we did not observe any of these L$_2$Pd(aryl)(OR) species in any of our reactions, we entertained the possibility that there could be a direct reaction between [L$_2$Pd(Ar$^+$)(I)] and [Ar'B(OR)$_3$]$^-$ or between [L$_2$Pd(Ar$^+$)]$^+$ and [Ar'B(OR)$_3$]$^-$. While the data show that [L$_2$Pd(Ar$^+$)]$^+$ disappears very rapidly upon addition of triesterboronate, it is possible that this process could simply be a fast recoordination of I$^-$ driven by consumption of [L$_2$Pd(Ar$^+$)(I)].[62] We could eliminate this possibility by adding AgNO$_3$ to efficiently remove any free iodide from solution,[14] and when this reaction is carried out, the reaction

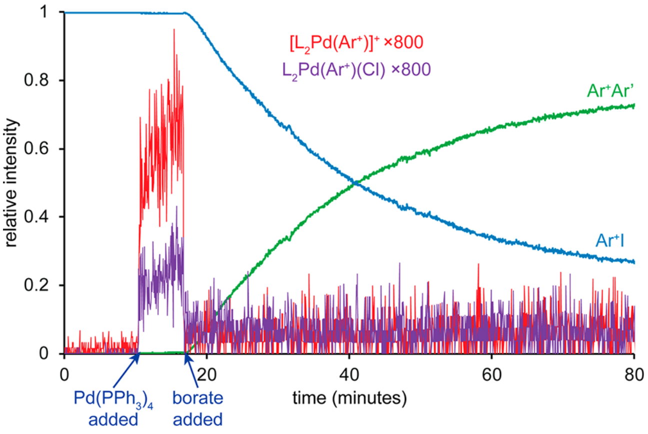


Figure 9. Relative species intensity over time in a sequential addition of $Pd(PPh_3)_4$ (5 mol % at 10 min) and $[NEt_4][PhB(O_3C_5H_9)]$ (1 equiv at 18 min) to an acetonitrile solution of Ar^+I (2.6 mM) monitored by PSI-ESI(+)-MS. Intermediate intensity is multiplied by a factor of 800.

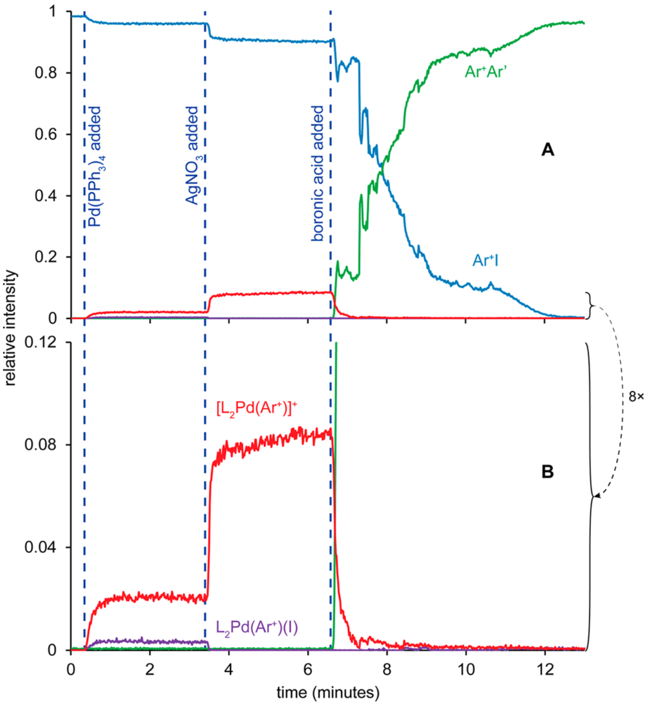
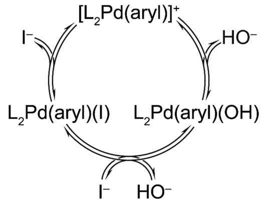


Figure 10. Relative species intensity over time for (A) reactant and product, and (B) palladium intermediates in a sequential addition reaction of $Pd(PPh_3)_4$ (8 mol % at 1 min), $AgNO_3$ (1.5 equiv at 4 min), and *p*-tolylboronic acid (1.1 equiv at 7 min) to a methanol solution of Ar^+I (0.5 mM) and solid Na_2CO_3 (9 equiv) monitored by PSI-ESI(+)-MS. Spray instability was observed after the addition of $AgNO_3$, which is likely due to clogging of the PEEK tubing by AgI particles.

still proceeds rapidly despite the complete absence of any detectable $L_2Pd(Ar)(I)$ (Figure 10). Note the disappearance of $[L_2Pd(Ar^+)I]$ and the boost in abundance of $[L_2Pd(Ar^+)]^+$ upon addition of $AgNO_3$. Subsequent introduction of $ArB(OH)_2$ resulted in the $[L_2Pd(Ar^+)]^+$ disappearing in favor of product $Ar^+{-}Ar'$. This observation is curious, as this does not appear to agree with either of the popular transmetalation mechanisms (Scheme 1A,B). A similar reaction using the caged boronate was performed, but upon boronate addition, precipitate immediately formed in the reaction flask, and no coupled product was observed (presumably the silver formed an insoluble salt with the boronate).

Locating the Hydroxyl-Palladium Species. We were particularly concerned that we had never observed the $L_2Pd(aryl)(OR)$ intermediate (or its respective dimer) in any of our reaction solutions, where so many other studies had assigned electrochemical or ^{31}P signals to this species. Accordingly, we set up an experiment that optimized conditions for its formation, namely, charge-tagged aryl iodide Ar^+I, $Pd(PPh_3)_4$, Na_2CO_3 base, and methanol. No source of boronic acid or boronate was added. Under these conditions, we expect the formation of the dimer species $L_2Pd_2(Ar^+)_2(\mu\text{-}OR)_2$, as it is should be preferably formed (with R = Me or H, L = PPh_3).[17] We collected data for 15 min, accumulating 1019 scans under conditions where the signal-to-noise ratio for $[L_2Pd(Ar^+)I]$ was ~7500 to 1. Under such conditions, we could detect no $[L_2Pd(Ar^+)(OMe)]$, $[L_2Pd(Ar^+)(OH)]$, or the dimers $[L_2Pd_2(Ar^+)_2(\mu\text{-}OR)_2]$ (R = H or Me), suggesting that if any of these species do form, the equilibrium between $[L_2Pd(Ar^+)I]$ and $[L_2Pd(Ar^+)(OR)]$ (or between $[L_2Pd(Ar^+)]^+$ and $[L_2Pd(Ar^+)(OR)]$) lies a long way to the former (Scheme 2; see Supporting Information).

Scheme 2. Equilibria between $L_2Pd(aryl)(I)$ and $L_2Pd(aryl)(OH)$[a]



[a]The $L_2Pd(aryl)(X)$ (X = I or OH) have the potential to dimerize to the form $[L_2Pd_2(aryl)_2(\mu\text{-}X)_2]$.

We reasoned that perhaps Na_2CO_3 was too weak a base to generate the hydroxyl-palladium species in detectable amounts, so we adjusted our conditions to resemble the conditions used by others for preparation of $L_2Pd(aryl)(OH)$. This species can be isolated if a dichloromethane solution of $L_2Pd(aryl)I$ is treated with sodium hydroxide,[17] so we tried those conditions with our charge-tagged aryl iodide, and $[L_2Pd(Ar^+)(OH)]$ appeared with excellent intensity. The MS/MS spectrum (Figure 11) of this species is entirely consistent with the assignment, first losing a PPh_3 ligand, then another, after which a species corresponding to $[Ar^+OH]$ was seen in addition to $[PPh_4]^+$. The fact that we can observe this species given the correct conditions (noncoordinating solvent and strong base) suggests that the observed $[L_2Pd(Ar^+)]^+$ is a separate species from $[L_2Pd(Ar^+)(OH)]$ and is not an artifact of the ESI process. It is important to note that $[L_2Pd(Ar^+)]^+$ is not part of the CID fragmentation pathway of $[L_2Pd(Ar^+)(OH)]$, adding weight to the assertion that the dication is a distinct species.

Under similarly forcing conditions, that is, excess sodium methoxide in CH_2Cl_2, $[L_2Pd(Ar^+)(OMe)]$ and the dimer species $[L_2Pd_2(Ar^+)_2(\mu\text{-}OMe)_2]$ could be readily observed (see Supporting Information). Sequential reactions with the boronic acid were attempted in CH_2Cl_2, but addition of the boronic acid to the strongly basic solution generated a large

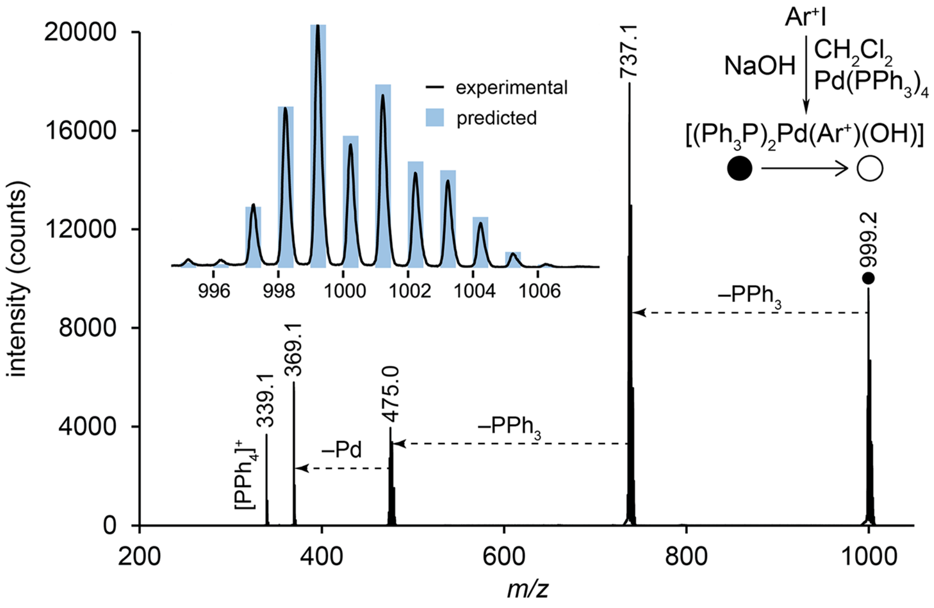


Figure 11. ESI(+)-MS/MS of $(PPh_3)_2Pd(Ar^+)(OH)$ at *m/z* 999.2 generated from a mixture of $Pd(PPh_3)_4$, Ar^+I (1 equiv relative to $Pd(PPh_3)_4$), and NaOH (excess) in dichloromethane. Inset: the predicted isotope pattern (bars) overlaid on the experimental mass spectrum (line) of $(PPh_3)_2Pd(Ar^+)(OH)$.

amount of precipitate (presumably insoluble boronates), and no product formed.

We found it difficult to reconcile our results with the popular mechanisms. We could not detect any amounts of $[L_2Pd(Ar^+)(OR)]$ in any reaction that resulted in product formation, which does not agree with the hydroxyl-palladium mechanism. However, it is of course possible that even though the equilibrium resulting in $L_2Pd(aryl)(OR)$ lies a long way toward $[L_2Pd(Ar)]^+$ (as evidenced by abundance below the detection limit of ESI-MS), the brief formation of this species and direct reaction with the arylboronic acid is a viable transmetalation process. At this stage, it seemed our results gave evidence for transmetalation through $L_2Pd(aryl)X$, except that transmetalation with arylboronate is preceded by halide dissociation. Some transmetalation mechanisms have been tested computationally, and the reaction of $[ArB(OH)_3]^-$ with $L_2Pd(Ar)X$ (Scheme 1B) should be favored over the reaction of $ArB(OH)_2$ with $L_2Pd(Ar)(OH)$ (Scheme 1A).[11,18,38,63] To our knowledge, no one has tried to calculate the $[L_2Pd(Ar)]^+$ and $[ArB(OH)_3]^-$ pathway (Scheme 1D).

Experiments without a Charged Tag. We are conscious of criticism of the fact that we invoke charged intermediates (because we use a technique that can only detect ions), but in this case, a cationic intermediate is observed *despite* the positively charged tag. We can make some predictions about what we ought to see when examining the reaction with reactants that are *not* charge-tagged if a cation is involved. For the untagged system, we would expect to see only $[L_nPd(Ar)]^+$ in the positive ion mode, and perhaps only if the transmetalation is a relatively slow step. In the negative ion mode, we would expect to see boronate replaced by iodide as the reaction proceeds. Both of these predictions play out (Figures 12 and 13). The only Pd-containing intermediate observed in the positive ion mode is $[L_2Pd(Ar)]^+$, and it disappears quickly upon addition of the boronic acid. In the negative ion mode, a small steady amount of iodide immediately appears upon addition of the catalyst to the phenyl iodide. Addition of the boronic acid results in the appearance of boronate species in the mass spectrum, which slowly goes away to be replaced by iodide (which appears with much lower intensity than the boronate species due to its much lower surface activity). Aggregate species are also noted in both ion modes and provide evidence that the reaction taking is place, even in the absence of a deliberately added charged tag.

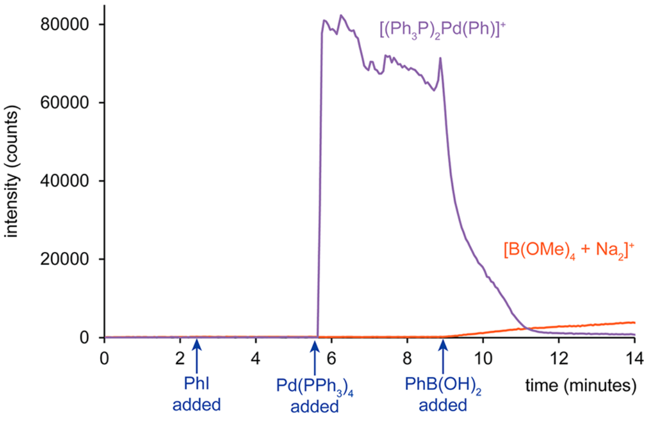


Figure 12. Species intensity over time in a sequential addition of iodobenzene (1.8 mM, 2.2 min), $Pd(PPh_3)_4$ (5 mol % at 5.6 min), and phenylboronic acid (1.4 equiv at 8.7 min) to methanol and solid Na_2CO_3 (5 equiv). Reaction was monitored by ESI(+)-MS and was plotted as raw counts due to changes in spray behavior of the species with each addition.

If we charge-tag the boron species with a positively charged tag, we would expect this to be in equilibrium with the zwitterionic charge-tagged boronate, but the product biaryl compound will experience no such complication. The only possible Pd-containing intermediates should be $[L_nPd(Ar)]^+$ and $[L_nPd(Ar)(Ar'^+)]$ (the latter charged now via Ar′ rather than Ar). Again, the speciation and reactivity is consistent with these predictions (see Supporting Information).

Reactivity of Cationic Palladium Complexes. Cationic palladium complexes are known and can be readily prepared in a form close to $[L_2Pd(Ar)]^+$ by stabilizing the complex with a

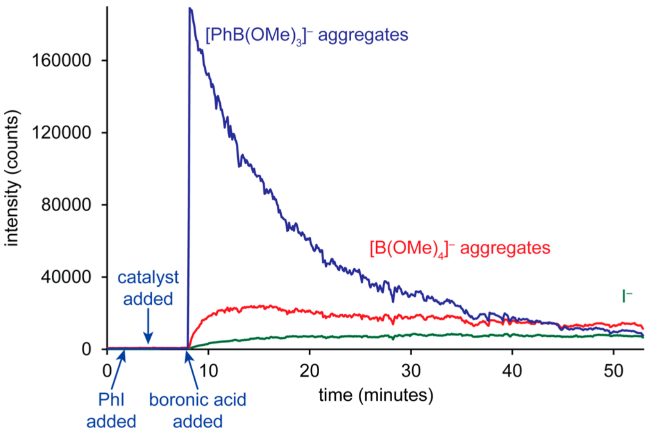


Figure 13. Species intensity over time for the sequential addition of iodobenzene (1.8 mM at 2.7 min), $Pd(PPh_3)_4$ (5 mol % at 4.8 min), and phenylboronic acid (1 equiv at 7.8 min) to methanol and solid Na_2CO_3. Reaction was monitored by ESI(−)-MS and was plotted as raw counts due to changes in spray behavior of the species with each addition. The large difference in intensity of $[PhB(OMe)_3]^-$ (starting material) and $[B(OMe)_4]^-$ (products) is due to the starting material being much more surface active.

weakly bound donor ligand.[64] Accordingly, an untagged palladium cation complex was independently synthesized and isolated as the 4-methylpyridine adduct (Figure 14).

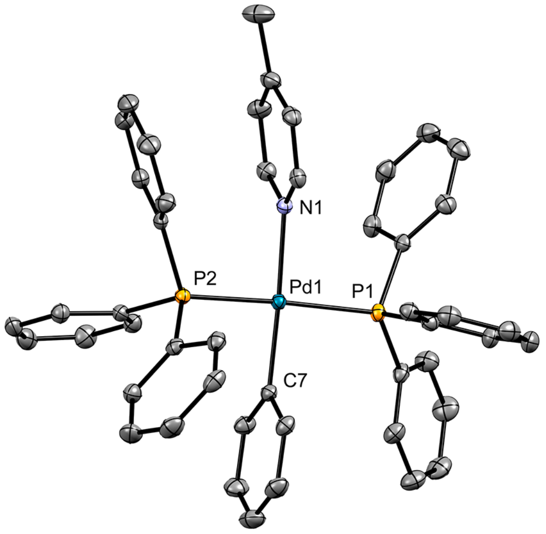


Figure 14. X-ray crystal structure of $[(Ph_3P)_2Pd(Ph)(C_6H_7N)]$-[OTf]. The triflate anion, solvent of crystallization (CH_2Cl_2), and hydrogens have been excluded for clarity. Key bond lengths and angles: Pd1−C7 2.0196(19) Å, Pd1−N1 2.1244(16) Å, C7−Pd1−N1 176.46(7)°, N1−Pd1−P2 89.85(4)°, N1−Pd1−P1 92.81(4)°, C7−Pd1P2 86.77(6)°, C7−Pd1−P1 90.45(6)°.

If the cationic mechanism were operative, we would expect that combining it with the caged boronate would result in transmetalation. However, when this reaction was performed in dry acetonitrile, *no* consumption of the $[L_nPd(Ar)(4\text{-methylpyridine})]^+$ was observed, instead requiring an aliquot of methanol to facilitate reaction (Figure 15). The lack of reactivity may be due to the difficulty of displacing pyridine, but the ease of displacing this ligand in the ESI process suggests it is much more labile than PPh_3.

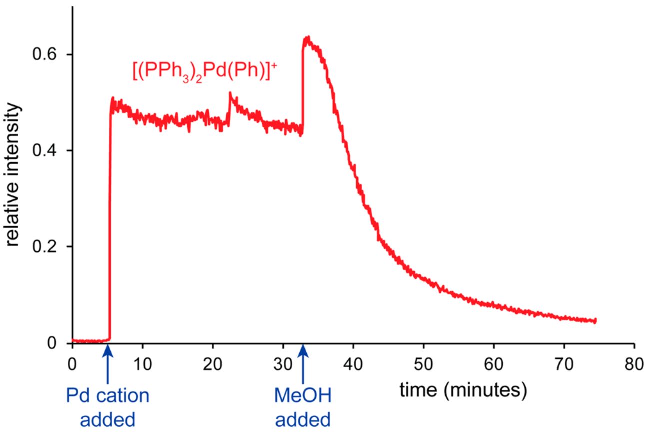


Figure 15. Relative species intensity in a sequential addition reaction of $[(Ph_3P)_2Pd(Ph)][OTf]$ (0.8 equiv at 5 min) and methanol (excess at 33 min) to a solution of $[NEt_4][PhB(O_3C_5H_9)]$ (0.5 mM) in dry acetonitrile monitored by PSI-ESI(+)-MS. The apparent jump in intensity upon addition of methanol arises from changes in spray conditions rather than through a change in abundance.

The Role of Water and Fluoride. Since the boronate is clearly not interacting directly with the palladium cation, the question then arose as to why we observed reactivity in Figure 9 (triesterboronate plus Ar$^+$I in acetonitrile, no added base). The reaction in Figure 9 was repeated, each time showing similar traces, and through adjustment of a variety of conditions, we found that the reactivity was likely due to catalytic concentrations of water present in the acetonitrile (see Supporting Information). This result indicates that the caged arylboronate must first be hydrolyzed prior to reaction, and does not directly react with the palladium cation, or that trace water is responsible for the formation of very reactive $[L_2Pd(Ar^+)(OH)]$. Additionally, the binding strength of triflate anion used for isolation may have inhibited the dissociation to a sufficient extent as to prevent reaction (a phenomenon noted in the recent work of the Carrow group).[26]

Instead, we turned our attention to the recent work from the Denmark group, who had observed Pd−O−B−aryl structures using low temperature NMR (Figure 16).[24,25] The proposed structure of this species effectively contained two subunits: the palladium cation $[L_2Pd(aryl)]^+$ and a deprotonated arylboronic acid $[O(HO)B(aryl)]^-$. We had observed in other work an arylboron species of mass corresponding to that of the deprotonated boronic acid, and considered that perhaps these two could exist separately in solution and interact to form the pretransmetalation intermediate.

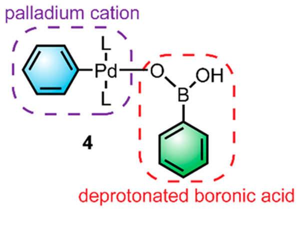


Figure 16. Intermediate structure determined by Denmark and co-workers.[24,25]

When the isolated palladium cation and arylboronic acid were dissolved in the presence of added base (NEt_3), no reaction was observed, again requiring the addition of methanol for reaction to occur (see Supporting Information). The negative ion mode indicated that the intended deprotonated arylboronic acid was not formed, and instead the base promoted the formation of arylboroxine species, which appear to be unreactive in Suzuki–Miyaura reactions (Figures 6 and 7). The arylboron speciation was studied in a titration experiment, and it was found that the arylboroxine species hydrolyze quickly and are mostly converted to other species by the addition of an excess of water (see Supporting Information). Several other bases were tested (K_2CO_3, Cs_2CO_3, DBU), but none resulted in the observation of the deprotonated arylboronic acid. We turned to the work of Amatore and Jutand, who found that the presence of fluoride ions could facilitate the reaction between $L_2Pd(aryl)(I)$ and $PhB(OH)_2$ in DMF and asserted that transmetalation occurred between $L_2Pd(aryl)(F)$ and the boronic acid (Scheme 1C).[32,65] We reasoned that this could also be facilitated by fluoride deprotonating boronic acid (as the pK_a of strong acids is increased significantly in nonaqueous conditions).[66] In that work, the authors used $[NBu_4][F]$ as a fluoride source, so we prepared a reaction to promote formation of the posited $L_2Pd(aryl)(F)$ using our charged aryl halide. Despite increasing the catalyst loading to 25 mol %, no trace of $[L_2Pd(Ar^+)(F)]$ was observed (see Supporting Information). It appears that fluoride is insufficiently nucleophilic to coordinate to palladium under these conditions, but perhaps in more weakly coordinating solvents (such as DMF), this coordination could occur. Despite the lack of observation of the putative intermediate, when arylboronic acid was added to the reaction solution, slow product formation was observed (Figure 17).

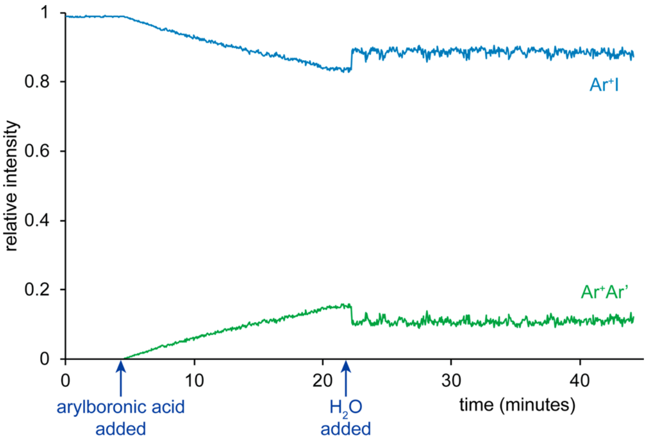


Figure 17. Relative species intensity over time in a sequential addition of *p*-tolylboronic acid (1 equiv, 4 min) and water (excess, 22 min) to a solution of $[Ar^+I][PF_6]$ (0.3 mM), $[NBu_4][F]$ (2 equiv), and $Pd(PPh_3)_4$ (25 mol % total) in methanol.

Since the $[NBu_4][F]$ was added as the trihydrate, we reasoned that the slow product formation was a result of low concentrations of water, so an aliquot of water was added, curiously halting the reaction. The palladium intermediate $[L_2Pd(Ar^+)(I)]$ was still observed after water addition, and the reaction solution remained clear and colorless, indicating that the catalyst had not decomposed.

If this reaction is followed by ESI-MS in the negative ion mode, a series of aggregates of the formula $Ar'B(OMe)_n(F)_m$ ($n + m = 3$, Ar' = *p*-tolyl) were observed after the addition of $[NBu_4]F$. The spectrum became significantly more complicated after the addition of water, with a series of aggregates with the formula $Ar'B(OMe)_n(F)_m(OH)_o$ ($n + m + o = 3$) being observed in addition to several other boron species, all of which eluded assignment (the CID spectra of these species provided no additional information). Additionally, an ion with mass corresponding to the deprotonated $[Ar'BO_2H]^-$ was observed only after the addition of water. The presence of both it and the palladium cation in solution simultaneously indicates that the direct reaction of these two components does not occur, and the Denmark intermediate must be approached from a different combination (perhaps the anionic oxygen is not nucleophilic enough to facilitate this coordination) or our structural assignment of $[Ar'BO_2H]^-$ is not an accurate representation of the ion in solution.

The halting of turnover is curious, as it appears that there is slow turnover in the presence of minimal water and fluoride (presumably fluoride-mediated), but turnover is halted when the conditions involve more water. Interestingly, this suggests that there must be at least two mechanisms that can accomplish Suzuki–Miyaura couplings (this fluoride-mediated mechanism cannot be active under most Suzuki–Miyaura conditions, as the majority contain large amounts of water). We were unable to detect any species under these conditions that provide evidence for a particular mechanism.

■ EXPERIMENTAL SECTION

$[4\text{-}IC_6H_4(CH_2)PPh_3][PF_6]$ was prepared through a previously published synthesis.[67] All other chemicals were used as obtained from Sigma-Aldrich. Solvents were purified on an MBraun solvent purification system. All gases used were obtained from Airgas. Mass spectra were processed with the assistance of ProteoWizard,[68] and species assignments were in part assisted by ChemCalc.[69] The Supporting Information contains more details including conditions for the various experiments described, additional mass spectra, NMR data, additional reaction traces, X-ray crystal structures, and structural data.

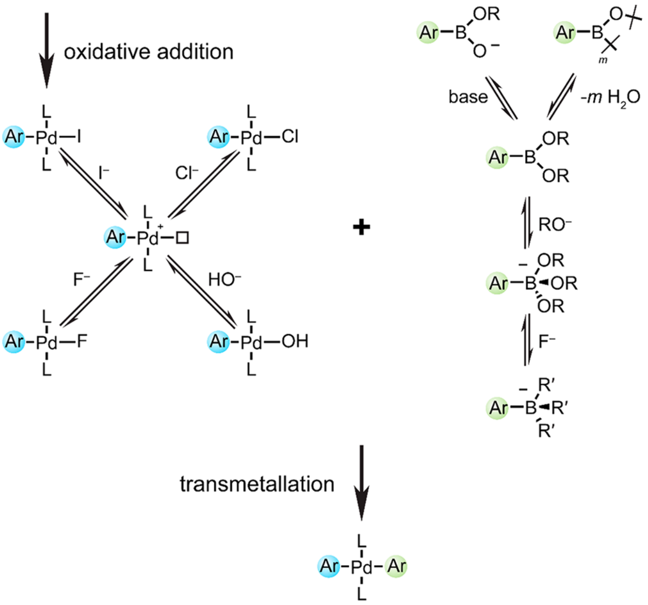
Synthesis of $[4\text{-}(B(OH)_2)C_6H_4(CH_2)PPh_3][PF_6]$. Triphenylphosphine (0.22 g, 1 mmol) and $4\text{-}(B(OH)_2)C_6H_4CH_2Br$ (0.40 g, 1.5 mmol) were dissolved in toluene (10 mL). The reaction mixture was stirred at room temperature for 16 h. The resulting white precipitate was filtered and washed with toluene to remove excess PPh_3, leaving the product $[4\text{-}(B(OH)_2)C_6H_4(CH_2)PPh_3][Br]$ (yield 0.3 g, 65%). A salt metathesis was performed with $[Na][PF_6]$ (0.55 g, 2 mmol) giving $[4\text{-}(B(OH)_2)C_6H_4(CH_2)PPh_3][PF_6]$ (yield 0.100 g, 50%) after stirring for 1 h in methanol. ^1H NMR (300 MHz, CD_2Cl_2) δ 4.35 (d, 2H, J = 14 Hz), 6.83 (dd, 2H, J = 3, 8 Hz), 7.30–7.65 (m, 6H), 7.80 (td, 8H, J = 2, 8 Hz). ^{31}P NMR (300 MHz, CD_2Cl_2) δ 22.38 (s). ESI(+)-MS: m/z 425.2 in MeOH (both OH groups are substituted with OMe).

Synthesis of $[4,4'\text{-}MeC_6H_4C_6H_4CH_2PPh_3][PF_6]$. Compound **1** (0.896 g, 1.6 mmol), *p*-tolylboronic acid (0.240 g, 1.8 mmol), sodium carbonate (1.67 g, 16 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.094 g, 0.4 mmol) were dissolved in MeCN (30 mL) and water (2 mL). The solution was refluxed for 1 h resulting in a pale yellow precipitate. The product was pumped to dryness *in vacuo*. A salt metathesis was performed with $[Na][PF_6]$ (0.795 g, 3 mmol) in methanol (5 mL) with stirring for 2 h (yield 0.300 g, 40%). ^1H NMR (300 MHz, CD_2Cl_2) δ 2.36 (s, 3H), 4.59 (d, 2H, J = 9 Hz), 6.93 (dd, 2H, J = 2, 8 Hz), 7.20 (d, 2H, J = 2 Hz), 7.34–7.40 (m, 4H), 7.49–7.56 (m, 6H), 7.60–7.67 (m, 6H), 7.76–7.79 (m, 3H). ^{31}P NMR (300 MHz, CD_2Cl_2) δ 22.70 (s). ESI(+)-MS: m/z 443.2. Crystals suitable for X-ray analysis (Figure 1) were prepared by dissolving the product in hot ethanol and allowing slow crystallization at room temperature.

■ CONCLUSIONS

Ultimately, what was intended to be a relatively simple investigation into the transmetalation step in the Suzuki reaction ended up being a broad survey of possible coupling partners. Despite combining a wide range of potential reactants (Scheme 3), we did not find a pair that could both be present in detectable quantities in separate solutions and produce immediate reactivity. However, we can offer suggestions about what *is* needed to enable rapid reaction to occur.

Scheme 3. Proposed Set of Equilibria Resulting from the Various Palladium and Boron-Containing Species Considered Herein[a]



[a]L = phosphine ligand, R = H or Me, and R′ = OR or F.

The boronic acid speciation is dynamic and greatly affected by reaction conditions (Scheme 3, right-hand side). Arylboronic acid $ArB(OH)_2$ is dehydrated to boroxine $[ArBO]_m$ (m = 3, 4) in anhydrous conditions. It may also be deprotonated to give $[ArBO_2H]^-$, which was unreactive with any palladium species, indicating that the intermediate proposed by Denmark, **4**, is likely not formed by the direct interaction of $[L_2Pd(Ar)]^+$ and $[ArBO_2H]^-$. In basic conditions, $ArB(OH)_2$ is in equilibrium with boronate $[ArB(OR)_3]^-$ (R = H or Me). In the presence of fluoride ions, the OR groups may be substituted for F. Given the variety of boronic species accessible via these equilibria, it is likely that many of these are simultaneously accessible under a given set of conditions and that the key for transmetalation lies in the palladium speciation.

The $L_2Pd(Ar)I$ complex showed no apparent reactivity with the boron containing species $Ar'B(OH)_2$, $[ArB(OR)_3]^-$, and $[ArBO]_n$ (n = 3,4). The addition of a protic solvent was required for reaction to occur in each of these cases. The behavior of $L_2Pd(Ar)Cl$ mirrored that of the I analogue, suggesting that in polar solvents at least, these species are in equilibrium with each other, probably via the cationic $[L_2Pd(Ar)]^+$, which is found contemporaneously in the same solutions. $L_2Pd(Ar)F$ was not observed even under conditions that ought to have favored its appearance (excess fluoride), but F^- was not competitive enough with I^- even under these conditions to produce detectable quantities of the fluoride complex. As the addition of protic solvent to these mixtures affects both the palladium and boron speciation simultaneously, we were unable to distinguish which speciation changes are ultimately responsible for reactivity.

Complexes of the type $[L_2Pd(Ar)]^+$ were similarly treated with different boron-containing substrates, including in a stoichiometric reaction between $[L_2Pd(Ph)(pyridine)]^+$, and proved unreactive toward all candidates. This result suggested that the role of $[L_2Pd(Ar)]^+$ is to serve as an intermediary between $L_2Pd(Ar)(I)$ and the unidentified pretransmetalation palladium intermediate.

Complexes of the type $L_2Pd(Ar)(OH)$ and $L_2Pd(Ar)(OMe)$ were not detectable under normal catalytic conditions, though both were readily observed as the most abundant species when generated via the addition of very strong base in nonpolar solvents.

In every case where the reaction turns over, the presence of H_2O or MeOH is required. What is the ROH (R = Me or H) doing? ROH perturbs the speciation of the boronic acid, especially in the presence of base, by facilitating the formation of $[ArB(OR)_3]^-$, but independent testing of preformed boronates of this type suggest that they are no more prone to react than boronic acids. ROH also provides a source of an alkoxide ligand. While we do not see any species of the type $L_2Pd(Ar)OR$, it is most likely in low concentration but in rapid equilibrium with some other Pd–Ar species such that its abundance never rises to detectable levels under catalytic conditions, even when those detectable limits are those of a technique as sensitive as mass spectrometry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00705.

Additional mass spectra, reaction monitoring, synthetic details, NMR spectra, and X-ray crystallographic data (PDF)

Dynamic visualization of the data depicted in Figure 3A (AVI)

Accession Codes

CCDC 1875028–1875029 and 967677 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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