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Distinguishing Between Pathways for Transmetallation in Suzuki-Miyaura Reactions

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Abstract

We report a systematic study of the stoichiometric reactions of isolated arylpalladium hydroxo and halide complexes with arylboronic acids and aryltrihydroxyborates to evaluate the relative rates of the two reaction pathways commonly proposed to account for transmetallation in the Suzuki-Miyaura reaction. Based on the relative populations of the palladium and organoboron species generated under conditions common for the catalytic process and the observed rate constants for the stoichiometric reactions between the two classes of reaction components, we conclude that the reaction of a palladium hydroxo complex with boronic acid, not the reaction of a palladium halide complex with trihydroxyborate, accounts for transmetallation in catalytic Suzuki-Miyaura reactions conducted with weak base and aqueous solvent mixtures

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The Suzuki-Miyaura reaction is one of the most practiced classes of catalytic C-C bond formation. Although this reaction is established to occur by oxidative addition, transmetallation and reductive elimination, the mechanism of the transmetallation step has been widely debated. Two pathways are typically considered for transmetallation: conversion of an organoboron compound by base to form a nucleophilic boronate, followed by attack on a palladium halide complex (Scheme 1, Path A) or conversion of a palladium halide to a nucleophilic palladium hydroxo complex that subsequently reacts with a neutral organoboron compound (Scheme 1, Path B).[1] A number of studies have led to the conclusion that transmetallation occurs between the palladium halide and boronate, but data that indicate transmetallation could occur between the boronic acid and palladium hydroxo species have also been reported.[2,3] Because transmetallation is often proposed to be turnover limiting and to dictate the choice of reaction conditions, a firm understanding of the mechanism of this step is important for the use of this common catalytic process.[4]

We report a systematic study involving the reactions of isolated arylpalladium hydroxo complexes and arylpalladium halide complexes containing the same ancillary ligands with arylboronic acids and aryltrihydroxyborates. Equilibrium data for the interconversion of boronic acid and trihydroxyborate, as well as equilibrium constants for the interconversion of palladium hydroxo and halide complexes containing PPh_3 and PCy_3 (Cy=cyclohexyl) as ligands have also been gained. Together, these data provide strong evidence that, in the typical mixtures of water and organic solvent, transmetallation between a palladium center that is ligated by common phosphines, such as PPh_3 or PCy_3, occurs between the palladium hydroxo complex and a boronic acid, not between the palladium halide complex and a trihydroxyborate, as often proposed.

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Supporting Information Available. Experimental procedures, preparation of organoboron and palladium compounds, and kinetic plots. This information is available free of charge via the Internet at www.pubs.acs.org.

Our experimental design to assess the different proposed pathways focused on comparing the relative rates of the different stoichiometric reactions between isolated arylpalladium complexes and arylboron species. We studied the stoichiometric reaction of an isolated arylpalladium halide complex and trihydroxyborate in one case and an isolated arylpalladium hydroxo complex and boronic acid in the other. For this design, stable, arylpalladium hydroxo and halide complexes containing the same phosphine ligand were needed. The dimeric $[(Ph_3P)Pd(Ph)(\mu\text{-}OH)]_2$ (**1**) and $(Ph_3P)_2Pd(Ph)(X)$ (X = I, Br, and Cl) are known and were the hydroxo and halide complexes we used for one study.[5] Alkali salts of aryltrihydroxyborates were found to be soluble in organic solvents in the presence of crown ether and were the boronates we used for this study.[6]

The reaction of hydroxo complex **1** with *p*-tolylboronic acid (eq 1) at room temperature without base formed 4-methylbiphenyl within minutes in high yield (81%)[7] from transmetallation and reductive elimination.[8,9] Similarly, the reaction of $(Ph_3P)_2Pd(Ph)(I)$ (**2**) with potassium *p*-tolyltrihydroxyborate at room temperature formed 4-methylbiphenyl rapidly within minutes in high yield (eq 2). The reaction of PhI with *p*-tolylboronic acid catalyzed by $Pd(PPh_3)_4$ occurred in 96% yield over 3 h at 80 °C (eq 3). Both stoichiometric reactions are much faster than the catalytic process and, therefore, could be the transmetallation step on the catalytic cycle.

The relative contribution of Path A and Path B to the transmetallation sequence in the catalytic reaction is dictated by the relative concentrations of the palladium halide and hydroxide, the relative concentrations of boronic acid and trihydroxyborate, and the relative rate constants for the two stoichiometric reactions between palladium halide and boronate and between palladium hydroxide and boronic acid (Scheme 2). The pathway with the largest product of the rate constant, concentration of palladium complex, and boron reagent would be the one by which transmetallation occurs. Thus, we studied the interconversion of palladium hydroxo and halide complexes under aqueous conditions common to the catalytic Suzuki-Miyaura reaction, the equilibrium between boronic acids and trihydroxyborates, and the rate constants for the two stoichiometric reactions.

The combination of 4-fluorophenylboronic acid (0.060 M) and the weak base potassium carbonate (0.03-0.15 M) typically used in Suzuki-Miyaura reactions (eq 4) formed a mixture of boronic acid and trihydroxyborate, as determined by ^{11}B and ^{19}F NMR spectroscopy at room temperature in a 1:1 mixture of acetone and water.[10] The equilibrium between boronic acid and trihydroxyborate occurred on the NMR time scale, as evidenced by a single resonance at a chemical shift between that of the boronic acid and trihydroxyborate. From the observed chemical shift and the known chemical shifts of the boronic acid and trihydroxyborate, the ratio of boronic acid to trihydroxyborate could be determined. This ratio varied from 1:1 to 1:3 when the concentration of base was increased from 0.03-0.15 M, respectively. Lloyd-Jones et al. have studied this equilibrium in aqueous THF mixtures; the populations of the free boronic acid and trihydroxyborate were similar to each other when the ratio of THF to H_2O was ca 1:1.[11,12] Thus, the concentrations of boronic acid and trihydroxyborate are close to each other in organic media containing weak base and water.

Our studies on the equilibria between palladium hydroxo and halide complexes are summarized in eq 5.[2e] The exchange of the halide in tetraalkylammonium halide salts (0.043 M) with the hydroxide in complex **1** (0.011 M) in aqueous THF (25:1) occurred upon mixing at room temperature, as determined by ^{31}P NMR spectroscopy (Eq 5). Equilibration was complete in the time required for acquisition of the ^{31}P NMR spectrum (<5 min). In addition to the formation of the corresponding aryl halide complex $(Ph_3P)_2Pd(Ph)(X)$ (X = I, Br, or Cl), monomeric $(Ph_3P)_2Pd(Ph)(OH)$ was detected.[13] The concentration of aryl halide complex was smaller (0.0028-0.0032 M) than the combined concentration of the dimeric and monomeric palladium hydroxo complexes (0.0077-0.0081 M) and appeared to be insensitive to the identity of the halide.

Direct comparison of the relative stabilities of hydroxo and halide complexes ligated by PPh_3 is complicated by the concurrent equilibrium between the monomeric and dimeric forms of the hydroxo complex. Thus, we also examined the equilibrium between the hydroxo and halide complexes for a related series of complexes ligated by PCy_3, which are both monomers.[13-14]

Equilibria between PCy_3-ligated hydroxo and halide complexes are summarized in eq 6 and eq 7. In a 25:1 mixture of THF and H_2O, the equilibrium constant for formation of $(Cy_3P)_2Pd(Ph)(I)$ (**6**) from the combination of $(Cy_3P)_2Pd(Ph)(OH)$ (**5**) (0.013 M) and tetrabutylammonium iodide (0.013 M) is approximately unity ($K = 1.1$) at 20 °C. Palladium bromide **7** and chloride **8** are more stable than iodide **6** ($K = 9.3$ and 23, respectively) (eq 6), but the equilibrium constants are still small. In a similar medium containing less water (THF:water = 50:1), the equilibrium between hydroxo **5** and each of the halide complexes (**6-8**) again contained substantial amounts of both halide and hydroxide complexes (eq 7), but the concentration of hydroxide **5** increased in all cases relative to the amount present in the 25:1 mixture of THF and H_2O. Presumably, the increased population of hydroxo complex at lower $[H_2O]$ results from the decreased hydration of free hydroxide ions. From these data, we conclude that the concentration of palladium halide complex is higher than the concentration of palladium hydroxide complex in catalytic Suzuki-Miyaura reactions conducted with aqueous solvent mixtures, but that the populations of the palladium hydroxo and halide complexes in eq 5-7 differ by less than an order of magnitude.

The observed rate constants for the reaction of hydroxide **1** with boronic acid and halide **3** with trihydroxyborate in a 50:1 mixture of THF/H_2O were measured by ^{31}P NMR spectroscopy. The reaction of **1** (0.015 M) with *p*-tolylboronic acid (0.15 M) in the presence of PPh_3 (0.15 M) was monitored (Fig 1) at −40 °C and occurred with an observed rate constant of 2.4×10^{-3} s^{-1}.[15] In contrast, no reaction was observed between halide complex **3** and potassium *p*-tolyltrihydroxyborate (0.15 M) in the presence of PPh_3 (0.15 M) and 18-crown-6 at −30 °C over the same period of time. In fact, less than 10% conversion of **3** occurred, even after 11 h. These data indicate that the rate constant for reaction of hydroxo complex **1** with boronic acid is much larger than that for reaction of halide complex **3** with trihydroxyborate.

The rate constant for reaction of halide complex **3** with *p*-tolyltrihydroxyborate at the −40 °C temperature of the reaction of hydroxo **1** with boronic acid was calculated from activation parameters for the reaction of **3** with trihydroxyborate (see Supporting Information). The estimated rate constant at −40 °C from these data is 1.7×10^{-7} s^{-1}. This rate constant is smaller than that for the reaction of hydroxo complex **1** with boronic acid at the same temperature by a factor of ca 1.4×10^4. Because the populations of hydroxo and halide complexes are similar and substantial amounts of boronic acid exist in media containing a mixture of organic solvent and water, this large difference in rate constant implies that the reaction of hydroxo complex **1** with boronic acid is the pathway that accounts for transmetallation in the catalytic Suzuki-Miyaura reaction. In fact, this large difference implies that the reaction would occur through the hydroxo complex, even under conditions that would generate low concentrations of hydroxo complex **1** relative to halide complexes **2-4**.

The reaction of hydroxo complex **1** with arylboronic esters was also monitored by ^{31}P NMR spectroscopy. The reaction of **1** with catechol and neopentyl glycol esters of 4-fluorophenylboronic acid at −55 °C occurred with rates that were similar to that of the reaction of **1** with free boronic acid (Scheme 3). The reactions of **1** with boronic esters formed an unidentified intermediate at low temperature as the initial product, in a similar fashion to the reaction of **1** with boronic acid (vide supra). This initial product decayed to $Pd(PPh_3)_n$ (n=3,4) upon warming to room temperature. 4-Fluorobiphenyl was also observed by ^{19}F NMR spectroscopy upon warming. The more sterically hindered 4-fluorophenylboronic acid pinacol ester also reacted with hydroxo complex **1** at −55 °C, albeit more slowly (>95% conversion after 1.5 h) than did the catechol and neopentyl glycol analogs. Thus, the reaction of **1** with all four neutral arylboron compounds occurs faster than the combination of halide complex **3** and trihydroxyborate. No reaction occurs between the latter combination over the same period of time, even at −30 °C. Assuming the borate analogs of the boronic esters do not react faster than the trihydroxyborates, these data suggest that transmetallation during Suzuki-Miyaura coupling of boronic esters also occurs by reaction of the neutral boron species with the palladium hydroxide (Path B).

In conclusion, we have shown that the reactions of isolated palladium hydroxide **1** with boronic acid and the reaction of palladium iodide **2** with aryltrihydroxyborate both form biaryl products rapidly in the absence of additives. Between these two classes of reactions, transmetallation between an arylpalladium hydroxo complex and a boronic acid would occur faster within the catalytic cycle because the populations of palladium halide and palladium hydroxo complex are similar to each other, the populations of boronic acid and trihydroxyborate are similar to each other in the presence of water and bases of the strength of carbonates, but the rate of reaction of hydroxo complex with boronic acid is several orders of magnitude faster than the reaction of halide complexes with trihydroxyborate. The fast reaction of hydroxo complex **1** with arylboronic esters suggests that Suzuki-Miyaura reactions with these substrates also proceed by reaction of the neutral arylboron species with a palladium hydroxo complex.

These results provide the first quantitative assessment of the rates of the two pathways and populations of the reactants in these two pathways, but our conclusions must be made with several caveats. First, the data we present here cannot be extrapolated to all metal-ligand systems. Second, reactions with stronger bases will contain more trihydroxyborate and if the base is sufficiently strong, then one might expect the borate pathway (Path A) to become competitive with the hydroxo pathway (Path B). Although this is likely to be true, the majority of catalytic Suzuki-Miyaura reactions are conducted with relatively weak bases such as carbonate or phosphate. Third, Lloyd-Jones et al have recently reported that Suzuki-Miyaura reactions of trifluoroborates occur through the free boronic acid after hydrolysis.[11] Thus, the mechanism for transmetallation in these systems could also proceed by reaction of a palladium hydroxo complex with boronic acid, but we have not yet assessed the rates of reaction under these conditions. Finally, our data do not reveal the intimate mechanism for transfer of the organic moiety from boron to palladium. Neverthe-less, we hope these data will provide an anchor point to guide further mechanistic and computational studies. Additional studies of the mechanism of transfer of the organic fragment from boron to palladium will be forthcoming.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(12). Lloyd-Jones et al. also reported that the population of free boronic acid increases when the concentration of water is decreased.

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(15). An intermediate ($\delta = 20.1$ ppm) was detected as the initial product, which decays to biaryl and $Pd(PPh_3)_4$ upon warming.

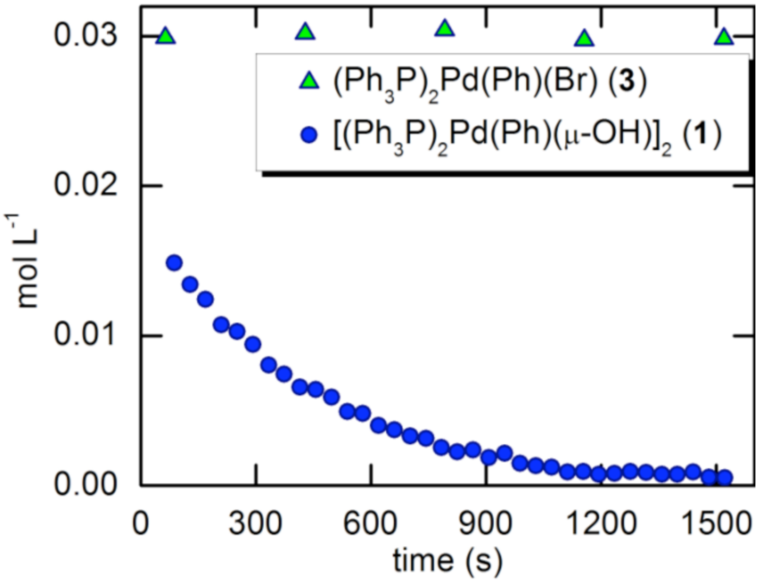
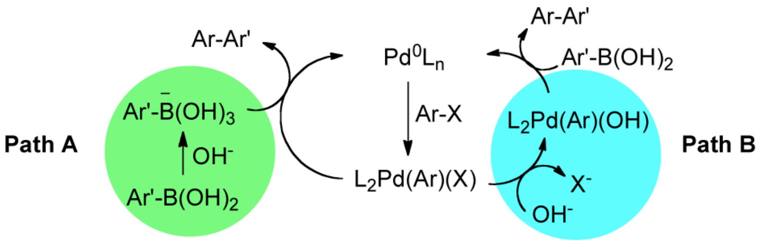
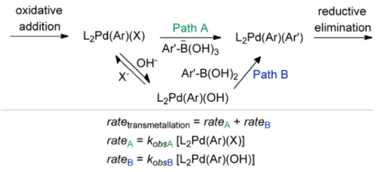


Figure 1.

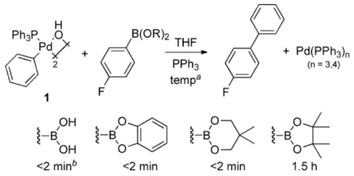
Decay of **1** (0.015 M) in the presence of *p*-tolylboronic acid (0.15 M) and PPh_3 (0.15 M) at −40 °C, and decay of **3** (0.030 M) in the presence of potassium *p*-tolyltrihydroxyborate (0.15 M), PPh_3 (0.15 M), and 18-crown-6 in THF/H_2O (50:1) at −30 °C as monitored by ^{31}P NMR spectroscopy.


Path A
Ar-Ar'
Ar'-B̄(OH)3
OH-
Ar'-B(OH)2
Pd0Ln
Ar-X
L2Pd(Ar)(X)
Ar-Ar'
Ar'-B(OH)2
L2Pd(Ar)(OH)
X-
OH-
Path B

Scheme 1.

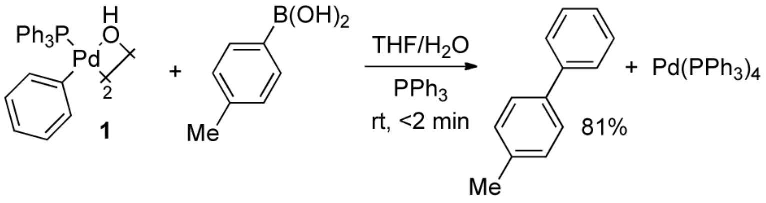

oxidative addition
$L_2Pd(Ar)(X)$
Path A
Ar'-$\bar{B}(OH)_3$
$L_2Pd(Ar)(Ar')$
reductive elimination
OH^-
X^-
Ar'-$B(OH)_2$
Path B
$L_2Pd(Ar)(OH)$
$rate_{transmetallation} = rate_A + rate_B$
$rate_A = k_{obsA}\,[L_2Pd(Ar)(X)]$
$rate_B = k_{obsB}\,[L_2Pd(Ar)(OH)]$

Scheme 2.

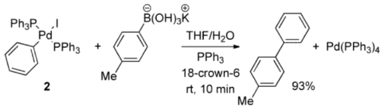


[a]-55 °C then rt. [b] Time to >95% conversion of **1** at -55 °C.

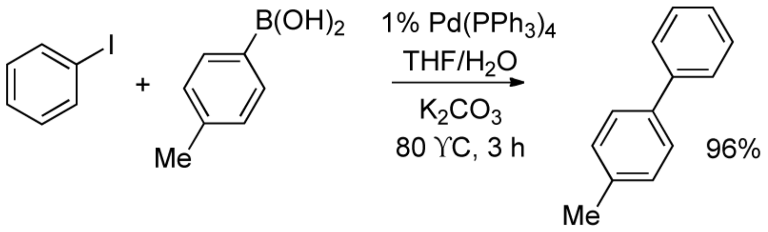
Scheme 3.



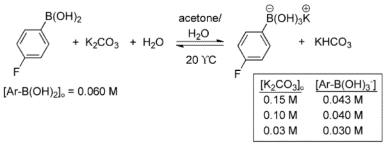
(1).


Ph3P
I
Pd
PPh3
2
+
B(OH)3K
Me
THF/H2O
PPh3
18-crown-6
rt, 10 min
Me
93%
+ Pd(PPh3)4

(2).

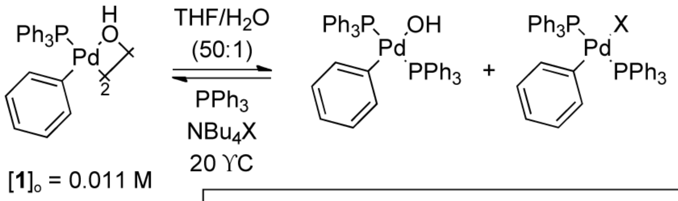


(3).



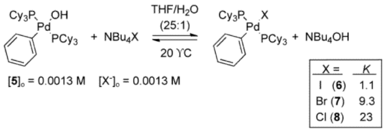
$[K_2CO_3]_o$	$[Ar\text{-}B(OH)_3^-]$
0.15 M	0.043 M
0.10 M	0.040 M
0.03 M	0.030 M

(4).



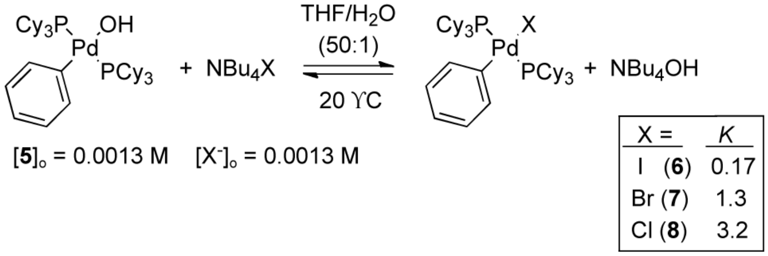
X=	[1]	[L_2Pd(Ph)(OH)]	[L_2Pd(Ph)(X)]
I (**2**)	0.0049 M	0.0028 M	0.0032 M
Br (**3**)	0.0043 M	0.0038 M	0.0028 M
Cl (**4**)	0.0032 M	0.0045 M	0.0031 M

(5).



X =	*K*
I (**6**)	1.1
Br (**7**)	9.3
Cl (**8**)	23

(6).



X =	K
I (**6**)	0.17
Br (**7**)	1.3
Cl (**8**)	3.2

(7).