

Solving the Riddle- the Mechanism of Suzuki Cross Coupling: A Review

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(Received 30 Oct, 2016; Accepted 01 Nov, 2016; Published 15 Nov, 2016)

ABSTRACT: Suzuki cross coupling reaction is one of the most celebrated organic reactions of 20th century. Even though it is generally assumed that the reaction proceeds via a sequence of steps oxidative addition, transmetalation and reductive elimination the actual mechanism is much more complex. Here in this review we discuss the mechanistic studies of Suzuki cross coupling reaction along with scientific criticism. We have here included the initial mechanistic studies as well the most recent studies. Overall we have focused different aspects of the mechanism along with the highly debated transmetalation mechanism.

Keywords: Suzuki Cross Coupling; Palladium catalysis; Mechanism and Organometallic Chemistry.

Pd-catalyzed cross coupling reactions revolutionize the field of organic synthesis. Among them, Suzuki cross coupling reaction is considered to be the most widely used cross coupling reactions in chemical industry as well as in academic settings.^{1,2} The applications of Suzuki reactions range from medicines to materials.³⁻¹⁷

In 2002 Fu reported Pd-catalyzed cross coupling of primary alkyl bromides with boronic acids.¹⁸ He also reported related enantioselective variety of Suzuki-coupling.¹⁹ Interestingly, in this work the metal used was nickel instead of palladium. The potency of first row transition metal was further exemplified by copper catalyzed Suzuki cross coupling.²⁰ The success of low cost first row transition metals greatly boosts future scope of related cross coupling reactions. Suzuki reaction was further extended to borylations.^{21,22} Recently, electrophilic chlorides have been successfully brought in coupling reactions.²³⁻²⁶ Lipshutz and other groups successfully employed aqueous coupling

reactions.²⁷⁻²⁹ Even though the initial results showed moderate yields eventual advancement is quite expected. In spite of its tremendous synthetic success until recently the understanding of the reaction was extremely superficial. Couplings associated with hetero arenes have been long standing problems as hetero atoms often bind to the metal center replacing the active phosphine ligands. This major limitation was successfully overcome by Buchwald when he coupled heterocyclic boronic acids with aryl halides.³⁰ This advancement was extremely significant as most of the drug candidates contain at least one heterocycles. The advancement regarding catalyst was further extended to heterogeneous variety. This was done either by silica embedded method or nano particle doping.^{28,31} In spite of its tremendous synthetic success until recently the understanding of the reaction was extremely superficial. This lack of knowledge, in turn limits the advancement of Suzuki and other related cross coupling reactions.



Dr. Bibaswan Biswas, born in West Bengal, India in 1985 received his B.Sc. and M.Sc. from University of Calcutta. In 2009 he started his doctoral study at Texas A&M University under the supervision of Dr. Daniel A. Singleton. His Ph.D. work is related to synthetic methodology development of bioactive molecules using computational calculations. After graduating with summa cum laude he joined Dr. M. P. Watson's group at University of Delaware, as a postdoctoral fellow in 2015.



Dr. Goutam Kulsi was born in West Bengal, India in 1983 and received his B.Sc. from University of Calcutta and M.Sc. from Tripura Central University. He started his doctoral study in 2009 at Indian Institute of Chemical Biology (CSIR-IICB), India, under the supervision of Dr. Partha Chattopadhyay and Dr. Krishnananda Chattopadhyay. During his Ph.D., he was engaged in design and synthesis of triazole based peptidomimetic macrocycles and other heterocycles and studied self-assembly and anion binding property of the macrocycles. After completion of his PhD degree in 2015 he joined Prof. Joon Myong Song's group at Seoul National University, South Korea, as a postdoctoral fellow where he is working on photodynamic therapy (PDT) for better cancer treatment.

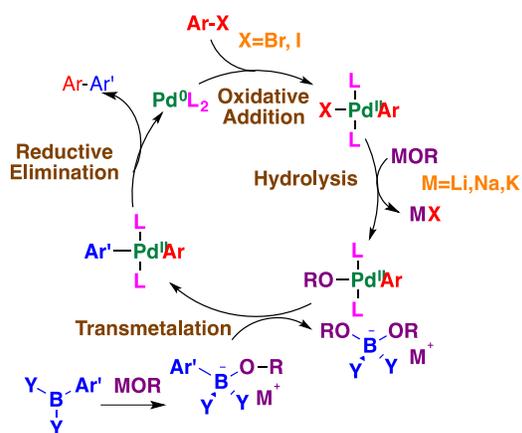
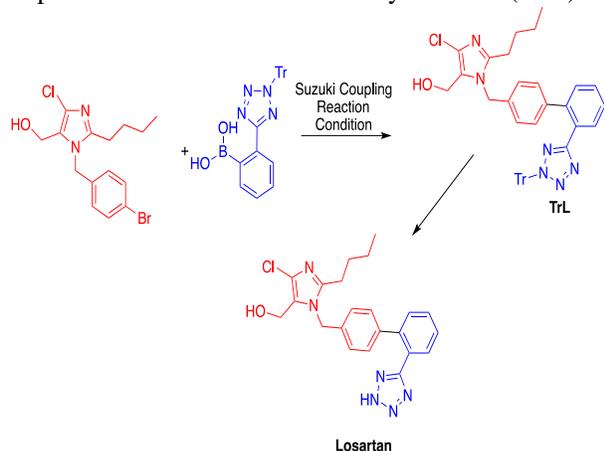


Figure 1: Suzuki Cross Coupling Catalytic Cycle.

The general catalytic cycle for Suzuki reaction is shown in Figure 1. In the first step $Ar-X$ is oxidatively added to coordinately unsaturated PdL_2^0 species. The second step is hydrolysis of $Pd(II)$ species. The third step involves the transmetalation of nucleophilic carbon from boron center to $ArPdL_2OH$. The final step is the reductive elimination leading to cross-coupled product and regeneration of the catalyst. Even though this generic mechanism is widely accepted. The underlying mechanism is far more complex than this generic version.

Even though Suzuki first reported this reaction in 1979, extensive mechanistic study was not carried out till 1994.¹

The process group in Merck Co first reported kinetic study on Suzuki coupling reaction for the production of pharmaceutical intermediate trityl losartan (**TrL**).³²



Scheme 1

The kinetic studies indicated that for aryl bromide electrophile the rate-limiting step is the oxidative addition step while in case of iodo-electrophiles the rate limiting step is the transmetalation step. This is quite understandable from the fact that carbon halogen bond

weakens as the size of the halogen increases. The study also indicated the necessity of the water for successful coupling even though they did not provide any in depth mechanistic rationale.

Soderquist studied the mechanism of the coupling of alkyl boranes with aryl bromides.³³ The study found that the transmetalation of the alkyl group proceeds through complete retention of the configuration at the alkyl center. The extremely high stereospecificity was attributed to the four membered μ_2 -bridged transition state model (Figure 2). The involvement of $Pd-OR$ species at the transmetalation process could potentially be able to explain the effect water and other alcoholic solvents in Suzuki reaction. They studied oxygenated and non-oxygenated boranes as coupling partners. In case of non-oxygenated borane (Figure 2 & 3) the reaction is first order with respect to the aryl bromide while zero order with respect to other substrates clearly indicating the oxidative addition as the rate-limiting step. While in case of oxygenated borane (Figure 2 & 5) hydrolysis of the initial oxidized $Pd(II)$ species is the rate limiting step. Based on their kinetic and NMR studies they proposed two different kinetic cycles involving different rate limiting steps. It is interesting to note that in case of oxygenated borane neither oxidative addition nor transmetalation step is the rate-limiting step.

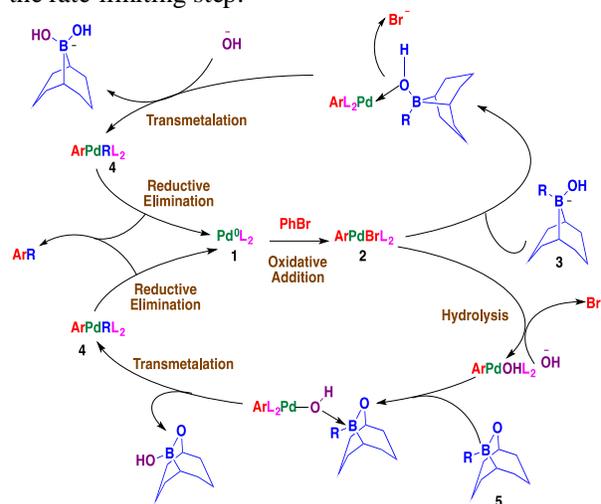


Figure 2: Soderquist Modified Suzuki Catalytic Cycle.

Among all the steps involved the mechanism of the transmetalation step has been highly debated. The understanding of the mechanism of the transmetalation step is extremely important as this step is often the turn over limiting step. Thus future advancement of this type of reactions requires understanding of the mechanism of transmetalation. There are two paths have been proposed Path A and Path B (Figure 3). Path A: Initial formation of tetra coordi-

nated boronate formed via reaction of tri coordinated boron species and base. This nucleophilic tetra coordinated boronate then attacks the Pd-halide complex. Path B: Initial hydrolysis of Pd-halide complex to Pd-hydroxo complex followed by reaction with tri coordinated organo boron species. Based on the necessity of the oxo or fluoride bases for successful coupling initially it was postulated that Path A is operative in catalytic cycle.¹ However, later findings suggested that Path B is followed in the catalytic cycle.³⁴ This was supported by the following observations, a) amine bases are incapable for coupling reactions, b) lithium salt of tetra alkyl boronates show very low reactivity.³⁵

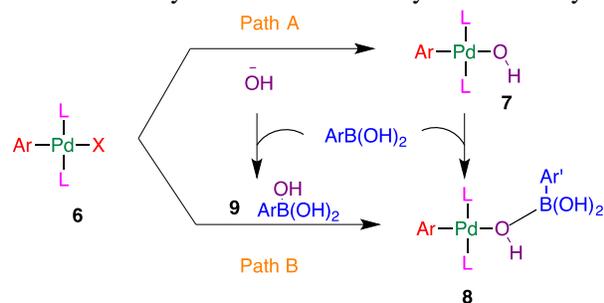
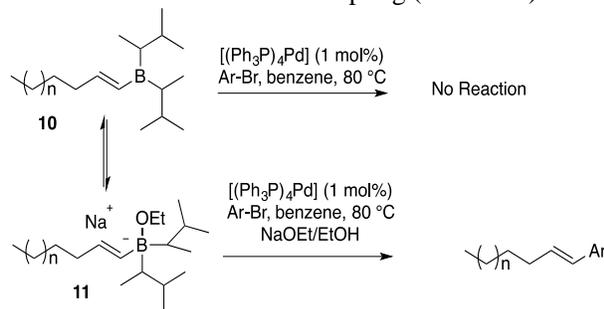


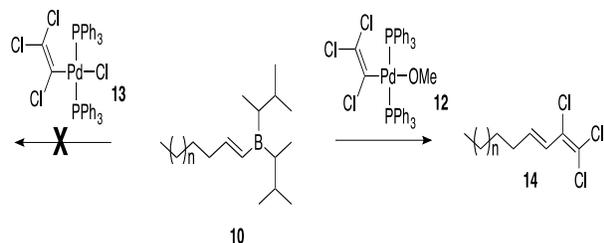
Figure 3: Alternative Mechanism for Transmetalation.

Whatever be the operative path the presence of a base is critical in case of Suzuki coupling (Scheme 2)



Scheme 1

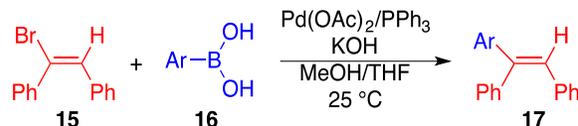
Finally stoichiometric reaction between the alkoxy-Pd species (**12**) and the organo borane (**10**) affords the coupled product quantitatively, while corresponding halogenated Pd-complex (**13**) was unable to take part in coupling reaction (Scheme 3).



Scheme 2

In mechanistic studies the direct detection of the intermediates are often helpful to unravel the actual mechanistic path. ESI-MS technique has been employed to analyze the transmetalation path. Anionic boronates and Pd-halide species were detected by ESI-MS analysis supporting Path A.³⁶⁻³⁸ The roles of these species in the catalytic cycle could not be explored. Even though the exact path of transmetalation has been highly debated both paths lead to the same intermediate **8**. However, this particular intermediate, **8** is highly elusive and have never been detected experimentally under ordinary catalytic reaction conditions.

As the key species **9** is anionic nature a series of Hammett plot was done to probe the mechanism of the transmetalation path.³⁹ For aryl boranes 2-aryl-1,3,2-dioxaborinane were the choice for the reaction because these boronic esters show considerable reactivity in coupling over wide range of substrates. When propargylic carbonates were used as coupling partner small negative charge was developed at the transition state as indicated from $\rho=+0.73$ value. In case of coupling between aryl boronic acids with 2-bromotoluene even smaller $\rho=+0.24$ was observed indicating marginal change of charge in the aryl group in the transition state with respect to the starting material, boronic acid. Even small amount of negative charge was developed, this observation cannot rule out the possibility of Path A or Path B as the exact identity of the intermediate that undergo transmetalation was not known. With vinyl electrophiles the ρ values were negative. For example with E-bromo stilbene $\rho=-0.7$ (Scheme 4) and vinyl bromide (generated in situ) $\rho=-1.3$. As the catalytic cycle might be extremely complex, consisting of a number of steps with comparable energy barriers the Hammett reaction constants mere gives the overall electronic effect at the transition state and that could explain the inconsistency in the ρ values. Furthermore it is possible that the catalytic cycle involving vinyl electrophile might be different from the aryl electrophile. Whatever be the reason results from Hammett plots were fairly inconclusive.



Scheme 3

Theoretical calculations have advantages over experiments to probe reaction mechanism as in theoretical calculation each step could be judged separately without the interference of the other steps.

Thiel in his work computationally studied coupling of acetic anhydride with boronic acid under Suzuki coupling conditions.⁴⁰ In the study two, catalytic cycles were investigated. These were a) catalytic cycle involving neutral Pd^0L_2 complex and b) cycle involving

Jutand type anionic species $[PdL_2X]^{41}$. Both cycles involve comparable energy barriers. However, the most important aspect of their study is that the computational results ruled out possibility of 5-coordinated Pd-species, often postulated to explain strong counter ion dependence of Pd-based transformations. It is worth to mention that the conclusion about coordination of the Pd-center could not be achieved by any experimental methods. Glaser regarding dissociation of the aryl anion from the anionic aryl boronates did another interesting study.⁴² The aryl dissociation from the boronate is thermodynamically feasible as the C-B bond in the boronates are quite weak (Figure 4). Their computational findings also suggest weak C-B bond ($<50 \text{ kcal mol}^{-1}$). However, further study predicted that this dissociation path is highly unlikely to occur kinetically under ordinary reaction condition eliminating the possibility of transmetalation via aryl dissociation followed by direct nucleophilic attack of aryl anion to Pd-center.

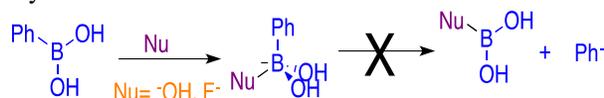


Figure 4 : Aryl anion dissociation mechanism.

Harvey studied the ligand effects on reactivity of a Suzuki catalyst. For the study four different phosphine ligands were chosen.⁴³ The ligands chosen were PMe_3 , P^tBu_3 , PPh_3 and $P(CF_3)_3$. In case of P^tBu_3 , dissociation of one P^tBu_3 molecule from the Pd-center is needed for oxidative addition. This is probably due to steric bulk of the tBu group. Interestingly, for every ligand the transmetalation step is the rate limiting step (computationally only Path A was explored). Considering the relative energy barrier of the steps associated with the catalytic cycle their results indicated that ligands with electron withdrawing group(s) decreases the energy barrier for the transmetalation process (Table 1).

Table 1 : Energy barriers for key catalytic Steps.

Step	P^tBu_3	$P(CF_3)_3$	PMe_3	PPh_3
Oxidative Addition	3.2	11	3.9	4.3
Transmetalation	19.8	14.4	18.3	16.4
Reductive Elimination	3.2	1.7	4.7	3.9

Recently Kozuch did an extensive computational study on Suzuki coupling reaction to unravel the origin of ligand dependency of catalyst reactivity.⁴⁴ They employed energetic span model to determine turnover frequencies (TOF) from the energy states obtained by theoretical calculations. The calculations suggest that monoligated metal center is the most reactive metallic species however the cis-diligated

species have comparable reactivity and population. The study predicted that PMe_3 ligand should fail to promote coupling due the possibility of formation of catalytically inactive trans-diligated Pd-center that cannot isomerize to the corresponding cis isomer due to its very high thermodynamic stability. This is in agreement with the experimental observations. The less reactivity of the PPh_3 ligand was attributed to the fact that it could form thermodynamically accessible catalytically inactive $Pd(PPh_3)_3$ species. The catalytic inactivity of $Pd(PPh_3)_3$ was attributed to the stacking interaction of the phenyl groups. This effect however could easily be minimized by decreasing the relative amount of the phosphine ligand with respect to the metal center or carrying out the reaction under dilute condition. In case of P^tBu_3 the monoligated species is only present as the diligated species is of very high energy. This could be the origin for faster rate with P^tBu_3 as ligand. It is noteworthy to mention that they expanded their model to include TON and off-cycle intermediates. The prediction of these off-cycle intermediates often very important to understand the catalyst decomposition process. The computation so far have been discussed did not address the most puzzling part, the transmetalation step of the catalytic cycle. Maseras published a series of computational studies in order to evaluate the relative preference of the pathways (Path-A and Path-B).⁴⁵⁻⁴⁸ His initial efforts dealt with transmetalation between $Pd(CH=CH_2)(PH_3)_2Br$ and $CH_2=CHB(OH)_2$ under basic conditions.⁴⁵ Even though these systems do not represent the actual reaction conditions considering the structural similarities the calculations will likely to provide insight about the favorability of either pathways. Theoretical calculations not only included the possibilities of Path A and Path B it also evaluate transmetalation between $Pd(CH=CH_2)(PH_3)_2OH$ and $CH_2=CHB(OH)_2$ (Path C) as well as $Pd(CH=CH_2)(PH_3)_2Br$ and $CH_2=CHB(OH)_2$ (Path D) in absence of any base. The results indicated very high energy barrier for Path D supporting the necessity of a base for successful coupling reaction. The calculations also predicted that kinetically the Path A is favored over Path C. However, unfortunately a direct comparison between Path A and Path B could not be made, as they were unable to locate the transition state for transmetalation for Path B. This might be due to the fact that their model system considerably differs from the experimental identities. Even though their study indicated kinetic feasibility of Path A under reaction condition it was not able to evaluate the competitiveness of Path A and Path B. Subsequently, the same group studied the transmetalation process by a combination of experiments and theoretical calculations. In that study coupling between 2(4)-bromopyridine and phenylboronic acid was investigat-

ed.⁴⁸ Their study indicated that Path A is operative. In the catalytic cycle and most importantly they were able to identify computationally predicted intermediate, $\text{trans-[Pd(Ph-B(OH)}_3\text{)(C}_5\text{H}_2\text{RN)(PR}_3\text{)}_2\text{]}$ by NMR technique (Figure 5). The study for the first time provided evidence of the key intermediate for transmetalation reaction.

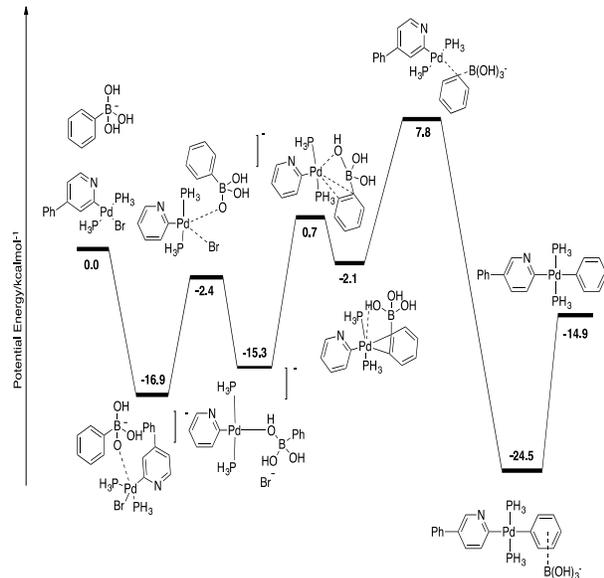
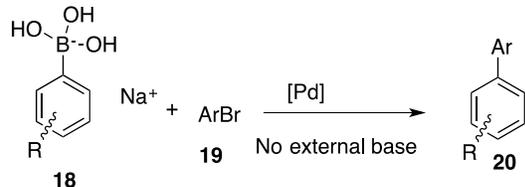


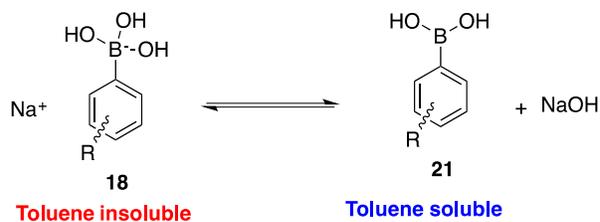
Figure 5 : Computational Energy Barriers

In order to solve this mechanistic problem it was suggested to examine the catalytic activity of preformed ArB(OH)_3^- (**18**) in absence of any external base. A group of chemists from GSK found that ArB(OH)_3^- are catalytically active species (Scheme 5). This observation apparently suggests that the transmetalation occurs via Path A.^{49,50}



Scheme 5

In that study toluene was used as the reaction solvent as well the solvent from which the boronate was precipitated. In fact in toluene the alkali boronates have very low solubility. For this reason it is quite possible that the 'active' boron species in the reaction medium is in fact the toluene-soluble tri coordinated boronic acid instead of the tetra coordinated boronate and the consumed boronic acid is replenished via fast boronic acid/boronate equilibration (Scheme 6). This possibility should particularly be considered, as the solid boronates are known to undergo this kind of equilibration when coupling reactions are carried out in methanolic or aqueous medium.^{38,50}

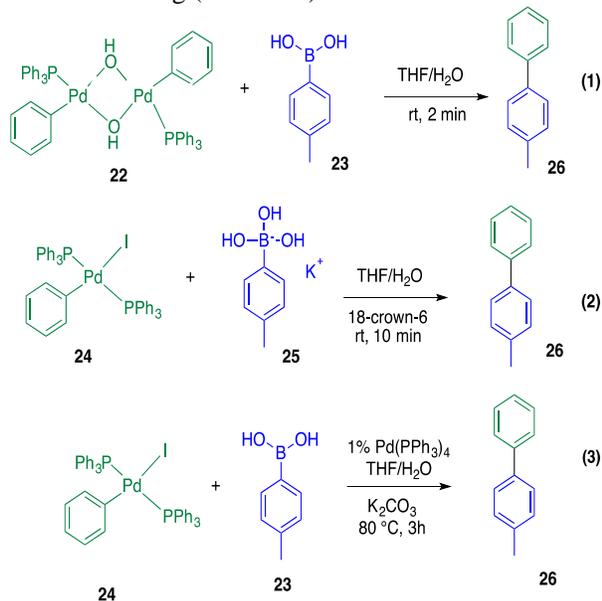


Scheme 6

Suzuki reported successful coupling of dimeric $(\text{Ph}_3\text{P})\text{Pd(OH)(Ph)}_2$ with p-anisyl boronic acid at room temperature to give homo- and cross-coupling products.⁵¹ The catalytic activity of the oxo species demonstrates that transmetalation could occur via Path B. Even though apparent feasibility of both transmetalation path was evaluated relative rate of the paths were not evaluated. A series of studies were performed to unravel the accurate mechanism of operating for transmetalation.

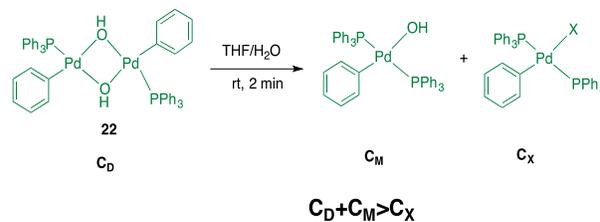
In 2011, Amatore published the first study regarding the role of hydroxide base in coupling reaction.⁵² They employed electrochemical and hetero-nuclear NMT techniques to detect and evaluate the concentration and reactivity of catalytically active Pd-species. They found three distinct roles of the base in catalysis activity. Two of them were positive and the other one is negative. The positive effects are, 1) to hydrolyze ArPdL_2Br to catalytically active ArPdL_2OH species, 2) to promote the reductive elimination step from the intermediate $\text{trans-[ArPdAr'(PPh}_3\text{)}_2]$. The negative effect was associated with the formation of Ar'B(OH)_3^- which reacts only very slowly with the reactive ArPdL_2OH (or ArPdL_2Br) species. This antagonistic effect of the base explains lower reactivity of catalysts with high loading of the base. Their study further established transmetalation step as the rate-limiting step. Overall, the study strongly suggested that the Path B is operative. As an anion is always associated with its counter cation the same research group further studied the effect of the counter cation. They found that as the size of the cation decreases the rate of the process decreases. This was attributed to the complexation of the Pd bound OH group with the counter cation.^{52,53} This possibly explains the inability of the Li-bases to promote Suzuki cross coupling reactions. The study also suggest that when carbonates were used as bases the *active base* involved in the catalytic cycle is still hydroxide, generated by reaction between carbonate and water. In the subsequent study they also found similar positive and negative roles of F^- , another widely used base in Suzuki cross coupling reactions.⁵⁴ Hartwig carried out an extensive investigation to solve the mechanistic problem associated with the transmetalation step by studying the kinetics of the reaction with the help of heteronuclear NMRs.⁵⁵

Firstly, three reactions were performed to gauge the feasibility of the Path A and B. As the stoichiometric reactions 1) $[\text{Ph}(\text{PPh}_3)_2\text{Pd-OH}]_2$ with *p*-tolylboronic acid and 2) trihydroxy(*p*-tolyl)boronate with $\text{Ph}(\text{PPh}_3)_2\text{PdI}$ are faster than the catalytic reaction either of the paths could potentially be the operative and rate limiting (Scheme 7).



Scheme 7

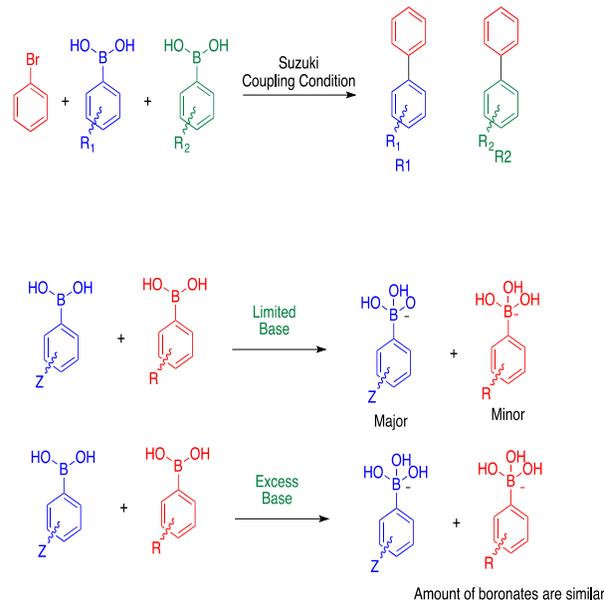
In principle the relative contribution of Path A and Path B depends on 1) relative population of the reacting species and also the 2) relative rate. In order to evaluate the relative population of the reacting species for Path A and Path B a series of equilibration experiments were performed. When the boronic acid was treated with a weak base K_2CO_3 in water/acetone (1:1) an equilibrium was established between boronic acid and corresponding boronate. The equilibrium is expectedly tilted towards boronate side when excess base was used. The equilibration between the oxo and halo Pd-complex was judged by reacting $[\text{Ph}(\text{PPh}_3)_2\text{Pd-OH}]_2$ with NBu_4X ($\text{X}=\text{Cl}, \text{Br}, \text{I}$). Unfortunately the reaction did not provide direct evaluation of relative population as in presence of halide ions the oxo-dimer decomposed to give one equivalent of $\text{Ph}(\text{PPh}_3)_2\text{PdX}$ and one equivalent of $\text{Ph}(\text{PPh}_3)_2\text{PdOH}$ (monomeric oxo species). Even though the relative population of the oxo species and halo species could not be evaluated accurately, the data showed that the total population of the oxo dimer and monomer is greater than the halo species (Scheme 8). However, this dimer monomer problem was avoided by using PCy_3 as the ligand where only monomeric oxo species exist. The equilibrium experiments suggest that unlike the previous case the equilibrium constant strongly depends on the identity of the halide used.



Scheme 8

The population of the monomeric oxo species increased as the size of the halide increases.

Interestingly, the relative amount of water in the mixture has strong effect on the relative population the oxo and halo species. As the proportion of the water increases the population of the oxo species decrease. This apparent anomaly could be rationalized by considering the hydration of hydroxide ion. With smaller amount of water hydroxide ion being less hydrated will be more available to form Pd-OH complex. After that they measured kinetics of the reaction 1) and 2) at $-40\text{ }^\circ\text{C}$. The rate of the reaction 1) is several order of magnitude greater than that of 2) ($\sim 10^4$). Considering the relative population of the reactive species and the relative rates of the competing path it could be inferred that the transmetalation occurs via Path B.



Scheme 9

Even though Hartwig's study provided compelling evidences for Path B, the kinetic measurements were not carried out at normal catalytic temperature rather at very low temperatures ($-40, -55\text{ }^\circ\text{C}$). In 2013 Lima et al. studied the mechanism of the transmetalation step under normal catalytic conditions.⁵⁶ In that work, at first relative acidity of different boronic acid was determined computationally. The computational results even though were not very accurate are qualita-

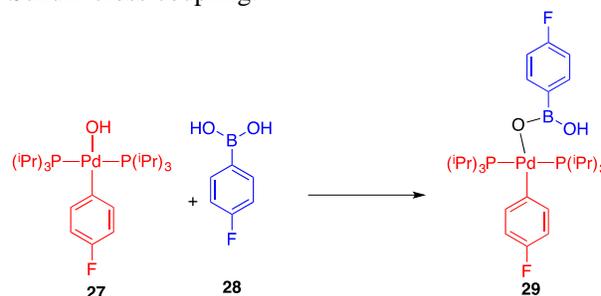
tively in agreement with the experimental values. The inaccuracy of the results could be attributed to the fact that the calculations were done in gas phase. Their NMR study found that the boronic acid-boronate equilibria is established quite fast. This fast equilibration was helpful to evaluate the relative population of different boronic acid-boronate species during the course of the reaction. The coupling reactions were performed with a mixture of two boronic acids having different acidity with varying equivalence of base. It was found that with lower base-loading, products originated from more acidic boronic acid is the major product (Table 2). However, as the equivalence of the base was increased the selectivity tilted towards the less acidic boronic acid (Table 2). This selectivity issue is more pronounced with the mixtures of boronic acids, differing widely in their acidity (Table 2).

With lower base loading more acidic boronic acid would preferentially transform to boronate. That means with low base loading the major boron species in the reaction medium is the boronate from more acidic boronic acid and the less acidic boronic acid. As the loading of the base was increased the less acidic boronic acid is now also converted into the corresponding boronates. Thus the dependence of selectivity on the base equivalence could only be explained by the greater reactivity of the boronate compared to the boronic acid. Even though the experiments did not rule out the possibility of the reaction associated with boronic acid it certainly suggested greater reactivity of the boronates compared to the boronic acids.

Table 2 : Selectivity dependence on base equivalence.

R ₁ /R ₂	K ₂ CO ₃ equiv	(R1/R2)
2-Ph/4-Ph	1	24/76
	2.5	32/68
	4.7	39/61
3-Ph/4-Ph	1	48/52
	2.3	48/52
	4.6	48/52
2-Ph/4-Ph	0.9	36/64
	2.4	43/57
	5	45/55
4-OCH ₃ /4-CHO	1	35/65
	2.5	68/32
	4.6	81/19
4-CH ₃ /4-NO ₂	1	34/66
	2.6	78/22
	4.9	83/17
4-CHO/4-NO ₂	1	46/54
	2.5	57/43
	3.5	58/42
	4.9	58/42

Very recently, Denmark group carried out an extensive experimental study to detect the key transmetalation intermediates via rapid injection NMR and other heteronuclear NMR techniques.⁵⁷ In that study [4-fluorophenyl(¹Pr₃)₂PdOH] (**27**) was reacted with (4-fluorophenyl)B(OH)₂ (**28**) at -78 °C. There was no new species observed even at -60 °C. However, heating to -30 °C leads to the formation of a new species (**29**) containing Pd-O-B bond (Scheme 10). The identity and the geometry of the new species was confirmed by two independent syntheses of the species from 1) 4-fluorophenylboroxine with [4-FC₆H₄(¹Pr₃)₂PdOH] and 2) trans [4-FC₆H₄(¹Pr₃P)₂PdI] with thallium 4-fluorophenylboronate. This newly detected species (intermediate) is structurally closely related to the highly elusive intermediate **8**. The generation and subsequent detection of the Pd-O-B complex could not confirm its competence as a reactive intermediate in Suzuki cross coupling reaction. The species is unreactive at -30 °C. However heating the reaction mixture to 20 °C the intermediate decomposed to give the cross coupled product, supporting its intermediacy in Suzuki cross coupling.



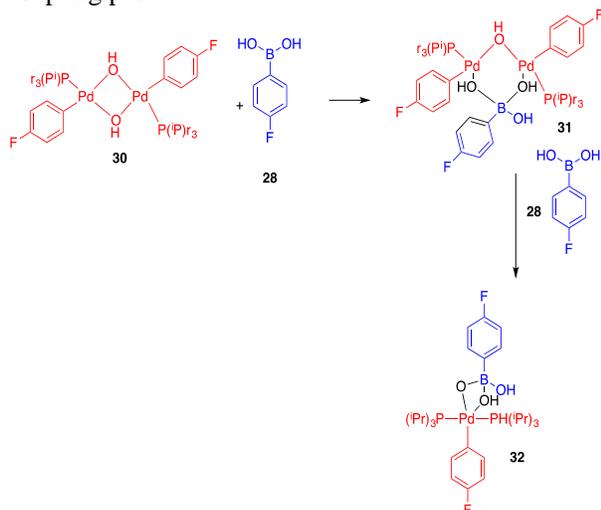
Scheme 10

The generation of this tri coordinated boron intermediate should occur via water loss from a tetra coordinated boron intermediate (**8** or similar species). However, the hydration of the species failed. This might be due to the steric effect from the two phosphine ligands. This observation prompted the researchers to study monoligated Pd-species. The mixing of [(¹Pr₃P)(4-FC₆H₄)Pd(OH)]₂ and (4-fluorophenyl)B(OH)₂ leads to the formation of bridged bis-arylpalladium arylboronate complex, **31** at -100 °C (Scheme 11).

This low temperature intermediate when reacted with one more equivalent boronic acid in methanol at -60 °C a new species was detected. The structure of the new species was assigned to be, **32** (Scheme 11).

Both the species were found to be catalytically active having similar first order decay to afford the cross coupled product. This study, for the first time provided compelling experimental evidences in favor of the existences of the elusive intermediate (**8**). The study

also showed that both tri and tetra coordinated boron species can undergo transformations leading to cross coupling product.



Scheme 11

CONCLUSION: The authors hope that this review provided a short account of the mechanistic studies regarding Suzuki cross coupling reaction. The most controversial part of the mechanism is no doubt the transmetalation step, which happened to be the rate limiting step in the cycle. Initial studies suggested that Path A is operative. However, studies by Hartwig and Amatore provided compelling evidences for the Path B. It is quite possible that Path B is dominant (exclusive) path for their system and reaction conditions and other alternatives might be operative for different reaction systems. For example the experimental results of Lima and Santos' work could only be explained by higher reactivity of boronates. Computational studies predicted different catalytically active species. The existence of most of those species is yet to be confirmed experimentally. However, computational work provided unique opportunities to understand the role of different short-lived species. The recent study by Denmark for the first time detected several catalytically active premetalation complexes. His study for the first time provided direct structural information of short-lived catalytically active transmetalation species. Overall, considerable effort has been done to unravel the mechanistic mystery a highly general and accurate mechanism for cross coupling reaction has yet to come.

ACKNOWLEDGEMENT: We thank to University of Delaware and Seoul National University for financial support. We also want to extend our gratitude to our doctoral and postdoctoral advisors. We are par-

ticularly thankful to Prof. Denmark for his generous discussion.

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