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Cross-Coupling

Transmetalation in the Suzuki–Miyaura Coupling: The Fork in the Trail

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The Suzuki–Miyaura coupling is one of the few transition-metal-catalyzed C–C bond-forming reactions that have been used in applications ranging from discovery chemistry to manufacturing processes. Although coupling proceeds through the generic three-stage 'oxidative addition, transmetalation, reductive elimination' sequence, there are a number of features that differentiate the Suzuki–Miyaura process from other transition-metal-catalyzed cross-couplings. Most of these features are centered around, or are a consequence of, activation of the boron reagent for transmetalation through one or both of two distinct pathways. This review focuses on the evidence that has been presented for this 'fork in the trail', and the potential to apply such mechanistic insight to the design of reaction conditions.

1. Introduction

1.1. Suzuki–Miyaura Coupling

Unlike many other metal or metalloid alternatives, organoboron compounds are usually inexpensive to prepare, have a broad functional-group tolerance, and generate co-products that are relatively environmentally benign. The ability of organoboron reagents to transmetalate with a variety of metal compounds has been known for many years.[1] However, it is their especially versatile transmetalation with palladium(II) complexes that has allowed the Suzuki–Miyaura reaction to develop into such an important coupling process in academic and industrial settings.

In general, the mechanisms of transmetalation in cross-coupling reactions have been much less extensively studied than the other major steps in these processes. For the Suzuki–Miyaura coupling, this study necessitates the identification, characterization, and measurement of the reaction rates of the key palladium(II) intermediate(s) with the active transmetalating agent. A recurrent theme is the general requirement of a base for the coupling to proceed. The precise role of this base, which is usually inorganic in nature, has been a matter of considerable debate over the past few decades. Moreover, some of the 'unintended consequences' of the use of such bases have become apparent only more recently.

1.2. The Fork in the Trail

The purpose of this Minireview is to compare and contrast mechanistic studies on this transmetalation event. As will become clear, there has been a dichotomy of opinion, complicated by the fact that while boronic acids are now the reagents that are most associated with the Suzuki–Miyaura coupling, a wide range of other organoboron reagents are also employed, in combination with an ever-increasing selection of ligands, organic electrophiles, bases, and additives.

The overarching mechanistic complexity in the transmetalation event arises from the fundamental property of three-coordinate boron species, which are Lewis acidic to varying degrees. Association of a fourth ligand to generate a four-coordinate "ate" complex is required to facilitate efficient transfer of the organic moiety from an organoboron species to a metal center, for example, Pd. The key question that then arises is the provenance of this "fourth ligand". The analysis can be subdivided to consider two distinct courses of events: A) a four-coordinate boron species is preformed, or generated through an equilibrium that is established in situ, and associates with the intermediate of the oxidative addition (**1**, Scheme 1) to transfer its organic moiety, the so-called 'boronate' pathway, or B) a ligand on the palladium catalyst

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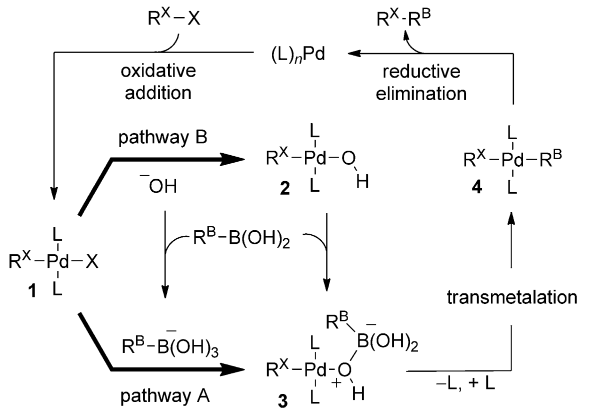


Scheme 1. Simplified generic mechanism for Suzuki–Miyaura coupling of a boronic acid ($R^BB(OH)_2$) with an organohalide (R^XX). L = ligand or solvent, X = halide; only *trans* isomers shown. The "Fork in the Trail" occurs at intermediate **1**, where pre-transmetalation intermediate **3** is either generated directly through the "boronate" pathway A, or indirectly via intermediate **2** on the "oxo-palladium" pathway B.

acts as a Lewis base toward a three-coordinate boron species, thus only generating the requisite four-coordinate species upon association with palladium. When this "tethering ligand" on the Pd is an alkoxy or hydroxy group (**2**), the pathway is referred to as the 'oxo-palladium' pathway. Ambiguity arises because inorganic bases, in aqueous or alcoholic media, are frequently employed in the Suzuki–Miyaura coupling, thus providing the requisite hydroxy or alkoxy ligands to facilitate either pathway A or B.

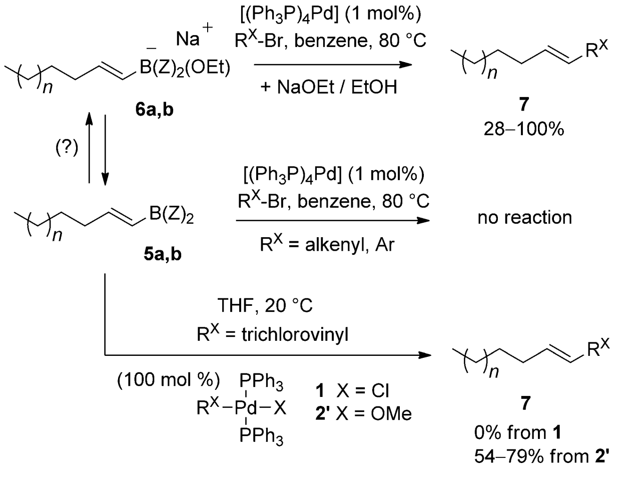
One might consider that the "fork in the trail" at intermediate **1** (Scheme 1) is merely of academic interest. After all, the pathways reconvene at **3** prior to transfer of the organic moiety and product-generating reductive elimination from **4**. However, a more general understanding of the evidence for both mechanisms and the factors that may affect catalytic transit through one or the other will naturally influence the optimization of reaction conditions. In particular, tailoring the conditions so that they are conducive to the most efficient pathway for that particular set of reagents can facilitate faster turnover and attenuate side reactions, such as protodeboronation, oxidation, and homocoupling.[2]

2. Pathways for Transmetalation

Elucidation of the dominant pathway to transmetalation is not at all straightforward: one must establish the kinetically active boron and palladium intermediates, and they may not necessarily be the most abundant species present in the medium. These difficulties are reflected in a large number of conflicting computational, spectroscopic/spectrometric, and kinetic studies. Below, we survey these studies, beginning with the early investigations by Suzuki and Miyaura,[3] and culminating in the most recent insights,[4] reported in 2011 by Amatore and Jutand,[4a] Hartwig,[4b] and Schmidt.[4c] We then move on to consider additional factors that lead to further dichotomies, intricacies, and physicochemical subtleties.

2.1. Early Observations

Pivotal to the development of the Suzuki–Miyaura coupling (1979) was the conclusion[3ab] that earlier attempts[5] to cross-couple organoboron reagents with organic halides had failed because the neutral three-coordinate boron species



Scheme 2. Early mechanistic conclusions regarding the pivotal role of alkoxide base for transmetalation, through pathway A[3ab] and pathway B.[3c] Z_2 = (3-methyl-2-butyl)$_2$ (**5a**/**6a**) or catechol (**5b**/**6b**).

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Guy Lloyd-Jones studied at Huddersfield Polytechnic (B.Sc. 1989) and Oxford University (D.Phil. with John M. Brown FRS, 1992) before tenure of a Royal Society postdoctoral fellowship at the University of Basel with Andreas Pfaltz. He joined the University of Bristol in 1996, was promoted to full Professor in 2003, and elected to the Royal Society (FRS) in 2013. Recent research includes Au- and Pd-catalyzed arylation, the chemistry of organotrifluoroborate salts, Tsuji–Trost allylation, metathesis, Ar–S bond-formation, amide activation, diazomethane reactions, aryne chemistry, and phosphine/amine borane complexes.

5a,**b** (Scheme 2) were insufficiently nucleophilic to efficiently transmetalate. Addition of NaOEt and NaOH, nominally to convert the organoboron reagents into more nucleophilic four-coordinate 'ate' complexes **6a**,**b**,[3c] resulted in the evolution of the most important transition-metal-catalyzed C–C bond-forming reaction to date, and a share of the 2010 Nobel Prize in Chemistry.

However, despite the preliminary[3ab] postulate that the coupling that generates **7** proceeds through pathway A and thus requires pregeneration of four-coordinate "ate" complexes **6a**,**b**, a detailed study on alkenyl–alkenyl couplings published six years later[3c] suggested that the alternative pathway B was active, involving turnover via alkoxo-palladium intermediates. Findings that led to these conclusions included: a) the lack of coupling when Et_3N was employed[6] as Lewis base; b) that the lithium salt of B-methylated hexenylboron reagent **5a** coupled with low yield (9%) in the absence of base, whereas the neutral 1-hexenyl dialkyl boron species **5a** coupled efficiently (49–73%) in the presence of NaOR/ROH (R = Me, Et); and c) that traces of alkene, the product of hydro-dehalogenation of the alkenyl bromide substrate, were obtained. The hydro-dehalogenation was interpreted as being indicative of a Pd–H species generated through β-H elimination in the alkoxo-palladium species **2**. Further supporting evidence was obtained by stoichiometric reactions of octenyl boron reagents **5** ($n = 2$) with isolated complexes **1** and **2′** (Scheme 2). Overall, it was concluded that after oxidative addition, alkoxo-palladium intermediates **2** (Scheme 1) are formed by metathetical displacement with, for example, sodium alkoxide, and that this species then captures the neutral three-coordinate organoboron reagent **5a**,**b**.[3c,d]

2.2. Computational Studies

Computational studies[7,8] on the coupling have tended to focus on the simplest collections of reactants, often with model ligands such as PH_3. In most studies, it has been assumed that transmetalation proceeds through the boronate pathway A,[7] with the motivation for the study being other mechanistic aspects, such as the effect of the phosphine ligand,[7c] or even the dissociation of the aryl anion from $[ArB(OH,F)_3]^-$ species.[7b] Only Maseras[8] has directly compared both pathways A and B. DFT[8a–c] (and DFT/MM)[8d] studies were conducted on the transmetalation of vinyl and phenyl boronic acids with $[L_2Pd(Ar)X]$ intermediates ($L = PH_3$, PPh_3; X = OH, Br; Ar = Ph, 4-phenylpyrid-2-yl).

For pathway A, formation of the boronate species $RB(OH)_3^-$ (**6c**) from $RB(OH)_2$ (**5c**, R = vinyl, Ph) was predicted to be almost barrier-less, and transmetalation begins through a coordinating interaction between the hydroxy group on the incoming boronate $[RB(OH)_3]^-$ and the $[L_2PdAr(Br)]$ species. This associative process ($[\mathbf{1}+\mathbf{6c}\rightarrow\mathbf{3}]^{\ddagger}$, Figure 1) induces the departure of the bromide ligand to generate key intermediate **3**, prior to the transfer of the organic moiety R from B to Pd. Similar profiles were determined for phenyl and vinyl boronic acids, except that the latter included η²-vinyl intermediates.

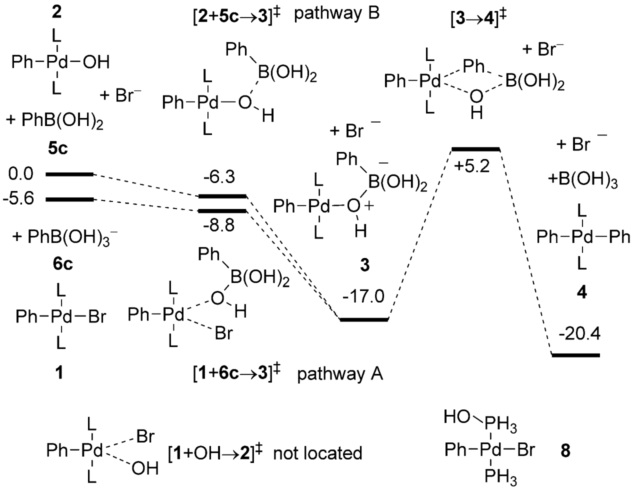


Figure 1. DFT (gas-phase) studies on the transmetalation of $[(PH_3)_2Pd(Ph)Br]$ with $Ph\text{-}B(OH)_2 + OH^-$ (no cation).[8] Pathways A and B have been normalized (-20.4 kcal mol^{-1}) at **4**; $L = PH_3$.

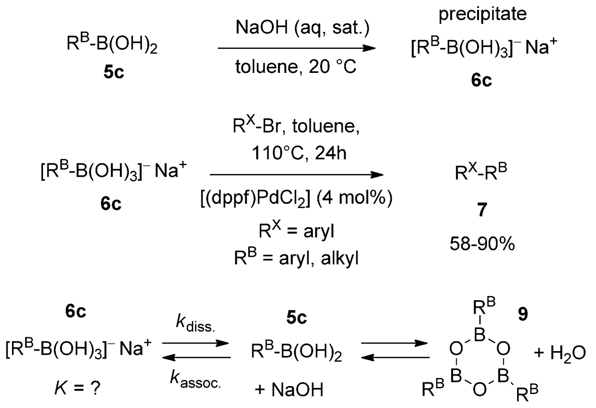
For pathway B, in all cases, transmetalation reactions begin with neutral $RB(OH)_2$ (**5c**) and $[L_2PdAr(OH)]$ (**2**) species and proceed with a similar or lower energetic barrier than pathway A. However, the transition state for the requisite associative displacement of Br with OH at Pd ($[\mathbf{1}+OH^-\rightarrow\mathbf{2}]^{\ddagger}$, Figure 1) could not be located. An alternative route, involving initial attack by hydroxide on the phosphine **8**, followed by a 1,2-shift to palladium to displace bromide, was found to be energetically feasible,[8a] but also facilitates oxidation of the phosphine ligand and concomitant reduction of Pd.[9,10] Thus, in all three studies,[8] it was concluded that the boronate pathway A is responsible for catalysis, because of a lack of ready access to the hydroxy–palladium intermediates **2** from nascent Pd–halide **1**, as would be required for turnover through pathway B.[8]

2.3. Detection of Intermediates

ESI-MS was used in a number of studies to analyze transmetalation. Negatively charged boronate species **6** and the halide–palladium complex **1** have both been detected in reaction mixtures using this technique, but not the oxo-palladium intermediate **2**.[11] Although this analysis confirms the presence of key species of pathway A, it does not reveal their reactivity characteristics. It is also of note that, irrespective of whether pathway A or B is followed, as written and indeed found computationally,[2a,7,8] both mechanisms should converge at **3**, the precursor to the transfer of R from B to Pd. To date, this key intermediate **3** has remained elusive,[8d] likely as a result of the favorable electronics for the transfer of the organic fragment from B to Pd (**3**→**4**). The barrier of this process was predicted computationally to be low (14–22 kcal mol^{-1}),[2a,7,8] suggesting specialist techniques will need to be applied to detect and confirm the identity of **3** experimentally.

2.4. Preformed Boronates

In principle, the ability to isolate preformed boronate reagents allows the direct assessment of the viability of pathway A.[11b,12] As noted above, early work from Suzuki and Miyaura showed the lithium salt of B-methylated alkenylboron species **5a** to give a much lower yield of coupling product than the neutral reagent **5a** in the presence of hydroxide, which was interpreted as evidence against the boronate pathway A.[3c] However, the possibility that the absence of a potentially Pd-coordinating heteroatom in the B-methylated alkenylboron species may be responsible for the much lower reactivity was apparently not considered at that time. Conversely, in a much more recent study, the sodium salts of trihydroxyboronate species **6c** could be readily prepared from boronic acids **5c**, which were isolated and then used in Suzuki–Miyaura coupling reactions under conditions that were free of additional base (Scheme 3).[12]



Scheme 3. Preparation of organotrihydroxyboronate reagents (**6c**), and their Suzuki–Miyaura coupling, nominally through pathway A.[12a]

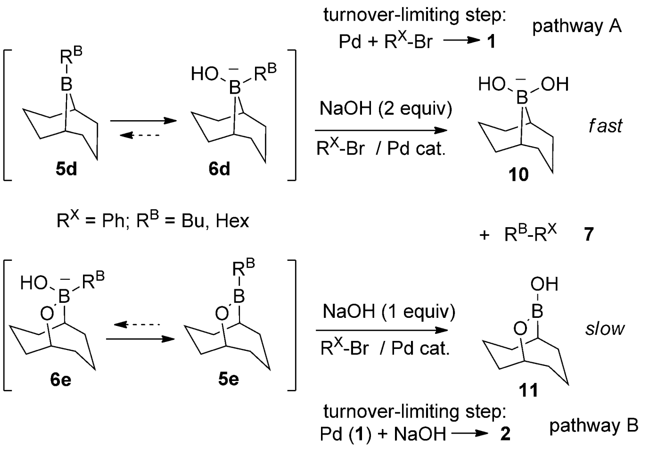
On first inspection, this result suggests that transmetalation readily occurs through the boronate pathway A. However, trihydroxyboronates **6c** were isolated by precipitation from toluene and their solubility in the coupling-reaction medium (anhydrous toluene) is very low. Thus, without probing the solution-phase associative equilibrium (both position and rate, K and k) for **6c** under the reaction conditions, it is unclear whether catalytic flux can also proceed with a small quantity of constantly replenished NaOH/boronic acid **5c**. Moreover, even starting with anhydrous toluene,[12a] liberation of toluene-soluble **5c** potentially facilitates the generation of a basic biphase, through the formation of boroxine **9** and aqueous solubilization of NaOH (Scheme 3). The ready dehydration of aryl boronic acids in toluene (**5c**→**9**, R^B = Ar) has previously been noted in the Suzuki–Miyaura coupling.[2a] Other examples of the coupling of **6c** have been conducted in methanolic[11b] or aqueous[12b] media, where the issues regarding pre-equilibria are even more apparent.

The trihydroxyboronate salts of **5c** are not the only preformed boronates that have been successfully coupled under conditions free of additional base. Miyaura[13a] and Buchwald[13bc] have both reported trialkoxyboronate salts that undergo very efficient Suzuki–Miyaura coupling in aqueous DMF or THF. Again, the possibility for a preceding equilibrium liberation of alkoxide (analogous to Scheme 3), and the generation of an aqueous basic biphase (see below) must be considered alongside their direct coupling.

2.5. Kinetic Studies: Catalytic Systems

One of the earliest kinetic studies on the Suzuki–Miyaura coupling was reported in 1994 by Smith.[14] Coupling of an aryl bromide with an aryl boronic acid forged the biaryl linkage in a precursor to losartan, a drug for the treatment of hypertension. Reactions were conducted in an aqueous diethoxymethane solvent mixture at 75 °C, using K_2CO_3 as a heterogeneous base with an in situ generated $[(Ph_3P)_nPd]$ catalyst. HPLC-derived kinetic data indicated that the oxidative addition of the aryl bromide was rate-limiting, whereas with iodotoluene, the rate-limiting event was a post-oxidative addition, possibly the transmetalation step. Interestingly, further analysis of the Pd speciation under both conditions (ArBr/iodotoluene) by kinetic modelling suggested that the proposed $[L_2PdX(Ar)]$ intermediates **1** (X = Br, I) were of similar reactivity toward transmetalation. This finding was interpreted as evidence against a mechanism in which halide dissociation preceded transmetalation, that is, via a cationic intermediate $[L_2Pd(Ar)]^+$. Two equivalents of both water and base were required for complete coupling, the second equivalent of base for boric acid sequestration. Although the reaction was relatively insensitive to the carbonate counterion (Na, K, Cs), it failed when bicarbonate was employed. The typical pK_a of an aryl boronic acid in water ($PhB(OH)_2$, $pK_a = 8.8$), relative to carbonate (10.3) and bicarbonate (6.4), was taken as evidence for the generation of the trihydroxyboronate as an essential step for coupling through pathway A.

A few years later, Soderquist[15] conducted systematic studies on the transmetalation step for coupling of primary alkylboranes **5d** and **5e** with bromobenzene + NaOH, in aqueous THF solutions (Scheme 4). This study revealed distinct sets of kinetic behavior, depending on the boron species used. According to ^{11}B NMR spectroscopy, Lewis acidic alkylborane **5d** readily formed boronate complex **6d** in the presence of base. ^{2}H-labeling at the primary alkyl carbon atom attached to the boron atom was elegantly employed to show that transmetalation proceeds stereospecifically (retention). The kinetics of the reaction of PhBr with **5d**/**6d** (initial rates, aqueous THF, NaOH, 65 °C, 2–3 mol% $[PdL_4]$; L = PPh_3) were found to be first-order in PhBr, and pseudo-zero-order in both **5d**/**6d** and NaOH. In contrast, the association of hydroxide was undetectable (^{11}B NMR spectroscopy) in alkylborinates **5e** that are of lower Lewis acidity. Rates of turnover were slower when **5e** was employed, and in competition experiments, **5d**/**6d** were orders of magnitude more reactive than **5e**. The kinetics of coupling of PhBr with **5e** (initial rates, aqueous THF, NaOH, 65 °C, 2–3 mol% $[PdL_4]$) were found to be distinctly different to **5d**, with a pseudo-zero-order dependency on both PhBr and **5e**, and a first-order dependency on NaOH. In separate stoichiomet-



Scheme 4. Pathways and stoichiometries for the Suzuki–Miyaura coupling (2–3 mol% [(PPh$_3$)$_4$Pd], aq NaOH, THF, 65 °C) of reagents **5d** and **5e**, which are of substantially different Lewis acidity.[15]

ric experiments, the rate of hydrolysis of in situ generated [L$_2$PdBr(Ph)] (**1**) to the hydroxy–palladium species [L$_2$PdOH(Ph)] (**2**) was found to be slow.

Another stark difference between **5d** and **5e** was found in a study of the stoichiometry of NaOH required to effect coupling: with **5d**, 2.0 equivalents are required, whereas with **5e**, reaction still proceeded effectively (92% conversion) with just 1.0 equivalent. Overall it was thus concluded that the transmetalation proceeds through the neutral pathway B for **5e**, with rate-limiting palladium-halide hydrolysis, but through the boronate pathway A for the more Lewis acidic **5d**. The mechanistic differentiation between **5d** and **5e** also explains the distinct difference in the stoichiometry of NaOH required to effect high conversion. The co-product of the reaction arising from **5d** is also substantially Lewis acidic, readily generating **10** and thus competing for the NaOH required to activate **5d**. In contrast, neither **5e**, nor its cross-coupling co-product **11**, sequester significant NaOH from the medium, leaving it available to effect salt metathesis with the catalytic palladium intermediate [PdBr(Ph)L$_2$] (**1**). The retention of configuration at the primary carbon atom in the coupling of **5d** is of course consistent with both pathways, as the alkyl group will be delivered through a four-membered transition state evolving from the elusive intermediate **3**. Finally, we note that Soderquist was careful to emphasize that "The energetics of the individual steps in this catalytic process are obviously very dependent upon the specific reagents and conditions employed."[15]

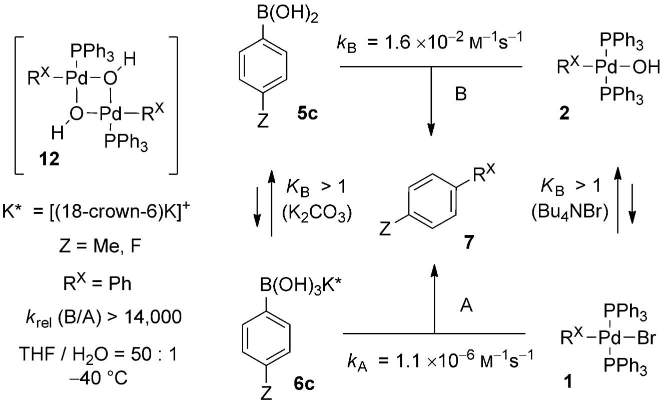
2.6. Kinetic Studies: Linear Free-Energy Relationships

A number of Hammett analyses have been conducted with Ar-B reagents to probe the linear free-energy relationships attending the transmetalation step. For example, coupling of 2-aryl-1,3,2-dioxaborinanes and a propargylic carbonate suggested a marginal build up of negative charge in the transition state ($\rho = +0.73$).[3e] A smaller effect was noted for the coupling of aryl boronic acids **5c** with 2-bromotoluene ($\rho = +0.24$).[16a] Conversely, a decrease in charge density was found for their coupling with both *E*-bromostilbene ($\rho = -0.7$)[11b] and in situ generated vinylbromide ($\rho = -1.3$),[16b] whereas coupling with 2-chlorotoluene was almost insensitive.[16a] The problem inherent in such analyses is that multiple steps are involved in systems that undergo catalytic turnover, with the boron reagent a common factor in the bifurcation between pathways A and B. For example, electron-donating substituents on the ArB(OH)$_2$ species **5c** would be expected to make the boron center less Lewis acidic, decreasing the rate of association with OH or Pd-OH moieties, but accelerating the R to Pd transfer step in **3** as a result of an increasing nucleophilicity.[3e] The opposite effects are of course expected with electron-withdrawing substituents. In summary, positive, negative, or zero Hammett ρ values can all be interpreted as fitting either pathway, through opposing electron demands in sequential processes (i.e. compensating effects). A more detailed kinetic interrogation of changes in electron density in discrete steps or equilibria[17] are anticipated to be very revealing.

2.7. Kinetic Studies: Stoichiometric Reactions

In 2002, Miyaura noted a previously unpublished[3f] result that [(Ph$_3$P)Pd(OH)(Ph)]$_2$ (**12**) reacts at room temperature with *p*-anisylboronic acid to give homo- and cross-coupling products in 85% yield, thus demonstrating viability of the second step in pathway B. Much more recently, independent reports from the groups of Amatore and Jutand,[4a] Hartwig,[4b] and Schmidt[4c] have detailed the kinetics of stoichiometric transmetalation. All three studies concluded that, at least for the systems tested, the oxo-palladium pathway B is kinetically the most favorable.

Amatore and Jutand employed electrochemical techniques in combination with heteronuclear NMR spectroscopy to study various transmetalation scenarios.[4a] Catalytic conditions were imitated by the use of a three-fold excess of aryl boronic acid **5c**, and reactions were conducted at room temperature in DMF. The generation, then decay, of each palladium species gives a characteristic voltammogram and the resulting reduction or oxidation currents are proportional to the concentrations of the electroactive species. The rate of transmetalation of the boronate species **6c** with the halide complex **1** (X = Br) was found to be very slow indeed (Scheme 5). In the presence of hydroxide, complex **1** was found to participate in a rapid equilibrium with the oxo-palladium complex **2**, which is in direct contrast to the high barriers predicted by DFT (Figure 1),[8] and transmetalation then proceeded efficiently with **5c**. Independently generated **2** behaved analogously. Two alternative transmetalation pathways, **1** + **5c** and **2** + **6c**, were ruled out by observation of rate attenuation on increasing concentrations of bromide (shifting the equilibrium from **2** back toward **1**) and hydroxide (shifting the equilibrium from **5c** back toward **6c**). Overall, the extracted kinetic data thus indicated that the only reaction that occurs at a significant enough rate to account for turnover, is that between the neutral boronic acid **5c** and the oxo-palladium species **2**.[4a]



Scheme 5. Approximate second-order rate constants for reaction of **1** and **2** with excess **5c** and **6c** (10 equiv, in THF/H_2O, 50/1, at -40 °C) and threshold equilibrium distributions for preceding salt metathesis and boron/OH^- association (THF/H_2O (50/1) at $+20$ °C.[4b] Analogous conclusions regarding reactions through pathways A and B, and the low reactivity of $\mathbf{2}+\mathbf{6c}$ and $\mathbf{1}+\mathbf{5c}$, are drawn from extensive electrochemical data in DMF at 22 °C.[4a]

Hartwig[4b] measured rates of the stoichiometric transmetalation of both the halide complex, $[(Ph_3P)_2Pd(Br)Ph]$ (**1**), with aryl trihydroxyboronate **6c**, and in situ generated $[(Ph_3P)_2Pd(OH)Ph]$ (**2**) with *p*-tolylboronic acid (**5c**). ^{31}P NMR spectroscopy was employed to monitor the rapid decay of both palladium species at low temperatures (from -55 to -30 °C). The transmetalation between *p*-tolylboronate **6c** and the bromide complex **1** was found to be around four orders of magnitude slower than that between boronic acid **5c** and the oxo-palladium complex **2**. It should be noted that these reactions were conducted in the presence of 18-crown-6, which may attenuate the availability of the K^+ counterion to **6c** for Br^- abstraction from Pd in **1**, and thus reduce the rate. The propensity for generation of the key Pd-OH species **2** from **1** was examined by measuring the equilibrium constant for salt metathesis with various halide complexes. Access to the oxo-palladium complex **2** was complicated by an equilibrium with the bridged hydroxy dimer **12**, but this could be manipulated through the addition of excess ligand (PPh_3), or by the use of the analogous Cy_3P complexes that are monomeric.

In the presence of $n$$Bu_4NX$, the oxo-palladium complexes underwent mildly endergonic equilibrium ($K \approx 2$) with the halide complex **1** (X = Cl, Br, I). Thus, taking into account the substantial differences in the bimolecular rate constant between the two transmetalation pathways, and the relatively unbiased equilibria between **5c**/**6c**, and **1**/**2**, the overall oxo-palladium pathway B was calculated as being substantially more favorable. Stoichiometric reactions of neopentyl glycol and catechol esters of *p*-fluorophenyl boronic acid **5c** with in situ generated Pd-OH complex **2** at -55 °C proceeded as rapidly as with the boronic acid; even the hindered pinacol ester reacted at this temperature, albeit in 1.5 h instead of just a few minutes. The overall conclusion was thus identical: the oxo-palladium pathway B is kinetically favored.

In a distinct but related study, Schmidt compared the rates of stoichiometric homocoupling of phenyl boronic acid (**5c**) in DMF/water (4:1) at ambient temperature by UV analysis, under phosphine-free conditions.[4c] The formation of biphenyl, in principle proceeding through two-fold transmetalation, was found to occur about two times more rapidly when **5c** was added to an equilibrium mixture of $[Pd^{II}(OAc)_2]$ and base (NaOAc), when compared to the addition of Pd to an equilibrium mixture of **5c** and base. The study added further weight to the conclusions of Hartwig,[4b] and Amatore and Jutand[4a] that pathway B is kinetically favored. Schmidt also noted that rates decreased when less-basic counterions were used ($OAc > Br \gg I$).[4c]

3. Additional Considerations

3.1. Boron Speciation and Biphasic Media

The fork in the trail (Scheme 1) arises from the exact role of the base, frequently an aqueous inorganic base, at one of the three key stages in the catalytic cycle. For both pathways, A and B, boron reagent speciation (Figure 2) will have an impact on the rate and efficiency of catalysis. Boron speciation is not only dependent on the pH value, but is also linked to the water concentration in the medium.[2a] With water-immiscible solvents, such as toluene, which forms two distinct phases in the presence or absence of base, the situation is clear. However, for water-miscible solvents, such as THF, dioxane, and DMF, which are also commonly employed in the Suzuki–Miyaura coupling, the addition of inorganic base can frequently induce phase splitting from what was initially a homogeneous aqueous-organic medium.[4b,18] In such cases, the volume of the minor phase is dependent on the amount of base added, and can commonly be just a few percent of the total reaction volume. Under these circumstances, the phenomenon is not always obvious on simple visual inspection, ranging for example from a hazy aspect through to agglomeration into a few small droplets that can adhere to vessel walls or stirrer bars, etc.

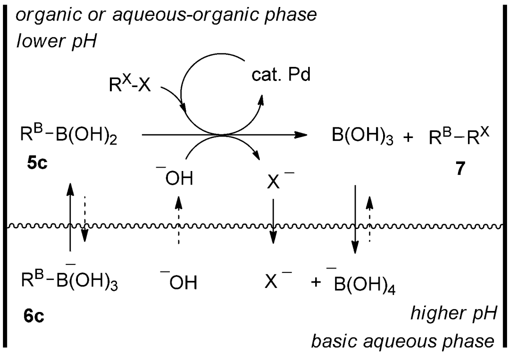


Figure 2. The potential influence of a biphasic medium, in which one of the two phases is predominantly aqueous and of much higher pH value, on boron speciation (**5c** versus **6c** and $B(OH)_3$ versus $B(OH)_4^-$) in Suzuki–Miyaura coupling through pathway B.

An analysis[18] of about forty thousand Suzuki–Miyaura couplings reported between 1981 and 2011 suggests that at least half are conducted in the presence of a basic aqueous biphase. A more detailed study of one specific system (THF-water-Cs_2CO_3) indicated that the Cs_2CO_3 was almost exclusively located in the predominantly aqueous minor phase, with the bulk phase being aqueous THF of much lower pH value. The difference in pH values between the phases results in the speciation of the boron reagent being much more strongly weighted toward the boronic acid in the bulk phase.[2a,18]

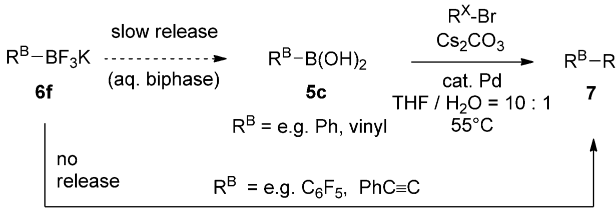
Biphasic media thus seem well-primed for Suzuki–Miyaura coupling, particularly through pathway B[18] (Figure 2). An aqueous phase with a higher pH value can act as a hydroxide reservoir for cross-coupling in the bulk organic phase, with the reaction conditions in the latter defined by the miscibility of the organic solvent with water. Although the two pathways for transmetalation place different initial demands for hydroxide in the minor basic phase, once the reaction is at a steady state, each turnover of the cycle formally consumes either one or two hydroxide anions (analogous to **10** in Scheme 4) and liberates one equivalent of halide (X^-) and boron co-product. When boronic acids are coupled, both co-products (X^- and $B(OH)_3$) are thermodynamically driven toward the aqueous minor phase, but until they are sequestered, they can potentially influence turnover. For example, $B(OH)_3$ can compete with R-$B(OH)_2$ for OH^- or Pd^{II}-X^-/OH^- intermediates **1** and **2**, while X^- can bias (common-ion effect) the equilibrium metathesis of Pd^{II}-X with OH^- (**1**→**2**).

Under these circumstances, the aqueous phase thus acts not only as a reservoir of base, but also as a repository for nascent halide and boron salts. As such, the reaction scale, vessel shape, and mode of agitation/stirring can all have a profound impact on the efficiency of phase contact. These parameters in turn then limit the macroscopic rates of transport of species, in both directions, between the bulk reaction medium and the minor split phase. These physical parameters, not usually of any consideration in homogeneous reactions, can potentially influence which of the two transmetalation pathways is followed, can govern the overall reaction rate directly, or indirectly through the rate of reagent release,[18] and affect selectivity for the desired cross-coupling over undesired reagent decomposition processes.[19]

Suzuki–Miyaura coupling in a single-phase (homogenous) medium is expected to be favorable when pathway A is dominant. A higher base concentration can be established in the medium, thus biasing the equilibrium between, for example, **5c** and boronate **6c**. However, a higher base concentration can also unfavorably bias the equilibrium between **1** and **2**, as well as facilitating higher net rates of proto-deboronation.[2]

3.2. Reagent Release

In terms of “atom economy” of the boron reagent in Suzuki–Miyaura cross-coupling, it is hard to beat a boronic acid. However, there are consequences to their use, including protodeboronation, direct and indirect aerobic oxidation, and generation of boroxines or other polymeric linear anhydrides.



Scheme 6. Coupling of R^BBF_3K reagents **6f**[20b] via the boronic acid **5c** under ‘slow-release’ aqueous biphasic conditions. When R^B is sufficiently electron-withdrawing, solvolytic release becomes so slow that direct coupling of R^BBF_3K **6f** occurs, possibly through pathway A rather than pathway B.[18]

These issues have led to a suite of “masked” boron reagents that are more amenable to isolation, purification, storage, and handling. The boronic acid, or other reactive species, is then released in situ through a solvolytic process, or the masked reagent participates directly in the coupling. Prime examples of the former are the B-MIDA system of Burke[20a] and the organotrifluoroborate salts (**6f**) developed extensively by Molander.[20bc] In most cases, engineering of the reaction conditions allows the solvolysis rate to be modulated from “instant release” through to “slow release” so as to best meet the specific demands of the reaction or process in question.[2d] The reaction conditions usually employ water (or alcohols) as both a reactant (release agent) and a cosolvent, and thus the bulk of the mechanistic features discussed in Section 2 can be transposed.

A further factor that clouds the distinction made above is that for some reagent release systems, specific organic moieties retard the solvolysis rate so extensively that the transmetalation must proceed predominantly or, for example, exclusively through the masked reagent (Scheme 6).[18] This ambiguity is likely to be present in a number of the “masked” boron systems, where the mode of transmetalation will be dictated by the identity of the masking group. For many reagents, no detailed studies on the mechanism have been published to date, so it is not clear whether either of the two pathways will be followed exactly, if indeed at all.

3.3. Counterions and Additives

Inorganic bases employed in Suzuki–Miyaura couplings inevitably contain a counter-cation, the most common of which are from the alkali earth series. The roles of these cations were investigated by Amatore and Jutand,[4d] again using electrochemical techniques. Rates of transmetalation of **2** with **5c** were compared when the counterion to the base was varied (Cs^+, K^+, Na^+, and NBu_4^+). In all cases, the use of alkali metal cations led to slower rates of reaction than with the NBu_4^+. This was attributed to alkali metal cations competing with boron for coordination to the hydroxy group in the key oxo-palladium complex **2**.

The use of thallium bases has been reported to greatly enhance the rates of transmetalation, with TlOH giving a 1000 times greater rate of turnover than KOH.[21] A possible explanation includes TlX precipitation aiding the formation of the oxo-palladium species, which is an effect similarly proposed when employing silver as an additive or base.[22] Alternatively, an efficient pre-transmetalation to form a Tl-R intermediate may be viable,[3g] similar to that proposed with Cu additives.[20a, 22c] When Tl_2CO_3 is employed as base, it has been suggested that decarboxylation generates a cationic palladium center (see below).[21]

3.4. The Roles of Fluoride

The oxo- or alkoxo-palladium species **2** cannot be universal catalytic intermediates in Suzuki–Miyaura cross-couplings as these are not exclusively conducted using water or alcohol as a co-solvent. Equally, when pseudohalides are employed as coupling partners, for example, organotriflates,[23] the situation may further deviate from the current mechanistic investigations. Fluoride sources are effective mediators of Suzuki–Miyaura couplings,[24] with reactions sometimes conducted under nominally[25] anhydrous conditions, using for example, CsF or KF. In parallel with their study, in which they used OH^- as base, Amatore and Jutand also examined the role of fluoride.[4e] Interestingly, they verified that in DMF, fluoride effected similar reactivity and had the potential to play the same antagonistic roles as hydroxide, that is, formation of inactive $R\text{-}B(OH)_2F^-$ and active $[PdArL_2F]$. This observation implies that a related oxo-palladium pathway operates under conditions employing fluoride. DFT calculations on the transmetalation step (**3**→**4**) in which all three inorganic anions on boron, not just the μ-bridged ligand between palladium and boron, were systematically permuted from OH to F, demonstrated that the lowest barrier along the reaction coordinate occurred when three hydroxides ligated boron.[2a] Fluoride was shown to bridge the two metals less proficiently, as well as reducing the migrating ability of the organic group. The role of fluoride in transmetalation may thus predominantly be to deliver OH^- (or RO^-) to Pd through strong hydrogen bonding of F^- with water (or ROH) in the bulk medium.

3.5. Cationic Palladium

There is a modification to the boronate pathway A that we have only briefly considered thus far, and that is the attack of a palladium cation by the organotrihydroxyboronate salt **6c**. This leads directly to the common intermediate **3**, either through a synchronous outer-sphere salt metathesis; or through pregeneration of a distinct but short-lived ion pair of the form $[R\text{-}Pd(L)]^+[R'\text{-}B(OH)_3]^-$. Transmetalation through this cationic manifold was dismissed in the Merck study,[14] however, with triflates and an ion-stabilizing solvent, the equilibrium between neutral and cationic palladium intermediates may become more viable.

A much clearer example stems from coupling of arenediazonium BF_4 salts[26] in a base-free anhydrous medium. Using these conditions, Genet found that organotrifluoroborate salts (**6f**) led to superior yields compared to the use of boronic acids.[26a] The process has been substantially expanded by Schmidt,[26bc] and the mechanism studied by Mastrorilli using ESI-MS/^{19}F NMR spectroscopy.[26d] Oxidative addition of the diazonium salt through nitrogen evolution leads to a palladium species with substantial cationic character. The anionic tetravalent organotrifluoroborate **6f** presumably undergoes more efficient transmetalation than the neutral trivalent boronic acid. Because of the presence of the additional ligand at the boron atom, higher nucleophilicity is engendered for transfer of the organic fragment upon formation of a bridged complex analogous to **3**. As hydroxide acts more proficiently than fluoride[2a] as a μ-bridging in **3**, it is anticipated that a combination of arenediazonium salts with preformed trihydroxyboronates **6c**[12] may result in a very efficient cross-coupling process, through the boronate pathway A.

4. Conclusions and Outlook

What has hopefully become clear in this Minireview is that from the inception of the Suzuki–Miyaura coupling (1979) to the current date, opinion has vacillated on how the key, but elusive, pre-transmetalation intermediate **3** is generated. Without doubt, the recent work of Hartwig,[4b] and Amatore and Jutand,[4a,d,f] provides compelling and conclusive evidence for the catalytic transit through pathway B, but only with any certainty for coupling of aryl boronic acids or selected esters, with simple aryl halides (Cl, Br, I) in aqueous DMF, acetone, or THF, with $[(L)_nPd]$ ($L = Ph_3P$, and possibly Cy_3P) as catalyst and M_2CO_3 as base. Even here, ambiguities remain regarding the effects of MX, when M^+ is Bu_4N^+ versus Na^+, K^+, or Cs^+, and the possibility for pathways to evolve from B to A, or vice versa, as co-products from catalytic turnover accumulate. Nonetheless, it should be noted that, except for the experiments of Soderquist using 9-BBN derivatives (Scheme 4), there is scant evidence for significant catalytic turnover through the boronate pathway A. This should not rule it out from consideration however, and we hope that this Minireview may stimulate further study to answer this important question for a wider range of substrates, ligands, and reaction conditions.

The increasing use of “masked reagents”, for example, B-MIDA[20a] and RBF_3K,[20b] means that the impact of the release products must also be taken into account. Bring in further considerations of biphasic media, the wide range of phosphine and carbene ligands now in common use, the effect of moving from aryl to alkenyl and alkyl reactants, and it is clear that there is still much to be discovered[27] for this key catalytic reaction. Nonetheless, although we do not yet have a unified mechanistic understanding, many of the features outlined herein influence the design and optimization of Suzuki–Miyaura coupling, in all its guises.

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