

# The catalytic mechanism of the Suzuki-Miyaura reaction

Juliet M. Macharia<sup>†</sup>, Chetan Joshi<sup>†</sup>, Joseph A. Izzo, Victor Wambua, Sungjin Kim, Jennifer S. Hirschi\*, Mathew J. Veticatt\*

Department of Chemistry, Binghamton University, Vestal, NY 13850, USA

\*Corresponding author. Email: jhirschi@binghamton.edu (J.S.H) veticatt@binghamton.edu (M.J.V)

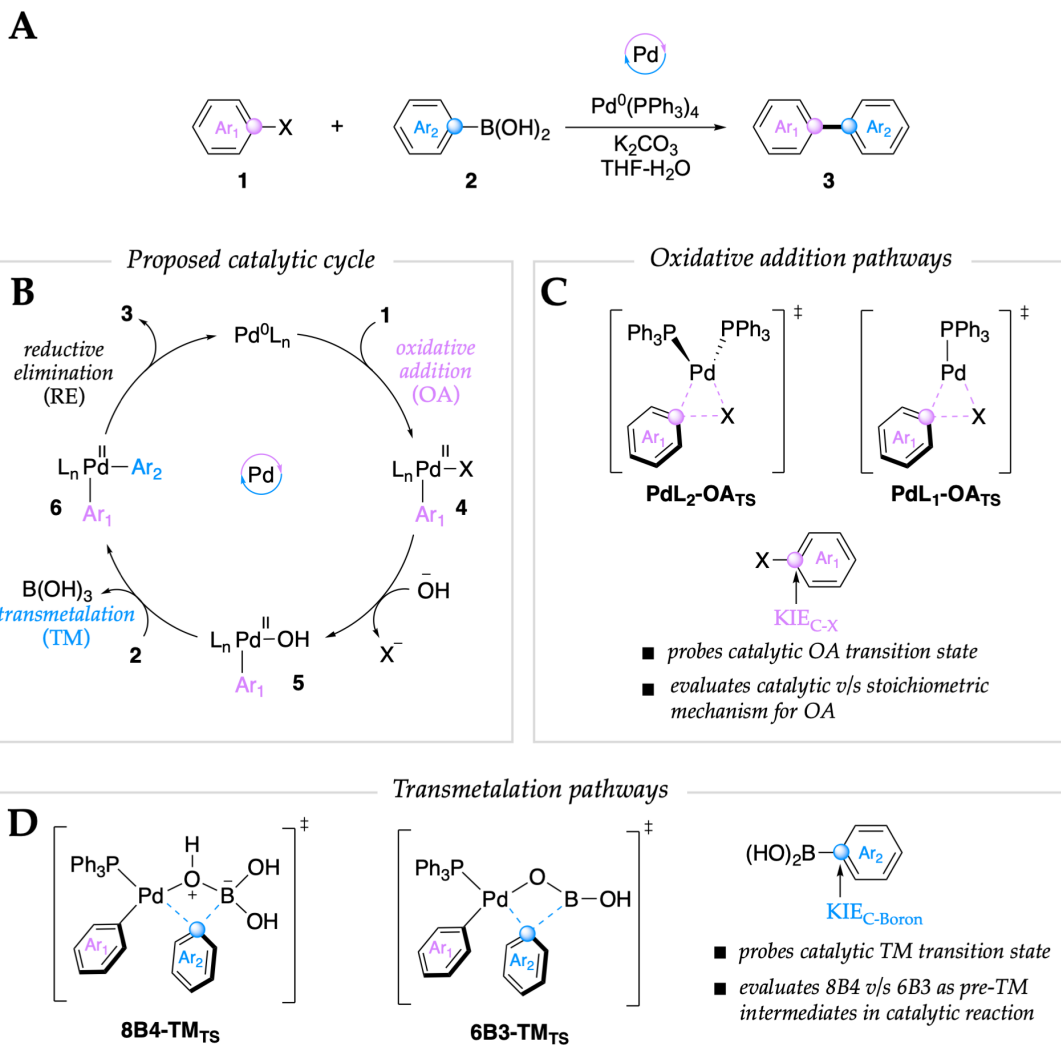
<sup>†</sup>Authors contributed equally

**Abstract:** Experimental and theoretical <sup>13</sup>C kinetic isotope effects are utilized to obtain atomistic insight into the catalytic mechanism of the Pd(PPh<sub>3</sub>)<sub>4</sub> catalyzed Suzuki-Miyaura reaction of aryl halides and aryl boronic acids. Under catalytic conditions, we establish that oxidative addition of aryl bromides occurs to a 12-electron monoligated palladium complex (Pd(PPh<sub>3</sub>)). For aryl iodides, the first irreversible step in the catalytic cycle precedes oxidative addition and is shown to be binding of the iodoarene to Pd(PPh<sub>3</sub>). Our results suggest that the commonly proposed oxidative addition to the 14-electron Pd(PPh<sub>3</sub>)<sub>2</sub> complex can occur only in the presence of excess added ligand or under stoichiometric conditions. The transmetalation step, under catalytic conditions, is shown to proceed via a tetracoordinate boronate (8B4) intermediate with a Pd-O-B linkage.

**One Sentence Summary:** The catalytic mechanism of the Suzuki-Miyaura reaction is resolved using <sup>13</sup>C kinetic isotope effects.

**Main Text:** Palladium catalyzed cross-coupling reactions, between an organic halide and an organometallic reagent, that forge carbon-carbon bonds constitute one of the central pillars of modern-day organic synthesis (1). Three sequential mechanistic events define the general catalytic cycle of most palladium catalyzed cross-coupling reactions: (a) oxidative addition (OA) of the organic halide to palladium (0) to form a palladium (II) complex; (b) transmetalation (TM), i.e. transfer of the organic portion of the organometallic reagent to the palladium (II) center; and (c) reductive elimination (RE) to form the new carbon-carbon bond and regenerate palladium (0) catalyst (2). High-resolution insight into the fine details of these fundamental steps is critical to the optimization of existing methodologies and development of novel catalytic cross-coupling reactions.

The palladium catalyzed Suzuki-Miyaura (S-M) reaction between an organic halide (1) and a boronic acid (2) has emerged as a versatile and robust cross-coupling process with broad application in the synthesis of high-value pharmaceuticals and fine chemicals (Fig. 1A) (3-5). The privileged status of the S-M reaction has inspired several high-quality experimental and theoretical investigations into the mechanism, leading to a constantly evolving view of this catalytic process (Fig. 1B) (6-14). OA has been extensively studied by a number of research groups (15-24) and the general consensus is that for simple phosphine ligands such as triphenylphosphine OA of 1 occurs to a palladium (0) center ligated to two phosphine ligands (PdL<sub>2</sub>) via PdL<sub>2</sub>-OATs to yield a PdL<sub>2</sub>ArX OA complex (Fig. 1C) (15). Alternatively, experimental (18) and computational studies (22, 23) have also suggested the possible involvement of a coordinatively unsaturated 12-electron PdL<sub>1</sub> complex as the active catalytic species in OA (Fig. 1C, PdL<sub>1</sub>-OATs).



**Fig. 1. Key mechanistic features of the catalytic Suzuki-Miyaura reaction** (A) Prototypical Suzuki-Miyaura reaction of aryl halide and aryl boronic acid catalyzed by a palladium (0) catalyst. (B) Widely accepted mechanism of the Suzuki-Miyaura reaction involving three key mechanistic events – oxidative addition, transmetalation, and reductive elimination. (C) Two possible pathways for oxidative addition involving either a 14-electron  $\text{PdL}_2$  or a 12-electron  $\text{PdL}_1$  palladium (0) complex. (D) Two viable pathways for transmetalation involving intermediates containing Pd-O-B linkages.

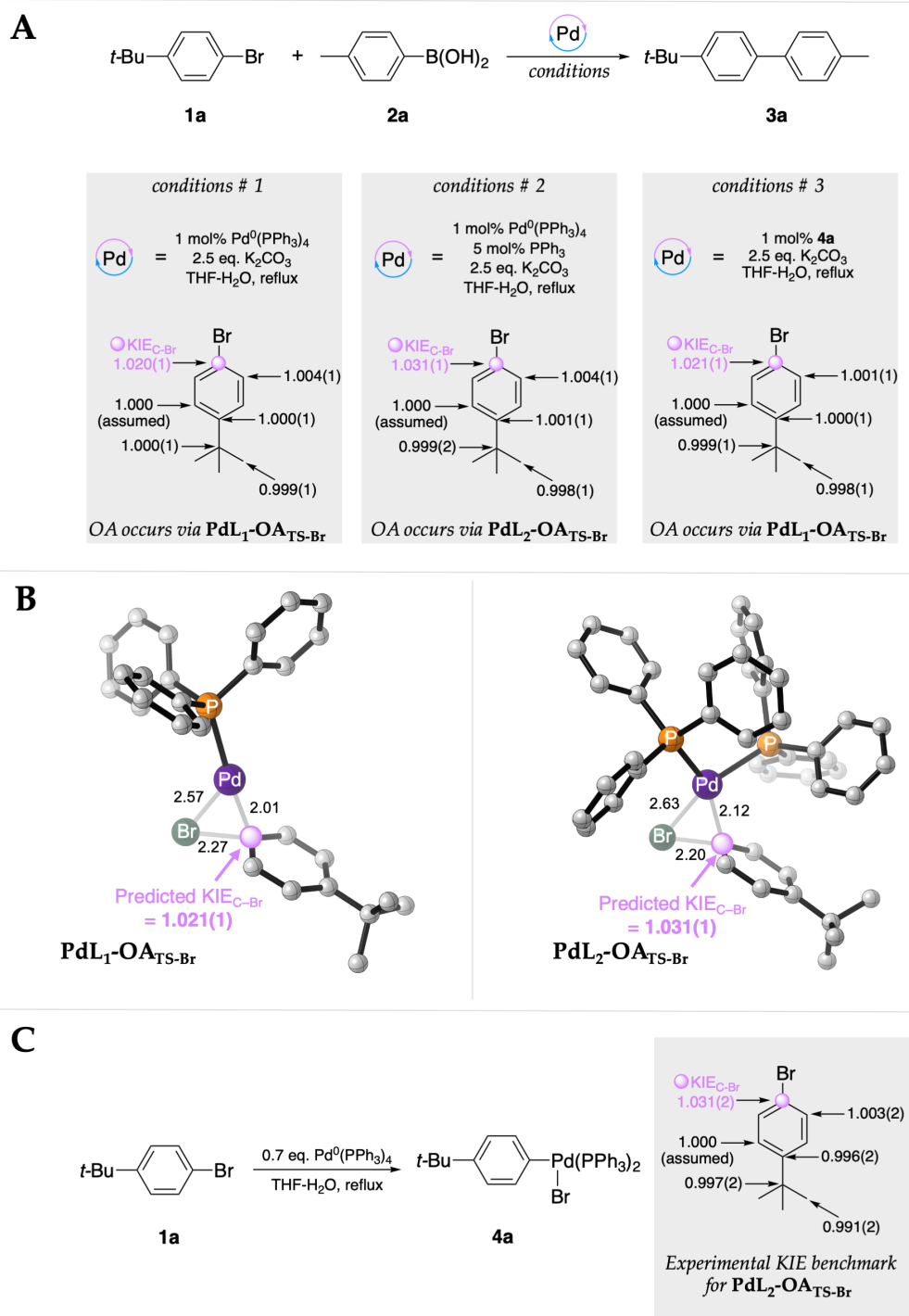
Elegant kinetic studies by Carrow and Hartwig, involving stoichiometric reactions of isolated OA complexes, have revealed that **4** is likely converted to a hydroxopalladium species **5** prior to the TM step by reaction with aqueous hydroxide generated in the THF-water reaction mixture containing an inorganic base such as  $\text{K}_2\text{CO}_3$  (25). Groundbreaking low-temperature NMR studies by Thomas and Denmark have shown that association of **2** and **5** leads to the formation of two key pre-TM intermediates containing Pd-O-B linkages – a tetracoordinate boronate (**8B4**) complex and a tricoordinate boronic acid (**6B3**) complex (12). However, since both intermediates readily convert to product **3** through TM (via **8B4-TM<sub>TS</sub>** or **6B3-TM<sub>TS</sub>**, Fig. 1D) and subsequent RE upon warming to room temperature, the exact identity of the pre-TM intermediate in the catalytic reaction remains ambiguous. Additional kinetic and computational studies by Denmark

and co-workers suggest that (a) both **8B4-TM<sub>TS</sub>** or **6B3-TM<sub>TS</sub>** are viable TM pathways depending on the concentration of ligand in solution, and (b) the TM event occurs only after dissociation of a ligand from these pre-TM intermediates (13). The final step in the catalytic cycle, C-C bond-forming RE, is extremely facile and thought to be accelerated by hydroxide ions in solution (26).

5 The currently accepted catalytic cycle for the S-M reaction (*vide supra*) is based predominantly on mechanistic observations from *stoichiometric* reactions of putative intermediate complexes (12, 15-19, 25). This approach is necessitated due to the low concentration of these intermediates under typical catalytic conditions (< 2 mol% palladium catalyst). Utilization of mechanistic observations from stoichiometric studies to interpret the catalytic mechanism is valid  
10 only if the intermediate complexes form under catalytic conditions. Kinetic studies can often provide valuable mechanistic information under catalytic conditions (7, 8); but this does not include atomistic information about the TS of the elementary steps. Computational studies provide detailed insight into the TS of each step of the catalytic S-M reaction (9, 10, 21, 22, 26-29). However, experimental validation of the calculated TSs in the catalytic S-M reaction has remained  
15 elusive.

A powerful experimental probe of transition structures in carbon-carbon bond-forming reactions is the determination of <sup>13</sup>C kinetic isotope effects (KIEs) at natural abundance (30-32). Despite this, there are limited examples of the use of <sup>13</sup>C KIEs among the vast literature of mechanistic studies of cross-coupling reactions (33-41). Given that each step in the proposed  
20 catalytic cycle of the S-M reaction involves bonding change at a carbon atom, determination of <sup>13</sup>C KIEs for the two bond-forming carbon atoms (Fig. 1, KIE<sub>C-X</sub> and KIE<sub>C-Boron</sub>) can provide vital insight into the transition structures of key steps under standard (catalytic) conditions. We describe herein a combined experimental and theoretical <sup>13</sup>C KIE study of the S-M reaction that provides unprecedented insight into the *catalytic* mechanism of this important reaction. Importantly, we  
25 find that <sup>13</sup>C KIEs are an exceptionally sensitive probe of the transition states involving bond-making or bond-breaking between carbon and palladium – *enabling the first experimental characterization of the transition structure of the OA and TM steps under catalytic conditions.*

*Probing the transition state geometry of OA in the catalytic S-M reaction:* Oxidative addition of aryl bromides to palladium (0) is highly exergonic and, barring some examples (42), is generally considered an irreversible step in the catalytic cycle. Therefore, <sup>13</sup>C KIEs determined for  
30 the aryl bromide in the S-M reaction should reflect the nature of the OA TS. We chose the prototypical S-M reaction of aryl bromide **1a** with boronic acid **2a** catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> for determination of <sup>13</sup>C KIEs for the aryl bromide (**1a**) via quantitative NMR analysis. Under catalytic conditions (Fig. 2A, conditions # 1), we observe a significant normal <sup>13</sup>C KIE on the carbon atom  
35 attached to the bromine (KIE<sub>C-Br</sub> = 1.020(1)). This result is qualitatively consistent with OA being the first irreversible step in the catalytic cycle and provides an experimental benchmark to probe the exact nature of the OA transition state using density functional theory (DFT) calculations.



**Fig. 2. Probing the oxidative addition step in the catalytic Suzuki-Miyaura reaction (A)**  $^{13}\text{C}$  KIE experiments to probe the OA TS as a function of ligand concentration and catalyst type. (B) Calculated TSs and predicted  $^{13}\text{C}$  KIEs for OA of **1a** to mono- and diligated palladium (0) with key bond distances shown in angstroms (Å). Predicted KIEs are expressed as an average from 12 DFT methods. (C) Stoichiometric experiment to establish a benchmark  $^{13}\text{C}$  KIE value for OA to PdL<sub>2</sub>. Experimental  $^{13}\text{C}$  KIEs are shown as an average of 12 measurements from two independent

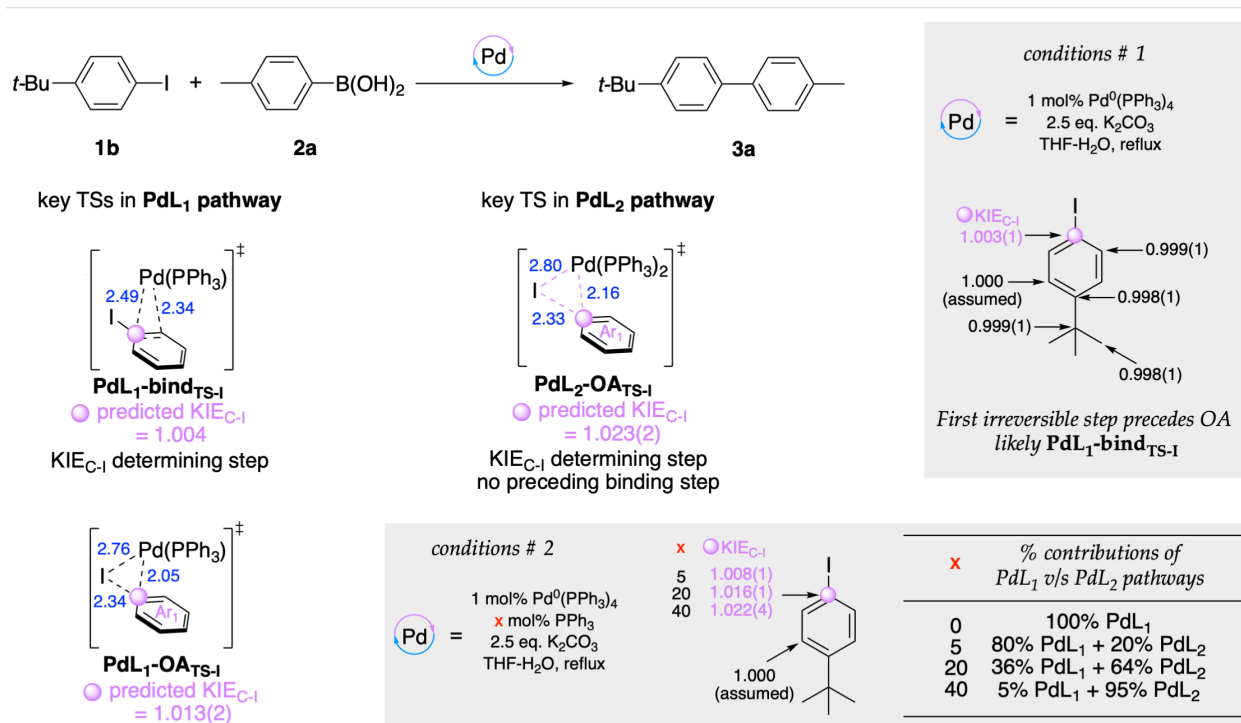
experiments. Experimental and predicted KIEs represent the 95% confidence range for the last digit shown in parentheses.

Key bond-distances and predicted KIEs for all transition structures presented in this study are displayed as an average from calculations implemented using 12 routinely employed DFT methods used to study these systems (see Supplementary Information for computational details). This ensures that the theoretical evaluation of our experimental results is not an artifact of one particular DFT method. For the quantitative interpretation of  $\text{KIE}_{\text{C-Br}}$  (Fig 2A, conditions # 1), we calculated the TS for OA of **1a** to both monoligated (**PdL<sub>1</sub>-OA<sub>TS-Br</sub>**) and diligated (**PdL<sub>2</sub>-OA<sub>TS-Br</sub>**) palladium (0) complexes. The two transition structures **PdL<sub>1</sub>-OA<sub>TS-Br</sub>** and **PdL<sub>2</sub>-OA<sub>TS-Br</sub>** are similar in terms of bond-making and bond-breaking distances (Fig. 2B). The Pd–C bond-forming distance in the mono-ligated **PdL<sub>1</sub>-OA<sub>TS-Br</sub>** is 2.01 Å compared to a slightly longer Pd–C bond-forming distance of 2.12 Å in the more electron-rich diligated **PdL<sub>2</sub>-OA<sub>TS-Br</sub>**. The greater extent of C–Pd bond-formation in **PdL<sub>1</sub>-OA<sub>TS-Br</sub>** also corresponds to a more advanced C–Br bond-breaking distance of 2.27 Å; C–Br bond-breaking distance in **PdL<sub>2</sub>-OA<sub>TS-Br</sub>** is 2.20 Å. Intriguingly,  $\text{KIE}_{\text{C-Br}}$  is exceptionally sensitive to these subtle differences in structure – the predicted  $\text{KIE}_{\text{C-Br}}$  for **PdL<sub>1</sub>-OA<sub>TS-Br</sub>** is 1.021(1) compared to a predicted  $\text{KIE}_{\text{C-Br}}$  of 1.031(1) for **PdL<sub>2</sub>-OA<sub>TS-Br</sub>** (Fig. 2B). Based on the excellent agreement of experimental and predicted KIEs for **PdL<sub>1</sub>-OA<sub>TS-Br</sub>**, our results suggest that OA in the catalytic S-M reaction (Fig. 2A, conditions # 1) occurs to a PdL<sub>1</sub> species. *Importantly, this result quantitatively rules out PdL<sub>2</sub> as the active species that undergoes OA in the catalytic reaction.*

To further support our finding that OA occurs to PdL<sub>1</sub> in the *catalytic* reaction, we conducted three additional experiments. The first experiment involves determination of  $\text{KIE}_{\text{C-Br}}$  for the *stoichiometric* OA of **1a** to Pd(PPh<sub>3</sub>)<sub>4</sub> to form the well-characterized PdL<sub>2</sub>(Ar<sub>1</sub>)(Br) complex (Fig 2C) (43). This stoichiometric experiment delivers an experimental benchmark  $\text{KIE}_{\text{C-Br}}$  value to unambiguously characterize **PdL<sub>2</sub>-OA<sub>TS-Br</sub>**. Gratifyingly, the  $\text{KIE}_{\text{C-Br}}$  for this reaction is 1.031(2) – a value consistent with the predicted  $\text{KIE}_{\text{C-Br}}$  for **PdL<sub>2</sub>-OA<sub>TS-Br</sub>**. *Importantly, this result provides unequivocal evidence that OA to Pd(PPh<sub>3</sub>)<sub>4</sub> occurs via different mechanisms under catalytic (Fig 2A, conditions # 1) versus stoichiometric (Fig. 2C) conditions.* In the second experiment, the catalytic S-M reaction of **1a** and **2a** was performed with added PPh<sub>3</sub> ligand (Fig. 2A, conditions # 2). Excess ligand is expected to decrease the probability of OA occurring to a PdL<sub>1</sub> by driving the PdL<sub>1</sub>/PdL<sub>2</sub> equilibrium towards the PdL<sub>2</sub> species. Consistent with our hypothesis, the  $\text{KIE}_{\text{C-Br}}$  for this reaction is 1.031(1) – a value consistent with the predicted  $\text{KIE}_{\text{C-Br}}$  for **PdL<sub>2</sub>-OA<sub>TS-Br</sub>**. The reaction with excess ligand is significantly more sluggish, suggesting that OA to PdL<sub>1</sub> is a faster process than OA to PdL<sub>2</sub>.(22) Finally, we performed the catalytic S-M reaction of **1a** and **2a** using the isolated complex **4a** as the catalyst (Fig. 1A, conditions # 3). Observation of an experimental  $\text{KIE}_{\text{C-Br}}$  of 1.021(1) illustrates that OA occurs via **PdL<sub>1</sub>-OA<sub>TS-Br</sub>** even when a PdL<sub>2</sub> complex is explicitly used as the catalyst for the S-M reaction.

Next, we turned our attention to studying the S-M reaction of aryl iodide **1b** and boronic acid **2a**. We determined  $\text{KIE}_{\text{C-I}}$  under standard catalytic conditions similar to ‘conditions # 1’ used for the bromo derivative (**1a**). The first key result is the near-unity  $\text{KIE}_{\text{C-I}}$  of ~1.003(1) (see Fig. 3, conditions # 1). This suggests there is no bonding change at this carbon in the first irreversible step of the catalytic cycle – a result qualitatively inconsistent with OA as the first irreversible step for **1b**. Oxidative addition of aryl iodides to palladium (0) is generally considered an irreversible process. Therefore, the absence of a significant normal  $\text{KIE}_{\text{C-I}}$  suggests the first irreversible step

for **1b** likely precedes OA, i.e. binding of **1b** to palladium (0) is irreversible and has a higher barrier than the ensuing OA step.



**Fig. 3. Using <sup>13</sup>C KIEs to probe contribution of concurrent pathways for oxidative addition in the catalytic Suzuki-Miyaura reaction of iodoarenes and boronic acids.** <sup>13</sup>C KIE experiments to probe the OA TS as a function of ligand concentration for aryl iodides along with predicted <sup>13</sup>C KIEs for all relevant TSs involved in the OA of **1b** under these conditions with key bond distances shown in angstroms (Å). Experimental <sup>13</sup>C KIEs are shown as an average of 12 measurements from two independent experiments. Experimental and predicted KIEs represent the 95% confidence range for the last digit, shown in parentheses.

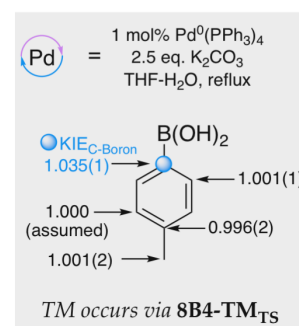
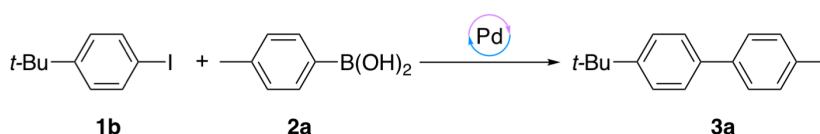
For the quantitative interpretation of the KIE<sub>C-I</sub>, we modeled the OA step of **1b** to both PdL<sub>1</sub> (**PdL<sub>1</sub>-OA<sub>TS-1</sub>**) and PdL<sub>2</sub> (**PdL<sub>2</sub>-OA<sub>TS-1</sub>**) complexes (Fig. 3A) using the theoretical methods described previously. Predicted KIE<sub>C-I</sub> for these two TSs are 1.013(2) and 1.023(2) respectively, both of which are inconsistent with the experimental KIE<sub>C-I</sub> value. Next, we located **PdL<sub>1</sub>-bind<sub>TS-1</sub>**, the transition structure for formation of the η<sup>2</sup> binding complex between PdL<sub>1</sub> and **1b**. Predicted KIE<sub>C-I</sub> for **PdL<sub>1</sub>-bind<sub>TS-1</sub>** is 1.004, which is in excellent agreement with the experimental KIE<sub>C-I</sub>. No such TS could be located for PdL<sub>2</sub> (IRC calculations from **PdL<sub>2</sub>-OA<sub>TS-1</sub>** result in separate starting materials) – consistent with prior investigations suggesting that OA of aryl halides to PdL<sub>2</sub> occurs without a preceding binding event (18, 22, 23). These results lend strong support to OA of **1b** to palladium (0) occurring via irreversible binding of **1b** to PdL<sub>1</sub> followed by a facile OA event.

To further confirm that the PdL<sub>1</sub> pathway is operative for **1b**, we determined KIE<sub>C-I</sub> in the presence of 5 mol% added PPh<sub>3</sub> (similar to Fig 2A, conditions # 2). Unlike in the case of aryl bromide **1a**, under conditions of excess ligand, we did not observe a KIE<sub>C-I</sub> corresponding to **PdL<sub>2</sub>-OA<sub>TS-1</sub>**; instead, we observed an experimental KIE<sub>C-I</sub> of 1.008(1) (Fig. 3, conditions # 2, x=5). A measurement greater than the predicted KIE<sub>C-I</sub> for **PdL<sub>1</sub>-bind<sub>TS-1</sub>** (the KIE-determining step in the

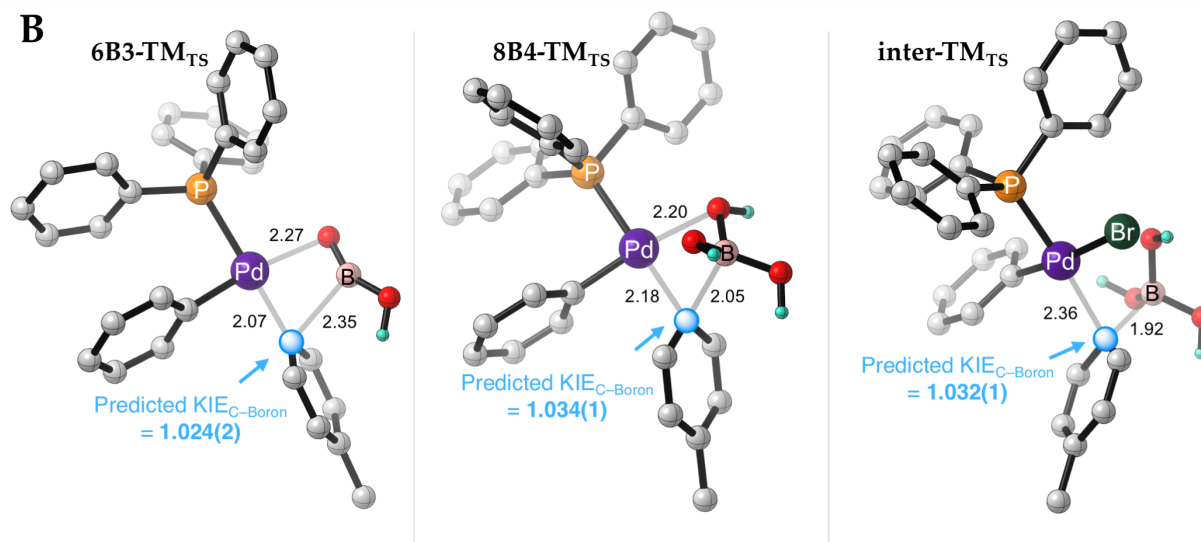
PdL<sub>1</sub> pathway) but significantly smaller than the predicted KIE<sub>C-I</sub> of 1.023(2) for PdL<sub>2</sub>-OATs-1 (likely the KIE-determining step in the PdL<sub>2</sub> pathway). This result can be interpreted as being consistent with ~85% of the reaction proceeding via the PdL<sub>1</sub> pathway and ~15% via the PdL<sub>2</sub> pathway. Increasing ligand concentrations to 20 and 40 mol% resulted in KIE<sub>C-I</sub> values of 1.016(1), and 1.022(4) (Fig. 3, conditions # 2, x=20, 40), respectively – reflecting the increasing contribution of the PdL<sub>2</sub> pathway in the catalytic reaction.

Collectively, these results provide support for OA of both aryl bromides and iodides occurring to a 12 electron PdL<sub>1</sub> species under standard catalytic conditions. This OA step is preceded by the formation of an η<sup>2</sup> binding complex between PdL<sub>1</sub> and the aryl halide. The key difference between aryl bromides and aryl iodides is the relative energies of the binding versus the OA step. Experimental KIE<sub>C-Br</sub> values (Fig. 2) suggest formation of the η<sup>2</sup> binding complex has a lower barrier than the OA step. In contrast, the weaker C-I bond results in the lowering of the OA barrier relative to that of the binding step (23). The PdL<sub>2</sub> pathway is operational only in the presence of excess PPh<sub>3</sub> ligand or under stoichiometric conditions.

**A**



**B**



**Fig. 4. Probing the transmetalation step in the catalytic Suzuki-Miyaura reaction from boronic acid KIEs** (A) <sup>13</sup>C KIE experiments to probe the TM TS in the catalytic S-M reaction of **1b** and **2a**. (B) Calculated TSs and predicted <sup>13</sup>C KIEs for possible TM TSs with key bond distances shown in angstroms (Å). Experimental <sup>13</sup>C KIEs are shown as an average of 12 measurements from two independent experiments. Experimental and predicted KIEs represent the 95% confidence range for the last digit shown in parentheses.

5 *Probing the transition state geometry of TM in the catalytic S-M reaction:* Having established the catalytic mechanism of OA, we turned our attention to the investigation of the TM step under catalytic conditions. In particular, we questioned whether we could distinguish between aryl transfer from the 8B4 (**8B4-TM<sub>TS</sub>**) versus the 6B3 (**6B3-TM<sub>TS</sub>**) pre-TM intermediates by determining the <sup>13</sup>C KIE on the carbon atom of **2** (Fig. 1, KIE<sub>C-Boron</sub>) that migrates from boron to palladium during the TM event. We speculated that KIE<sub>C-Boron</sub> will be different for these two TSs due to the difference in nucleophilicity of the aryl group in the respective intermediates. We chose the prototypical S-M reaction of aryl iodide **1b** and boronic acid **2a** catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> for determination of KIE<sub>C-Boron</sub> via NMR analysis. Observation of a significant KIE<sub>C-Boron</sub> of 1.035(1) (Fig. 4A) is qualitatively consistent with TM being the first irreversible step in the catalytic cycle for **2a**.

10 For the quantitative interpretation of this KIE, we modeled the intramolecular TM event (Fig. 4B) from both the tetracoordinate boronate complex (**8B4-TM<sub>TS</sub>**) and the tricoordinate boronic acid complex (**6B3-TM<sub>TS</sub>**). In **8B4-TM<sub>TS</sub>**, the forming Pd-C bond distance ( $r_{\text{Pd-C}}$ ) is 2.18 Å and the breaking B-C bond ( $r_{\text{B-C}}$ ) is 2.05 Å. The corresponding distances in **6B3-TM<sub>TS</sub>** are 2.07 Å and 2.35 Å, respectively. Therefore, TM from the 8B4 intermediate has an earlier transition state than the 6B3 intermediate – consistent with the more nucleophilic migrating aryl group in 8B4. We also observed a clear correlation between  $r_{\text{Pd-C}}$  in the transition structures and KIE<sub>C-Boron</sub> – increased proximity of the migrating carbon atom to the palladium center in **6B3-TM<sub>TS</sub>** (compared to **8B4-TM<sub>TS</sub>**) results in a lower predicted KIE<sub>C-Boron</sub> (Fig. 4B). The average KIE<sub>C-Boron</sub> from 12 DFT predictions for **6B3-TM<sub>TS</sub>** is 1.024(2) – a value that is in variance with the experimental KIE of 1.035(1). On the other hand, the predicted KIE<sub>C-Boron</sub> for **8B4-TM<sub>TS</sub>** is 1.034(1), which is in excellent agreement with experimental KIE<sub>C-Boron</sub>. On a side note, we also explored the intermolecular TM TS for transfer of the aryl group from an aryltrihydroxyborate to the PdL<sub>1</sub>(Ar<sub>1</sub>)(Br) OA complex (**inter-TM<sub>TS</sub>**). While the predicted KIE<sub>C-Boron</sub> for this TS is in reasonable agreement with experiment, it is 7.0 kcal/mol higher in energy than **8B4-TM<sub>TS</sub>** – suggesting that **inter-TM<sub>TS</sub>** is likely not the operative TM pathway (25). The quantitative match of experimental (~1.035) and predicted (~1.034) KIE<sub>C-Boron</sub> for **8B4-TM<sub>TS</sub>** provides the first quantitative evidence for the transition structure of the TM step in the Suzuki-Miyaura reaction under *catalytic* conditions. We obtained identical KIE<sub>C-Boron</sub> (1.035(2)) when the reaction was performed with aryl bromides and in the presence of 5 mol% added triphenylphosphine, suggesting that the TM step was unaffected by these modifications to reaction conditions (see Table S10 in Supplementary Information for details of these experiments).

20 25 30 35 40 45 In conclusion, we have utilized a combination of experimental and theoretical <sup>13</sup>C KIEs to delineate the fine details of the *catalytic* mechanism of the Pd(PPh<sub>3</sub>)<sub>4</sub> catalyzed Suzuki-Miyaura reaction of aryl halides and aryl boronic acids. Our studies provide the first experimentally validated transition structures for both the OA (**PdL<sub>1</sub>-OA<sub>TS-Br</sub>**/ **PdL<sub>1</sub>-bind<sub>TS-I</sub>**) and TM (**8B4-TM<sub>TS</sub>**) steps in the catalytic reaction, leading to a more detailed description of the catalytic cycle (Fig. 5). The reaction is initiated by dissociation of two phosphine ligands (L) from PdL<sub>4</sub> to form the 14-electron PdL<sub>2</sub> complex. During the first turnover, our experimental KIE<sub>C-Br</sub> from the stoichiometric OA reaction (Fig. 2C) suggests that PdL<sub>2</sub> is likely the palladium (0) species that undergoes OA to the aryl halide to deliver the palladium (II) complex **4L<sub>2</sub>**. Displacement of the halide ligand by hydroxide likely results in the hydroxo-palladium complex **5L<sub>2</sub>**, which presumably undergoes ligand dissociation and coordination to **2a** to form the pre-TM **8B4** intermediate. Our experimental KIE<sub>C-Boron</sub> supports transmetalation occurring from **8B4** resulting in the pre-RE



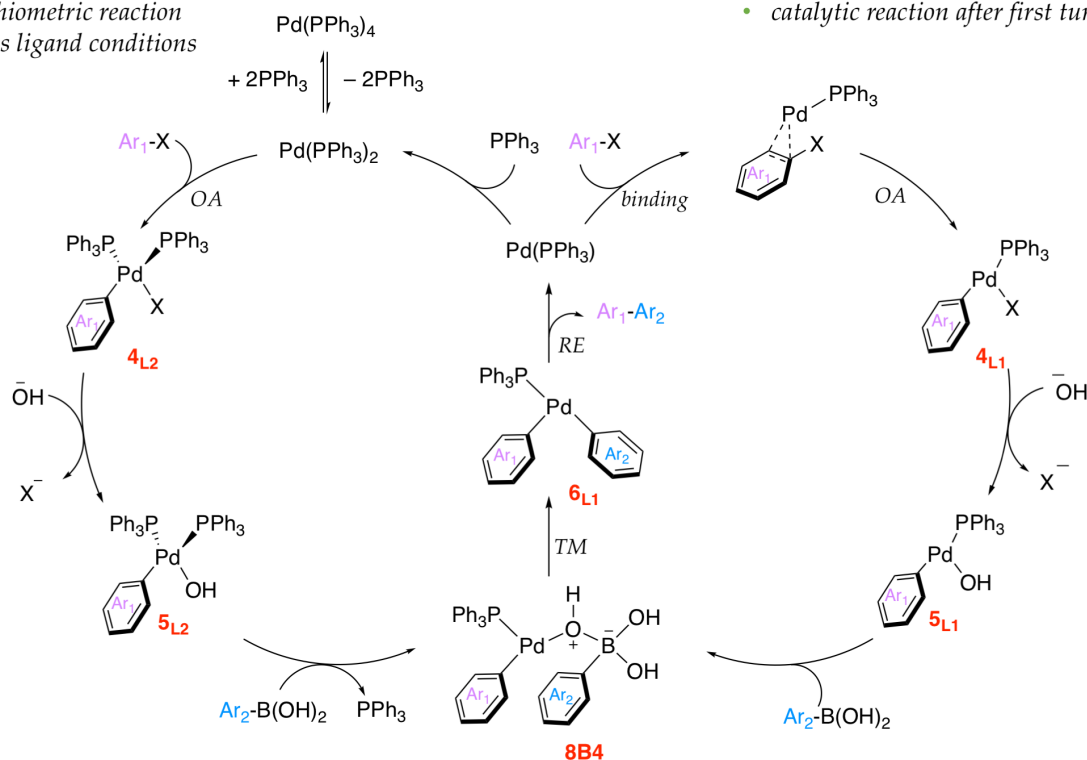
intermediate **6<sub>L1</sub>**. Subsequent facile RE delivers the cross-coupled biaryl **3** and generates the highly reactive, 12-electron PdL<sub>1</sub> complex.

### PdL<sub>2</sub> pathway

- stoichiometric reaction
- excess ligand conditions

### PdL<sub>1</sub> pathway

- catalytic reaction after first turnover



**Fig. 4.** The catalytic mechanism of the Suzuki-Miyaura reaction as determined herein using a combination of <sup>13</sup>C KIEs and DFT calculations

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After the first turnover, the mechanism of subsequent catalytic cycles depends on the nature of the aryl halide and the concentration of the phosphine ligand in solution. Experimental KIE<sub>C-Br</sub> and KIE<sub>C-I</sub> determined under standard catalytic conditions (1 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and no added PPh<sub>3</sub>) support OA occurring to the PdL<sub>1</sub> complex via a two-step process – (i) formation of an η<sup>2</sup> binding complex between PdL<sub>1</sub> and the aryl halide, and (ii) OA of PdL<sub>1</sub> into the C-X bond to form the palladium (II) complex **4<sub>L1</sub>**. For aryl iodides, we have shown that the binding event is the first irreversible step whereas aryl bromides proceed via reversible binding followed by OA as the first irreversible step. Displacement of the halide from **4<sub>L1</sub>** by hydroxide results in the mono-ligated hydroxopalladium complex **5<sub>L1</sub>**, which coordinates to the aryl boronic acid to directly yield the pre-TM intermediate **8B4**. Subsequent TM and RE completes the catalytic cycle and regenerates PdL<sub>1</sub>. We anticipate that this unprecedented insight into the S-M reaction under *catalytic* conditions will inspire similar investigations of long-standing mechanistic questions in other areas of transition-metal catalysis.

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#### Supplementary Materials:

Materials and Methods

Tables S1-S22

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