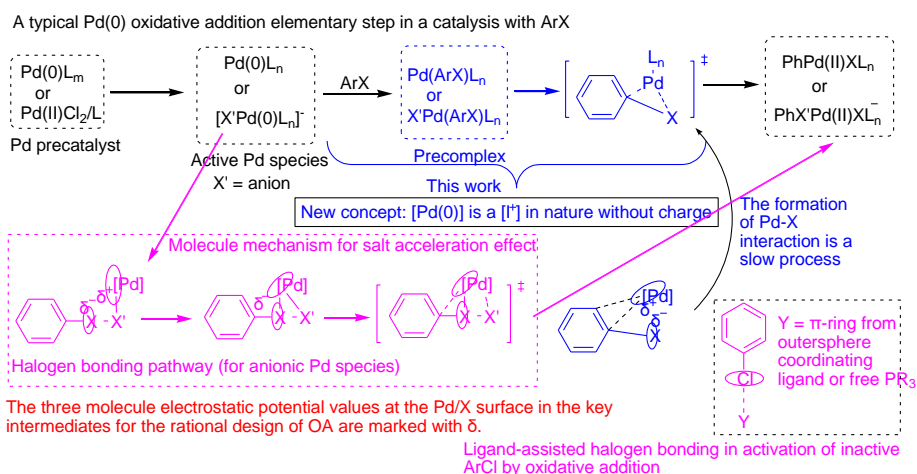


# An Integrated Study of Pd(0)-Halide Interactions in Pd Oxidative Addition to Organic Halides: Uncovering the “Super Iodine” Character of Pd(0)

Liuqun Gu

## Abstract

*Note: the oval atom shape of the Pd (or X) atom in all schemes is an illusion to draw an attention on the shape/volume change of atom upon bonding, not the actual shape of Pd (or X) in bonding.*



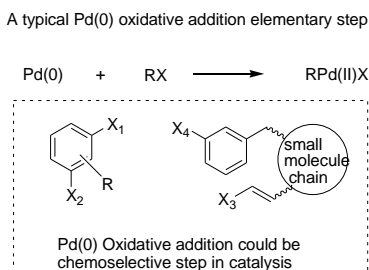
Pd(0) oxidative addition (OA) to organic halides is a fundamental step in many catalytic organic transformations. Previous mechanistic studies have shown that the electronic/steric nature of ligand, metal coordination unsaturation, halide identity and the presence of an additive all have sizable influences on reaction reactivity and selectivity. A single parameter-based rational design fully integrating all important factors in a quantitative manner remains elusive, due to the complex nature of Pd(0) OA. To address this challenge, a study of Pd(0)-halide interactions which are crucial for the 3-centered concerted mechanism, is initiated in this work by integrating the key progress in organometallic chemistry and the relatively well-established halogen bonding knowledge, mimicking the “data-driven” method. The achieved advanced understanding of the mechanisms in this work includes five key parts: 1) uncovering the “super iodine” character of Pd(0), 2) uncovering the bonding nature of Pd-halide (organic halide) interaction and its essential role in Pd(organic halide) precomplex before OA; 3) a molecular mechanism for the additive effect, and a theoretical prediction of a halogen transfer pathway for OA to specific organic halides; 4) demystifying the known super

reactivity of the ligand-controlled Pd catalysis with inactive aryl chlorides; and ultimately 5) proposing a proof-of-concept of surface molecule electrostatic potential-based rational design of OA.

## Introduction

The Suzuki-Miyaura coupling reaction, the Buchwald-Hartwig coupling reaction, and the Sonogoshira coupling reaction are among the most frequently used synthetic reactions in drug discovery according to recent statistical analysis<sup>1-3</sup>, arguably because of “retrosynthetic simplicity”<sup>4</sup>. Pd catalysis is currently dominant for coupling reactions in both academia and industry, but with increasing interest in sustainable reactions at very low catalytic loading under aqueous solution along with an organic co-solvent or even in the absence of any organic solvent.<sup>5-7</sup> In most of the coupling reactions, Pd(0) oxidative addition (OA) to an organic halide is the first elementary step (Scheme 1)<sup>8,9</sup> and often is also the rate-determining step<sup>10-15</sup> or/and the stereo-determining step<sup>14-16</sup> in the overall Pd catalysis of coupling reactions involved with organic halides. In addition, selective Pd(0) OA in the presence of two or more organic halides will usually determine the chemo-selectivity in many Pd catalyzed domino/one-pot reactions<sup>17-24</sup> resulting into complex functional molecules in an efficient manner.

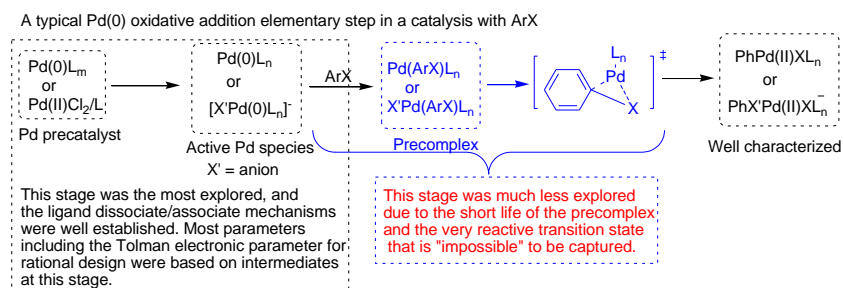
Scheme 1. Pd(0) Oxidative addition to organic halides.



Due to the essential role of OA for the rational design and development of the Pd catalysis as well as the curiosity-driven theoretical interest, extensive mechanistic work<sup>8,9,14,25-29</sup> has been done in the past five decades in organometallic catalysis. As one of the key factors influencing the OA process, the steric and electronic nature of the ligands was the most studied. Active Pd(0) species generated from in situ reduction from Pd<sup>2+</sup> by the present ligand and water<sup>30-31</sup>, or from ligand dissociation/association of bench stable Pd(0) complexes<sup>9,14,25,26,33-36</sup>, was well established recently (Scheme 2). The key concepts of electron count and coordinative unsaturation are fundamental in mechanism-based development in organometallic chemistry, and they were frequently used in reported ligand design for Pd catalysis.<sup>25,26,34</sup> The Tolman electronic parameters (TEL)<sup>26,37</sup> and Tolman cone angle<sup>34,38,39</sup> have been used widely as quantitative descriptors for the electronic donor capability and the bulkiness of new ligands, in the following pursuit of highly efficient catalysts under mild conditions since the pioneering reports by Hartwig<sup>40</sup> and Buchwald<sup>41</sup>. Very recently, “minimum percent buried volume” [%V<sub>bur</sub> (min)]

developed by Sigman and Doyle<sup>38</sup> was demonstrated to be a distinctive ligand steric descriptor for prediction of active, inactive, mono- and bis-ligating phosphines before synthesis. The molecular electrostatic potential at the metal center  $V_{Pd}$  and at the ligand center  $V_{min}$ , was reported by Suresh<sup>42</sup> as good parameters to characterize the electron-rich/-poor character of the ligands and complexes, providing another quantitative measure of the reactivity of the catalyst. An important advancement was recently from Paci/Leitch<sup>43</sup>, in which they developed a quantitative structure–reactivity model for reaction reactivity prediction, focusing on fundamental mechanistic steps in catalytic mechanisms. The model used a combinative calculation of free energies of activation ( $\Delta G^{\ddagger}_{OA}$ ) by integrating of average molecular electrostatic potentials as electronic descriptors for specific atoms in the substrate, A-values as steric descriptors, and the intrinsic bond strength index as a bond energy descriptor. Despite all the progress that has been achieved toward quantitative predictions, other species like solvent molecules, salt additives, nitrogen-containing compounds, olefin et.al, which are normally present in real-life catalytic conditions, make the rational design and optimising of catalysts a still challenging task<sup>25,26</sup>. A single parameter-based rational design of Pd-catalyzed coupling reactions fully integrating all important factors in a quantitative manner remains elusive, and is currently highly desirable in order to minimize the resource-intensive experimental developments and optimizations for almost all new catalytic systems.

Scheme 2. The current mechanistic studies and the stages based-rational design of Pd(0) oxidative addition to aryl halides.

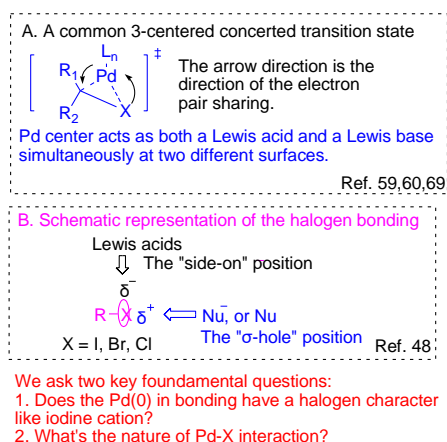


The reactivity acceleration of halide additives in transition metal catalysis<sup>44</sup> is well-known. A theoretic mechanism study by Amatore/Jutand<sup>45</sup> and a later experimental mechanism study by Hartwig<sup>46</sup> have provided strong evidence on the role of tricoordinated anionic complexes Pd(0)L<sub>2</sub>Cl<sup>-</sup> and Pd(0)L<sub>2</sub>(OAc)<sup>-</sup> or the dimer general structure [Pd(Ar)Br<sub>2</sub>]<sub>2</sub><sup>2-</sup> as the effective catalysts instead of the usually postulated Pd(0)L<sub>2</sub> complex in Heck coupling reactions. However, the molecular mechanism of these anionic species counterintuitively interacting with the same electronegative halide atom of organic halides and resulting into OA, is still missing<sup>26,47</sup>.

On the other hand, the halogen bonding knowledge (Scheme 3B)<sup>48</sup> was relatively well established in the past decades due to its broad applications in different fields including crystal engineering<sup>49</sup>, drug design<sup>50</sup>, biomolecular recognition/biochemistry<sup>51</sup>,

organocatalysis<sup>52</sup>. Though organic halides or/and transition metal halides were frequently involved in many studies<sup>48-52</sup>, surprisingly, the halogen bonding knowledge was rarely brought into the mechanistic studies in Pd(0) OA of organic halides to our best knowledge. We speculate two possible reasons (Scheme 2 and Scheme 3): 1) Pd(0)-X (ArX) interaction is very weak and unstable in nature since organic halides are very weak bases<sup>53</sup>, and it is challenging to be measured technically; 2) Pd(0) arene precomplexes were known to be extremely shorted-life intermediates in OA, undetectable by NMR spectroscopy under standard conditions<sup>54-57</sup>. In fact, currently there is no known experimental technique for directly detecting Pd(0)-X (RX) interaction in Pd catalytic systems<sup>58</sup>, even though the Pd(0)-X interaction is a must for the widely proposed 3-centered concerted mechanism (Scheme 3A)<sup>16,59-61</sup> for Pd(0) OA to RX.

Scheme 3. The dual roles of Pd(0) in 3-centered concerted transition state and the feature of the halogen bonding.



It is widely known that it is dangerous to solely depend on isolated intermediates for both identifying active catalyst species and proposing a catalytic cycle in mechanistic study of catalysis. It is particularly true for the typically more reactive organometallic catalysis due to the complex nature, like the tenet from Halpern, "a preeminent scholar and father of modern organometallic chemistry and homogeneous catalysis"<sup>62</sup>, "if you can identify a compound from a catalytic system, it is probably not the catalyst"<sup>62</sup>. In order to fill the gap between formation of Pd(0)(organic halide) neutral complexes and the final Pd(II) aryl complexes in fundamental understanding of Pd(0) OA to organic halides, an integrated study on the nature of Pd(0)-halide interactions would be carried out in this work in an interdisciplinary manner, mimicking the desired data-driven methods<sup>25</sup> but picking up literatures manually. We also asked another fundamental question: does Pd(0) in bonding have a halogen character like an iodine cation? In our following study, "atom in molecule" concept<sup>63,64</sup> would be adopted generally and we will present evidences that Pd(0) metal in coordination could be seen as iodine cation ( $I^+$ ) with the similar characteristic of anisotropically distributed electron density across the polarized atom, just like the halide atom in organic halide (Scheme 3)<sup>48-52</sup>. With a new

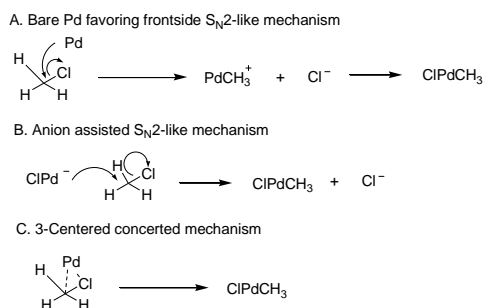
concept of the existence of both the positive molecule electrostatic potential and the negative one in different surfaces of a Pd atom, the known halide identity effect<sup>65</sup>, the salt additives effect<sup>47,66,67</sup> and the solvent effect<sup>67</sup> may also be better explainable and potentially included in consideration in a quantitative manner, improving understanding of real-life catalytic systems.

After achieving systematical understanding of Pd(0) OA to organic halides, other aims are to demystify the known super reactivity of the ligand-controlled Pd catalysis with inactive aryl chlorides, and to discover the molecular mechanism for the salt additive effect, ultimately to introduce a proof-of-concept of molecular electrostatic potential at Pd/halide surface-based rational design of OA in real-life Pd catalytic systems.

## Results and discussion

The mechanisms of Pd(0) OA to organic halides are generally well established under controlled conditions and three main mechanisms were summarized in the very recent comprehensive review<sup>25</sup> on Pd(0) OA: 1) S<sub>N</sub>2-like mechanism through a backside approach; 2) 3-centered concerted mechanism involving a side attack to the carbon center (C-X bond); 3) a radical process. The first two mechanisms are both important for Pd(0) OA to alkyl halides (Scheme 4)<sup>26,56,61</sup>, meanwhile the second 3-centered concerted mechanism is found to be the most favorable one for Pd(0) OA to aryl halides (Scheme 2)<sup>59-61,69</sup>. From a mechanistic view, a close Pd(0)-X (ArX) interaction could enable the Pd(0) center accepting an electron pair from the halide atom, and subsequently it would enhance Pd(0) sharing an electron pair with a π-antibonding molecular orbital, transferring negative charge from the halide to the ring and eventually stabilizing the 3-centered transition state (Scheme 3A).<sup>59-60,69</sup> Lack of Pd(0)-X (ArX) interaction would lead to either an alternative S<sub>N</sub>2-like mechanism, or no OA at all.

Scheme 4. S<sub>N</sub>2-like mechanism and 3-centered concerted mechanism initially proposed by Bickelhaupt<sup>61</sup> for Pd(0) oxidative addition to CH<sub>3</sub>Cl.



In the initial proposed 3-centered transition state, Pd(0) has both characteristics of electron donor (Pd-C) and electron acceptor (Pd-I) in the overall electron density change with directionality (Scheme 3A).<sup>59,60</sup> Expanded literatures' research indicated that Pd(II) centers with ligands as nucleophiles are not uncommon in crystal engineering.<sup>70-73</sup> Such

double characters are very similar to those of halogen atoms in halogen bonding (XB) (Scheme 3B); the halogen atoms can interact attractively with negative sites (nucleophiles) along the extensions of their bonds ( $\sigma$ -hole position<sup>74</sup>) and with positive sites (electrophiles) in lateral (“side-on”) directions, because of simultaneous presence of both positive and negative regions quantified with surface molecule electrostatic potential as an indicator<sup>75,76</sup>. The bonding similarity intrigues us to further explore both atoms’ (Pd, I) sizes, electronegativity and chemical properties, and their similarity.

#### *The “super iodine” (I<sup>+</sup>) character of Pd(0)*

This comparison data<sup>77</sup> shows that the atomic radius (empirical) of palladium (1.40 Å) and that of iodine (1.40 Å) is exactly same. And the covalent radius of both atoms (atom in molecule), which is more relevant in this study, is also very similar (1.20 Å for Pd in the single bond with a coordination number of 3, and 1.33 Å for iodine in a single bond with a coordination number of 1). Van der Waals radius of an atom, which is useful for evaluation of an effective non-covalent interaction between the two atoms, is also very close (Pd: 2.15 Å; I: 2.04 Å). A relatively higher Pauling electronegativity (2.66 Pauling units) of iodine atom than that of Pd atom (2.20 Pauling units) is consistent with the electron density shift from iodine atom to the more electrophilic Pd(0) atom proposed in the 3-centered concerted transition state<sup>59,60</sup>.

Table 1. The atom sizes and electronegativity of Pd and I.<sup>77</sup>

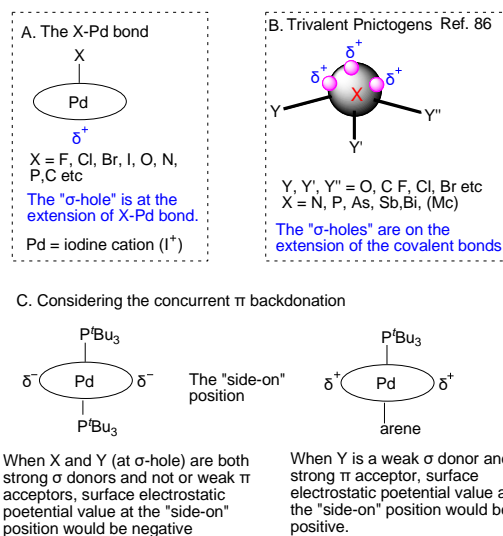
	Atomic radius (empirical)	Covalent radius (single bond)	Van der Waals radius	Pauling electronegativity (Pauling units)
Palladium	1.40 Å	1.20 Å (coordination number: 3)	2.15 Å	2.20
Iodine	1.40 Å	1.33 Å (coordination number: 1)	2.04 Å	2.66

Two common bonding modes of [D...X<sup>+</sup>...D] (or in frameworks of [D...X...D]<sup>+</sup>)<sup>78,79</sup> and [D<sup>-</sup>...X<sup>+</sup>...D<sup>-</sup>] (or in frameworks of [D...X...D]<sup>-</sup>)<sup>80,81</sup> with an iodine cation (I<sup>+</sup>) at the center were common in Cambridge Structural Database (CSD) searches or literatures. The bonding is linear and symmetrical in both modes with neutral electron donors or anionic electron donors. And it is well known that Pd(0) also favors such two types of bonding modes in a *trans* position with either neutral electron donors or anionic electron donors.<sup>25,26,45,46,48</sup> In addition, bifurcated XBs of an iodine center with two oxygen, two nitrogen, or one oxygen and one nitrogen were all known in literatures<sup>82</sup>. Such bifurcated XBs are very similar to Pd(0) with bidentate oxygen/nitrogen ligands in structure<sup>8,33,35</sup>.

On the other hand, surface electrostatic potential (SEP) indicating simultaneous presence of both positive and negative regions at the iodine (R-I, R = electron withdrawing

group)  $V(r)$ , is created at any point  $r$  in the space of a molecule by its nuclei and electrons, given by a known Equation<sup>75,76</sup>. The electrostatic potential is a real physical property, and observable. It can be determined experimentally by diffraction techniques<sup>83</sup> as well as computationally<sup>75,76</sup>. The used computation methods were mostly based on molecular orbital theory<sup>43,75,76</sup>, which is quantum mechanics modelling. Because "it is the atom and its properties that are defined by quantum mechanics"<sup>84</sup>, we here concluded that *Pd(0) atom in the 3-centered transition state should also have more than two surfaces (rather than be a sphere) depending on coordinated ligands, and at which there is simultaneous presence of both positive and negative regions based on the "atom in molecules" theory<sup>84</sup>. Specifically, the Pd(0) atom is an equivalence of iodine cation ( $I^+$ ) in halogen bonding, however it is a neutral "super iodine" with a balance of nucleophilicity and electrophilicity.* This fundamental understanding of this new type of  $\sigma$ -hole interactions is essential to identify the " $\sigma$ -hole" positions in a typical Pd(0)-containing 3-centered transition state as well as general frameworks of Pd(0) $X_n$  ( $X = I, Br, Cl$ ); in other words, the " $\sigma$ -hole" positions would be at the metal Pd(0) sides, the extension of X-Pd bond, similar to those in pnictogen bond (Scheme 5A,B)<sup>85,86</sup>. Our new understanding could provide a theoretical support "in its greatest simplicity (a saying from J. W. Gibbs)"<sup>87</sup> for the well-known "*trans* effect" (another name is "push-pull interaction") in transition metal complexes (Pd, Pt, Ir et.al)<sup>88</sup>; and it is also consistent with an experimental fact that there is no  $\sigma$ -hole at the extension of M-X bonds in crystal engineering<sup>89,90</sup> and gold catalysis<sup>91</sup>. Regarding the nature of X-Pd bond, there is a significant charge transfer character along with the electrostatic interaction, similar with the strong  $[I^+-I^-]$  bond<sup>48,52,81</sup>.

Scheme 5. The anisotropic distribution of electron density in Pd atom in bonding and the trivalent pnictogens (the oval in A/C is an illusion, not a real shape of Pd in bonding).



In fact, the simultaneous presence of both positive and negative regions at different surfaces of Pd was clearly visible in the computed HOMO structure of dimeric Pd(0)<sub>2</sub>L<sub>2</sub>Cl<sup>Li</sup>

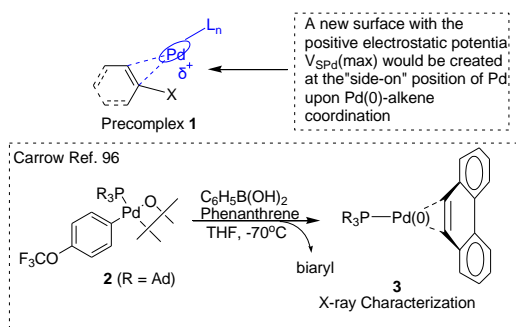
complex, by Perrin/Payard<sup>47</sup>. The “super iodine” nature of Pd(0) could also be evidenced indirectly by the high similarity of Pd(0)/Pd(II) catalysis with I(I)/I(III) catalysis<sup>92</sup> (in which, Pd(II) is an equivalence of I(III)), which is out of scope of this work.

A key difference of X-Pd-Y bonding with the XB with a charge transfer character (RX...Y) is that the electrostatic potential of “side-on” (the belt) position of Pd atom could be the negative as the XB, or be positive, depending the type of ligand Y (Scheme 5C). The concurrent  $\pi$  backdonation from Pd atom should also be included into consideration. This point is crucial for the below discussion.

#### *Pd(0)-alkene interactions in Pd(0)(organic halide) precomplex*

After uncovering the “super iodine” nature of Pd(0) in the 3-centered concerted transition state in OA, we next move to investigate Pd(0)-alkene interaction in Pd(0)(organic halide) precomplex **1** (Scheme 6). For organic halides (RX) with saturated alkyl groups (R), there would be no alkene functional group for coordinating with Pd(0). And Pd(0)-halide interaction instead would be the dominant force in the precomplex<sup>61</sup>, which would be discussed in later section. For alkene-containing alkyl halides (RX), an adduct where the Pd(0) is ligated to the C=C bond of RX as in a neutral framework of Pd(0) ( $\eta^2$ -RX)(L)<sub>n</sub> complex, is generally believed to form<sup>33,35,56,57</sup> reversibly before the intramolecular OA, though none of the neutral complexes was successful to be characterized by spectroscopy due to their too short half-life time. And the complexation step of the Pd(0) by the alkyl halide with a C=C bond was found to be much faster than the oxidative addition/ionization step<sup>56,57</sup>. A general trend is that the more electron-deficient the alkene, the more stable the formed neutral Pd(0) ( $\eta^2$ -RX)(L)<sub>n</sub> would be<sup>33,35,56,57</sup>. This trend is consistent with the trend of  $\sigma$ -hole interaction (or the “push pull effect”) of X-Pd...( $\eta^2$ -alkene) bond uncovered in the previous section in this work.

Scheme 6. The generally agreeable Pd(0)(organic halide) precomplex **1** via Pd-alkene interaction.



The olefin effect is relatively well understood<sup>33,35,57,93,94</sup>. “It is generally accepted that coordination of an olefin results in the removal of electron density from the metal center concurrent  $\pi$  backdonation occurs from an occupied metal d orbital to the lowest unoccupied molecular orbital (LUMO) of the olefin, the vacant  $\pi^*$  orbital.”<sup>94</sup> Based on this



general understanding and the uncovered “super iodine” nature of Pd(0), we speculate that a new Pd surface with the positive SEP  $V_{\text{SPd}}(\text{max})$  would be created upon Pd(0)-alkene coordination, favoring the subsequent intramolecular Pd(0)-halide interaction generating the 3-centered concerted transition state (Scheme 6).

Similar with Pd(0) OA to alkene-containing alkyl halides, the Pd(0)-arene interaction was also rarely observed directly; and the proposed neutral complex Pd(0)( $\eta^2$ -ArX) has never been characterized by spectroscopy in our searches, though such  $\eta^2$ -arene complex had been used in theoretic study with density functional theory<sup>95</sup>. Very recently, a linear complex (Ad<sub>3</sub>P)Pd(0) ( $\eta^2$ -C<sub>33</sub>,C<sub>46</sub>-phenanthrene) was isolated by Carrow<sup>96</sup> as a crystal by mixing (Ad<sub>3</sub>P)Pd(0) complex with the phenanthrene, which is the only intermolecular  $\eta^2$ -arene complex (without a halide functional group) with a full spectroscopy characterization so far, to our best knowledge (Scheme 6). The partial removal of electron density from the metal center via  $\eta^2$ -arene complex is important for Pd(0) OA to aryl halides in creating a surface with a positive SEP  $V_{\text{SPd}}(\text{max})$ , when a very strong electron-rich ligand is employed in the OA systems.

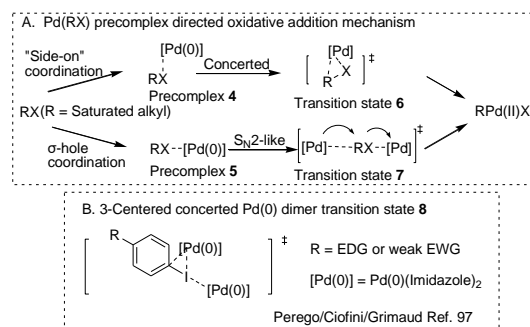
In general, a reversible/slipped  $\eta^2$ -arene complex with a very short life is suitable for describing the neutral framework of Pd(0) ( $\eta^2$ -RX)(L)<sub>n</sub> intermediates in OA. Pd(0) species with electron-rich ligands or anionic Pd(0) species are favorable in forming the neutral complex intermediates.

#### *Pd-halide (RX) interaction and a new halogen ion transfer mechanism*

Pd-halide (RX) interaction plays an essential role in facilitating the last oxidative insertion of the C-X bond in the overall Pd(0) OA to organic halides via a 3-centered concerted mechanism (Scheme 2, Scheme 3, Scheme 4C)<sup>16,59-61</sup>, and it has been well recognized as we discussed in the early section. Meanwhile, without Pd-halide (RX) interaction in Pd(0) OA to organic halides, both a frontside S<sub>N</sub>2-like mechanism with a bare metal and a backside S<sub>N</sub>2-like mechanism in the presence of chloride anions (Scheme 4C) was proved to be feasible depending on condition by Bickelhaupt<sup>61</sup> computed with density functional theory. Because the frontside S<sub>N</sub>2-like mechanism was rarely found and proposed in Pd catalysis<sup>25,26</sup>, unlike the common backside S<sub>N</sub>2-like mechanism, here we will not further discuss this possibility in this work. Theoretically, a Pd(0) interaction with either the “side-on” or the “ $\sigma$ -hole” position of the halide atom, would largely determine the OA mechanisms in the catalytic systems (Scheme 7A). For alkyl halides with an electron-poor alkene group or aryl halides, the electron density removal effect from the electron-rich Pd(0) center toward a more stable precomplex could be sizable and non-negligible. On the contrary, for alkyl halides without an alkene group for favorably coordinating with the Pd(0) center or with an electron-rich alkene group, the electronic nature of ligands likely would be essential in favoring either type of the coordination in the precomplex stage.

Report of OA mechanism with Pd(0) species at the “ $\sigma$ -hole position” of ArX remained blank until a cooperative mechanism involving two Pd(0) centers in the oxidative addition of iodoarenes in the presence of imidazole ligands appeared in 2018 proposed by Perego/Ciofini/Grimaud (Scheme 7B)<sup>97</sup>. In the novel mechanism, both Pd(0)-iodine interaction at the “side-on” position of iodine and the Pd(0)-iodine interaction at “ $\sigma$ -hole position” of C-I bond co-existed cooperatively, creating a “super palladium” with both an excellent nucleophilicity and an excellent electrophilicity at the two different Pd centers.

Scheme 7. Pd-halide interaction directed Pd(0)(RX) precomplex formation and the subsequent oxidative addition, as well as the known halogen bonding transition state **8**.

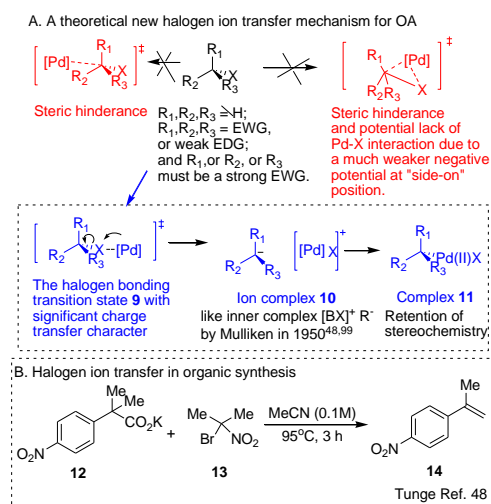


A Pd-halide (alkylX) interaction is not involved in the common  $S_N2$ -like mechanism<sup>16</sup> via a backside attack to the carbon atom (C-X bond) (Scheme 4B) if a Pd(AlkylX) precomplex could not form in a fast manner. However, if R is an alkyl group with a less bulky electron-withdrawing group, it would not be surprising to see that a nucleophilic Pd atom could occupy at the extension of a C-X bond ( $\sigma$ -hole position) based on the XB knowledge<sup>48,74-76</sup>. As shown in Scheme 7A, XB formation would likely result into elongation of the C-X bond, assisting the backside attack to the carbon atom by another Pd(0) species. In this modified mechanism Pd-halide (RX) interaction plays an additive or a catalytic activation role in accelerating the halide leaving, rather than a decisive role. And the formation of this  $\sigma$ -hole interaction could be much faster if a “side-on” Pd-halide interaction is not favored in the presence of strong electron-rich ligands, due to the lack of relatively positive SEP.

When alkyl halides with a strong electron-withdrawing group at  $\alpha$ -quaternary carbon are used for oxidative addition by Pd(0) species, a new halogen ion transfer OA mechanism could be very feasible in case the bulkiness resulted in hindrance following a common  $S_N2$ -like mechanism or a 3-centered concerted mechanism (Scheme 8A). In this new mechanism, the Pd(0) species approaches and occupies the  $\sigma$ -hole position by offering an electron pair to share with the halogen atom, and a halogen bonding with a common bonding mode of  $[Pd(0) \cdots X^+ \cdots R^-]$  forms in a linear manner. Then a formation of  $Pd(0)X^+$  intermediate is quite likely before a charge transfer in generating Pd(II)X and a free R<sup>-</sup>; subsequently the free R<sup>-</sup> would be captured by Pd(II)X, eventually giving the OA product  $RPd(II)X$  complex. The overall OA process is similar to Pd(0) OA ( $S_N2$ -like) to allylic

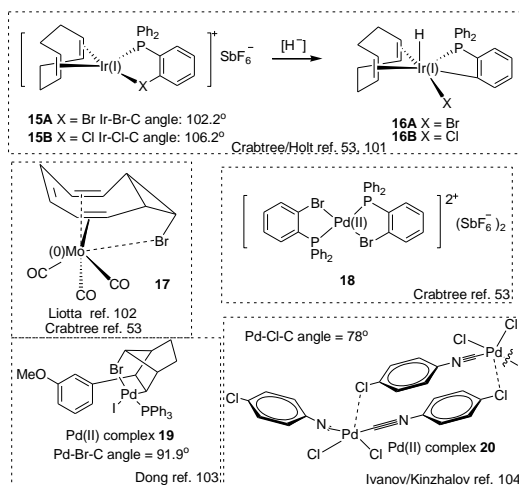
acetate<sup>56,57</sup>, however, the oxidative insertion targets at the “X<sup>+</sup>”, rather than allylic cation in the latter process. Another key difference is in the stereochemistry of the  $\alpha$ -quaternary carbon in the OA product. An overall retention of stereochemistry would be expected by following the new halogen ion transfer OA mechanism (Scheme 8A); on the other hand, an overall reverse of stereochemistry at the carbon center was observed by following a S<sub>N</sub>2-like mechanism via an anti-attack to the allylic carbon<sup>57</sup>. This mechanism is not yet known<sup>25,26</sup>, to our best of knowledge, probably because such highly bulky organic halides were rarely explored in Pd catalysis development or mechanistic studies. A literature study (Scheme 8B) showed such halogen ion transfer mechanisms were already used for catalytic organic synthesis even in the absence of transition metal.<sup>98</sup> The known chemistry under relatively mild conditions indicates that the activation barriers for our proposed new OA mechanism would be low and it could be dominant in OA of specific organic halides, though the new OA mechanism is currently a theoretical speculation. It is worthy to mention that the charge transfer might play a much bigger role in the proposed halogen bonding intermediate [Pd(O)⋯X<sup>+</sup>⋯R<sup>-</sup>], along with the electrostatic interaction. In fact, this intermediate structure is more like the “inner complex” [BX]<sup>+</sup>R<sup>-</sup> with significant charge redistribution, proposed by Mulliken in 1950<sup>48,99</sup>. The significant charge transfer nature in these complexes was also confirmed by a very recent detailed Valence Bond-Spin Coupled analysis of a series of halogenated molecules for the physical origin of halogen bonding<sup>100</sup>. The results showed the negative belt around the halogen atom (“side-on” position) usually observed when bonded to electron-withdrawing groups of medium strength, could disappear if bonded to a strong electron-withdrawing group like CN (like NCBR), prohibiting the “side-on” Pd-X interaction and the subsequent 3-centered concerted pathway.

Scheme 8. A theoretical new halogen ion transfer mechanism for oxidative addition and the known mechanism in organic synthesis.



The essential role of Pd(0)-halide interaction in OA of aryl halides or alkene/alkenyl halides via a 3-centered concerted mechanism and the technical difficulty in characterization of the interaction as we discussed in the previous sections, intrigues us to explore the similar but well characterized Pd-halide interactions in crystal engineering and other metal-halide interactions in organometallic chemistry, in order to get new insights of the nature of Pd(0)-halide (organic halides) interaction. Only Pd-halide interactions with the Pd-X-C angle at or close to 90° (70-110°) in the crystal characterized by X-ray would be counted since only such orthogonal interactions could be able to facilitate the 3-centered transition state for a concerted OA. An important early review by Crabtree<sup>53</sup> on coordination chemistry of halocarbons indicated that positively charged transition metals (like Pd, Ir) could form weak complexes with halocarbons involving secondary bonding with the M-X-R angle in the complex close to 90°, rather than true coordination complexes (Scheme 9). A very relevant study by Crabtree/Holt<sup>53,101</sup> suggests that the positive charge on the Ir<sup>+</sup> species (cod)Ir(Ph<sub>2</sub>PC<sub>6</sub>H<sub>4</sub>-O-X)<sup>+</sup> **15A,B** prevents oxidative addition of C-X bond, addition of hydride anion induces rapid oxidative addition, following a 3-centered concerted mechanism (the mechanism was proposed as a direct migration of aryl group for the halogen atom to the metal in the literature<sup>101</sup>). This rare result provides a good direct evidence on the essential role of the metal-halide interaction as well as the importance of zero-valent transition metal as a reductant in the OA to C-X bond.

Scheme 9. Transition metal (Ir, Mo, Pd) complexes (characterized by X-ray analysis) with organic halides involving secondary Pd-X bonding.

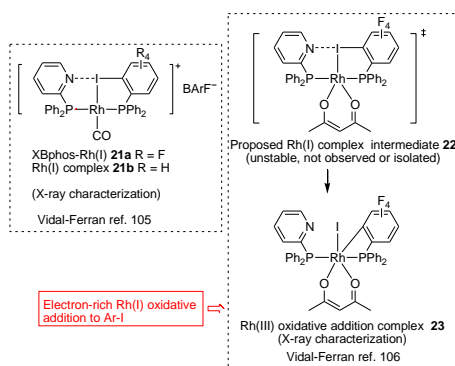


A very rare stable zero-valent transition metal complex Mo(CO)<sub>3</sub>(C<sub>9</sub>H<sub>9</sub>Br) **17** with a Mo-Br bond was characterized (Scheme 9)<sup>53,102</sup>, probably due to the stabilization effect from the three CO ligands significantly decreasing the nucleophilicity of Mo atom at any surface. Pd(0) complex with Pd-X bond is not found in our searches, but positive charged Pd(II) complexes like complex **18** were common<sup>53</sup>. Very recently, a Pd(II)-Br bond with the M-X-

C angle of 91.9° in the similar strained complex **19** was also characterized by X-ray crystallography by Dong<sup>103</sup>. In all three complexes, the length of M-X bond is within the range of a normal coordination bond. However, a “semicoordination” of Pd(II)-Cl interaction<sup>104</sup> (Ar-Cl) with the M-X-C angle of 78° was found in the crystal of isocyanide complex *cis*-[PdCl<sub>2</sub>(CNC<sub>6</sub>H<sub>4</sub>Cl)<sub>2</sub>] **20** and the length of Pd-Cl bond is significantly longer (3.645 – 3.745 Å).

In another work, a stable and well-characterized Rh(I)-I interaction<sup>105-107</sup> with the M-X-C angle in several complexes close to 90°, was found in halogen-bond assembled supramolecular catalyst XBphos-Rh and its analogs (Scheme 10). Similar with the Ir<sup>+</sup> species<sup>53,101</sup>, the positive charge on Rh center proved to be essential to stabilize the metal-I bond (RX). The use of an electron-rich Rh(I) complex instead of the electron-poor one as raw material, gave oxidative addition product IRh(III)RL<sub>1</sub>L<sub>2</sub> complex **23**, and an unstable Rh(I) complex **22** with a similar halogen bonding along with a metal-organic halide bond that is believed to be the intermediate or the transition state before OA. An interesting fact is that a metal-P(Ph<sub>2</sub>)Ar bond is the primary interaction in both Rh(I) complexes **21**, **22** and Ir(I) complexes **15A,B**, not the Pd-alkene interaction in normal η<sup>2</sup>-arene complexes. The smooth oxidative insertion of Ir/Rh to C-X bond by direct reduction with a hydride or by direct use of a Rh(I) with an electron-rich ligand, *provides strong evidences for a new insight that formation of Pd(0)-X interaction is likely the rate-determining step (RDS) from the active Pd(0) species approaching an organic halide (precomplex stage) to the OA product formation. And the subsequent Pd(0)-C (C-X) interaction step forming the 3-centered concerted transition state and the subsequent oxidative insertion by Pd(0) is very fast.* This new insight is compatible with the early mechanistic studies<sup>59-61</sup> and the recent studies<sup>29,108</sup> on the 3-centered concerted mechanism and the halogen effect in reactivity order (ArI > ArBr > ArCl).

Scheme 10. The halogen-bond assembled supramolecular Rh(I) complexes **21**, **22**.



The surface potential at the belt of a halogen atom (X) in an organic halide (CF<sub>3</sub>X) are very different depending on the identity of the halide (X = Cl, Br, I) based on the computed data (Table 2) by Politzer<sup>75,76</sup> and Clark<sup>74</sup>. The most negative potential was observed when X is I (between 0.00045 to -0.00270 Hartrees); meanwhile, the least negative potential

was observed when X is Cl (between 0.00360 to 0.00045 Hartrees). The halogen depending negative surface potential at the coordination position of organic halides and the RDS role of Pd(0)-X interaction, along with the polarization difference (Hartwig had pointed out the polarization as a major cause<sup>65</sup>) could better explain the obvious halide identity effect observed by Hartwig<sup>65</sup>. The chloroarenes has a much higher potential value (poor electronegativity) at the “side-on” position of Cl atom, which needs a higher positive value at the surface of Pd(0) created by a lower-coordination of phosphine ligands or a higher-coordination of electron-deficient olefin (or arene). The combination of both insights could also result into *a conclusion that the ligand dissociation/association*<sup>9,25,26,32,34-36,65</sup>, *the olefin dissociation/association*<sup>25,26,33,57,93,94,109</sup> *and the amine dissociation/association*<sup>108</sup> (in the Buchwald-Hartwig coupling reactions) *are all driven by creating a coordination accessible surface of Pd(0) atom with a suitable positive potential toward the formation of the essential Pd(0)-X interaction. And the formation of the Pd(0)-X interaction is an exit toward OA from the reversible Pd(0)-arene interaction.*

Table 2. The most negative molecular electrostatic potential on the “side-on” (“Belt”) position of halogen, in Hartrees, at the 0.001 electrons Bohr<sup>-3</sup> isodensity surface of CF<sub>3</sub>X (X = I, Br, Cl)<sup>74</sup>.

	I (CF <sub>3</sub> I)	Br (CF <sub>3</sub> Br)	Cl (CF <sub>3</sub> Cl)
V <sub>SX</sub> (min) (range, X 10 <sup>-3</sup> )	0.45 ~ -2.70	0.45 ~ -2.70	3.60 ~ 0.45

Generally speaking, our new insights pave a way for future rational design focusing on Pd(0)-X interaction, an alternative for the current prevailing Tolman electronic parameter<sup>110</sup>-based rational design. The detail of the overall framework for a rational design will be discussed in later section. And we are clearly aware that the threshold difference could be large for different haloarenes in the coordination of the accessible surface of Pd(0) atom (with a suitable positive potential V<sub>SPd</sub>(max)) with the “side-on” surface of the halogen (with the negative potential V<sub>SX</sub>(min)), due to the polarization capability difference. For iodoarenes and bromoarenes, there is evidence<sup>111</sup> that visualization of the polarization could occur in distances greater than 1.2 times than Van der Waals radii. And this might partially explain the observed higher reactivity of iodo/bromoarenes in Pd(0) OA following a 3-centered concerted mechanism<sup>59,60</sup>.

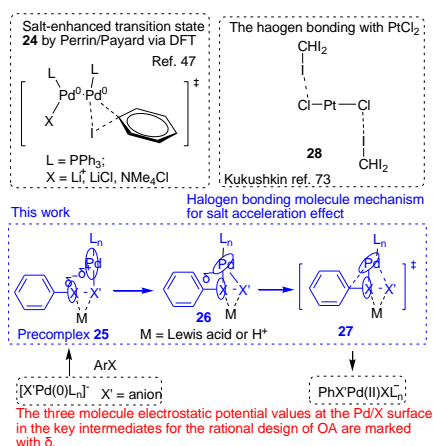
#### *The XB mechanism for the salt acceleration effect*

As described in the introduction section the molecular mechanism for the reactivity acceleration by the halide additives has not been established<sup>26,44,47</sup>. Very recently, Perrin and Payard<sup>47</sup> pointed out that stabilization of the di-ligated Pd(0) intermediate was the first reason of the salt effect on the OA to Pd(0), and a transition state including the cations and anions (LiCl or NH<sub>4</sub>Cl salt) was proposed based on a computation. However,

the linear XB interaction (or the  $\sigma$ -hole interaction)<sup>48,49</sup> was not included in the transition state.

Inspired by the recent successful organocatalysis developments through XB<sup>52,112</sup>, and the activation of gold precatalysts via XB with the anion<sup>91,113,114</sup>, we here propose a XB mechanism for explaining the salt acceleration effect in the OA to Pd(0) in a general manner (Scheme 11). In the proposed intermediate **25**, a free halide anion prefers to occupy the “ $\sigma$ -hole” position of an aryl halide in a linear manner according to the previous observance of such interaction in XB between PtX<sub>2</sub> and CHI<sub>3</sub> by Kukushkin<sup>73</sup>, and the metal involved halogen bonding by Brammer<sup>90</sup>. On the other hand, a free cation like a proton or quaternary amine cation, could stabilize the XB via an orthogonal binary bonding with both the halide anion and the halogen atom in organic halide. Such polarization enhanced XB was extensively investigated by Berryman/Ho in the recent review<sup>51</sup>. The further interaction of the intermediate with Pd(0) species would also likely be in the binary manner as shown in Scheme 11, such binary interaction would likely increase the chance for formation of Pd(0)-X (ArX) bond and eventually promote the 3-centered concerted mechanism, because the early review<sup>53</sup> on the coordination chemistry of Pd and halocarbons indicated that a secondary bonding would favor Pd(0)-X bonding. In addition, the XB formation would also result into elongation of the C-X bond further lowering the oxidative insertion energy barrier by Pd(0). It should be noted that the XB accelerated OA was proposed as the major cause in a brief manner by Vidal-Ferran in electron-rich Rh(I) oxidative insertion of Ar-I bond in complex **22** (Scheme 10) even at 25°C, since the OA of the ortho-iodoarylphosphine (2-IC<sub>6</sub>F<sub>4</sub>PPh<sub>2</sub>) by Rh(I) without XB could only occur at high temperatures or under UV/Vis radiation.<sup>106</sup>

Scheme 11. The known salt-enhanced transition state **24** and the general halogen bonding mechanism for salt promotion effect proposed in this work.



With this molecular mechanism in hand, the remarkable promotion effect of those active anionic species Pd(0)L<sub>2</sub>Cl<sup>-</sup>, Pd(0)L<sub>2</sub>(OAc)<sup>-</sup> and [Pd(Ar)Br<sub>2</sub>]<sub>2</sub><sup>2-</sup> in Heck coupling reactions reported by Amatore/Jutand<sup>45</sup> and Hartwig<sup>46</sup>, respectively, are now better explainable

(Scheme 11). The halogen anion  $\text{Cl}^-$ ,  $\text{OAc}^-$ , or  $\text{Br}^-$  would occupy the “ $\sigma$ -hole” position of an aryl halide in a linear manner as a nucleophile, meanwhile maintaining the halide anion-Pd interaction. The negative charge on the anion would significantly enhance the negative potential on the “side-on” position of X atom (organic halide), favoring the Pd(0)-X (RX) interaction in a binary manner, as described in the proposed intermediates **25**, **26**. Moreover, the very early report of LiCl promotion effect in Pd( $\text{Ph}_3\text{P}$ )<sub>2</sub> OA to  $\text{PhI}$  by Negishi<sup>66</sup> is also very explainable with the proposed common intermediates **25-27**.

The XB mechanism could not only explain the efficiency of tetraalkylammonium salts in Heck type reactions reported by Jeffery<sup>67</sup> in a general manner, but also could explain the surprising high efficiency of the hydrogen sulfate anion. Like a halide anion, the hydrogen sulfate anion (oxygen anion) could also act as an XB acceptor (nucleophile) in the absence of water; however, the presence of water would favor strong hydration of sulfate<sup>115,116</sup>, and water may likely act as an acceptor instead forming a much weaker XB bond<sup>117</sup>. The good tolerance of  $\text{Cl}^-$  to water is likely due to its relatively low hydration capability<sup>118</sup>, still preferring to be involved in the linear XB. Alkali metal salts like LiCl, KCl proved to be inactive in reactivity promotion in Heck coupling reactions in Jeffery’s optimization, probably due to the very low concentration of “free  $\text{Cl}^-$ ” in the organic phase of the reaction system, evidenced by the later additive study by Neufeldt<sup>119</sup>. Meanwhile the coexistence of organic Li ( $n\text{-BuLi}$ ) in Negishi<sup>66</sup> could lead to a complexation with LiCl improving the “free  $\text{Cl}^-$ ” in organic solvent. The remarkable salt effect of KI in promotion of Catellani Reaction by  $\text{Ca}^{120}$  is also hypothesized to be associated with the improved solubility of “free  $\text{I}^-$ ” resulted by the high temperature (120°C) and the XB with toluene solvent molecules.

Importantly, the sizable salt effect could be able to be included in physical measurement or a computation of surface molecular electrostatic potential ( $V_{\text{SPd}}(\text{max})$  and the negative potential  $V_{\text{SX}}(\text{min})$  at the “side-on” surface of the halogen) by the proposed intermediate with our new XB mechanism (Scheme 11).

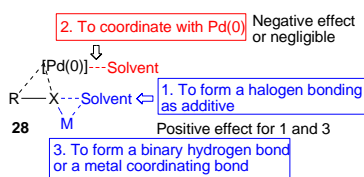
### *Solvent effect*

The solvent effect on Pd(0) OA to organic halides is complex and is usually difficult to be predicted. The role of solvents had been hypothesized to relate to their polarity<sup>121,122</sup>. However, the recent studies by Neufeldt<sup>68,119</sup> revealed a more complicated mechanistic picture and a solvent coordination to Pd was found to be more reasonable in Pd/ $\text{P}^t\text{Bu}_3$ -catalyzed Suzuki-Miyama coupling reactions, supported by strong experimental evidence. In fact, solvent molecule coordination to Pd center had been proposed in several early studies<sup>16,57</sup>, which could switch the reaction mechanism from a 3-centered concerted mechanism to a  $\text{S}_{\text{N}}2$ -like mechanism. On the other hand, depending on the reaction system, solvent polarity was also proved to be insensitive to the OA by Pd(0) in many studies<sup>12,32</sup>. An advanced understanding on the solvent effect is still in great need, in order



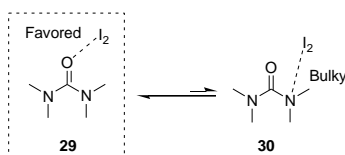
to put the solvent effect into consideration in a quantitative manner in the future rational design of OA by Pd(0).

Scheme 12. A rational analysis of the possible pathways for the solvent molecules affecting the Pd(0) oxidative addition to organic halides.



By uncovering the “super iodine” nature of Pd(0) and the essential role of Pd(0)-X (RX) interaction in the 3-centered concerted mechanism in this work, we could define the Pd(0)-X interactions as “I-X” interactions. The solvent effect to XB is clearly insightful to understand the solvent effect in OA by Pd(0). Based on the 3-centered concerted mechanism and the XB mechanism for additives, we envisage that *the solvent molecules could affect the OA in three possible pathways (Scheme 12): 1) as an additive to the lone pair electrons (or  $\pi$  electrons for aromatic solvents) of a solvent molecule occupying the “ $\sigma$ -hole” position of an aryl halide in a linear manner as a weak nucleophile, following the XB mechanism for the salts acceleration effect; 2) as a ligand coordinating with the Pd(0) center by the lone pair electrons in the solvent molecules as proposed by Neufeldt<sup>119</sup>, destabilizing or destroying the essential Pd(0)-X interaction; 3) protonation of organic halide via a hydrogen bonding as a Lewis acid, the bonding could only be binary after an XB forms as we proposed in Scheme 11, because of the rather weak basic nature of the halide atom in most of organic halides.* For the first possible pathway, the solvent effect would be positive more or less, enhancing the Pd(0)-X interaction depending on the basicity of the solvent molecule. The existence of another lone pair of electrons enabling an addition co-ordination with the Pd(0) center or a proton forming a hydrogen bonding with the organic halide (combining with the third pathway), would largely enhance the Pd(0)-X interaction as well, as we discussed in “The molecular mechanism for additive effect” section. For the second possible pathway, the solvent effect could be negligible or very negative, depending on the competitive affinity of the coordination in comparison with the Pd(0)-X bonding. The higher affinity for solvent coordinating with Pd(0), the more negative effect; in extreme case, the solvent effect could be able to inhibit the Pd(0)-X interaction and the subsequent 3-centered concerted pathway.

Scheme 13. The two halogen bonding complexes of molecule iodine and tetramethylurea<sup>123</sup>



The early studies<sup>59,60,69</sup> show that the solvent effect for Pd(0) OA to aryl iodide is small and negligible, and a conclusion was drawn that OA following a 3-centered concerted pathway would be insensitive to solvent polarity. A recent investigation (Scheme 13) by Perutz/Brammer/Hunter<sup>123</sup> on the solvent effect on XB between molecule iodine and tetramethylurea showed that the associate constant is extremely low (< 1 in most commonly used organic solvents). Because of the tetramethylurea containing both nitrogen atoms with a lone pair of electrons and an oxygen atom with two lone pairs of electrons, the extremely low associate constant could result into a conclusion that the I-O and I-N interactions are both very weak and could be easily replaced even by the same weak (or even weaker, but massive) I-solvent interaction or by a strong I-I interaction. In other words, *the essential strong Pd(0)-I (equivalent to I<sup>+</sup>-I) interaction would remain intact in either non-polar or polar solvents, ensuring the 3-centered concerted OA by Pd(0) unaffected.*

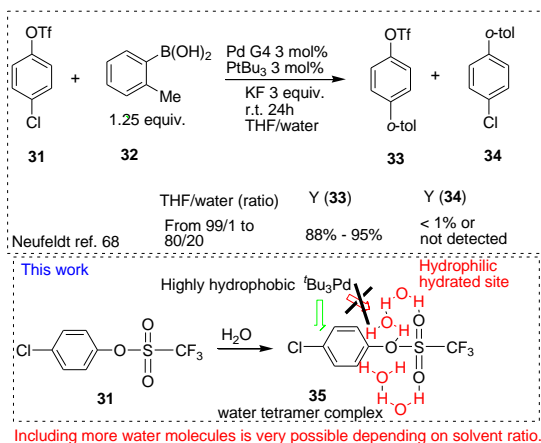
The observed solvent effect in Pd(0) OA to aryl chloride in the recent studies by Fu<sup>121</sup> and Neufeldt<sup>68,119</sup> could be due to the easily distorted nature of the rather weak Pd(0)-Cl (ArCl) interaction as we have discussed in the “Pd(0)-X interactions” section. The weak Pd(0)-Cl (ArCl) interaction could possibly belong to the “semicoordination” as observed in Pd(II)-Cl (Ar-Cl) interaction as reported in literature<sup>104</sup> at least in certain cases. The recent comprehensive solvents screening DFT calculation, and the Hammett-type plot analysis by Neufeldt<sup>68,119</sup> proved that the coordination capability to Pd(0) center rather than the polarity of the solvent was responsible for switching the OA mechanism and subsequently inverting the selectivity. The work<sup>68,119</sup> was an advanced understanding of the molecular mechanism of solvent effect in a qualitative manner, however, the method to quantify such capability for rational design is still missing.

Here we would like to discuss the potential of solvent additive effect via an XB molecular mechanism and the potential correlation between polar coordinating capability and the solvent structure, in order to gain more insights in structure-property based rational design. Based on the solvent structure and its potential to be involving with both XB and coordinating with Pd, there are three common types of solvents. 1) Saturated alkane solvents like hexane, pentane, etc. These solvents would not be able to form XB or to coordinate with the metal center. 2) Aromatic arenes like toluene, and polar solvents with two or more lone pairs of electrons like alcohols, ketones, carbonates, nitromethane, water, THF, dioxane, and halosolvents. These solvents are generally good XB acceptors via the lone pairs or aromatic  $\pi$  clouds, and they could all act as a positive additive to the OA, following both the first and the third possible pathway. Their coordinating capability (oxygen with Pd center<sup>124</sup>) is weak/negligible and would not be able to compete with the Pd(0)-Cl (ArCl) interaction. 3) Polar solvents with a single electron pair like PhCN, NMP, DMF, CH<sub>3</sub>CN and DMSO, etc (nucleophilicity of oxygen atoms in both DMF and NMP was enhanced by the adjacent N lone pair) are better XB acceptors theoretically. They could also be able to coordinate with the Pd center as proved by Neufeldt<sup>68,119</sup>. *A key difference*

of this discussion is the identification of the additive mechanism for elucidation of the solvent effect partially and subsequently providing a method for quantifying the effect via future measurement or computation of the negative potential  $V_{Sx}(min)$  at the “side-on” surface of the chlorine atom in aryl chloride. Another point that we uncovered is the key structure difference (the number of the lone pair electrons) between the polar coordinating solvents and the polar non-coordinating solvents, making the solvent (particularly for new solvents with unknown property of the nucleophilicity) selection more predictive in the future.

The water effect (Scheme 14) on the selectivity of Pd/P<sup>t</sup>Bu<sub>3</sub>-catalyzed Suzuki-Miyama coupling reaction of chloroaryl triflate with o-tolylboronic acid discovered by Neufeldt<sup>68</sup> deserves a separate discussion, due to the potential of *adding water as a general strategy in suppressing the reactivity at the more hydrophilic site*. It was found<sup>68</sup> that in the presence of large amounts of water, the Pd source was not a factor in the selectivity, and the coupling reaction occurred exclusively at the chloride site. The molecular mechanism for this water-controlled chemo-selectivity is not clear. Based on our recent work on the hydration of chloride anion<sup>118</sup> and the hydration resulted water organic complexes study<sup>115,116</sup>, a selective hydration of oxygen atoms (OTf) resulted enhanced hydrophilicity could account for the selectivity. The reversible coordination of the strong hydrophobic active Pd(0) species with the alkene bonds close to the hydrated OTf group would be inhibited as shown in the intermediate **35**; and subsequently the OA to C-OTf bond could be totally suppressed (Scheme 14).

Scheme 14. The water effect on the selectivity of Pd/P<sup>t</sup>Bu<sub>3</sub>-catalyzed Suzuki-Miyama coupling and the molecule mechanism proposed in this work.



### Demystifying the efficient Pd(0) OA to inactive aryl chlorides

Reactivity of aryl chloride in transition metal-catalyzed cross-coupling reactions is generally much lower than that of its aryl bromide/iodide counterpart, mainly due to the

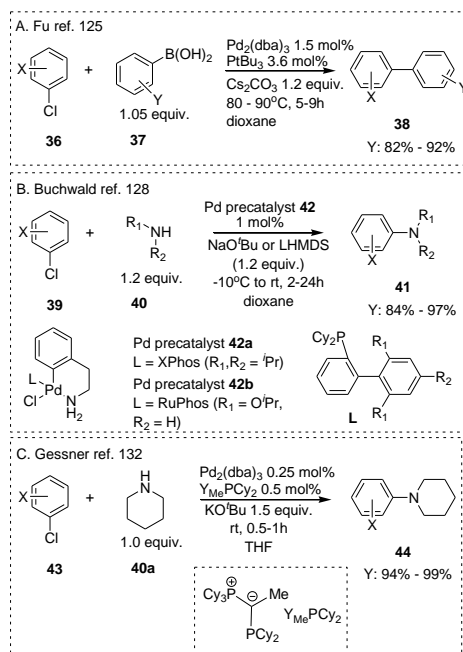
C-Cl bond reluctance to oxidative addition by Pd(0)<sup>125</sup>. Developments of catalytic systems with Pd that are able to couple aryl chlorides were major achievements in organometallic catalysis in recent decades<sup>8,37,55</sup>; the pioneering studies with <sup>t</sup>Bu<sub>3</sub>P as an electron-rich and steric bulky ligand were initially reported in 1998 independently by Fu<sup>124</sup> and Nishiyama/Yamamoto<sup>126,127</sup>. Further developments by design of new ligands with similar electron-rich and steric bulky feature quickly appeared in literatures<sup>5,6,8-10,36,37,54,55,128-133</sup>, notably like biaryl ligands<sup>8-10,55,128,130,133</sup>, NHC (N-heterocyclic carbene) ligands<sup>8-10,36</sup>, ylide-functionalized ligands<sup>37,132</sup> and some of them could even activate aryl chlorides at room temperature<sup>132,133</sup> or even below zero degree<sup>128</sup>. Because aryl chlorides are much cheaper and available in large volumes worldwide, compared to their bromide/iodide counterparts. Their involved Pd-catalyzed coupling reactions are particularly attractive and were quickly utilized in the chemical/pharmaceutical industry<sup>5,8</sup>.

Later mechanistic studies suggested that dissociation of Pd precatalysts to the active monoligated Pd(0) species<sup>8,9,25,26,54</sup> and the subsequent Pd(0) OA to ArCl is the rate-determining step<sup>9,10,36,37</sup>. This suggests that further enhancement of OA rate would allow for an even faster reaction in the aryl chloride-involved coupling reactions. The likely formation of Pd(0)(XPhos)(ArCl) precomplex as a neutral intermediate by Grimand<sup>54</sup> and a proposed concerted three-centered mechanism supported by the Hammett study of OA of ArCl to the XPhosPd(0) complex by Buchwald<sup>128</sup>, indicates that our current approach focusing on Pd(0)-Cl (ArCl) interaction is suitable for further investigation of the mystery molecular mechanism in efficient OA of ArCl not limited on the donor ability of the ligand. Because the strong electron-richness of the ligand was well known as an essential factor, we will not discuss this part separately in following elucidation.

We will demystify the observed enhancing activation of ArCl by focusing on three typical ligands (Scheme 15): <sup>t</sup>Bu<sub>3</sub>P, XPhos/RuPhos, Y<sub>Me</sub>PCy<sub>2</sub>; the first two were mostly explored in previous mechanistic studies and Y<sub>Me</sub>PCy<sub>2</sub> is one of the most successful ligands developed in the recent five years. Pd(0)-arene interaction was found by DFT calculation<sup>54,55</sup> with either <sup>t</sup>Bu<sub>3</sub>P or XPhos as a ligand, and Norrby<sup>55</sup> found that the reactivity difference with <sup>t</sup>Bu<sub>3</sub>P as a ligand between electron-deficient and electron-rich aryl chlorides was due to the higher ligating ability of the electron-deficient aryl chlorides. Norrby's finding is consistent with our data-driven research results on Pd(0)-arene interaction. However, this is likely not the full picture. Our study on Pd(0)-Cl interaction suggests that the further enhancement in Pd(0)-Cl (ArCl) interaction via creating a suitable Pd surface with positive molecular electrostatic potential is more important in the rate increase of the OA step. In addition, a XB would likely form via a free <sup>t</sup>Bu<sub>3</sub>P occupying the  $\sigma$ -hole position of ArCl (Scheme 16A), increasing the potential in generating the essential Pd(0)-Cl (ArCl) interaction as we discussed in previous sections. It is well known<sup>8-10</sup> that the steric bulky nature of the <sup>t</sup>Bu<sub>3</sub>P ligand would favor a dissociation of Pd(<sup>t</sup>Bu<sub>3</sub>P)<sub>2</sub> to active monoligated Pd(0) species, by a release of free <sup>t</sup>Bu<sub>3</sub>P. The electronic nature of the <sup>t</sup>Bu<sub>3</sub>P ligand would only allow for coordination of weak bases like the chlorine atom in ArCl or

solvent molecules like MeCN, but not strong bases like amines, to the Pd(0) surface with positive potential and thus assisting the formation of concerted 3-centered transition state or S<sub>N</sub>2-like transition state (recently a concerted S<sub>N</sub>2-like mechanism for substitution of ArX was proved to be not uncommon<sup>134</sup>).

Scheme 15. Three Pd-catalyzed coupling reactions involved of ArCl with three different ligands (<sup>t</sup>Bu<sub>3</sub>P, XPhos, Y<sub>Me</sub>PCy<sub>2</sub>)

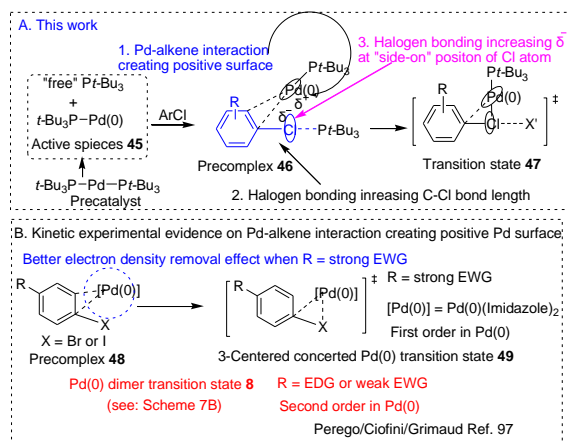


Such fine tuning phenomena of electronic property at Pd(0) surfaces was clearly observed in Pd oxidative addition to iodobenzenes with strong donor ligand imidazole; the kinetic data by Perego/Ciofini/Grimaud<sup>97</sup> suggested that a 3-centered concerted transition state **49** could only form in OA with iodobenzenes with a strong electron-withdrawing group due to a stronger electronic removal effect (Scheme 16B). Meanwhile, an unusual Pd(0) dimer-involved concerted transition state **8** likely forms in OA with a weak electron-withdrawing group or an electron-donating group (Scheme 7). It is estimated that the much weaker electronic removal effect in the latter case might not be able to create a Pd surface with enough positive potential for formation of Pd-X interaction in the absence of XB enhancement.

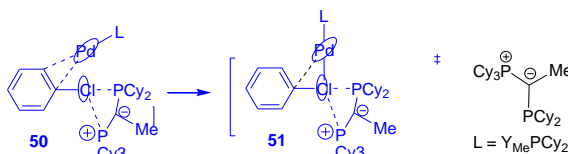
For the OA of ArCl by Pd(0) with ylide-functionalized-phosphine ligand Y<sub>Me</sub>PCy<sub>2</sub> developed by Gessner<sup>37,132</sup>, a similar XB mechanism for OA with <sup>t</sup>Bu<sub>3</sub>P ligand by Y<sub>Me</sub>PCy<sub>2</sub> occupying the σ-hole position of ArCl is also quite likely (Scheme 17). A key difference with a strong reactivity promotion effect is the potential assistance of the positive charge P (in Y<sub>Me</sub>PCy<sub>2</sub>) by bonding with the chlorine atom at the “side-on” position as shown in intermediate **50**, which could explain the extraordinary efficiency in the amination of ArCl even at room temperature. A similar proton assistance to the “side-on” position of the

free  $t\text{BuPCy}_2$  participated XB might also account for the high efficiency in the Suzuki-Miyaura coupling with water as a solvent by Schaub<sup>5</sup>, and the proton could come from a water molecule via a hydration of a orthogonal  $\text{NO}_2$  group of ArCl as the water-organic complexes we proposed before<sup>115</sup>.

Scheme 16. Demystifying the strong ligand ( $t\text{Bu}_3\text{P}$ ) promotion effect in Suzuki coupling reported by Fu<sup>125</sup>.



Scheme 17. Binary halogen bonding intermediate **50** and the transition state **51** for elucidation of the efficient oxidative addition step enabled by ligand  $\text{YMePCy}_2$  (Gessner<sup>132</sup>).

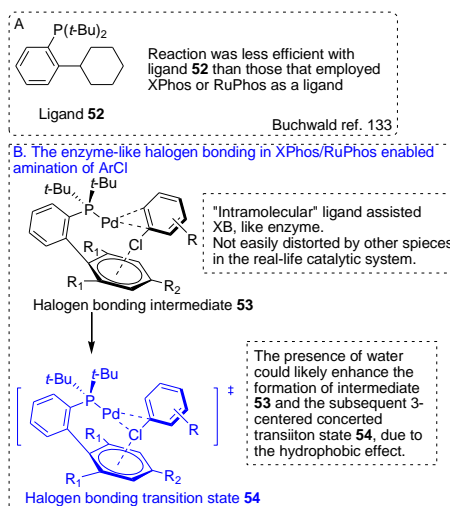


Except the free bulky and electron-rich phosphines like  $t\text{BuPCy}_2$ ,  $\text{YMePCy}_2$  and  $t\text{Bu}_3\text{P}$ , other donors like alkoxide base ( $\text{MO}^t\text{Bu}$ ), water, sulfate salt and some amines could also compete for occupying the  $\sigma$ -hole position as a XB acceptor in facilitating the OA step by Pd(0), depending on the specific catalytic system, as we discussed in the XB additive mechanism section. And the  $t\text{BuO}^-$  anion as a XB acceptor respectively in the catalytic amination systems developed by Hartwig<sup>9,135</sup>, could possibly explain the observed high efficiency following the anionic pathway. Meanwhile, the  $\text{SO}_4^{2-}$  anion (in form of  $(\text{NH}_4)_2\text{SO}_4$ ) might also participate in the amination of aryl chlorides again developed by Hartwig<sup>130</sup>, along with the  $t\text{BuO}^-$  anion in the catalytic system.

An outer sphere  $\pi$ -ring(from coordinated phosphine ligand)-involved XB is proposed (Scheme 18) as a driving force for the activation of C-Cl bond and lowering the barrier in forming the 3-centered transition state **54**, in the amination of aryl chlorides under the very mild condition enabled by the ligand XPhos, RuPhos, or other analogues developed by Buchwald<sup>128,133</sup>. In fact the possibility of the  $\pi$ -ring participation in the intermediate

had been predicted by Buchwald<sup>133</sup> evidenced by a control study that the room-temperature reactions were much less efficient with a ligand **52** without an outer sphere  $\pi$ -ring (Scheme 18A).

Scheme 18. The enzyme-like intramolecular ligand assisted hydrogen bonding intermediate **53** and the transition state **54** for oxidative addition of aryl chloride by XPhosPd or RuPhosPd.

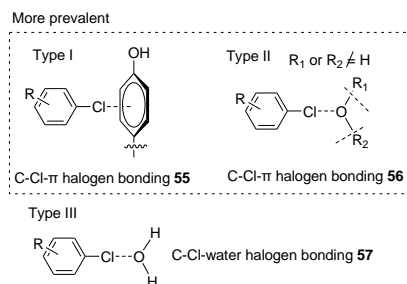


Though C-X... $\pi$  XB is weaker in bonding nature and is less prevalent in biological systems according to the statistical analysis of organic halides and XB in Protein Data Bank (PDB)<sup>136</sup>, in comparison with C-X...Y (Y = O, N, S) XB, the "template effect" linked by the coordinated biaryl phosphine ligand would likely make the generation of "intramolecular" C-X... $\pi$  XB more favorable, and more tolerant to other species in the catalytic systems (Scheme 18B). This enzyme-like XB activation could be the potential reason why an unactivated aryl chloride can undergo oxidative addition to SPhosPd(0)/RuPhosPd(0) at a temperature as low as  $-40\text{ }^\circ\text{C}$ <sup>128</sup>. The dominance of C(Ar)-Cl...Tyr interaction (46.4%) in all the C-X... $\pi$  XB (total number: 211 in PDB) suggests that electron-rich arenes as a  $\pi$  donor and a XB acceptor is clearly more favorable in biological media (Scheme 19). Such XB trends are consistent with the results in the experimental study of catalyst screening that the biaryl ligands with an electron-rich arene like XPhos ligand and RuPhos ligand could enable more efficient amination at room temperature or even lower temperatures (Scheme 15B)<sup>128</sup>. The high ratio of C(Ar)-Cl...O interaction in the general type of C-Cl...Y XB in the PDB also acts as evidence for our suggested XB mechanism for oxygen atom-containing additives' (like anions  $t\text{BuO}^-$  and  $\text{SO}_4^{2-}$ ) accelerated effect in the amination reactions<sup>9,130,135</sup>.

In term of a fact that synthesis of the more electron-rich and steric bulky ligand guided by the Tolman electronic parameter for Pd catalysis of aryl chloride<sup>37</sup> can be very challenging now, an alternative pathway for future rational design of Pd ligands is clearly in great need. With the proposed theoretic XB mechanisms in the activation of C-X bond

and enhancing the 3-centered concerted pathway in this work, future rational design of new ligands by incorporation of aromatic functional group offering  $\pi$ -ring as a XB acceptor, or by adding an enable functional group at the geometrically suitable position offering proton or Lewis acid assistance in orthogonal bonding, is clearly possible in a qualitative manner. And it is desirable since the XB was relatively less explored as an important non-covalent interaction in design of small-molecule catalysts<sup>137</sup>.

Scheme 19. The halogen bonding types involved with aromatic chloride in biological system<sup>136</sup>.



Water and alcohols are obviously solvents of choice in future solvent optimization in Pd catalyzed coupling reactions, particularly for Suzuki coupling reaction, not only for a green and sustainable process, but also for a better efficiency in favoring the Pd(0) OA of ArCl by forming a XB (Scheme 19). Future detection of the proposed XB with those aryl chlorides that are inert exposing to oxidative addition by Pd(0) in a specific catalytic system, might be possible by NMR technique, according to a recent tutorial review<sup>138</sup> summarizing hydrogen bonding in solution. But it would be impractical to capture intermediates for those substrates vulnerable to the Pd(0) OA because the life span of the intermediates can be very short.

#### *The surface electrostatic potential parameter for rational design*

To control the reaction selectivity when two or more halogen reaction sites are present in the complex real-life catalytic systems, it is essential to identify the dominant OA pathway. Currently, it is challenging and there is no practical method to predict whether the OA by Pd(0) is to follow a 3-centered concerted pathway or a  $S_N2$ -like pathway, although there are some general guidelines based on the nature of ligand (like monodentate or bidentate)<sup>139</sup>. To address this challenge, a surface electrostatic potential parameter-based rational design of OA is introduced here as a potential practical method in the future. A proof-of-concept, rather than a case study is presented here since the expertise in quantum mechanics-based computation and AI is quite necessary for the rational design of OA and it is out of our knowledge/technical capability.

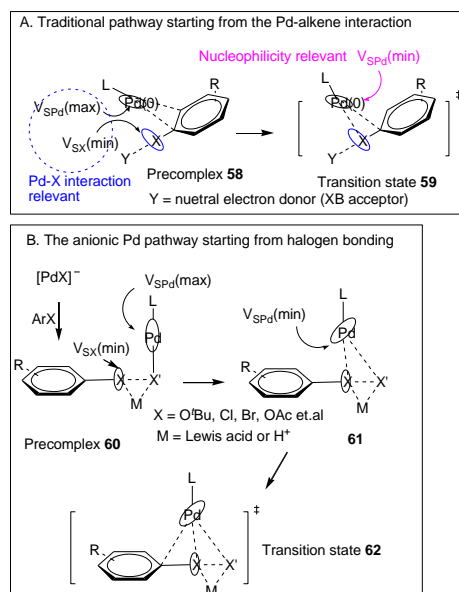
Pd-X interaction is essential for a 3-centered concerted mechanism of OA as shown in Scheme 11 and Scheme 16A. Pd-arene interaction is a very fast and reversible process generating the Pd(ArX) neutral complexes initially and not all the neutral complexes have



an equal chance to facilitate the essential Pd-X interaction. Only the Pd-arene interaction at the two adjacent alkenes ( $\eta^2$ -complex) have a good chance to form a binary Pd-X interaction, and subsequently a fast switching from a Pd-arene interaction ( $\eta^2$ -complex) to a Pd-C (C-X) interaction leads to the well-known 3-centered concerted transition state. We have demonstrated that the electronic removal from the Pd atom by Pd-arene interaction would be crucial in creating a new surface with relatively positive electrostatic potential ( $V_{SPd(max)}$ : the maximum surface potential value on all surfaces of Pd(0)), which is likely located close to the organic halide geometrically, facilitating a Pd-X interaction at the “side-on” surface of the halogen atom via the electrostatic force and polarization (Scheme 20A). The uncovered “super iodine” nature of Pd(0) is essential to understand the shape/volume change of Pd(0) in coordination, proposed in the intermediates/transition states. By forming XB with the organic halide at the  $\sigma$ -hole position, the presence of electron donors like free anions, free ligands, neutral molecules, solvent molecules, and  $\pi$ -rings could all have sizable influences on the negative electrostatic potential ( $V_{SX(min)}$ : the minimum surface potential value on the belt surfaces) at the “side-on” surface of the halogen atom, and the bond length of C-X in organic halides. We envisage that only when both  $V_{SPd(max)}$  and  $V_{SX(min)}$  lie within a suitable range, a meaningful Pd-X interaction could be able to be generated. And there are different thresholds for the two surface potential values for different halogens, due to the polarization difference of them. The third surface electrostatic potential value ( $V_{SPd(min)}$ : the most negative electrostatic potential value at the surface of Pd upon Pd-X coordination) is for quantifying the nucleophilicity of the Pd in subsequent Pd-C interaction within the 3-centered concerted transition state. *Both values of  $V_{SPd(max)}$ ,  $V_{SX(min)}$  are observable physical properties, which could be determined experimentally or computationally<sup>76</sup>.  $V_{SPd(min)}$  could only be achieved computationally since the transition state **59** upon Pd-X formation is impractical to be captured. A general trend is that the lower the negative potential value of  $V_{SPd(min)}$ , the more favorable for OA of inactive ArCl could be expected because of the better nucleophilicity of the eligible Pd surface toward the carbon atom (C-X). Meanwhile, the higher the positive potential value of  $V_{SPd(max)}$  with a better Lewis acidity at Pd surface orthogonal to the halide atom (C-X), and a lower negative potential value of  $V_{SX(min)}$  at “side-on” position of the halide atom (C-X) with a better coordination capability, would also be more favorable for OA of inactive ArCl by promotion of Pd-X interaction. However, it should be noted that all three surface electrostatic potential values are actually interlinked via the electron density sharing between aryl group (ArX) and Pd (Pd-arene interaction) and between aryl group and X.* For example, decreasing the negative potential value of  $V_{SPd(min)}$  to maximize the nucleophilicity of the Pd surface, by making the ligand more electron-rich, may possibly decrease the Lewis acidity at the Pd surface (a lower  $V_{SPd(max)}$ ) where it is supposed to form an essential Pd-X interaction (ArX) and eventually a lower reactivity of OA is observed. A future combination of the traditional quantum mechanics-based computation with artificial intelligence (AI) is highly desirable, in order to look for the

goldilocks values of  $V_{SPd(max)}$ ,  $V_{SX(min)}$  and  $V_{SPd(min)}$  toward a systematic rational design of OA.

Scheme 20. The proof-of-concept for rational design of Pd(0) OA to ArX at the precomplex stage to the transition state stage in systematic way with three surface electrostatic potential values of  $V_{SPd(max)}$ ,  $V_{SX(min)}$  and  $V_{SPd(min)}$ .



An alternative XB pathway to generate the common 3-centered concerted transition state without forming the Pd(arene) precomplex via Pd-arene interaction, is theoretically also very possible for the anionic palladium species<sup>45,46,140</sup> as we proposed in “the XB mechanism for salt acceleration effect” section (Scheme 11 and Scheme 20B). The anion coordinating with Pd(0) is known to be an excellent XB acceptor<sup>90</sup> by occupying the  $\sigma$ -hole position of the organic halide in a linear manner, the relative long distance between Pd and the arene moiety would unlikely result into a subsequent Pd-arene interaction, but instead could possibly favor a binary coordination with the nearby organic halide atom forming a 3-centered intermediate **61**. A fluctuation resulted breaking of the Pd-anion bond and quick formation of the required Pd-C bond, eventually generates the common 3-centered concerted transition state **62**. The directionality of the linear XB and the potential stronger nucleophilicity (lack of electron density removal effect by Pd-arene interaction) of the Pd(0) surface targeting to the carbon atom (C-X), very likely makes the formed 3-centered concerted transition state **62** even more reactive due to following this alternative pathway. Similarly, within intermediate **60** upon XB formation, a positive molecular electrostatic potential at the Pd surface ( $V_{SPd(max)}$ ) that faces the organic halide (likely induced by the charge transfer from the coordinated anion X' to X (the organic halide)), and the negative molecular electrostatic potential ( $V_{SX(min)}$ ) at the “side-on” surface of the organic halogen would be essential in favoring the Pd-X interaction. In the resulted new 3-centered intermediate **61**, the negative molecular electrostatic

potential at Pd surface ( $V_{SPd}(\text{min})$ ) that faces the the carbon atom (C-X) would also be an important element in quantifying the nucleophilicity of the Pd surface.

Importantly, in our new concept for rational design, the surface molecular electrostatic potential could be able to include the ligand effect (regardless of the type of the ligand), additive effect, and solvent effect in a systematic and quantitative manner. The “halogen” character of Pd(0) in bonding not only could be expanded to Pd(II) (the planar square feature of Pd(II) in coordination of 4 is well known<sup>44</sup>) in bonding, but also could potentially be transferrable for OA by other soft transition metal complexes like Au, Ir, Rh, Pt, Ni complexes. Hence, the data pool is expected to be large enough for future computation and AI training due to the relatively well-explored OA by these soft transition metal complexes.

Typically the active Pd(0) species must be known in our above single parameter-based rational design of OA. In regards to this limitation, the quantitative analysis as shown above with Pd(0)L and Pd(0)L<sub>2</sub> (L = electron-rich ligand) respectively, could also be promising to determine the real active Pd species and a ligand dissociate or associate mechanism, by comparing the three values whether are suitable for a 3-centered concerted transition state, when AI training is available in the future. To speed up the process to identify the active Pd(0) species in a catalytic system via employing a newly designed ligand, a practical method is suggested here, by mixing the stable Pd(COD)(DQ) (COD = 1,5-cyclooctadiene, DQ = duroquinone) with a stoichiometric amount of new ligand. A ligand exchange would be expected as reported very recently by Eagle<sup>141</sup>, and usually a complex formula of Pd(0)L<sub>n</sub>(DQ) (n = 1 or 2) would be obtained as a bench stable Pd complex, in which Pd(0)L<sub>n</sub> could be seen as the active Pd(0) species at the initial stage for our single parameter-based analysis. The similar Pd(0)L<sub>n</sub>(nq) or Pd(0)L<sub>n</sub>(pbq) or Pd(0)L<sub>n</sub>(ma) (n = 1 or 2, nq = 1,4-naphthoquinone, pbq = *para*-benzoquinone, ma = maleic anhydride) were also reported before by Elsevier<sup>142,143</sup> and Leitch<sup>144</sup>, respectively. In all complexes except Pd(<sup>t</sup>Bu<sub>3</sub>P)<sub>2</sub><sup>141</sup>, Pd(0)L<sub>n</sub> is indeed the active Pd(0) species evidenced by the reported kinetic studies<sup>8-9</sup>. It is likely because Pd(0) shows a tendency to be trigonal planar<sup>142</sup>. Besides, the crystal data might provide important information on the coordination geometry, which is valuable for identification of feasible non-covalent interactions in the catalyst-substrate complex. For example, in all stable Pd(0)L<sub>n</sub>(DQ) or Pd(0)L<sub>n</sub>(nq) or Pd(0)L<sub>n</sub>(pbq) or Pd(0)L<sub>n</sub>(ma) complexes, the metal-alkene bond is approximately perpendicular to the plane of the quinone, but within the same plane of the ligand framework. Particularly in the crystal of Pd(L) (DQ) (L = JohnPhos, XPhos, Brettphos)<sup>141</sup>, the plane of the DQ is also approximately perpendicular to the outsphere  $\pi$ -ring; this indicates that the proposed Cl(in ArCl)- $\pi$  in the previous section (Scheme 18B) is geometrically very feasible.

## Conclusions

An integrated study of Pd(0)-halide interactions in Pd(0) OA to organic halides is carried out in this work in an interdisciplinary manner, mimicking the desired data-driven methods but picking up literatures manually. The new fundamental understanding achieved has filled the gap between formation of Pd(0)(organic halide) neutral complexes and the final Pd(II) aryl complexes. We discovered that under coordination, a Pd(0) atom is equivalent to an iodine cation (I<sup>+</sup>) in halogen bonding, more precisely, it is a neutral “super iodine” with both positive and negative regions at different surfaces. This new concept could provide a theoretical basis for the well-known “*trans* effect” (another name is “push-pull interaction”) in transition metal complexes (Pd, Pt, Ir et.al), and for an experimental fact of the simultaneous presence of both nucleophilicity and electrophilicity in Pd(0) coordination.

A new halogen ion transfer OA mechanism is demonstrated to be very feasible theoretically when both a common S<sub>N</sub>2-like mechanism and a 3-centered concerted mechanism are not favored due to the bulkiness resulted hindrance. In this new mechanism, the Pd(0) species approaches and occupies the σ-hole position by offering an electron pair to share with the halogen atom, and a halogen bonding with a common bonding mode of [Pd(0) ⋯X<sup>+</sup>⋯R<sup>-</sup>] forms in a linear manner. The assistant or catalytic role of another Pd(0) in OA of RX by Pd(0) in OA following a S<sub>N</sub>2-like mechanism is also proposed to be feasible in a general manner.

The nature of the Pd(0)-X interaction (organic halides) is uncovered via an interdisciplinary approach. We provided strong pieces of evidence for a new insight, that the formation of Pd(0)-X interaction is the rate-determining step (RDS) from the formation of Pd(0) precomplex stage to the OA product formation. And the subsequent Pd(0)-C (C-X) interaction forming the 3-centered transition state and the oxidative insertion by Pd(0) is very fast. Broadly speaking, the ligand dissociation/association, the olefin dissociation/association and the amine dissociation/association (in the Buchwald-Hartwig coupling reactions) are all driven by creating a coordination accessible surface at the Pd(0) atom with a suitable positive potential toward the formation of the essential Pd(0)-X interaction. And the formation of the Pd(0)-X interaction is an exit toward OA from the reversible Pd(0)-arene interaction.

A halogen bonding mechanism for explaining the salt acceleration effect in the OA to Pd(0) in a general manner is also proposed. A free halide anion prefers to occupy the “σ-hole” position of an aryl halide in a linear manner, and a free cation like proton or quaternary amine cation, could stabilize the halogen bonding in the catalyst-substrate intermediate, via an orthogonal binary bonding with both the halide anion and the halogen atom in organic halide. With this molecular mechanism in hand, the remarkable promotion effect of active anionic species Pd(0)L<sub>2</sub>Cl<sup>-</sup>, Pd(0)L<sub>2</sub>(OAc)<sup>-</sup> and [Pd(Ar)Br<sub>2</sub>]<sub>2</sub><sup>2-</sup> in coupling reactions are now better explainable. The halogen bonding mechanism could

also better explain the “solvent effect” partially along with our new solvent classification methods based on the numbers of lone pairs in solvent molecules.

The molecular mechanism in enhancing activation of ArCl is demystified by focusing on three typical ligands:  $t\text{Bu}_3\text{P}$ , XPhos, and  $\text{Y}_{\text{Me}}\text{PCy}_2$ . A halogen bonding formed via a free  $t\text{Bu}_3\text{P}$  (or its analogues) occupying the “ $\sigma$ -hole” position of ArCl, increases the potential in generating the essential Pd(0)-Cl (ArCl) interaction. For catalysis with  $\text{Y}_{\text{Me}}\text{PCy}_2$ , A similar halogen bond mechanism could explain the high efficiency as well. An additional reactivity promotion effect is the potential assistance of the positive charge P by bonding with the chlorine atom at the “side-on” position, which could explain the extraordinary efficiency in the amination of ArCl even at room temperature. An outer sphere  $\pi$ -ring (from coordinated phosphine ligand)-involved halogen bonding is proposed as a driving force for enzyme-like activation of the C-Cl bond, lowering the barrier in forming the 3-centered transition state, in the amination of aryl chlorides under very mild conditions enabled by the ligand XPhos/RuPhos or other analogues. With the new insights in hand, the rational design of new ligands with a feature of ligand-assisted halogen bonding is demonstrated to be very promising qualitatively in future development of inactive ArCl-involved coupling reactions.

Our new concept of the surface molecular electrostatic potential-based rational design of oxidative addition focusing on the key intermediates just before the formation of the essential Pd-X interaction (ArX), including the ligand effect (regardless of the type of the ligand), additive effect, and solvent effect in a systematic and quantitative manner, is also introduced as an alternative for the Tolman electronic parameter-based design. Three surface values ( $V_{\text{SPd}}(\text{max})$ ,  $V_{\text{SX}}(\text{min})$  and  $V_{\text{SPd}}(\text{min})$ ) are defined separately based on the traditional Pd( $\eta^2$ -arene) precomplex pathway and an unprecedented halogen bonding pathway in generating the common 3-centered concerted transition state. Importantly, the “halogen” character of Pd(0) in bonding not only could be expanded to Pd(II) in bonding, but also could also potentially be applicable for other soft transition metal complexes like Au, Ir, Rh, Pt, Ni complexes. Hence, the data pool is expected to be large enough for future computation and AI training due to the relatively well-explored OA by these soft transition metal complexes.

#### Author Information

Liuqun Gu --- currently unaffiliated, Singapore, ORCID: 0000-0002-4254-6824.

#### Reference

- 1) Wang, Y.; Haight, I.; Gupta, R.; Vasudevan, A. “What is in Our Kit, An Analysis of Building Blocks Used in Medicinal Chemistry Parallal Libraries” J. Med. Chem. 2021, 64, 17115 – 17122.

- 2) Brown, D. G.; Boström, “Analysis of Past and Present Synthetic Methodologies on the Medicinal Chemistry: Where Have All the New Reactions Gone” *J. Med. Chem.* 2016, 59, 4443 – 4458.
- 3) Roughley, S. D.; Jordan, A. M. “the Medicinal Chemist’s “Toolbox”, An Analysis of Reactions Used in the Pursuit of Drug Candidates” *J. Med. Chem.* 2011, 54, 3451 – 3479.
- 4) Levin, M. D. “Retrosynthetic Simplicity” *Synlett* 2023, 34, A – D.
- 5) Orecchia, P.; Petkova, D. S.; Goetz, R.; Rominger, F.; Hashimi, A. S. K.; Schaub, T. “Pd-Catalysed Suzuki-Miyaura Cross-Coupling of Aryl Chlorides at Low Catalyst Loadings in Water for the Synthesis of Industrial Important Fungicides” *Green Chem.* 2021, 23, 8169 – 8180.
- 6) Palladino, C.; Fantoni, T.; Ferrazzano, L.; Tolomelli, A.; Cabri, W. “Copper-Free Heck–Cassar–Sonogashira and Suzuki–Miyaura Reactions of Aryl Chlorides: A Sustainable Approach” *ACS Sustainable Chem. Eng.* 2023, 11, 15994 – 16004.
- 7) Luescher, M. U.; Gallou, F.; Lipshutz, B. “The Impact of Earth-abundant Metals as A Replacement for Pd in Cross coupling Reactions” *Chem. Sci.* 2024, 15, 9016 – 9025.
- 8) Firsan, S. J.; Sivakumar, V.; Colacot, T. J. “Emerging Trends in Cross-Coupling: Twelve-Electron-Based  $L_1Pd(0)$  Catalysts, Their Mechanism of Action, and Selected Applications” *Chem. Rev.* 2022, 122, 16983 – 17027.
- 9) Christmann, U.; Vilar, R. “Palladium Species as Catalysts in Cross-Coupling Reactions” *Angew. Chem. Int. Ed.* 2005, 44, 366 – 374.
- 10) Palladino, C.; Fantoni, T.; Ferrazzano, L.; Muzzi, B.; Ricci, A. Tolomelli, A.; Cabri, W. “New Mechanistic Insights into the Copper-Free Heck–Cassar–Sonogashira Cross-Coupling Reaction” *ACS Catal.* 2023, 13, 12048 – 12061.
- 11) Crociani, B.; Antonaroli, S.; Canovese, L.; Uguagliati, P. “Kinetic Studies of the Oxidative Addition and Transmetalation Steps Involved in the Cross-Coupling of Alkynyl Stannanes with Aryl Iodides Catalysed by  $\eta^2$ -(Dimethyl fumarate)(iminophosphane)palladium(0) Complexes” *Eur. J. Inorg. Chem.* 2004, 732 – 742.
- 12) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. “Mechanistic Studies of the Palladium-Catalyzed Amination of Aryl Halides and the Oxidative Addition of Aryl Bromides to  $Pd(BINAP)_2$  and  $Pd(DPPF)_2$ : An Unusual Case of Zero-Order Kinetic Behavior and Product Inhibition” *J. Am. Chem. Soc.* 2000, 122, 4618 – 4630.
- 13) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. “Mechanistic Studies of the Suzuki Cross-Coupling Reaction” *J. Org. Chem.* 1994, 59, 8151 – 8156.
- 14) Stille, J. K.; Lau, K. S. Y. “Mechanisms of Oxidative Addition of Organic Halides to Group 8 Transition- Metal Complexes” *Acc. Chem. Res.* 1977, 10, 434 – 442.
- 15) Milstein, D.; Stille, J. K. “Palladium-Catalyzed Coupling of Tetraorganotin Compounds with Aryl and Benzyl Halides. Synthetic Utility and Mechanism” *J. Am. Chem. Soc.* 1979, 101, 4992 – 4998.
- 16) Wolf, L. M.; Thiel, W. “Origin of Inversion versus Retention in the Oxidative Addition of 3-Chloro-cyclopentene to  $Pd(0)L_n$ ” *J. Org. Chem.* 2014, 79, 12136 – 12147.

- 17) Catellani, M.; Frignani, F.; Rangoni, A. "A Complex Catalytic Cycle Leading to a Regioselective Synthesis of o,o'-Disubstituted Vinylarenes" *Angew. Chem. Int. Ed. Engl.* 1997, 36, 119 – 122.
- 18) Motti, E.; Ca', N. D.; Xu, D.; Piersimoni, A.; Bedogni, E.; Zhou, Z.-M.; Catellani, M. "A Sequential Pd/Norbornene-Catalyzed Process Generates o-Biaryl Carbaldehydes or Ketones via a Redox Reaction or 6H-Dibenzopyrans by C-O Ring Closure" *Org. Lett.* 2012, 14, 5792 – 5795.
- 19) Wang, J.; Dong, G. "Palladium/Norbornene Cooperative Catalysis" *Chem. Rev.* 2019, 119, 7478 – 7528.
- 20) Liu, X.; Wang, J.; Dong, G. "Modular Entry to Functionalized Tetrahydrobenzo[b]azepines via the Palladium/Norbornene Cooperative Catalysis Enabled by a C<sub>7</sub>-Modified Norbornene" *J. Am. Chem. Soc.* 2021, 143, 9991 – 10004.
- 21) Rago, A. J.; Ye, R.; Liu, X.; Dong, G. "A four-component reaction to access 3,3- disubstituted indolines via the palladium– norbornene-catalyzed ortho amination/ipso conjunctive coupling" *Chem. Sci.*, 2024, 15, 1318 – 1323.
- 22) Mahendar, L.; Krishna, J.; Reddy, A. G. K.; Ramulu, B. V.; Satyanarayana, G. "A Domino Palladium-Catalyzed C-C and C-O Bonds Formation via Dual O-H Bond Activation: Synthesis of 6, 6-Dialkyl-6H-benzo[c]chromenes" *Org. Lett.* 2012, 14, 628 – 631.
- 23) Chai, D. I.; Lautens, M. "Tandem Pd-Catalyzed Double C-C Bond Formation: Effect of Water" *J. Org. Chem.* 2009, 74, 3054 – 3061.
- 24) Monteferrante, E.; Houghthing, K. E.; Kropiwnicki, A. R.; Paradine, S. M. "Urea Ligand-promoted chainwalking Heteroannulation for the Synthesis of 6- and 7-membered Azaheterocycles" *ChemRxiv*. 2024, DOI: 10.26434/chemrxiv-2024-5dz98.
- 25) Rio, J.; Liang, H.; Perrin, M.-E.; Perego, L.; Grimaud, L.; Payard, P.-A. "We Already Know Everything about Oxidative Addition to Pd(0) - Do We?" *ACS Catal.* 2023, 13, 11399 – 11421.
- 26) Labinger, J. A. "Tutorial on Oxidative Addition" *Organometallics* 2015, 34, 4784 – 4795.
- 27) Hansen, T.; Sun, X.; Dalla Tiezza, M.; van Zeist, W. J.; van Stralen, J. N. P.; Geerke, D. P.; Wolters, L. P.; Poater, J.; Hamlin, T. A.; Bickelhaupt, F. M. "C-X Bond Activation by Palladium: Steric Shielding versus Steric Attraction." *Chem. Eur. J.* 2022, 28, e202201093.
- 28) Hansen, T.; Sun, X.; Dalla Tiezza, M.; van Zeist, W.-J.; Poater, J.; Hamlin, T. A.; Bickelhaupt, F. M. "C(Sp<sup>n</sup>)-X (n = 1 - 3) Bond Activation by Palladium" *Chem. Eur. J.* 2022, 28, e202103953.
- 29) Moloto, B. P.; Vermeeren, P.; Dalla Tiezza, M.; Esterhuysen, C.; Poater, J. Bickelhaupt, F. M.; Hamlin, T. A. "Palladium-Catalyzed Activation of Carbon–Halogen Bonds: Electrostatics-Controlled Reactivity" *Eur. J. Org. Chem.* 2022, e202200722.
- 30) Ozawa, F.; Kubo, A.; Hayashi, T. "Generation of Tertiary Phosphine-Coordinated Pd(0) Species from Pd(OAc)<sub>2</sub> in the Catalytic Heck Reaction" *Chem. Lett.* 1992, 2177 – 2180.
- 31) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. "Water-Mediated Catalyst Preactivation: An Efficient Protocol for C-N Cross-Coupling Reactions" *Org. Lett.* 2008, 10, 3505 – 3508.
- 32) Hartwig, J. F.; Paul, F. "Oxidation Addition of Aryl Bromide after Dissociation of Phosphine from a Two-Coordinate Palladium(0) Complex, Bis(tri-o-tolylphosphine)palladium(0)" *J. Am. Chem. Soc.* 1995, 117, 5373 – 5374.

- 33) Van Asselt, R.; Vrieze, K.; Elsevier, C. J. "Oxidative addition of organic halides to zerovalent palladium complexes containing rigid bidentate nitrogen ligands" *J. Organometal. Chem.* 1994, 480, 27 – 40.
- 34) Norman, J. P.; Larson, N. G.; Neufeldt, S. R. "Different Oxidative Addition Mechanisms for 12- and 14-Electron Palladium(0) Explain Ligand-Controlled Divergent Site Selectivity" *ACS Catal.* 2022, 12, 8822 – 8828.
- 35) Amatore, C.; Broecker, G.; Jutand, A.; Khalil, F. "Identification of the Effective Palladium(0) Catalytic Species Generated in Situ from Mixtures of Pd(dba)<sub>2</sub> and Bidentate Phosphine Ligands. Determination of Their Rates and Mechanism in Oxidative Addition" *J. Am. Chem. Soc.* 1997, 119, 5176 – 5185.
- 36) Lewis, A. K. K.; Caddick, S.; Cloke, F. G. N.; Billingham, N. C.; Hitchcock, P. B.; Leonard, J. "Synthetic, Structural, and Mechanistic Studies on the Oxidative Addition of Aromatic Chlorides to a Palladium (N-Heterocyclic Carbene) Complex: Relevance to Catalytic Amination" *J. Am. Chem. Soc.* 2003, 125, 10066 – 10073.
- 37) Knyszek, D.; Gessner, V. H. "Ylide-Substituted Phosphines in Palladium-Catalyzed Coupling Reactions" *Aldrichimica ACTA* 2024, 57, 17 – 28.
- 38) Newman-Stonebraker, S. H.; Smith, S. R.; Borowski, J. E.; Peters, E.; Gensch, T.; Johnson, H. C.; Sigman, M. S.; Doyle, A. G. "Univariate classification of phosphine ligation state and reactivity in cross-coupling catalysis" *Science* 2021, 374, 301 – 308.
- 39) Tolman, C. A. "Steric effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis" *Chem. Rev.* 1977, 77, 313 – 348.
- 40) Paul, F.; Patt, J.; Hartwig, J. F. "Palladium-Catalyzed Formation of Carbon-Nitrogen Bonds. Reaction Intermediates and Catalyst Improvements in the Hetero Cross-Coupling of Aryl Halides and Tin Amides" *J. Am. Chem. Soc.* 1994, 116, 5969 – 5970.
- 41) Guram, A. S.; Buchwald, S. L. "Palladium-Catalyzed Aromatic Aminations with in situ Generated Aminostannanes" *J. Am. Chem. Soc.* 1994, 116, 7901 – 7902.
- 42) Anjali, B. A.; Suresh, C. H. "Interpreting Oxidative Addition of Ph-X (X = CH<sub>3</sub>, F, Cl, and Br) to Monoligated Pd(0) Catalysts Using Molecular Electrostatic Potential" *ACS Omega* 2017, 2, 4196 – 4206.
- 43) Lu, J.; Donnecke, S.; Paci, I.; Leitch, D. C. "A Reactivity Model for Oxidative Addition to Palladium Enables Quantitative Predictions for Catalytic Cross-Coupling Reactions" *Chem. Sci.*, 2022, 13, 3477 – 3488.
- 44) Fagnou, K.; Lautens, M. Halide Effects in Transition Metal Catalysis" *Angew. Chem. Int. Ed.* 2002, 41, 26 – 47.
- 45) Amatore, C.; Jutand, A. "Anionic Pd(0) and Pd(II) Intermediates in Palladium-Catalyzed Heck and Cross-Coupling Reactions" *Acc. Chem. Res.* 2000, 33, 314 – 321.
- 46) Carrow, B. P.; Hartwig, J. F. "Ligandless, Anionic, Arylpalladium Halide Intermediates in the Heck Reaction" *J Am Chem Soc.* 2010, 132, 79 – 81.
- 47) Liang, H.; Rio, J.; Perrin, L.; Payard, P.-A. "Salt-Enhanced Oxidative Addition of Iodobenzene to Pd: An Interplay Between Cation, Anion, and Pd-Pd Cooperative Effects" *Inorg. Chem.*, 2022, 61, 7935 – 7944.
- 48) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. "The Halogen Bond" *Chem. Rev.* 2016, 116, 2478 – 2601.



- 49) Brammer, L.; Peuronen, A.; Roseveare, T. M. "Halogen bonds, chalcogen bonds, pnictogen bonds, tetrel bonds and other r-hole interactions: a snapshot of current progress" *Acta Cryst.* 2023, C79, 204 – 216.
- 50) Chiodi, D.; Ishihara, Y. "'Magic Chloro': Profound Effects of the Chlorine Atom in Drug Discovery" *J. Med. Chem.* 2023, 66, 8, 5305 – 5331.
- 51) Riel, A. M. S.; Rowe, R. K.; Ho, E. N.; Carlsson, A.-C. C.; Rappe, A. K.; Berryman, O. B.; Ho, P. S. "Hydrogen Bond Enhanced Halogen Bonds: A Synergistic Interaction in Chemistry and Biochemistry" *Acc. Chem. Res.* 2019, 52, 2870 – 2880.
- 52) Sutar, R. L.; Huber, S. M. "Catalysis of Organic Reactions through Halogen Bonding" *ACS Catal.* 2019, 9, 9622 – 9639.
- 53) Kulawiec, R. J.; Crabtree, R. H. "Coordination Chemistry of Halocarbons" *Coord. Chem. Rev.* 1990, 99, 89 – 115.
- 54) Wagschal, S.; Perego, L. A.; Simon, A.; Franco-Espejo, A.; Tocqueville, C.; Albaneze-Walker, J.; Jutand, A.; Grimaud, L. "Formation and Reactivity of XPhos-Ligated Palladium(0) Complexes in Oxidative Additions" *Chem. Eur. J.* 2019, 25, 6980 – 6987.
- 55) Ahlquist, M.; Norrby, P.-O. "Oxidative Addition of Aryl Chlorides to Monoligated Palladium(0): A DFT-SCRF Study" *Organometallics* 2007, 26, 550 – 553.
- 56) Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Mottier, L. "Reactivity of palladium(0) complexes in the oxidative addition of allylic acetates" *Electrochimica Acta* 2001, 46, 3237 – 3244.
- 57) Kurosawa, H.; Kajimaru, H.; Ogoshi, S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. "Novel Syn Oxidative Addition of Allylic Halides to Olefin Complexes of Palladium(0) and Platinum(0)" *J. Am. Chem. Soc.* 1992, 114, 8417 – 8424.
- 58) Koszinowski, K. "Observation and Characterization of Single Elementary Reactions of Organometallics" *Organometallics* 2024, 43, 205 – 218.
- 59) Fauvarque, J.-F.; Pfluger, F.; Troupel, M. Kinetics of Oxidative Addition of Zerovalent Palladium to Aromatic Iodides" *J. Organometal. Chem.* 1981, 208, 419 – 427.
- 60) Semmelhack, M. F.; Ryono, L. Carbon-Carbon Bond Formation Via Transition Metals: Addition-Elimination of Aryl and Alkenyl Halides to Methytris(Triphenylphosphine)Rhodium(I)" *Tetrahedron Lett.* 1973, 31, 2967 – 2970.
- 61) Bickelhaupt, F. M.; Ziegler, T.; Scheyer, P. R. "Oxidative Insertion as Frontside S<sub>N</sub>2 Substitution: A Theoretical Study of the Model Reaction System Pd + CH<sub>3</sub>Cl" *Organometallics* 1995, 14, 2288 – 2296.
- 62) Bercaw, J. E. "Jack Halpern (1925–2018): Pioneer of homogeneous catalysis" *PNAS* 2018, 115, 5049 – 5050.
- 63) Bader, R. F. W.; Carroll, M. T.; Cheeseman, J. R.; Chang, C. "Properties of Atoms in Molecules: Atomic Volumes" *J. Am. Chem. Soc.* 1987, 109, 7968 – 7979.
- 64) Bader, R. F. W.; Matta, C. F. "Atoms in molecules as non-overlapping, bounded, space-filling open quantum systems" *Found. Chem.* 2013, 15, 253 – 276.
- 65) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. "Effect of Ligand Steric Properties and Halide Identity on the Mechanism for Oxidative Addition of Haloarenes to Trialkylphosphine Pd(0) Complexes" *J. Am. Chem. Soc.* 2009, 131, 8141 – 8154.

- 66) Negishi, E.; Takahashi, T.; Akiyoshi, K. "Bis(triphenylphosphine)palladium: Its Generation, Characterization, and Reactions" *J. Chem. Soc., Chem. Commun.* 1986, 1338 – 1339.
- 67) Jeffrey, T. "On the Efficiency of Tetraalkylammonium Salts in Heck Type Reactions" *Tetrahedron* 1996, 52, 10113 – 10130.
- 68) Reeves, E. K.; Bauman, O. R.; Mitchem, G. B.; Neufeldt, S. R. "Solvent Effects on the Selectivity of Palladium-Catalyzed Suzuki-Miyaura Couplings" *Isr. J. Chem.* 2020, 60, 406 – 409.
- 69) Amatore, C.; Pfuger, F. "Mechanism of Oxidative Addition of Palladium(0) with Aromatic Iodides in Toluene, Monitored at Ultramicroelectrodes" *Organometallics* 1990, 9, 2276 – 2282.
- 70) Baykov, S. V.; Dabranskaya, U.; Ivanov, D.; Novikov, A. S.; Boyarskiy, V. P. "Pt/Pd and I/Br Isostructural Exchange Provides Formation of C–I•••Pd, C–Br•••Pt, and C–Br•••Pd Metal-involving Halogen Bonding" *Cryst. Growth Des.* 2018, 18, 5973 – 5980.
- 71) Ivanov, D. M.; Bokach, N. A.; Kukushkin, V. Y.; Frontera, A. "Metal Centers as Nucleophiles: Oxymoron of Halogen Bond-Involving Crystal Engineering" *Chem. Eur. J.* 2022, 28, e202103173.
- 72) Zierkiewicz, W.; Kizior, B.; Michalczyk, M.; Jezierska, A.; Scheiner, S. "Pd and Pt Metal Atoms as Electron Donors in  $\sigma$ -Hole Bonded Complexes" *Phys. Chem. Chem. Phys.* 2023, 25, 26172 – 26184.
- 73) Ivanov, D. M.; Novikov, A. S.; Ananyev, I. V.; Kirina, Y. V.; Kukushkin, V. Y. "Halogen bonding between metal centers and halocarbons" *Chem. Commun.* 2016, 52, 5565 – 5568.
- 74) Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P. "Halogen bonding: The  $\sigma$ -hole" *J. Mol. Model.* 2007, 13, 291 – 296.
- 75) Brinck, T.; Murray, J. S.; Politzer, P. "Surface electrostatic potentials of halogenated methanes as indicators of directional intermolecular interactions" *Int. J. Quantum Chem.* 1992, 44, 57 – 64.
- 76) Murray, J. S.; Politzer, P. " $\sigma$ -Hole Interactions: Perspectives and Misconceptions" *Crystals* 2017, 7, 212.
- 77) The data of element physical properties was taken from Prof. Mark J. Winter's group website (<https://winter.group.shef.ac.uk/webelements>), Department of Chemistry, the University of Sheffield.
- 78) Velasquez, J. D.; Echeverria, J.; Alvarez, S. "Structure and Bonding of Halonium Compounds" *Inorg. Chem.* 2023, 62, 8980 – 8992.
- 79) Erakovic, M.; Cincic, D.; Molcanov, K.; Stilinovic, V. "Crystallographic Charge Density Study of the Partial Covalent Nature of Strong N•••Br Halogen Bonds" *Angew. Chem. Int. Ed.* 2019, 58, 15702 – 15706.
- 80) Noyes, W. A. "Iodine Cations" *J. Am. Chem. Soc.* 1934, 56, 1819 – 1819.
- 81) Jimenez-Gravalos, F.; Gallegos, M.; Pendas, A. M.; Novikov, A. S. "Challenging the Electrostatic  $\sigma$ -Hole Picture of Halogen Bonding Using Minimal Models and the Interacting Quantum Atoms Approach" *J. Comput. Chem.* 2021, 42, 676 – 687.
- 82) "Electrophilic–Nucleophilic Dualism of Nickel(II) toward Ni•••I Noncovalent Interactions: Semicoordination of Iodine Centers via Electron Belt and Halogen Bonding via  $\sigma$ -Hole" *Inorg. Chem.* 2017, 56, 13562 – 13578, and therein references.

- 83) Stewart, R. F. "On the mapping of electrostatic properties from bragg diffraction data" *Chem. Phys. Lett.* 1979, 65, 335 – 342.
- 84) Bader, R. F. W. "Atoms in Molecules" *Acc. Chem. Res.* 1985, 18, 9 – 15.
- 85) Resnati, G.; Bryce, D. L.; Desiraju, G. R.; Frontera, A.; Krossing, I.; Legon, A. C.; Metrangolo, P.; Nicotra, F.; Rissanen, K.; Scheiner, S.; Terraneo, G. "Definition of the pnictogen bond (IUPAC Recommendations 2023)" *Pure Appl. Chem.* 2024; 96, 135 – 145.
- 86) Renno, G.; Chen, D.; Zhang, Q.-X.; Gomila, R. M.; Frontera, A.; Sakai, N.; Ward, T. R.; Matile, S. "Pnictogen-Bonding Enzymes" *Angew. Chem. Int. Ed.* 2024, e202411347.
- 87) Quagliano, J. V.; Schubert, L. "The Trans Effect in Complex Inorganic Compounds" *Chem. Rev.* 1952, 50, 201 – 260.
- 88) Politzer, P.; Murray, J. S.; Clark, T. "Halogen Bonding and Other  $\sigma$ -Hole Interactions: a Perspective" *Phys. Chem. Chem. Phys.*, 2013, 15, 11178 – 11189.
- 89) Scheiner, S. "On the Capability of Metal-Halogen Groups to Participate in Halogen Bonds" *CrystEngComm* 2019, 21, 2875 – 2883.
- 90) Brammer, L.; Espallargas, G. M.; Libri, S. "Combining metals with halogen bonds" *CrystEngComm*, 2008, 10, 1712 – 1727.
- 91) Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. "Activation of a Metal-Halogen Bond by Halogen Bonding" *Angew. Chem. Int. Ed.* 2020, 59, 16496 – 16500.
- 92) Neufeld, J.; Daniliuc, C. G.; Gilmour, R. "Fluorocyclisation of Oximes to Isoxazolines Through I(I)/I(III) Catalysis" *Helv. Chim. Acta* 2023, 106, e202200183.
- 93) Jutand, A. "Dual role of nucleophiles in palladium-catalyzed Heck, Stille, and Sonogashira reactions" *Pure Appl. Chem.* 2004, 76, 565 – 576.
- 94) Johnson, J. B.; Rovis, T. "More than Bystanders: The Effect of Olefins on Transition-Metal-Catalyzed Cross-Coupling Reactions" *Angew. Chem. Int. Ed.* 2008, 47, 840 – 871.
- 95) Green, J. C.; Herbert, B. J.; Lonsdale, R. "Oxidative addition of aryl chlorides to palladium N-heterocyclic carbene complexes and their role in catalytic arylation" *J. Organometal. Chem.* 2005, 690, 6054 – 6067.
- 96) Lau, S. H.; Chen, L.; Kevlishvili, I.; Davis, K.; Liu, P.; Carrow, B. "Capturing the Most Active State of a Palladium(0) Cross-Coupling Catalyst" *ChemRxiv*, 2021, DOI: 10.26434/chemrxiv-2021-477kn.
- 97) Perego, L. A.; Payard, P.-A.; Haddou, B.; Ciofini, I.; Grimaud, L. "Evidence for a Cooperative Mechanism Involving two Palladium(0) Centers in the Oxidative Addition of Iodoarenes" *Chem. Eur. J.* 2018, 24, 2192 – 2199.
- 98) Joseph, E.; Brar, D. S.; Stuhlsatz, G.; Tunge, J. A. "Transition Metal-Free Decarboxylative Olefination of Carboxylic Acid Salts" *Chem. Sci.* 2024, 15, 9353 – 9360, and therein references.
- 99) Mulliken, R. S. "Structures of Complexes Formed by Halogen Molecules with Aromatic and with Oxygenated Solvents" *J. Am. Chem. Soc.* 1950, 72, 600 – 608.
- 100) Franchini, D.; Forni, A.; Genoni, A.; Pieraccini, S.; Gandini, E.; Sironi, M. "The Origin of the  $\sigma$ -Hole in Halogen Atoms: a Valence Bond Perspective" *ChemistryOpen* 2020, 9, 445 – 450.

- 101) Burk, M. J.; Crabtree, R. H.; Holt, E. M. "Halocarbon Chelation in  $[\text{Ir}(\text{cod})(\eta^2\text{-o-HalC}_6\text{H}_4\text{PPh}_2)]\text{SbF}_6$  (Hal = Br, Cl): Structural and Chemical Studies" *J. Organomet. Chem.* 1988, 341, 495 – 509.
- 102) Liotta Jr., F. J.; Duyne, G. Van; Carpenter, B. K. "Structures and Rearrangement Mechanisms for Some Bicyclo[6.1.0]nona-2,4,6-triene Complexes of Chromium, Molybdenum, and Tungsten" *Organometallics*, 1987, 6, 1010 – 1023.
- 103) Liu, X.; Wang, J.; Dong, G. "Modular Entry to Functionalized Tetrahydrobenzo[b]azepines via the Palladium/Norbornene Cooperative Catalysis Enabled by a C<sub>7</sub>-Modified Norbornene" *J. Am. Chem. Soc.* 2021, 143, 9991 – 10004.
- 104) Kashina, M. V.; Ivanov, D. M.; Kinzhalov, M. A. "The Isocyanide Complexes  $\text{cis-}[\text{MCl}_2(\text{CNC}_6\text{H}_4\text{-4-X})_2]$  (M = Pd, Pt; X = Cl, Br) as Tectons in Crystal Engineering Involving Halogen Bonds" *Crystals* 2021, 11, 799.
- 105) Carreras, L.; Serrano-Torné, M.; van Leeuwen, P. W. N. M.; Vidal-Ferran, A. "XBphos-Rh: a halogen-bond assembled supramolecular catalyst" *Chem. Sci.* 2018, 9, 3644 – 3648.
- 106) Carreras, L.; Benet-Buchholz, J.; Franconetti, A.; Frontera, A.; van Leeuwen, P. W. N. M.; Vidal-Ferran, A. "Halogen Bonding Effects on the Outcome of Reactions at Metal Centres" *Chem. Commun.* 2019, 55, 2380 – 2383.
- 107) Trouve, J.; Gramage-Dora, R. "Beyond Hydrogen Bonding: Recent Trends of Outer Sphere Interactions in Transition Metal Catalysis" *Chem. Soc. Rev.* 2021, 50, 3565 – 3584.
- 108) Alcazar-Roman, L. M.; Hartwig, J. F. "Mechanistic Studies on Oxidative Addition of Aryl Halides and Triflates to  $\text{Pd}(\text{BINAP})_2$  and Structural Characterization of the Product from Aryl Triflate Addition in the Presence of Amine" *Organometallics* 2002, 21, 491 – 502.
- 109) Motti, E.; Ca', N. D.; Deledda, S.; Fava, E.; Panciroli Fr.; Catellani, M. "Palladium-catalyzed unsymmetrical aryl couplings in sequence leading to o-teraryls: dramatic olefin effect on selectivity" *Chem. Commun.*, 2010, 46, 4291 – 4293.
- 110) Besora, M.; Gourlaouen, C.; Yates, B.; Maseras, F. "Phosphine and solvent effects on oxidative addition of  $\text{CH}_3\text{Br}$  to  $\text{Pd}(\text{PR}_3)$  and  $\text{Pd}(\text{PR}_3)_2$  complexes" *Dalton Trans.* 2011, 40, 11089 – 11094.
- 111) Murray, J. S. "The Formation of  $\sigma$ -Hole Bonds: A Physical Interpretation" *Molecules* 2024, 29, 600.
- 112) Das, T. K.; Ghosh, A.; Aguinaga, U.; Yousufuddin, M.; Kürti, L. "Organocatalytic Electrophilic Arene Amination: Rapid Synthesis of 2-Quinolones" *ChemRxiv*, 2024, DOI: 10.26434/chemrxiv-2024-5902g.
- 113) Jónsson, H. F.; Sethio, D.; Wolf, J.; Huber, S. M.; Fiksdahl, A. Erdelyi, M. "Halogen Bond Activation in Gold Catalysis" *ACS Catal.* 2022, 12, 7210 – 7220.
- 114) Carreras, L.; Franconetti, A.; Grabulosa, A.; Frontera, A.; Vidal-Ferran, A. "Selective Functionalisation of Aromatic Alcohols with Supramolecularly Regulated Gold(I) Catalysts" *Org. Chem. Front.*, 2020, 7, 1626 – 1634.
- 115) Gu, L. <sup>1</sup>H NMR shift of single molecular water and its water ligand interactions in organic solvents. Preprint deposited at *ChemRxiv* 2023, DOI: 10.26434/chemrxiv-2023-s1.
- 116) Gu, L. On Rational Design of Stereodivergent Organocatalysis Controlled by Selective Hydration. *ChemRxiv* 2023, DOI: 10.26434/chemrxiv-2023-6vbn.

- 117) Zhou, P.; Lv, J.; Zou, J.; Tian, F.; Shang, Z. "Halogen–Water–Hydrogen Bridges in Biomolecules" *J. Struct. Bio.* 2010, 169, 172 – 182.
- 118) Zhu, G.; Li, H.; Li, Y.; Gu, L. <sup>1</sup>H NMR Elucidation of observed stable sugar-NaCl-water complexes in aqueous solution. *Chemistry- Methods* 2023, 3, e202200063.
- 119) Elias, E. K.; Rehbein, S. M.; Neufeldt, S. R. "Solvent Coordination to Palladium Can Invert the Selectivity of Oxidative Addition" *Chem. Sci.* 2022, 13, 1618 – 1628.
- 120) Botla, V.; Fontana, M.; Voronov, A.; Maggi, R.; Motti, E.; Maestri, G.; Ca', N. D. "Closing the Cycle as It Begins: Synthesis of ortho-Iodobiaryls via Catellani Reaction" *Angew. Chem. Int. Ed.* 2023, 62, e202218928.
- 121) Littke, A. F.; Dai, C.; Fu, G. C. "Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions" *J. Am. Chem. Soc.* 2000, 122, 4020 – 4028.
- 122) Schoenebeck, F.; Houk, K. N. "Ligand-controlled Regioselectivity in Palladium-Catalyzed Cross-Coupling Reactions" *J. Am. Chem. Soc.* 2010, 132, 2496 – 2497.
- 123) Robertson, C. C.; Perutz, R. N.; Brammer, L.; Hunter, C. A. "A Solvent-Resistant Halogen Bond" *Chem. Sci.* 2014, 5, 4179 – 4183.
- 124) Vignolle, J.; Gornitzka, H.; Donnadiou, B.; Bourissou, D.; Bertrand, G. "Palladium-Oxygen and Palladium-Arene Interactions in Complexes Derived from Biaryl Aminocarbenes: Comparison with Biaryl phosphanes" *Angew. Chem. Int. Ed. Engl.* 2008, 47, 2271 – 2274.
- 125) Littke, A. F.; Fu, G. C. "A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids" *Angew. Chem. Int. Ed.* 1998, 37, 3387 – 3388, and therein references.
- 126) Nishiyama, M.; Yamamoto, T.; Koie, Y. "Synthesis of N-Arylpiperazines from Aryl Halides and Piperazine under a Palladium Tri-tert-butylphosphine Catalyst" *Tetrahedron Lett.* 1998, 39, 617 – 620.
- 127) Yamamoto, T.; Nishiyama, M.; Koie, Y. "Palladium-Catalyzed Synthesis of Triaryl amines from Aryl Halides and Diaryl amines" *Tetrahedron Lett.* 1998, 39, 2367 – 2370.
- 128) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. "A New Class of Easily Activated Palladium Precatalysts for Facile C-N Cross-Coupling Reactions and the Low Temperature Oxidative Addition of Aryl Chlorides" *J. Am. Chem. Soc.* 2008, 130, 6686 – 6687.
- 129) Daugulis, O.; Chiong, H. A. "Palladium-Catalyzed Arylation of Electron-Rich Heterocycles with Aryl Chlorides" *Org. Lett.* 2007, 9, 1449 – 1451.
- 130) Green, R. A.; Hartwig, J. F. "Palladium-Catalyzed Amination of Aryl Chlorides and Bromides with Ammonium Salts" *Org. Lett.* 2014, 16, 4388 – 4391.
- 131) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shaha, H. P.; Tudge, M. T. "Design of a Versatile and Improved Precatalyst Scaffold for Palladium Catalyzed Cross-Coupling: ( $\eta^3$ -1-<sup>t</sup>Bu-indenyl)<sub>2</sub>( $\mu$ -Cl)<sub>2</sub>Pd<sub>2</sub>" *ACS Catal.* 2015, 5, 3680 – 3688.
- 132) Scharf, L. T.; Rodstein, I.; Schmidt, M.; Scherpf, T.; Gessner, V. H. "Unraveling the High Activity of Ylide-Functionalized Phosphines in Palladium-Catalyzed Amination Reactions: A Comparative Study with CyJohnPhos and PtBu<sub>3</sub>" *ACS Catal.* 2020, 10, 999 – 1009.

- 133) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. "Simple, Efficient Catalyst System for the Palladium-Catalyzed Amination of Aryl Chlorides, Bromides, and Triflates" *J. Org. Chem.* 2000, 65, 1158 – 1174.
- 134) Kwan, E. E.; Zeng, Y.; Besser, H. A.; Jacobsen, E. N. "Concerted Nucleophilic Aromatic Substitutions" *Nat. Chem.* 2018, 10, 917 – 923.
- 135) Alcazar-Roman, L. M.; Hartwig, J. F. "Mechanism of Aryl Chloride Amination: Base-Induced Oxidative Addition" *J. Am. Chem. Soc.* 2001, 123, 12905 – 12906.
- 136) Xu, Z.; Yang, Z.; Liu, Y.; Lu, Y.; Chen, K.; Zhu, W. "Halogen Bond: Its Role beyond Drug-Target Binding Affinity for Drug Discovery and Development" *J. Chem. Inf. Model.* 2014, 54, 69 – 78.
- 137) Neel, A. J.; Hilton, M. J.; Sigman, M. S.; Toste, F. D. "Exploiting Non-Covalent  $\pi$  Interactions for Catalyst Design" *Nature* 543, 637 – 646.
- 138) Erdelyi, M. "Halogen Bonding in Solution" *Chem. Soc. Rev.* 2012, 41, 3547 – 3557.
- 139) Kania, M. J.; Reyes, A.; Neufeldt, S. R. "Oxidative Addition of (Hetero)aryl (Pseudo)halides at Palladium(0): Origin and Significance of Divergent Mechanisms" *ChemRxiv* 2024, DOI: 10.26434/chemrxiv-2024-h2s9s-v2.
- 140) Proutiere, F.; Schoenebeck, F. "Solvent Effect on Palladium-Catalyzed Cross-Coupling Reactions and Implications on the Active Catalytic Species" *Angew. Chem. Int. Ed.* 2011, 50, 8192 – 8195.
- 141) He, W.-J.; Qin, W.-Z.; Yang, S.; Ma, S.; Kim, N.; Schultz, J. E.; Palkowitz, M. D.; He, C.; Ma, A.; Schmidt, M. A.; Gembicky, M.; Wisniewski, S. R.; Engle, K. M. "Pd(COD)(DQ): A Stable, Versatile, and Monometallic Palladium(0) Source for Organometallic Synthesis and Catalysis" *ChemRxiv* 2024, DOI: 10.26434/chemrxiv-2024-sj081.
- 142) Kleina, R. A.; Wittea, P.; van Belzena, R.; Fraanjeb, J.; Goubitzb, K.; Numanb, M.; Schenkb, H.; Ernstinga, J. M.; Elsevier, C. J. "Monodentate and Bridging Coordination of 3,39-Annulated 2,29-Bipyridines in Zerovalent Palladium- and Platinum-p-quinone Complexes" *Eur. J. Inorg. Chem.* 1998, 319 – 330.
- 143) Kluwer, A. M.; Elsevier, C. J.; Buhl, M.; Lutz, M.; Spek, A. L. "Zero-Valent Palladium Complexes with Monodentate Nitrogen s-Donor Ligands" *Angew. Chem. Int. Ed.* 2003, 42, 3501 – 3504.
- 144) Huang, J.; Keenan, T.; Richard, F.; Lu, J.; Jenny, S. E.; Jean, A.; Arseniyadis, S.; Leitch, D. C. "Chiral, Air Stable, and Reliable Pd(0) Precatalysts Applicable to Asymmetric Allylic Alkylation Chemistry" *Nat. Commun.* 2023, 14:8058.