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Versatile Reactivity of Pd-Catalysts: Mechanistic Features of the Mono-N-Protected Amino-Acid Ligand and Cesium-Halide Base in Pd-Catalyzed C-H Bond Functionalization

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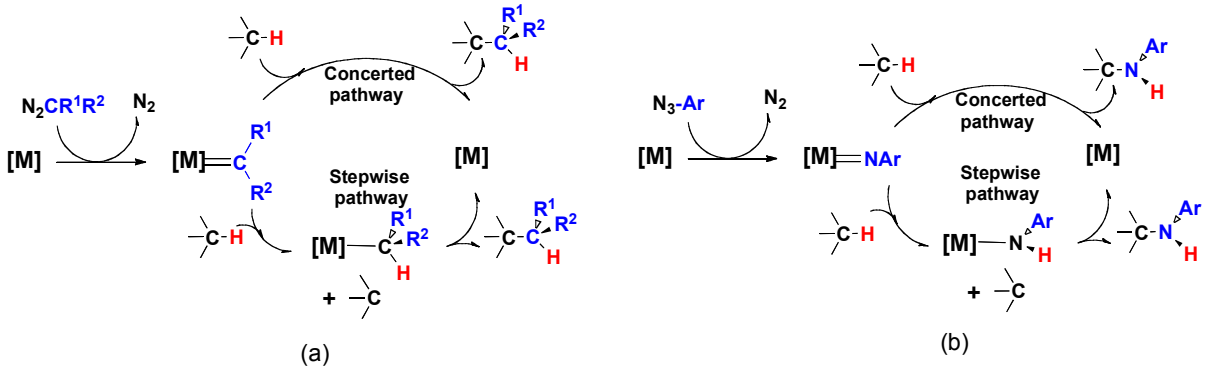
Abstract.

The widely used C-H functionalization strategies and some complexities in the Pd-catalyzed chemical transformations were analyzed. It was emphasized that, in the course of catalysis various Pd-intermediates (including nano-scale Pd-clusters) could act as an active catalyst. However, both identification of these catalytically active species and determination of factors controlling the overall catalytic process require more comprehensive and multi-disciplinary approaches. Recent joint computational and experimental approaches were instrumental to: (1) demonstrate that the addition of $Pd(OAc)_2$ as a catalyst precursor to RSeH and RSH reagents forms the $[Pd(SeR)_2]_n$ and $[Pd(SR)_2]_n$ clusters, respectively, which show an unprecedented ability for selective synthesis of Markovnikov-type products starting with a mixture of reagents RSH/RSeH and acetylenic hydrocarbons; (2) predict a valid mechanism of the amino-acid ligand-assisted Pd(II)-catalyzed C–H activation that is shown to proceed via the formation of the catalytically active Pd(II) intermediate with a bidentately coordinated dianionic amino-acid ligand; (3) demonstrate that the amino-acid ligand plays crucial roles in the ligand-assisted Pd(II)-catalyzed C–H activation by acting as: (a) a weakly coordinating ligand to stabilize desirable Pd(II)-precatalyst, (b) a soft proton donor and bidentately coordinated dianionic ligand in the catalytically active Pd(II) intermediate, and (c) a proton acceptor accelerating the C-H deprotonation via the CMD mechanism; and (4) reveal the roles of the CsF base (and "cesium effect") in the $Pd(0)/PCy_3$-catalyzed intermolecular arylation of terminal β-$C(sp^3)$-H bond of aryl amide and predict the unprecedented "Cs_2-I-F cluster" assisted mechanism for this reaction.

I. Intoduction

Search for new reactions and new synthetic methodologies for making C-C and C-heteroatom bonds in fine chemical synthesis, and discovery of new materials and drugs has always attracted the attention of chemists. In the last several decades, extensive studies have led to development of numerous fundamental and powerful synthetic strategies, such as oxidative addition-reductive elimination[1-12] and 2010 Nobel prize winning cross-coupling [containing of oxidative addition, transmetalation and C-X bond formation].[13-23] However, the former procedure is found to be energy-demanding, while the latter reactions require pre-activated expensive starting materials and generate stoichiometric amount of waste/byproduct (such as H-halides or their base salts).

A potentially *greener and environmentally benign* alternative to the aforementioned strategies is the direct C−H bond functionalization, *i.e.* direct transformation of inert C-H bonds into the useful C-C and C-X (where X=heteroatom) bonds, which does not generate hazardous byproducts and avoids pre-functionalization stages.[24-67] However, the C-H bonds are highly stable, generally resistant to reactions with acid, bases, electrophiles and nucleophiles, and consequently, are very difficult to be directly functionalized. This monumental task requires atomistic level understanding of the: (a) important steps of the targeted processes, (b) controlling factors of the catalysis (including but not limited to the rate of the reaction, rate limiting step, catalyst stability and turnover cycles, factors affecting selectivity and yield of the reaction and more), (c) nature of catalytic active intermediates, (d) role of ligand environments, solvent and additives, and more. Knowing that the C-H bond functionalization, in general, is a two-electron oxidation process, chemists have developed several strategies for direct C−H bond functionalization, such as use of "free" (*i.e.* un-coordinated) 2-electron oxidants (carbenes, CR^1R^2, and nitrenes, NR)[57-61] and application of visible-light to generate free radicals for further use in functionalization of inert C-H bonds.[62-67] However, neither the "free 2-electron oxidant" approach nor photocatalysis allows a greater control selectivity and yield of the C-H functionalization reactions.

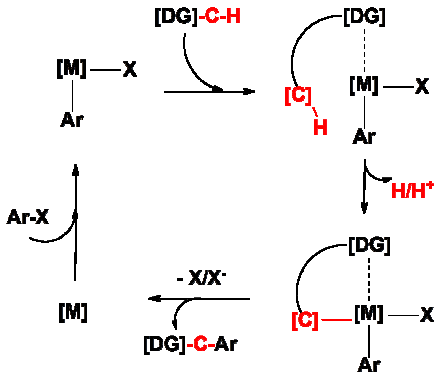


Scheme 1. Schematic presentation of transition metal catalyzed intermolecular C(sp^3)-H bond functionalization via the atom-transfer strategy. Here, we presented C-H bond (a) alkylation by diazocarbene, and (b) amination by aryl azide.

Therefore, currently, the most extensively used synthetic methodology is the metal-catalyzed direct functionalization of stable C−H bonds,[24-56] which is more efficient and selective than the "free 2-electron oxidant" and photocatalytic approaches. This strategy has opened new horizons of synthetic chemistry due to its simplicity in designing synthetic routes to complex molecules in a stereoselective manner. Impressive achievements have been made in enhancing the efficiency of the direct C(sp^2)–H and C(sp^3)–H bond alkylation, amination, aziridination and oxidation. The

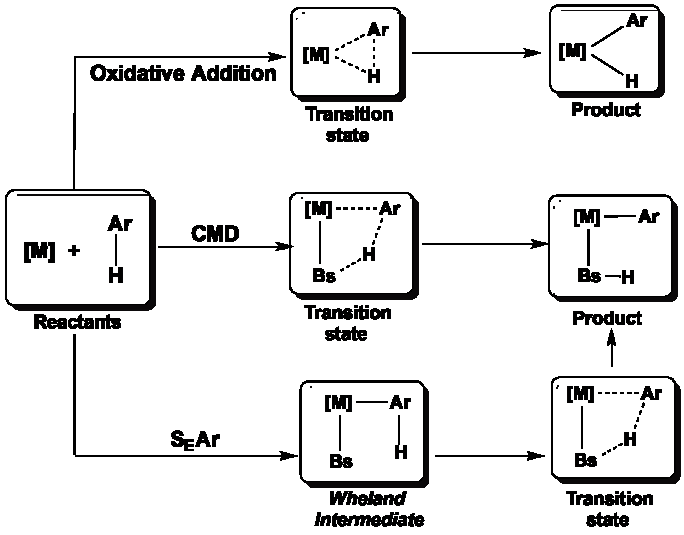
existing transition metal-catalyzed direct C-H bond functionalization strategies can be divided into two major classes.

One of such strategies is *the atom (or group) transfer or outer-sphere C-H bond functionalization strategy*,[32,40,68,69] which includes two major stages (Scheme 1): (i) preparation of reactive metallocarbene, metallonitrene, and metallooxene intermediates from widely available reagents (such as diazocarbenes, various azides, etc.), and (ii) insertion of X = carbene (C-terminal), nitrene (N-terminal) or oxene (O-terminal) fragment of the resulted [M]-X reactive intermediates into the C-H bond of substrate. This process, where the complexes of Ru, Rh, Cu, Co, Fe, Ir, Ag, Au are widely utilized catalysts,[24-26,32-34,70-93] is shown to be both intermolecular (utilizing the external substrate) and intramolecular (utilizing the reactive centers of the coordinated carbene or nitrene fragments), and proceed via two distinct mechanisms: concerted and stepwise. In the concerted C-H bond utilization mechanism the X fragment directly inserts into the C-H bond to form final product with the C-X-H subunit. The stepwise mechanism includes the H-atom abstraction (from the C-H bond by X-fragment), diradical intermediate formation and radical-radical coupling steps (Scheme 1).



Scheme 2. Schematic presentation of the directing group (DG) assisted transition metal-catalyzed C-H bond activation

Another actively utilized direct C-H bond functionalization strategy is the *directing group assisted C-H bond functionalization or inner-sphere C-H bond functionalization strategy.*[4,32,40,51] Several accounts have described recent advances of this strategy.[5,6,27,29,36,40,47,51,56] Briefly, this strategy (Scheme 2) includes: (a) substrate coordination to transition metal center of the previously prepared oxidative addition product with its directing electron-rich group (N, O, S-centers), (b) C-H bond cleavage, and (c) C-X bond formation. Later steps of the reaction could be very complex and may proceed via multiple mechanisms for different substrates and transition metal complexes.[40,47,51,56,94-97] The C-H oxidative addition, electrophilic aromatic substitution (S_EAr), and concerted proton abstraction (concerted metalation-deprotonation, CMD) are three main mechanisms reported in the literature (Scheme 3). In the oxidative addition mechanism the C-H bond oxidatively adds to metal-center to generate a short-



Scheme 3. Widely applicable mechanisms for metal-catalyzed C-H bond activation: Oxidative addition, concerted metalation-deprotonation (CMD) and electrophilic aromatic substitution (S_EAr).

lived oxidative addition intermediate. The S_EAr mechanism consists of two steps: a metal-carbon bond formation resulting in a stable Wheland intermediate and the C-H bond cleavage by the base to generate a cyclometalated intermediate. In CMD, the formation of metal-carbon bond and proton abstraction from C-H bond by the base occur simultaneously. In this strategy of the C-H bond functionalization, the complexes of Pd, Rh and Ir are among the widely utilized catalysts. [5,6,27,29,36,40,45,47,51,56,98-122]

Previously, both transition metal catalyzed C-H functionalization strategies were subject of seminal review articles.[24-67] Therefore, here, we only briefly revisit and expand some of the latest developments in our laboratory on studies of the Pd-catalyzed C-H bond functionalization. For completeness of our discussion, at first, we briefly comment on an important related issue, namely, the true nature of active catalyst in Pd-catalyzed chemical transformations, which still needs more comprehensive analysis.

II. Brief overview of the true nature of active catalyst in the Pd-catalyzed transformations

In spite of extensive use of palladium in catalysis, in general, the true nature of active catalyst in vital catalytic processes is still subject of extensive discussion. This is mainly because Pd is a versatile element that forms complexes at (0), (I), (II), (III) and (IV) oxidation states corresponding to its s^0d^{10}, s^0d^9, s^0d^8, s^0d^7 and s^0d^6 electronic configurations, respectively. Its rich catalytic activity has emerged over the many years ago by: (a) mostly involving mononuclear Pd(0) and Pd(II) species, particularly in relation of discovery of reactions involving of Pd(0)/Pd(II) redox couples, and (b) facile reductive elimination from the complexes with high oxidation states (+2 and +4) of Pd. [123-126] However, recently, the complexes of Pd with odd oxidation states (+1 and +3), as well as the nano-scale Pd-clusters ("naked" and ligated) have also attracted interest of researchers.[127-130]

II.a Reactivity of Pd(I) complexes.

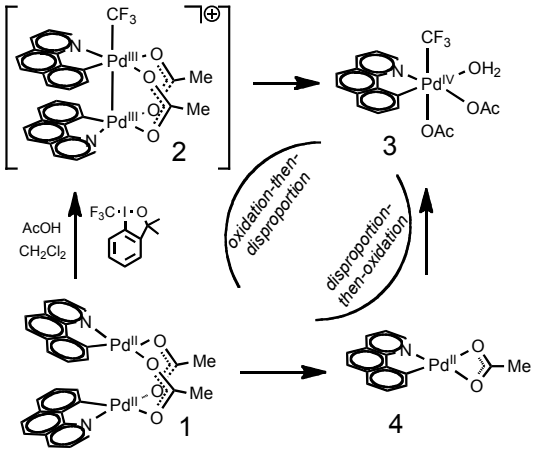
No mononuclear Pd(I) complexes have been isolated to date, while the formation of a few transient Pd(I) species has been proposed based on spectroscopic studies.[131-135] Therefore, in the literature, special attention was devoted to the dinuclear Pd(I)−Pd(I) complexes. Although the first dinuclear Pd(I)-Pd(I) complex was synthesized over 70 years ago,[136-138] and its formation as side products from mononuclear Pd(II) intermediates has also been proposed long ago,[139,140] the catalytic activity of the numerous dinuclear Pd(I)−Pd(I) complexes become subject of extensive discussion only a few years ago.[141-147] For example, Schoenebeck and coworkers[143] have demonstrated that the use of di-tert butylphosphane-ligated Pd(I) dimer, $\{[P^tBu_3]PdBr\}_2$, previously synthesized by Vilar, and coworkers,[148-152] as a pre-catalyst increases rates of the Pd-catalyzed transformations of aryl bromides in Suzuki and amination reactions.[153,154] The employed computational and experimental methods have provided[143,146] data convincingly suggesting the oxidative addition of ArI by the dinuclear metal complex as a favored mechanism of the halide exchange reaction between $\{[P^tBu_3]PdBr\}_2$ and ArI in THF (*i.e.* the direct reactivity of the dinuclear Pd(I) complex with aryl iodides). In contrast, the reactivity of the same Pd(I) dimer with ArBr and ArCl is inconsistent with direct catalytic involvement of the Pd(I)-dimer but is consistent with catalytic activity of mononuclear Pd(0) catalysis. Thus, the nature of catalytic active species in the $\{[P^tBu_3]PdBr\}_2$ catalyzed halide exchange (in THF) depends on the nature of X in ArX. Another factor controlling the nature of true catalytic active species in reactivity of the dinuclear Pd(I) complex with aryl halides is found to be the nature of solvent

and base: for example, Schoenebeck and coworkers have demonstrated that in a non-polar solvent the reactivity of Pd(I) dimer with ArBr and ArCl is consistent with direct catalytic involvement of Pd(0)-P^tBu_3, but in a polar solvent it is consistent with the involvement of mononuclear anionic Pd(0)(P^tBu_3)X^- species. [143,147]

II.b Reactivity of Pd(III) complexes.

Other Pd-complexes with odd oxidation number of palladium are mononuclear and binuclear Pd(III) complexes. Since the first discovery[155] of mononuclear Pd(III) complex in 1982, its synthesis, characterization and reactivity became the subject of numerous seminal articles.[127,128] Discovery of binuclear Pd(III) complex by Powers and Ritter[128,156] has significantly advanced discussion of involvement of binuclear Pd(III) intermediates in various catalytic processes.[157-164]

For example, Yates and co-workers[161] have reported the C-CF_3 bond formation reaction catalyzed by binuclear Pd-Pd complex **1** (Scheme 4).



Scheme 4. Schematic presentation of mechanisms the C-CF_3 bond formation reaction catalyzed by binuclear Pd-Pd complex **1**, proposed by Yates and coworkers [161]. Adapted with permission from reference [161].

The authors proposed the oxidation-then-disproportionation of bimetallic complex **1** to be favored over the disproportionation of **1** to mononuclear Pd(II) complex followed by the oxidation to Pd(IV) complex **3**. The C-CF_3 bond formation is proposed to proceed from complex **3** with a high oxidation state of Pd. The results provided in this paper, once again, illustrate the complexities observed in the mechanisms available for arene functionalization. Canty and Yates have provided[162-164] a theoretical model that describes fragmentation of dinuclear Pd(II) complexes, which is based on valence asymmetry of binuclear complexes bearing different apical ligands.

Another interesting example for involvement of Pd(III)-complex into catalysis is the Pd-catalyzed coupling of 3-methyl-2-phenylpyridine (mppH) with $[Ph_2I]BF_4$ to form mppPh.[164] The computational studies of mechanism of this reaction fully support conclusions of a prior synthetic and kinetic study implicating involvement of binuclear Pd-species in a rate-limiting oxidation step. Detailed analysis shown that the $Pd(OAc)_2$ pre-catalyst forms the ortho-palladated di-palladium complex $[Pd(mpp)(\mu\text{-}OAc)]_2$ as the active catalyst, which later is

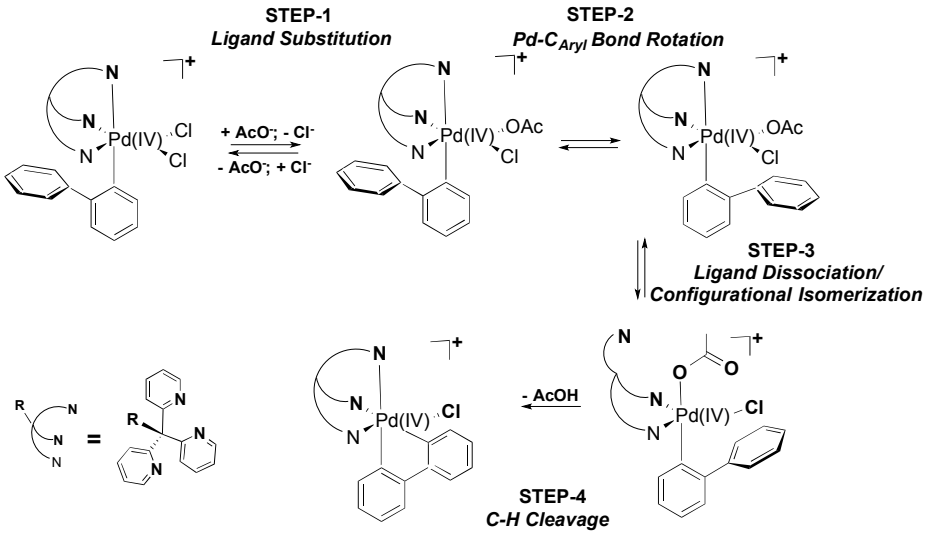
oxidized by $[Ph_2I]^+$. As a result of this oxidation a reactive binuclear Pd(III) cation complex, $[Ph(mpp)Pd(\mu\text{-}OAc)_2Pd(mpp)]^+$, with a Pd−Pd bond was formed. [164]

II.c Reactivity of Pd(IV) complexes.

Still, the vast majority of the reported Pd-catalyzed chemical transformations (such as C-H bond activation, C-C and C-heteroatom formation, and more) are believed to involve a Pd(0) and Pd(II) catalysts.[13-23] Applications of high oxidation state palladium catalysis in organic synthesis have focused primarily on reductive elimination from Pd(III) and/or Pd(IV) species. More comprehensive studies of other organic transformations at high oxidation states Pd have just commenced. Recently, several groups have proposed a C-H activation at a transient Pd(IV) intermediate.[165-175] Remarkably, many of these catalytic reactions proceed under unusually mild conditions[165-169] and/or exhibit unprecedented site selectivities.[165-170] These findings suggest that harnessing C-H activation at Pd(IV) could provide opportunities for achieving distinct and complementary reactivity relative to analogous (and much more common) transformations at Pd(II) centers. Available limited results show that C-H activation at Pd(IV) centers often proceed with markedly different site selectivity than Pd(II)-mediated C−H functionalization processes. Therefore, it is of great importance to understand whether these differences are the result of novel mechanistic pathways for C−H activation at Pd(IV), different ligand environments at octahedral Pd(IV) versus square planar Pd(II) complexes, or other factor(s).

As example, here, we wish to emphasize recent seminal papers by Sanford and co-workers.[172,173] The authors prepared a Pd(IV) complex (Scheme 5) and studied (by a series of experiments) a mechanism of carboxylate-assisted C-H activation at Pd(IV)-centers. The insights obtained from these studies could ultimately prove valuable in accelerating the design and optimization of catalytic processes involving C−H activation at Pd(IV) as a key step. Briefly, the authors proposed and experimentally supported a mechanism of the C-H bond activation in $[(Py_3CR)Pd(biphenyl)Cl_2]X$ system that involves four steps: (1) chloride-to-acetate ligand substitution, (2) rotation around the $Pd-C_{Aryl}$ bond, (3) pyridine ligand dissociation and configurational isomerization via Berry pseudorotation, and (4) carboxylate-assisted C−H cleavage (Scheme 5). A key feature of this reaction is the semi-labile tridentate Py_3CR ligand (for R = H) since both the ligand substitution (step 1) and configurational isomerization (step 3) of the proposed mechanism requires a reversible dissociation of one arm of the Py_3CR ligand. Furthermore, this ligand stabilizes octahedral cationic Pd(IV) centers toward reductive elimination. Importantly, the extremely mild conditions necessary for acetate assisted C−H cleavage at Pd(IV) centers renders this process attractive for applications in catalytic C−H functionalization processes mediated by a high oxidation state palladium.

More insightful computational and experimental studies of the mechanism and controlling factors of the Pd(IV)-catalyzed C-H bond activation are still required and could significantly advance our ability to design better and more efficient catalysis for C-H bond functionalization. Outstanding research activities in this field are anticipated in near future.



Scheme 5. Schematic presentation mechanism of acetate-assisted C-H bond activation in Pd(IV) complex, $[(Py_3CR)Pd\text{-}(biphenyl)Cl_2]X$ proposed by Sanford and coworkers [173]. Adapted with permission from reference [173].

II.d Reactivity of Pd-clusters and nanoparticles.

Catalytic flexibility of palladium is not just limited to its aptitude to form mono- and di-metallic complexes at the Pd(0), Pd(I), Pd(II), Pd(III) and Pd(IV) oxidation states. Its rich catalytic activity is also a result of its ability to form structurally flexible oligomers/small clusters in catalysis mixture.[129,130, 176-180]

Extensive investigations of various *in situ* generated Pd-catalyzed fundamental transformations (for example, cross-coupling reactions) under ligand-free conditions have demonstrated that different palladium compounds (*i.e.* catalyst precursors), such as salts, complexes in oxidized or reduced form, and nanoparticles are equally capable of catalyzing these reactions.[129] Based on these findings, it is reasonable to assume that the same catalytic active species are involved in these processes, regardless of the Pd-source. This assumption is consistent with latest findings of Corma and coworkers.[130] The authors have convincingly demonstrated (by utilizing various experimental techniques) that regardless of the starting palladium source, that is, whether it is a salt, a complex, or nanoparticles, C-C bond-forming reactions, such as Heck, Sonogashira, Suzuki, and Stille coupling reactions, of iodo and bromo derivatives do not proceed with a higher rate until small palladium clusters of three and four atoms are formed. Furthermore, they have shown that water and other nucleophiles (for example, cyclohexylamine) introduced into the reaction media dislodge palladium clusters from nanoparticles (and/or from other Pd-sources used). These findings provide a plausible explanation for the positive effect of water on the rate of these reactions. The authors have suggested that the limiting step in the initiation of the reaction is the efficient removal of palladium atoms from the nanoparticle surface and the subsequent formation of the atomic clusters, which is consistent with previous mechanistic proposals.[181-185] To prove this concept, the authors separately prepared and stored Pd-clusters with three and four atoms, which showed almost the same reactivity as the Pd-nanoparticles generated *in situ*.

Despite these (and many other) significant advances, the mechanism of the palladium-catalyzed

cross-coupling reactions under ligand-free conditions, that may involve an oxidative addition–reductive elimination cycle of a Pd(0) species generated *in situ*, as well as the exact nature of the Pd(0) catalytic species, still requires comprehensive investigations. In order to shed light onto the mechanism and controlling factors of the σ-bond oxidative addition in Pd-clusters [in the literature (see Ref.[130] and references therein) it is accepted that the oxidative addition step controls the overall rate of the coupling reactions) Musaev and colleagues[186-189] conducted extensive computational studies of the mechanism of reaction of Pd_n (where n=1-4) with H_2 and CH_4 molecules. These calculations showed that the oxidative addition of H-H and H-CH_3 bonds to the Pd atom is not feasible. In contrast, the addition of the H-H bond to the Pd-dimer is a barrier-free process and is highly (36.6 kcal/mol) exothermic. Interestingly, the resulted Pd_2H_2 product has a rhombic structure, Pd-(μ_1-H)$_2$-Pd, where H atoms bridged to the Pd-centers. It was found that the increase in number of the Pd atoms in the cluster to 3 and 4 increases the H-H activation barrier to 3.7 and 10.5 kcal/mol, and reduces exothermicity of the reaction to 26.4 and 11.0 kcal/mol, respectively. Thus, the smaller clusters of Pd are more reactive toward H-H bond. For the case of methane, the C-H oxidative addition to Pd_2 requires *ca* 5.0 kcal/mol energy barrier and leads to MePd-(μ_1-H)-Pd complex. This reaction is found to be only slightly, *ca* 7.0 kcal/mol, exothermic. Comparison of these values with those for the reaction $Pd_2 + H_2$ shows that C-H oxidative addition is a more energy demanding process.

Recently, Ananikov, Musaev and coworkers[190] found a similar degree of complexity even in the palladium cluster catalysts with an adaptive tuning ability. The authors utilized various experimental (including FE-SEM and microanalysis) and computational techniques and found that the addition of $Pd(OAc)_2$ as a catalyst precursor to RSeH and RSH reagents forms the $[Pd(SeR)_2]_n$ and $[Pd(SR)_2]_n$ clusters, respectively. These clusters are similar to the Pd nanoparticle catalyst generated *in situ* under ligand-free conditions because of their high reactivity and dynamic nature; however, catalyst operation in Ananikov's experiments was performed in a controlled manner.

As seen in Figure 1, the $[Pd(SeR)_2]_n$ and $[Pd(SR)_2]_n$ clusters can have at least two stable structures: chain and cyclic. In cyclic structures all Pd centers are equivalent and contain only μ_2-(bridging) ZR ligands (where Z = S and Se). On the contrary, in chain structures two different types of metal centers exist: two unsaturated Pd-centers at the ends of the chain each with one μ_1-(terminal) ZR ligand and one coordination vacancy, and *n*-2 saturated Pd-centers with four μ_2-ZR ligands each. Extensive computations have shown that (a) at lower numbers of *n* (but higher than 3) the most stable structure of the $[Pd(ZR)_2]_n$ cluster is its cyclic conformer, while at larger numbers of *n* the chain structure may become energetically as stable as, or even more stable than the cyclic structure, and (b) reactivity of the μ_1-(terminal) and μ_2-(bridging) ZR groups (Z = S and Se) are very different: the terminal (or surface) μ_1-ZR groups are significantly more reactive than the bridging (or core) μ_2-ZR groups. Thus, $[Pd(ZR)_2]_n$ clusters with a chain structure and reactive terminal μ_1-ZR groups are predicted and experimentally proven to be reactive with various organic substrates including hydrocarbons with alkenes and alkynes. These catalytic systems show unprecedented ability for selective synthesis of Markovnikov-type products starting with a mixture of reagents RSH/RSeH and acetylenic hydrocarbons. Importantly, two key factors: i) selective capture of a reagent from the mixture; and ii) highly selective transformation of each reagent to vinyl monomer were achieved within a single catalyst. The developed procedure shows high efficiency and selectivity towards RSH and RSeH groups and tolerance to oxygen species and water (Z = O), which may be present in the initial

reagents.

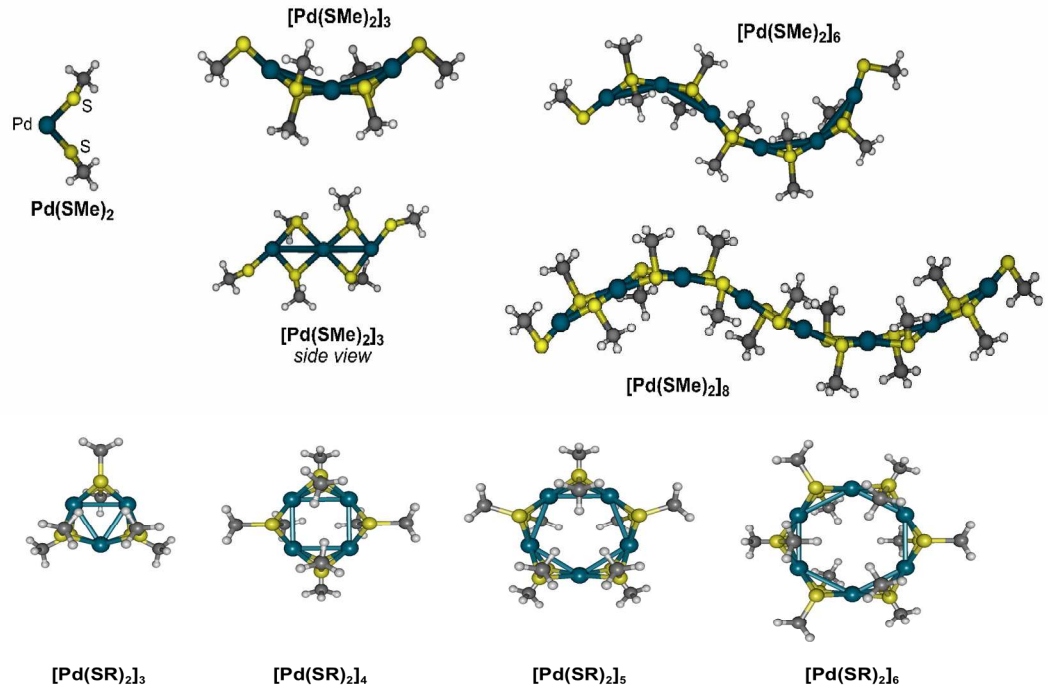


Figure 1. Optimized structures of chain (n = 2, 3, 6, 8) and cyclic (n = 3-6) $[Pd(SR)_2]_n$ clusters. Adapted with permission from reference [190].

The observed high selectivity of the catalytic system is explained by palladium catalyst's ability for adaptive tuning. The difference in the Pd−Z bond energies leads to the formation of the palladium catalyst with only one type of reactive μ_1-chalcogenide groups on the surface which facilitates the addition of the corresponding chalcogen-containing compound. Therefore, only one catalytic transformation is mediated at a time. After completion of a preceding reaction the active site of catalyst rebuilds and the next transformation starts (see also Ref. 129 and 185, and references therein).

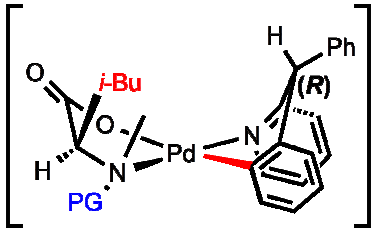
Despite these and many other advances in Pd chemistry the understanding of the precise nature of active Pd-species in catalytic mixtures (catalyst, substrate, additives, solvent, base, etc.), mode of action of Pd-sites in catalysis, as well as roles of base, ligands and additives requires additional and more comprehensive multi-disciplinary approaches. Below we provide two additional examples on mechanistic complexity of the Pd-catalyzed reactions stemming from our recent computational studies, namely, the roles of weakly coordinated amino-acid ligands, as well as Cs-base in the Pd(II)-catalyzed C-H activation. The first example demonstrates multiple roles played by the amino acid in the [chiral mono-*N*-protected amino acid] ligand-assisted Pd(II)-catalyzed arene C-H bond activation, while the second example highlights the role of base (Cs-halide) in the Pd(0)-catalyzed C-H bond arylation.

III. Enantioselective C-H bond activation catalyzed by [(chiral mono-*N*-protected amino acid)-Pd(II)] complexes.

As mentioned above, in the early 1970's several carbon-carbon and carbon-heteroatom formation

reactions were developed by utilizing Pd(0)-catalyst, based on the Pd(0)/Pd(II) redox catalysis.[13-23] It was shown that the diverse reactivity of the oxidative addition [Pd(II)-R] intermediates is one of the major driving forces of this class of reactions. Inspired by this diverse reactivity of [Pd(II)-R] intermediates, several research groups have initiated synthetic methodology on mimicking the Pd(II)/Pd(0) redox catalysis directly from the well-defined [Pd(II)-R] complex generated by C-H bond activation.[2,5,6,29,35,36,51,94,98,191,192] In spite of notable achievements, a major limitation of this synthetic strategy becomes the designing of suitable ligand scaffolds that can stabilize Pd(II) complex and accelerate C-H cleavage and formation of reactive [Pd(II)-R] intermediates.

Recently, Yu and co-workers have discovered that the mono-*N*-protected amino acid ligands (MPAA) do promote the $Pd(OAc)_2$-catalyzed enantioselective C–H activation of 2-benzhydrylpyridine and 2,2-diphenylpropanoic acid and control selectivity of the reaction.[51,193,194] [The catalytic C–H activation reactions using a chiral auxiliary are well documented[195-201]]. The reported absolute configuration of the products is consistent with a major C–H insertion intermediate that has been observed and characterized only for the pyridine-containing substrate (Chart 1).[194]



Intermediate characterized by ^{1}H NMR

Chart 1

However, no information has been obtained from the experiments on the mechanisms, the role of weakly bound amino acid ligand, and the nature of the reactive species and transition states of the C–H cleavage step, as well as factors controlling the observed product selectivity. In order to gain insights into aforementioned problems Musaev and coworkers recently reported computational studies on the mechanism of this reaction.[202,203]

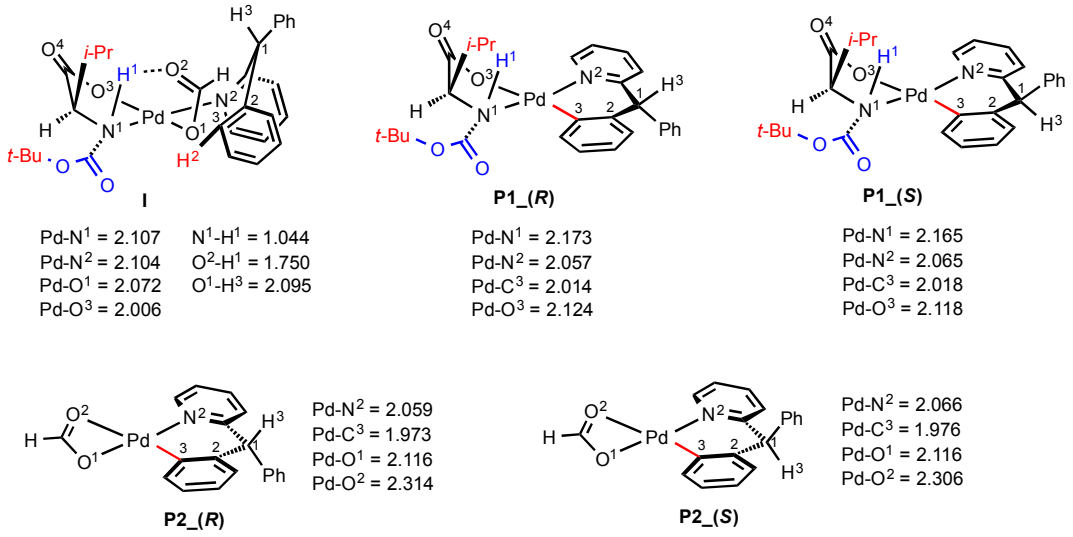


Figure 2. The calculated structures of reactant [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine], **I**, and (*R*) and (*S*) stereoisomers of possible C-H activation products **P1** and **P2.** Distances are in Å. Adapted with permission from reference [202].

Briefly, they have shown that the reactant, *i.e.* [(chiral mono-*N*-protected amino acid)-Pd(II)]

complex with substrate and acetate, [Boc-Val-O]-Pd(II)-[Sub](HCOO), where Sub = 2-benzhydrylpyridine, may have numerous isomers, among which isomer **I** is energetically the most favorable (Figure 2), where the $(HCO^1O^2)^-$ ligand is coordinated to Pd-center (by its O^1 atom) and H^1-atom of amino-group (by its O^2 atom). This coordination mode of $(HCO^1O^2)^-$ has facilitated the formation of a weak Pd-N^1 donor-acceptor bond with a 2.107Å bond distance. Following ^{1}H NMR experiments on the mixture of $Pd(OAc)_2$, substrate and amino acid ligand support the aforementioned structural motive of complex **I** obtained from the computation.[202] *Thus, in this structure, the amino-acid ligand acts as a weakly coordinating ligand that stabilizes Pd(II)-complex **I**.*

As mentioned above, the experimentally observed[51,194] product of the arene C-H bond activation in **I** is complex **P1** (Figure 2). Computations[202] have revealed several isomers of **P1.** Overall, its (*S*) stereoisomer **P1_(*S*)** is found to be ΔH_{gas}=2.7/ ΔG_{gas}=2.7// ΔG_{sol}=2.5 kcal/mol lower in energy than the (*R*) stereoisomer **P1_(*R*).** In the course of these computational studies[202] the authors also located another possible product of the reaction, complex **P2**, where Pd is ligated by $HCOO^-$ (instead of amino-acid) and substrate (Figure 2). The (*S*) stereoisomer **P2_(*S*)** is found to be 4.2/4.6//9.8 kcal/mol more stable than the (*S*) stereoisomer of the **P1** product, *i.e.* **P1_(*S*).** Comparison of these computational findings with available experiments have raised the question: Why do experiments lead to the thermodynamically less favorable (*R*) stereoisomer **P1_(*R*)**, rather than thermodynamically more stable **P1_(*S*)** and/or **P2** product?

The provided extensive computation[202] of all possible mechanisms of the C-H bond activation in complex **I** was intended to answer this question. At first, under the influence of the available experimental data, namely, the reported absolute configuration of the C–H insertion intermediate, the authors have investigated the "direct arene C^3-H^2 bond activation" pathway. In general, this pathway is found to proceed via a CMD mechanism with assistance of the base ($HCOO^-$), which is consistent with conclusions of numerous previous studies of the C-H bond activation by other Pd(II)-complexes.[36,40,212-224]

The authors have demonstrated[202] that the first step of this pathway, *i.e.* the "direct arene C-H bond activation" pathway, is the C^3-H^2 bond activation at the transition state **TS1**, which controls the formation of (*R*) and (*S*) stereoisomers (Figure 3). Overcoming the **TS1_(*R*)** and **TS1_(*S*)** transition states, which requires 21.0/22.8//22.9 and 18.6/19.8//20.2 kcal/mol energy barriers**,** leads to the formation of the kinetically less stable intermediate **Int1.** Among the several located isomers of **TS1** and **Int1**, those leading to the thermodynamically more stable, but experimentally not observed, **P1_(*S*)** stereoisomer are found to be kinetically more favorable: the formation of experimentally observed **P1_(*R*)** product is kinetically *2.4/ 3.1//2.7 kcal/mol less favorable than the formation of the* **P1_(*S*)** *product.*

Furthermore, comparison of the Pd-O^3 bond distance in reactant **I** and intermediates **Int1** shows that in the latter the amino-acid ligand is effectively detached from the Pd-center: the calculated Pd-O^3 bond distances are by 0.25-0.30 Å longer in intermediates than in reactants. Meantime, the Pd-O^1 bond distance is only 0.06-0.07 Å longer in **Int1** than in **I**. These geometry changes indicate that the dissociation of an amino-acid ligand from intermediates **Int1** is easier than dissociation of HCOOH. In other words, the formation of **P2** product from **Int1** is the most likely process.

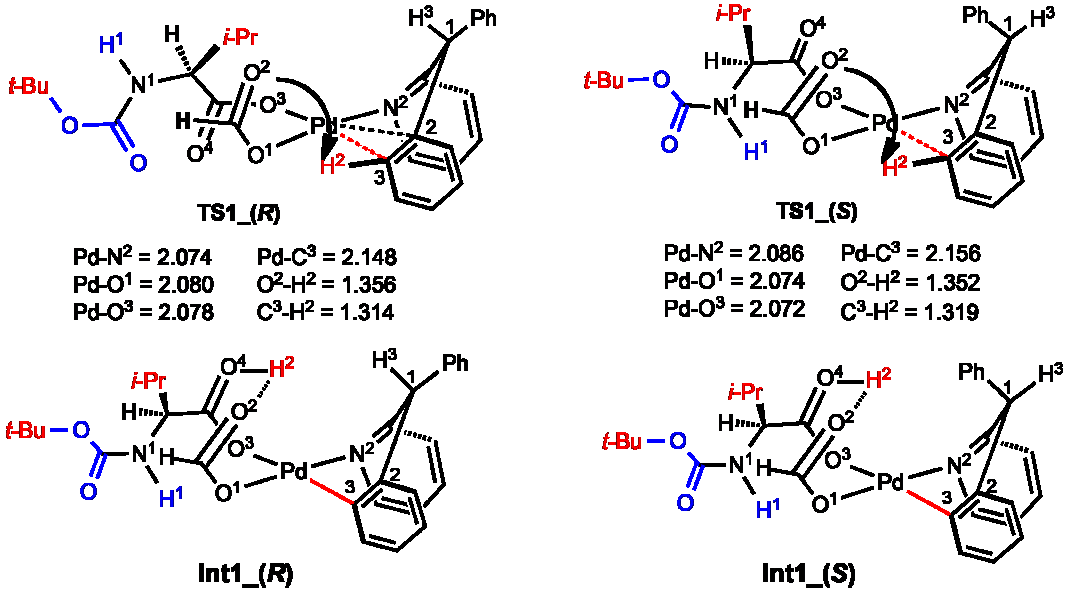
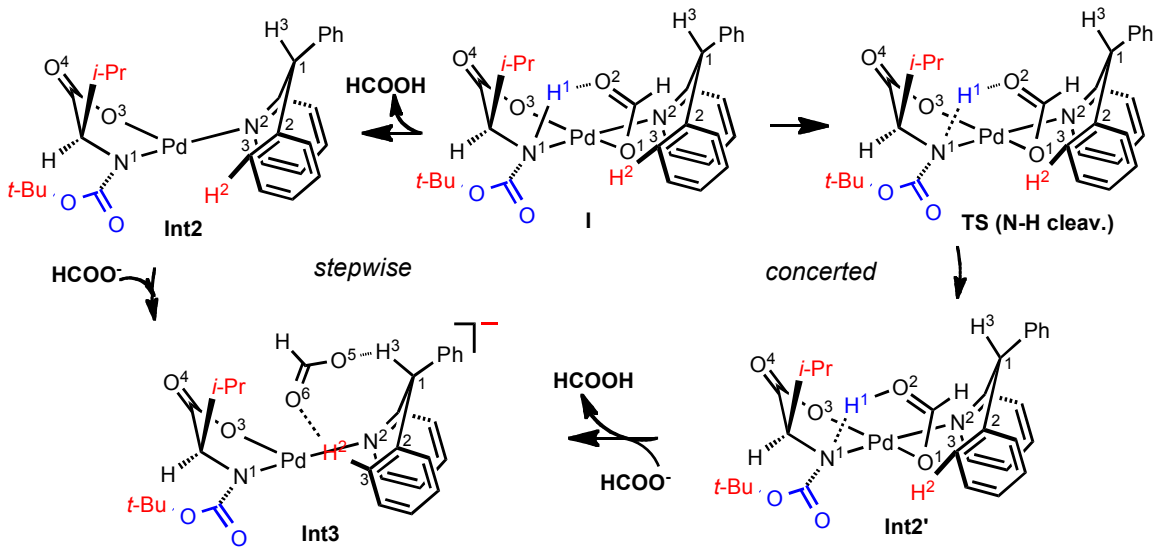


Figure 3. The calculated structures of the two isomers of transition state **TS1**, and (*R*) and (*S*) stereoisomers of intermediate **Int1.** Distances are in Å. Adapted with permission from reference [202].

Thus, if the arene C-H bond activation in **I** proceeded via the "direct arene C-H bond activation" pathway then: (1) the formation of experimentally observed **P1_(*R*)** product would be kinetically less favorable than the formation of **P1_(*S*)** product, and (2) the final product of the reaction would be complex **P2** [Pd(II) complex with AcO and substrate] rather than experimentally reported complex **P1** [Pd(II) complex with amino-acid and substrate]**.** However, both of these conclusions derived from the computation contradict the available experimental data.[51,194] Therefore, Musaev and coworkers[202] have reasoned that: the "direct arene C-H activation" in complex **I** is unlikely to be a valid mechanism of the recently discovered [chiral-mono-N-protected-amino-acid]Pd(II)-catalyzed enantioselective C–H bond activation reaction because it fails to explain the experimentally observed product formation and selectivity.[51,194]

The N-H bond cleavage and subsequent C-H bond activation mechanism. Close examination of the calculated structure of reactant **I** {showing strong [r(O^2-H^1) = 1.750Å] hydrogen-bonding between the coordinated acetate and amino-group, which results in elongation of N^1-H^1 bond [r(N^1-H^1) = 1.044Å]} has led Musaev and coworkers to investigate an alternative, the "N-H bond cleavage and subsequent C-H bond activation", mechanism.[202] For the sake of simplicity, they have divided the discussion of this mechanism into two parts: **Part-1**, where the active catalyst, Pd(II) intermediate **Int2 (**and/or **Int3)** with a bidentately (with O and N-ends) coordinated amino-acid ligand is generated (Scheme 6); and **Part-2**, where the arene C^3-H^2 bond cleavage occurs in the newly generated Pd(II) intermediate **Int2 (**and/or **Int3)** (see below).



Scheme 6. Schematic presentation of intermediates and transition states involved in the **Part-1** of the "N-H bond cleavage and subsequent C-H bond activation" pathway of the C-H bond activation in the [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine] system.

Part-1. This part of the reaction may proceed via two distinct pathways: concerted and stepwise. The concerted pathway includes: (a) the N^1-H^1 bond cleavage by base at the transition state (**TS(N-H cleav.)** leading to the formation of intermediate **Int2′**, and (b) the HCOOH-to-$HCOO^-$ substitution (*i.e.* **Int2′**-to-**Int3** rearrangement) leading to the formation of intermediate **Int3** (see Scheme 6). The stepwise pathway proceeds via the formation and dissociation of HCOOH to form intermediate **Int2**, which, at the next step, may coordinate acetate to form **Int3**. The formation of **Int2**, *i.e.* the reaction **I** → **Int2,** is found to be exergonic by ΔG_{THF} = 12.9 kcal/mol [In this article, for the sake of consistency with the presented discussion, we re-optimized the geometries of the reactant **I**, and intermediates **Int2** and **Int3** in THF solution at the same level of theory]. The formation of intermediate **Int3** from **Int2** is only 1.7 kcal/mol ΔG_{THF} = endogenic (see Figure 4).

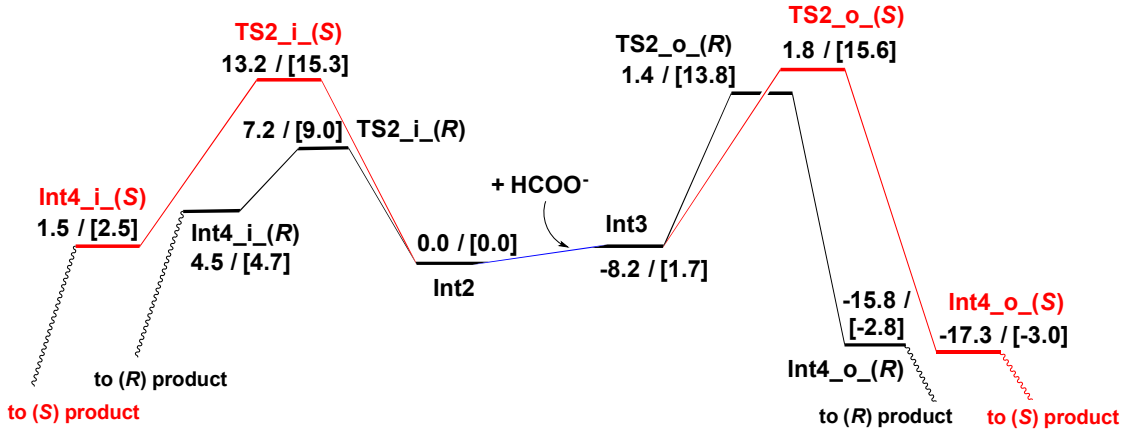


Figure 4. Schematic presentation of the relative energies of the inner-sphere and outer-sphere C-H concerted metalation-deprotonation (CMD) steps of the "N-H bond cleavage and subsequent C-H bond activation" pathway in the [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine] system. The presented energies are the ΔH / ΔG (in kcal/mol) calculated in THF.

Noteworthy, the intermediates **Int3** and **Int2** may have several isomers, which were extensively discussed previously.[202] In Figure 5 we present only their energetically most favorable isomers.

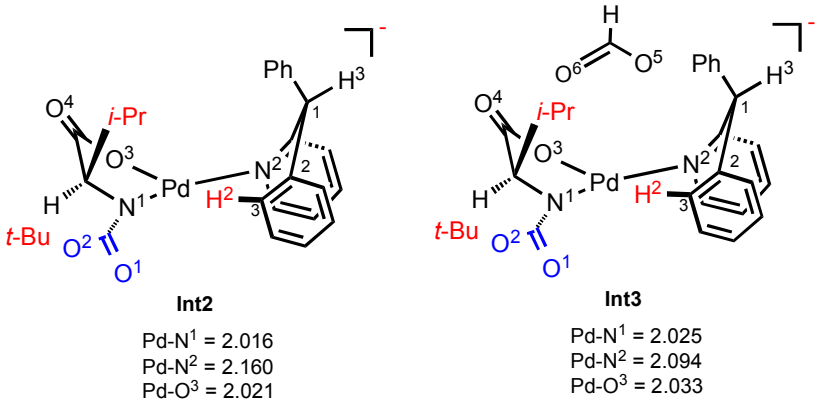


Figure 5. The most favorable isomer of the Pd(II) intermediates **Int2** and **Int3** with a bidentately coordinated dianionic amino-acid ligand. These intermediates are proposed to be active catalysts for enantioselective C–H bond activation in the [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine] system.

The first step of the concerted pathway, *i.e.* the N^1-H^1 bond cleavage **I** → **Int2′**, requires an energy barrier of a few kcal/mol. However, the authors[202] did not report the transition state either for the **I** → **Int2′** transformation or for the following HCOOH-to-$HCOO^-$ substitution step. Therefore, here we take the ΔG_{THF} = 12.9 kcal/mol energy, required for the stepwise process, *i.e.* **I** + **HCOO**$^-$ → **Int2** + **HCOOH** + **HCOO**$^-$, as a value of the energy required for the entire **I** → **Int2** reaction, *i.e.* the reaction for the formation of Pd(II) intermediate with a bidentately coordinated (by O- and N-ends) amino-acid ligand. As was previously concluded,[202] the energy (ΔG_{THF} = 12.9 kcal/mol) required for the **I** → **Int2** transformation is significantly smaller than ΔG_{THF} = 22.9 and ΔG_{THF} = 20.2 kcal/mol barriers reported for the "direct arene C-H bond activation" pathway, which also starts from the same reactant **I**. Based on these computational findings, Musaev and co-workers, for the first time in the literature, have concluded[202] that the first possible bond breaking event in the reactant **I** would be the N-H bond cleavage leading to the formation of the Pd(II) intermediate **Int2** (and/or **Int3)** with a bidentately coordinated dianionic amino-acid ligand, rather than the "direct arene C-H bond activation". *Thus, at this stage, the amino-acid ligand of* ***I*** *acts as a soft proton donor leading to the formation of the Pd(II)-intermediate,* ***Int2*** *(and/or* ***Int3),*** *with a bidentately (via its both O-and N-terminals) coordinated dianionic amino-acid ligand.*

Part-2 of the "N-H bond cleavage and subsequent C-H bond activation" pathway starts from the newly formed intermediate **Int2**. The arene C^3-H^2 bond activation in this intermediate may proceed via two possible pathways: outer-sphere CMD, with assistance of external acetate, and inner-sphere CMD, with assistance of carbonyl of the NCO^{t}Bu-group of the coordinated amino-acid ligand. Previously Musaev and coworkers[202] have shown that this step of the reaction [*i.e.* C-H bond activation in the Pd(II)-intermediate **Int2** (and/or **Int3)** with a bidentately coordinated dianionic amino-acid ligand] is crucial and controls the stereoselectivity of entire reaction. However, the authors previously reported only the outer-sphere CMD transition states **TS2_o_(*R*)** and **TS2_o_(*S*),** as well as resulted corresponding intermediates **Int4_o_(*R*)** and **Int4_o_(*S*).** (Figures 6 and 7)

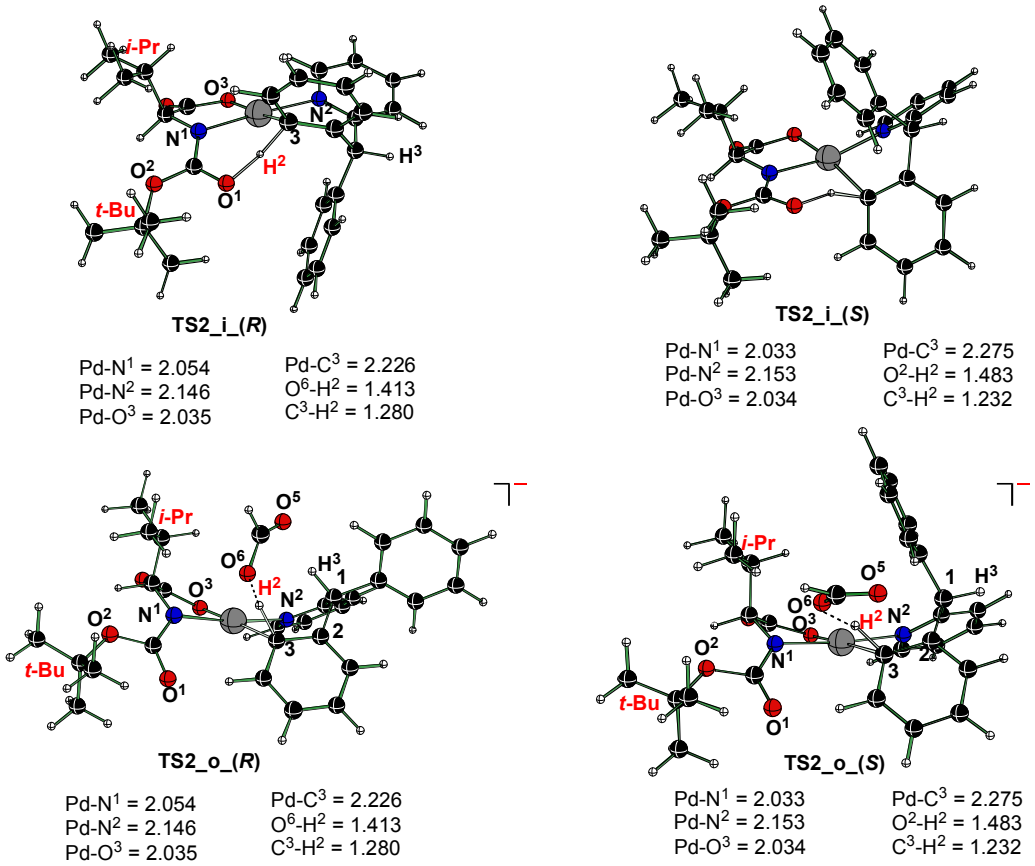


Figure 6. The calculated inner-sphere [**TS2_i_(*R*)** and **TS2_i_(*S*)**] and outer-sphere [**TS2_o_(*R*)** and **TS2_o_(*S*)**] C-H activation transition states of the "N-H bond cleavage and subsequent C-H bond activation" pathway in the [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine] system. The distances are in Å.

For the sake of completeness, in the present paper, we extended our calculations to the transition states [**TS2_i_(*R*)** and **TS2_i_(*S*)**] and resulted intermediates [**Int4_i_(*R*)** and **Int4_i_(*S*)**] of the inner-sphere C-H activation mechanism in the [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine] system. These calculations were performed in THF solution (treated at the PCM level) at the B3LYP level of theory in conjunction with {lanl2dz (for Pd) plus 6-311+G(d,p) (for other atoms)} basis sets. For consistency, we also re-optimized the geometries of the previously reported[202] transition states [**TS2_o_(*R*)** and **TS2_o_(*S*)**] and resulted intermediates [**Int4_o_(*R*)** and **Int4_o_(*S*)**] of the outer-sphere CMD mechanism at the same level of theory in THF solution.

Comparison of the calculated energy barriers (see Figure 4) shows that the formation of (*R*) product, in general, is kinetically less energy demanding regardless of the inner-sphere or outer-sphere C-H CMD mechanism. This finding is consistent with experimental findings[51,194] and provides additional evidence for proposing the "N-H bond cleavage and subsequent C-H bond activation" mechanism for C–H bond activation in [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine].

Furthermore, as seen in Figure 4, the inner-sphere and outer-sphere C-H bond deprotonation in [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine] require similar energy barriers. Therefore, both outer-sphere and inner-sphere C-H activation can be operative mechanisms of the arene C-H bond deprotonation in the [chiral-mono-N-protected-amino-acid]-Pd(II)-complexes. However,

several factors, such as the nature of substrate and N-protecting group, the length of amino-acid chain, steric bulkiness of chiral ligands and more, could strongly impact the mechanism of this reaction. Elucidating the role of these factors in the [chiral-mono-N-protected-amino-acid]-Pd(II)-catalyzed enantioselective C-H bond activation requires additional and more comprehensive studies which are in progress in our group (also see below).

Overcoming transition states **TS2_i_(*R*)**, **TS2_i_(*S*)**, **TS2_o_(*R*)** and **TS2_o_(*S*)** completes the formation of (*R*) and (*S*) stereoisomers at the intermediate **Int4**, respectively (see Figure 7). As seen in Figure 4, between the resulted **Int4** intermediates those formed via the outer-sphere mechanism, *i.e.* **Int4_o_(*R*)** and **Int4_o_(*S*)**, are thermodynamically more stable than the **Int4_i_(*R*)** and **Int4_i_(*S*)** structures formed via the inner-sphere mechanism. Furthermore, in both cases, the (*S*) stereoisomers of **Int4** are slightly more stable than their (*R*) counterparts.

As shown previously,[202] the formation of final product **P1** from the **Int4** intermediate requires only an insignificant energy barrier and is an exergonic process. This step of the reaction does not contribute to the overall rate and selectivity of the reaction. Therefore, here we will not discuss transition states and intermediates involved in the **Int4** → **P1** transformation.

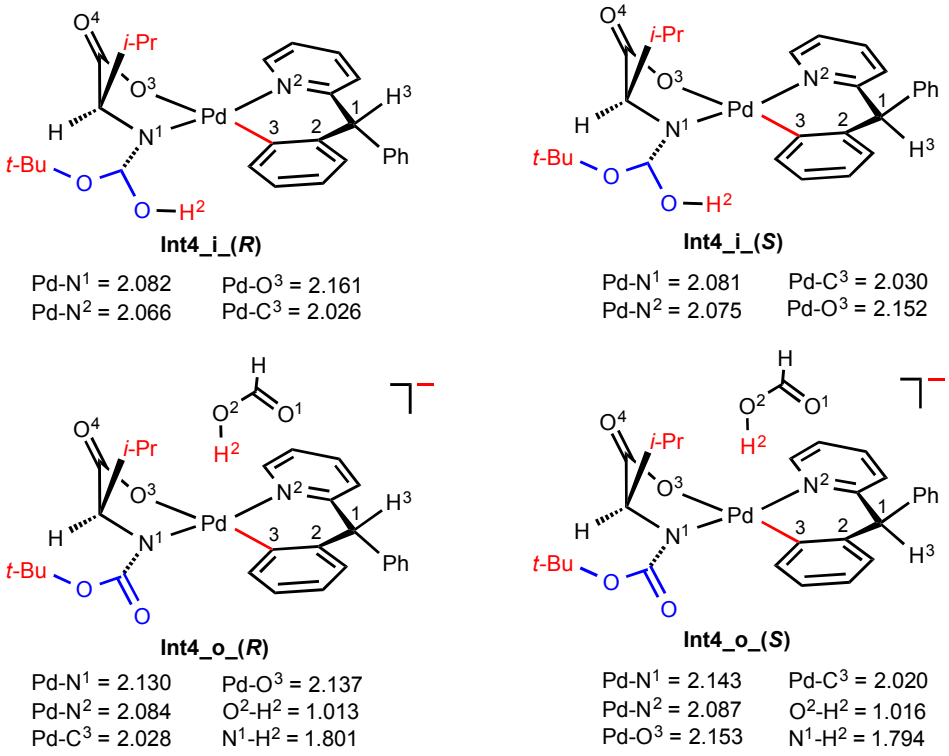


Figure 7. The calculated intermediates (**Int4**) resulted from the inner-sphere and outer-sphere C-H bond activation on the "N-H bond cleavage and subsequent C-H bond activation" pathway in the [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine] system. The distances are in Å.

Thus, based on their aforementioned computational findings, for the first time in the literature, Musaev and coworkers have predicted[202] the "N-H bond cleavage and subsequent C-H bond activation" mechanism for the [(chiral mono-*N*-protected amino acid)-Pd(II)]-catalyzed enantioselective C–H bond activation in [Boc-Val-O]-Pd(II)-[2-benzhydrylpyridine]. This mechanism proceeds via the formation of the catalytically active Pd(II) intermediate with a

bidentately coordinated dianionic amino-acid ligand. This computational finding is consistent with the conclusion of experiments by Yu and coworkers: The performed two sets of experiments, (i) measuring the intermolecular KIE, and (ii) observing the relationship between the initial rate and the electronic properties of the substrate through competition experiments suggested that the amino acid ligands are not merely enhancing the TON (turnover number) but are generating a more reactive catalyst.[194]

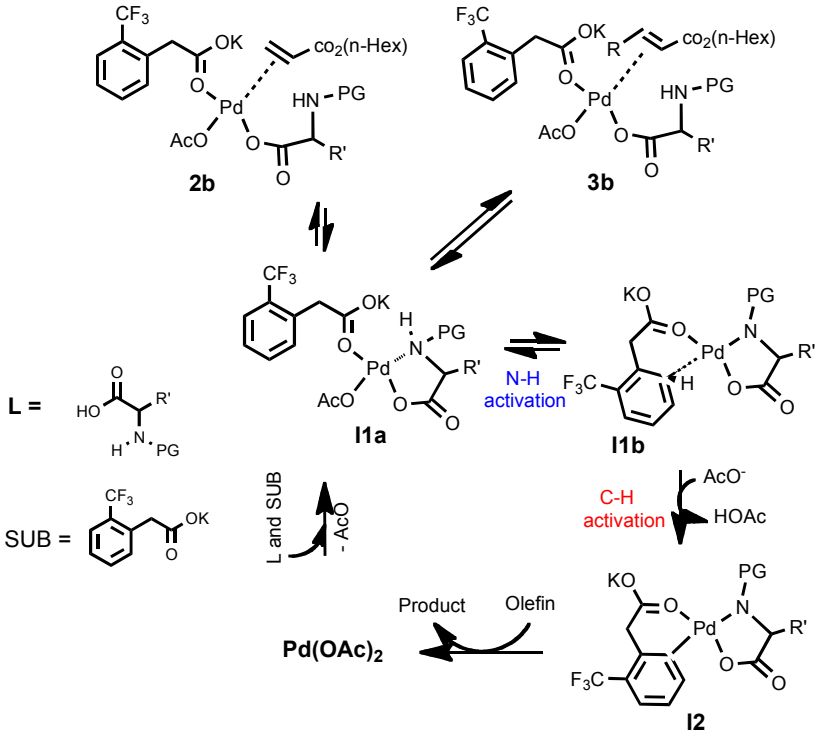
Furthermore, previous[202] and current studies of the Musaev group have shown that the amino-acid ligand plays multiple roles in the [(chiral mono-N-protected amino acid)-Pd(II)]-catalyzed C–H bond activation by acting as: (i) a weakly coordinating ligand to stabilize the Pd(II)-precatalyst; (ii) a soft proton donor (from the N-terminal) and bidentate (O- and N-terminals) ligand to facilitate the formation of the catalytically active Pd(II) intermediate **Int2** (and/or **Int3)**, and (iii) a proton acceptor from the arene C-H bond via the concerted metalation-deprotonation (CMD) mechanism. *It is important to emphasize that the Pd-center, in the course of the reaction, acts as a coordinatively and electronically flexible metal center that holds the substrate and amino acid ligand in close vicinity to promote the chemical transformation.*

Additional experimental confirmation of these computational findings came from the detailed kinetic studies of the Pd(II)-catalyzed C-H bond olefination in the presence of mono-N-protected amino acid ligands (such as Ac-Ile-OH, Ac-Val-OH, Boc-Val-OH and Boc-Ile-OH), performed by Blackmond and coworkers.[225] Utilization of the computational results, namely, the prediction that reaction proceeds through an "N-H bond cleavage and subsequent C-H bond activation" pathway via the formation of catalytically active Pd(II) intermediate with a bidentately coordinated amino-acid ligand rather than through a "direct arene C-H bond activation" has helped to rationalize the presented[225] kinetic rate laws: The determined overall kinetic rate law holds if the formation of two kinetically indistinguishable species **I1a** and **I1b** upon coordination of **SUB** to the catalyst followed by N−H activation is assumed (Scheme 7).

In the paper,[225] the observed anomalous concentration dependences (zero order in substrate concentration, zero order in oxygen pressure, negative orders in both olefin and product concentrations, and positive order in the catalyst concentration) of the reaction are attributed to the presence of off-cycle reservoirs (initiated from the weakly coordinated species **I1a,** prior to N−H activation) containing the substrate and product olefin species bound to a weakly coordinated Pd-species **I1a,** prior to N−H activation. The proposal that the rate-determining step involves an interplay between N−H and C−H activation processes has also helped to explain both the similar form of the rate expression and the observed differences in the absolute magnitude of the rate for the different amino acid ligands (namely, increase in the reaction rate in the following order: Ac-Ile-OH > Ac-Val-OH > Boc-Val-OH ≈ Boc-Ile-OH).[225] In addition, the authors demonstrated[225] that suppressing formation of a stable mixed acetate species (similar to **P2** product reported by Musaev and coworkers[202]) accounts for the observed rate of acceleration.

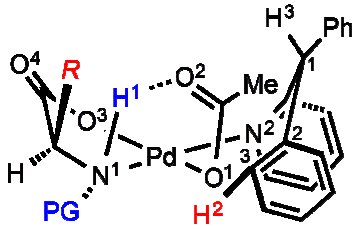
Just recently (after this paper was submitted for publication), Houk-Yu-Wu and coworkers[226] reported mass-spectrometry and computational studies, which provide an additional confirmation of our findings presented above. Indeed, mass spectrometry experiments of a 1:1 mixture of $Pd(OAc)_2$ and *N*-acetyl-glycine (or *N*-Boc-glycine) dissolved in CH_3OH (or CH_3CN), and following isotope pattern and fragmentation analysis via collision-induced dissociation (CID) have suggested that in this mixture the deprotonated amino acid ligand is coordinated to Pd-center in a bidentate fashion. The accompanied influential DFT studies utilizing $Pd(OAc)_2$ and *N*-acetyl-glycine (*i.e.* MPAA) have confirmed this experimental finding: These calculations[226]

have shown that deprotonation of the MPAA N–H bond by the acetate is highly favored and leads to the formation of a stable bidentate Pd-MPAA complex, which is consistent with mass-spectrometry studies[226] and previous computational results.[202]



Scheme 7. Proposed reaction mechanism from the kinetic studies in [225]. Adapted with permission from reference [225].

Furthermore, comparison of our computational findings with those provided by Houk-Yu-Wu and coworkers[226] demonstrates the impact of the nature of the amino-acid ligand and substrate on the mechanism of C-H activation in the [mono-N-protected-amino-acid]-Pd(II) systems. Indeed, by utilizing $Pd(OAc)_2$ (as a catalyst), *N*-acetyl-glycine (as an amino-acid ligand) and *N*,*N*-*bis*(2-cyanophenyl)-3-phenylpropanamide (as a substrate) Houk-Yu-Wu and coworkers[226] have found the inner-sphere C-H activation to be kinetically more favorable than the outer-sphere C-H activation by 12.3 kcal/mol. However, as shown by Musaev and coworkers in the present and previous papers[202] for the $Pd(OAc)_2$ (as a catalyst), *N*-Boc-valine (as an amino-acid ligand) and 2-benzhydrylpyridine (as a substrate), the formation of the (*R*) product via the inner-sphere C-H activation pathway requires only 4.9 kcal/mol (*i.e.* almost three times less than in Houk and coworkers studies[226]) less energy barrier than that via the outer-sphere C-H activation pathway. Interestingly, the formation of the (*S*) product via the both outer-sphere and inner-sphere C-H activation pathways requires very similar energy barriers.



Scheme 8. Schematic presentation of protecting (PG) and alkyl (R) groups used in these studies.

As mentioned above, the predicted[202] and later experimentally confirmed[225,226], "N-H bond cleavage and subsequent C-H bond activation" mechanism of the C-H bond activation in the {[

mono-*N*-protected amino acid]-Pd(II)[Substrate]} system proceeding via the formation of the catalytically active Pd(II) intermediate with a bidentately coordinated dianionic amino-acid ligand offers an opportunity for the C-H bond cleavage through a concerted metalation deprotonation (CMD) mechanism.[40,47,51,56,94-97] Although a similar deprotonation mechanism was computed with Pd(0)/ArI/PPh_3 catalytic system,[220-224] C-H cleavage by newly formed Pd(II) catalyst with a bidentately coordinated dianionic amino-acid ligand provides a valuable set of tools for further optimization of the amino acid ligands with respect to the *N*-protecting group and development of new and more efficient C-H activation reactions.

Therefore, in the present paper, we further investigated the effect of the nature of *N*-protecting group on the energies of the **Part-1** of aforementioned "N-H bond cleavage and subsequent C-H bond activation" mechanism: *i.e.* steps of the N-H bond cleavage and the active catalyst **Int2** formation. In these calculations we used the **PG** = H, COOH, Ac, Boc and Ac-CF_3 as a protecting group, **R** = ^{i}Pr as an alkyl group, and $MeCOO^-$ as a base (see Scheme 8 for clarity). We found that the energy required for the **Int2** formation decreases via **PG** = **H** [ΔH_{gas}=39.2/ΔG_{gas}=29.0 kcal/mol] > **Boc** [ΔH_{gas}=26.3/ΔG_{gas}=14.9 kcal/mol] ~ **COOH** [ΔH_{gas}=25.7/ΔG_{gas}=14.0 kcal/mol] > **Ac** [ΔH_{gas}=23.5/ΔG_{gas}=12.7 kcal/mol] > **Ac-CF_3** [ΔH_{gas}=20.7/ΔG_{gas}=9.0 kcal/mol]. The alkyl **R** substitution has no significant effect on the **Int2** formation: by varying R as Me, ^{i}Bu, ^{i}Pr, but fixing PG as HCOO and base as $MeCOO^-$, we found that the energy required for the **Int2** formation in **I** changes only slightly: R = Me [ΔH_{gas}=24.3/ΔG_{gas}=12.3 kcal/mol], ^{i}Bu [ΔH_{gas}=25.5/ΔG_{gas}=12.3 kcal/mol] and ^{i}Pr [ΔH_{gas}=25.7/ΔG_{gas}=14.7 kcal/mol].

Ironically, the above provided computational trend in the energy required for the **Int2** formation, *i.e.* PG = H > Boc ~ COOH > Ac > Ac-CF_3, well correlates with the experimentally reported[194] conversion rate (the conversion was determined by ^{1}H NMR analysis of the crude reaction mixture) of the C-H cleavage in complex **I** which changes as PG= H(0%) < MeOOC(21%) < Boc (46%) < Ac (57%).

The effect of electronic and steric properties of the substituents on the bidentate MPAA ligand and on the calculated reaction rate and yield were also elucidated by Houk and coworkers.[226] by replacing Ac-Gly-OH (R1 = Ac, R2 = H) with Boc-Gly-OH (R1 = Boc, R2 = H) in the reaction with *N*,*N*-*bis*(2-cyanophenyl)-3-phenylpropanamide. It was found that the barrier of C–H bond activation with the Boc-Gly-OH ligand is 2.7 kcal/mol higher than with the Ac-Gly-OH ligand. This finding is in good agreement with experiment showing a significant (from 95% to 10%) decrease in the yield.[227]

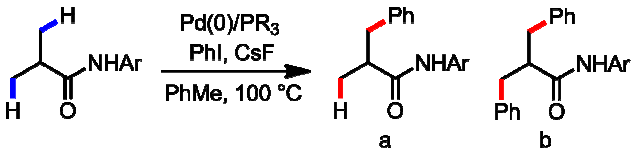
Armed with this computational and experimental knowledge, we currently continue our joint computational and experimental efforts on a more detailed interpretation of the role of protecting group (PG) and chain amino acid ligand, in the ligand-accelerated Pd(II)-catalyzed C-H bond functionalization.

IV. Role of the Cs-halide in the Pd(0)/PR_3-catalyzed C-H bond arylation.

This example demonstrates roles of the Cs-base in the Pd-catalyzed chemical transformations. Delineation of the role of base in C-H bond arylation is currently under debate.[214-224, 228-234] In general, multiple experimental and computational studies suggest a crucial role of base in the C-H bond activation, as well as in many other chemical transformations, where the substrate/ligand deprotonation step is a vital and necessary step of the entire reaction. Among the numerous bases

used in experiments the Cs-bases (Cs-halides, Cs-acetates, Cs-carbonates, etc.) have attracted a special attention.[40, 235-238] Cesium reagents/additives are generally superior to their alkali metal counterparts with respect to reaction time and yield, and most such conversions proceed under mild conditions. In particular, cesium bases have excelled at controlling reaction chemoselectivity and have been demonstrated to be highly compatible with a wide range of functional groups. This enhanced reactivity under mild conditions has been defined as the "cesium effect", and it is believed that this phenomenon stems from: (i) better solubility of cesium bases, the generation of highly reactive "naked" anions, (ii) large size of Cs, and (iii) its facile polarizability. [235-238] However, the understanding of the precise role of base (including Cs-bases) in Pd-catalyzed direct C-H bond functionalization still requires more analysis. For this purpose, computations, including both cationic and anionic components of the bases into the calculations, are expected to be extremely valuable. Recently, Musaev and coworkers demonstrated this in a study of mechanism of Pd(0)/PR_3 catalyzed intermolecular C-H bond arylation in the presence of CsF.[239, 240]

We should note that, in the literature, the Pd(0)/PR_3-catalyzed arylation of C(sp^2)-H bonds with aryl halides have been extensively described.[51] Pioneering works on Pd(0)/PR_3 catalyzed *intramolecular* arylation of C(sp^3)-H bonds with a tethered aryl halides have also been reported.[242-247] However, examples for Pd(0)/PR_3-catalyzed *intermolecular* arylation of C(sp^3)-H bonds are still very rare. Just recently, Yu and coworkers have reported the first examples of the Pd(0)/PR_3 catalyzed *intermolecular* selective C(sp^3)-H functionalization with aryl iodides[248] (Scheme 9) and alkynyl halides.[249] The reaction conditions (*i.e.*, ligands, bases, solvents, and coupling partners) were screened to improve the yield for the desired mono-arylated products.



Scheme 9. Selective β-C(sp^3)-H bond arylation using N-aryl amides in conjunction with Pd(0)/PR_3 catalysts, PhI, CsF and Ar = C_6F_5. Adapted with permission from reference [239].

For example, for the Pd(0)/PR_3 catalyzed *intermolecular* selective C(sp^3)-H functionalization with aryl iodides (below we only summarize findings on the reaction with aryl iodides, our computational study on the reaction with alkynyl halides is in progress)[248]: (1) Bulky electron-rich PR_3 ligands such as PCy_3 and Buchwald ligands were found to be optimal; (2) CsF is reported to be the most efficient base and gave appreciable amounts of the desired products; (3) Only aryl iodides were found to give the desired product. Other aryl halides and pseudohalides such as aryl bromides, chlorides, triflates, and tosylates did not carry out the reaction; and (4) The substrate (**SM** = EtCONH-Ar), containing an aryl component (Ar = C_6H_5 and C_6F_5), was found to greatly improve the reactivity when decorated with electron withdrawing substituents. Subsequent ^{1}H NMR and computational efforts have demonstrated[239] that the deprotonation of the amide directing group of **SM,** *i.e.* EtCONH-Ar, by CsF to form **DG′** = [EtCON-Ar]Cs^+ is necessary for coordination of substrate to Pd-center and for success of the reaction. Furthermore, it is established that deprotonation of EtCONH-Ar by CsF becomes a facile process upon replacing Ar = C_6H_5 by Ar = C_6F_5. These finding are in excellent agreement with previously reported experimental data.[248]

However, the experiments[248] left the following questions unanswered: (1) what is the mechanism of this reaction?, (2) Does the directing group **DG′** and/or PR_3 group dissociate in the course of the reaction?, and (3) Why is CsF the most efficient base for this reaction? A better understanding of the aforementioned problems could facilitate the design of more efficient catalysts that will expand the substrate scope of the Pd(0)/PR_3 catalyzed *intermolecular* selective C(sp^3)-H functionalization. Recently reported computational study by Musaev and coworkers[239] intended to shed light on the mechanistic aspects of the Pd(0)/PCy_3-catalyzed *intermolecular* arylation of terminal β-C(sp^3)-H bond of aryl amide (**SM** = EtCONH-Ar) in presence of CsF base. Below, we summarize the findings of Musaev and coworkers for Ar = C_6F_5.[239]

Oxidative addition of aryl iodides (Ph-I) to Pd(0)/PCy₃, which is proposed to be an initial step of the reaction, Pd(0)/PCy_3 (**5**) + Ph-I (**6**) → I-Pd(II)(PCy_3)Ph (**7**), is found to be exergonic (ΔG = -20.4 kcal/mol) and proceeds essentially without an energy barrier. This finding is in excellent agreement with the results of previous experimental and computational studies.[250]

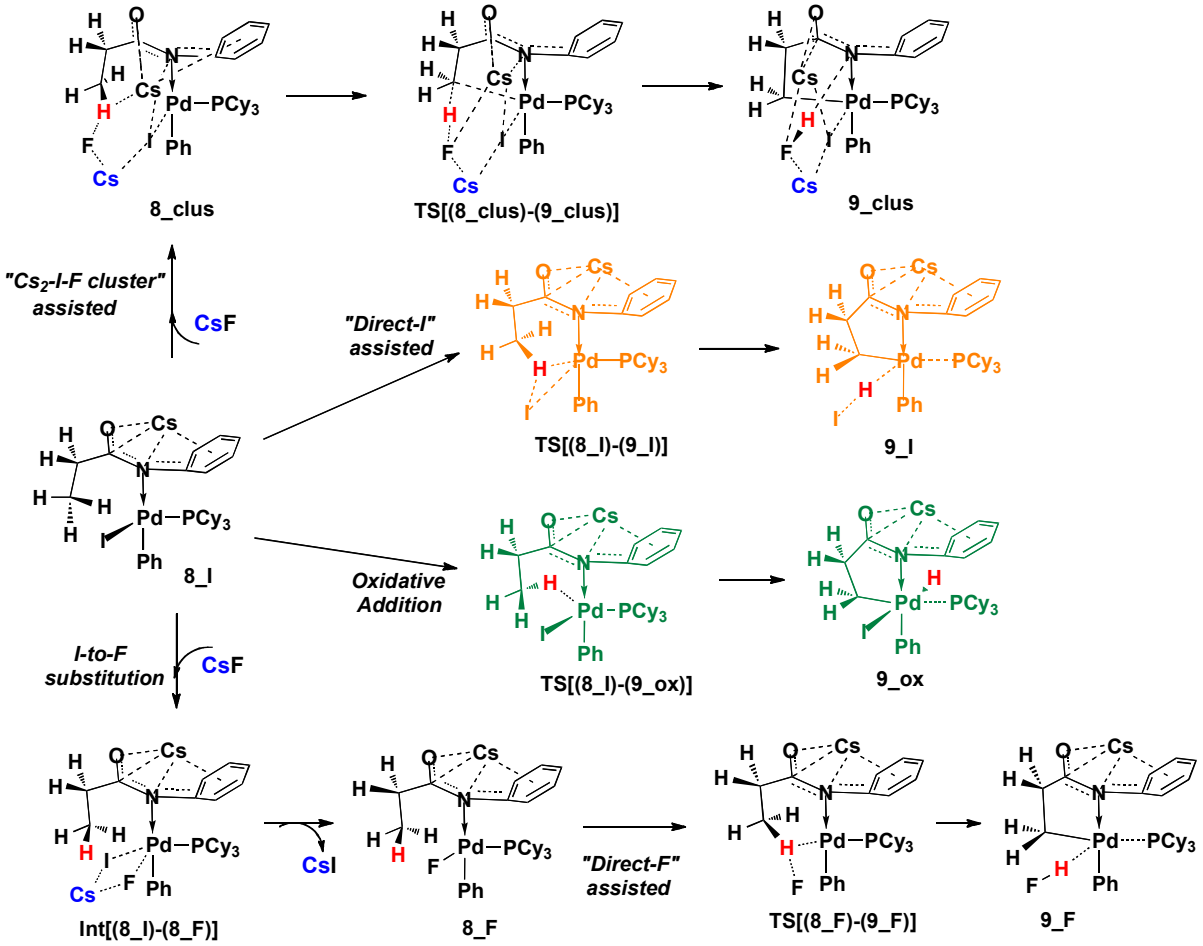
At the next stage, the previously deprotonated substrate coordinates to the Pd-center of **7** to give complex **8_I**, which is the pre-reaction complex for the C(sp^3)-H bond activation (see Figure 8). The authors have investigated several possible mechanisms of the C(sp^3)-H bond activation in intermediate **8_I** (Scheme 10), among which the classic C-H oxidative addition pathway leading to the formation of intermediate **9_ox** (Figure 8) with a Pd-H bond, where the H-ligand is *trans* to the I-ligand, requires a large activation barrier of $\Delta G^{\ddagger}$ = 49.1 kcal/mol. An alternative pathway, dubbed the "direct-I" assisted pathway, which proceeds via H insertion into the Pd-I bond and concomitant formation of the Pd-C bond (see structure **9_I** in Figure 8), is also found to require a high (44.1 kcal/mol) energy barrier. Thus, both mechanistic pathways require very high-energy barriers and cannot be the operative mechanisms of this reaction.

Since experiments[248] show that CsF plays a special role in this reaction, the authors also explored the effect of the CsF on the β-C(sp^3)-H bond activation.[239] At first, they studied the CsF-mediated I-to-F ligand substitution in intermediate **8_I** to form structure **8_F** with Pd-F bond followed by the "direct-F" assisted C-H bond activation (instead of the "direct-I" assisted pathway), i.e. reaction:

$$L_nPd\text{-}I,\ \mathbf{8\_I} + CsF \rightarrow L_nPd\text{-}F,\ \mathbf{8\_F} + CsI \qquad (1)$$

It was found[239] that this reaction (Eq. 1) is thermodynamically favorable, ΔG = -31.2 kcal/mol and proceeds via a relatively small, $\Delta G^{\ddagger}$ = ~10.0 kcal/mol, energy barrier. This result indicates that the Pd(II)-F bond is stronger than Pd(II)-I bond for the given Pd(II)-coordination environment. Similar results were found by Sakaki et. al,[251] and Yates et al.[252] in a study on the role of fluoride anion in the transmetalation between vinylsilane and Pd(II)-vinyl complex, and in the Stille cross-coupling reaction of Ph-Cl catalyzed by Pd(P^tBu_3)$_2$, respectively. Furthermore, Sanford et al.[253] have recently reported a successful Pd(II) mediated I-to-F substitution reaction with AgF.

To further elaborate the Pd-halide bond strength, they also calculated the I-to-Cl and I-to-Br substitution. These calculations showed that the substitution of I by Cl and Br is favorable by ΔG = -5.8 and -1.5 kcal/mol, respectively. Thus, the stability of the $L_nPd(II)$-X bond reduces as X = F >> Cl > Br > I.



Scheme 10. Possible β -C(sp^3)-H activation pathways from intermediate (**8_I**): "oxidative addition" (green), "direct-I" assisted (orange), the "direct-F" assisted, and "Cs_2-I-F cluster" assisted C-H activation pathways. Adapted with permission from reference [239].

The next step of this pathway is the β-C(sp^3)-H bond activation in **8_F** and formation of **9_F**, called the "direct-F" assisted C-H activation step. The calculations predicted the "direct-F" assisted C-H activation in **8_F** to be 21.4 kcal/mol endothermic and proceed with a 33.7 kcal/mol energy barrier.[239] Comparison of these energy parameters with those (39.8 and 44.1 kcal/mol, respectively) for the "direct-I" assisted β-C(sp^3)-H bond activation in **8_I** shows that the "direct-F" assisted β-C(sp^3)-H bond activation in **8_F** is kinetically and thermodynamically less demanding than the "direct-I" assisted C-H bond activation in **8_I**.

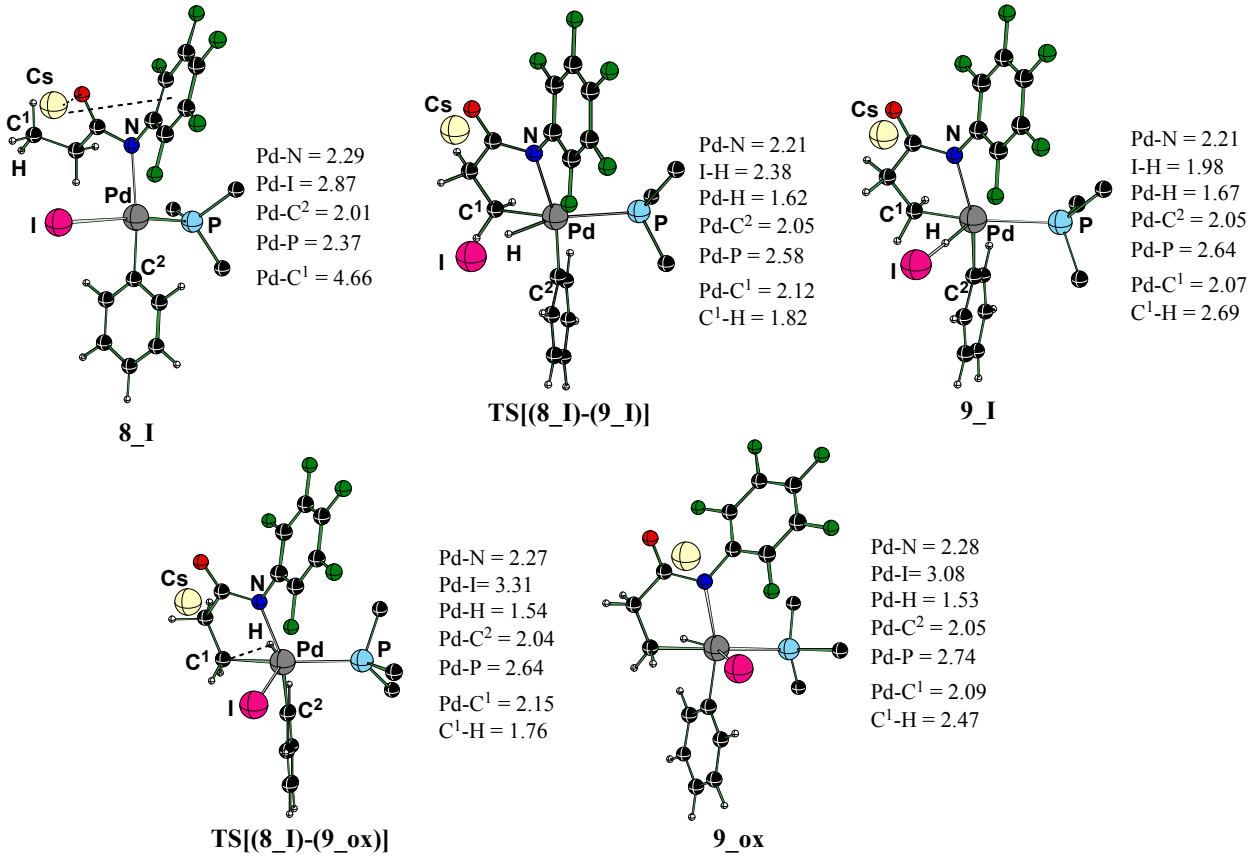


Figure 8. Optimized important geometries of the "oxidative addition" and "direct-I" assisted C(sp^3)-H bond activation transition state, reactant and respective products. For clarity, PCy_3 ligands are presented as PC_3. Bond lengths are given in Å. Adapted with permission from reference [239].

Although the CsF-mediated I-to-F substitution, *i.e.* Eq. 1, reduces the "direct-halide" assisted β-C(sp^3)-H bond activation barrier, it also creates an opportunity for the competing Ph-F bond formation. The calculated barrier for the Ph-F reductive elimination in **8_F** is found to be 21.8 kcal/mol, *i.e. c.a.* 12 kcal/mol lower than that required for the "direct-F" assisted C-H bond activation. However, the Ph-F bond formation was not observed experimentally.[248] Thus, the CsF-mediated I-to-F substitution followed the "direct-F" assisted β-C(sp^3)-H bond activation is not expected to be the operative mechanism of this reaction either.

Thus, all three above reported mechanisms should be ruled out as operative mechanisms of the Pd(0)/PCy_3-catalyzed *intermolecular* arylation of terminal β-C(sp^3)-H bond of aryl amide for various reasons. This raises the question: what is an operative mechanism of this reaction? Since in experiments,[248] the success of the reaction requires an excess of CsF, at the next stage of their computational study, the authors included[239] one more CsF molecule directly into the calculations. This led to formation of intermediate **8_clus** with a "Cs_2-I-F" cluster. Therefore, they have also explored the *"Cs_2-I-F cluster" assisted β-C(sp^3)-H activation process* started

from intermediate **8_clus** which ultimately allowed them to resolve the issue related to the operative mechanism of this important reaction.[239]

In the "Cs_2-I-F cluster" assisted β-C(sp^3)-H activation pathway *(see* Figure 9 and 10) the formed "Cs_2-I-F" cluster abstracts (via its F-atom) a proton from the terminal methyl group at the transition state **TS[(8_clus)-(9_clus)].** The free energy barrier at this transition state is calculated to be small, $\Delta G^{\ddagger}$ = 10.2 kcal/mol. Inclusion of dispersion corrections (see reference[239,240] for more details) increases it to $\Delta G^{\ddagger}_{disp}$ = 11.8 kcal/mol. Overcoming this barrier leads to formation of a diamond shaped "Cs_2-I-FH" cluster complex, **9_clus**.

The optimized geometries of **8_clus**, **TS[(8_clus)-(9_clus)]**, and **9_clus**, given in Figure 9, reveal several key points: (a) In **8_clus**, the Pd-I bond is still intact (Pd-I = 2.91 Å) and the F atom of CsF is weakly interacting with a terminal methyl hydrogen atom (F-H(Me) = 1.91 Å). Noteworthy, both Cs atoms are interacting with the halide atoms; the calculated F-Cs^1/F-Cs^2 and I-Cs^1/I-Cs^2 bond lengths are 2.83/2.85Å and 3.84/3.99Å, respectively. Thus, in **8_clus**, the Cs cations, and F and I anions are formed in a "Cs_2-I-F" cluster; (b) In **TS[(8_clus)-(9_clus)]** the F atom is not coordinated to the Pd center (Pd-F = 2.70 Å), and is weakly bound to Cs^1 (Cs^1-F = 3.13 Å). Furthermore, in **TS[(8_clus)-(9_clus)]** the iodide ligand is dissociating, as a part of the "Cs_2-I-F" cluster (presumably assisted by cesium cation), and the Cs_2-I-(F-H) (*i.e.* with the F-H bond) and Pd-C bonds (Pd-C = 2.42 Å) are forming, and (c) In product **9_clus,** the newly formed Cs_2-I-(F-H) fragment is hydrogen bonded to the nitrogen atom of the aryl amide ligand (F-H--N = 1.75 Å).

The C(sp^3)-Ph coupling in intermediate **7_clus** completes the reaction. The calculations showed that this process is a facile process only after the protonation of the N-center of directing group **DG′** group in **9_clus.** The source of protonation is likely to be H_2O from the reaction solution (Figure 10). Thus, the computations have revealed that Cs-F plays a dual role in this reaction, that is: (1) it facilitates deprotonation, subsequently, coordination of the substrate to Pd-center, and (2) it forms the *unprecedented "Cs_2-I-F" cluster* that involves in the C-H bond activation and significantly reduces the activation barrier of the terminal β-C(sp^3)-H bond of aryl amide. Based on these results the authors have predicted the *unprecedented "Cs_2-I-F cluster" assisted mechanism* for the Pd(0)/PCy_3-catalyzed *intermolecular* arylation of terminal β-C(sp^3)-H bond of aryl amide. To the best of our knowledge this is a first example reported in the literature,[239] on the "Cs-halide" cluster-mediated C-H bond activation.

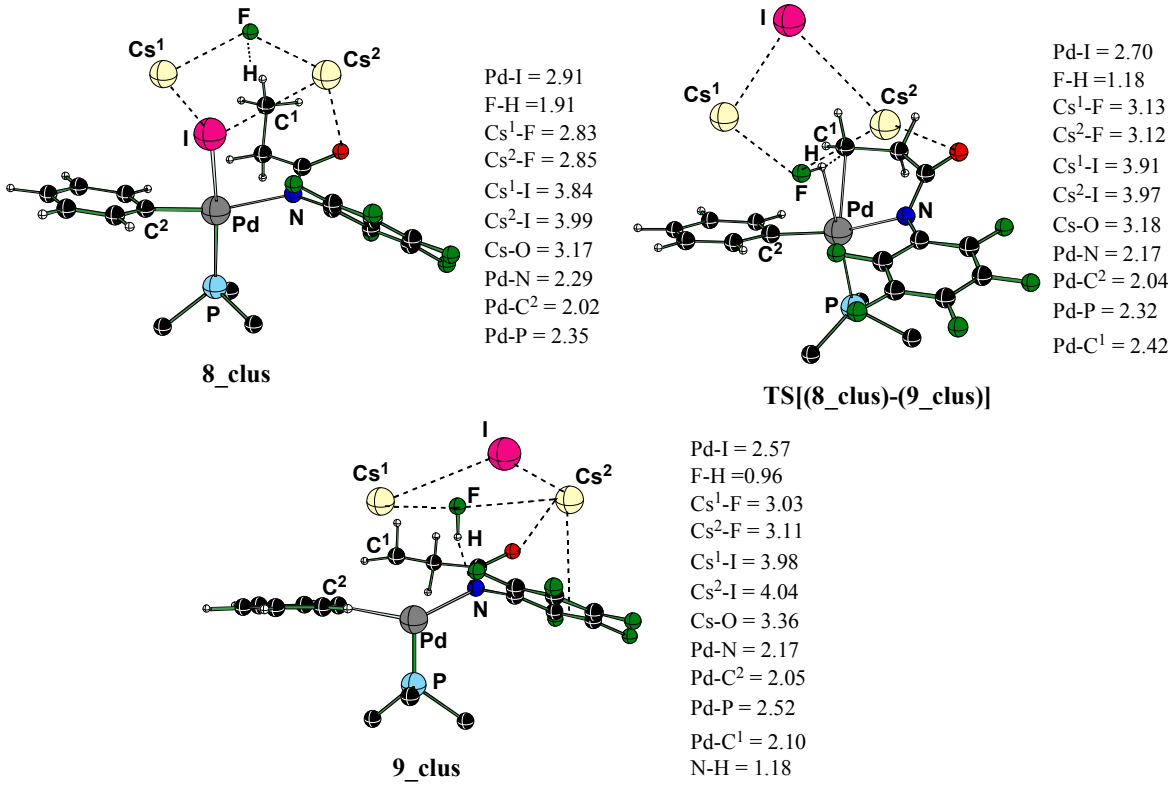


Figure 9. Optimized geometries of intermediates **8_clus**, **9_clus** and the "Cs_2-I-F cluster" assisted hydrogen atom abstraction transition state **TS[(8_clus)-(9_clus)]**. For clarity, PCy_3 ligands are presented as PC_3. Bond lengths are given in Å. Adapted with permission from reference [239].

Furthermore, close examination of geometry of the transition states **TS[(8_ox)-(9_ox)], TS[(8_I)-(9_I)], TS[(8_F)-(9_F)]** and **TS[(8_clus)-(9_clus)]** showed that upon C-H bond activation via the oxidative addition, "direct-I" assisted, "direct-F" assisted and "Cs_2-I-F cluster" assisted pathways the Pd-P bond elongates, but *does not dissociate*.

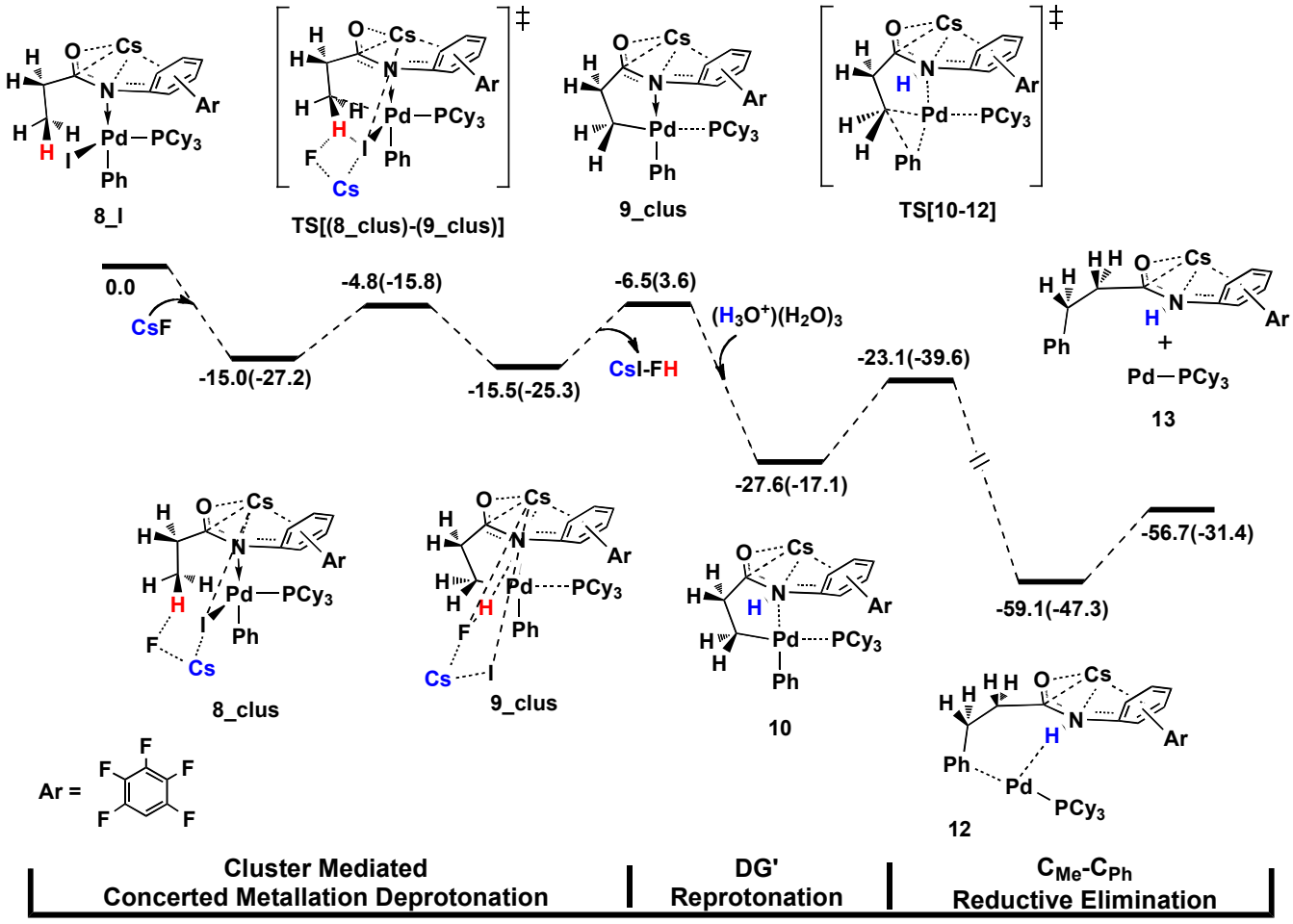


Figure 10. Proposed catalytic cycle for the arylation of methyl C(sp^3)-H bonds. Energetics, ΔG(ΔH), are with respect to **8_I** and are given in kcal/mol. Adapted with permission from reference [239].

V. Conclusions and Perspectives

Above we summarized the most widely used strategies and mechanistic details for the C-H bond functionalization reactions, as well as some of the complexities in the Pd-catalyzed chemical transformations, in general, and Pd-catalyzed C-H bond functionalization, in particular. We have demonstrated that, in the course of catalysis various Pd-containing intermediates with 0, +1, +2, +3 and +4 oxidation states of palladium, as well as nano-scale Pd-clusters could become active catalysts. However, both identification of these catalytically active species and determination of factors controlling the overall catalytic process require more comprehensive and multi-disciplinary approaches. The use of high-level computational methods is an invaluable part of these approaches.

Indeed, recent joint computational and experimental efforts made it possible to identify active species in several important Pd-catalyzed reactions, and to determine the mechanisms and controlling factors of these reactions:

1. It was demonstrated[190] that the addition of $Pd(OAc)_2$ as a catalyst precursor to RSeH and RSH reagents forms the $[Pd(SeR)_2]_n$ and $[Pd(SR)_2]_n$ clusters, respectively, which shows an unprecedented ability for selective synthesis of Markovnikov-type product starting with a mixture of reagents RSH/RSeH and acetylenic hydrocarbons. Importantly, two key-factors: i) selective capture of a reagent from the mixture, and ii) highly selective transformation of each reagent to vinyl monomer, were achieved within a single catalyst.
2. Musaev and coworkers, the first time in the literature, have predicted[202] the "N-H bond cleavage and subsequent C-H bond activation" mechanism for the [(chiral mono-*N*-protected amino acid)-Pd(II)]-catalyzed enantioselective C–H bond activation that proceeds via the formation of the catalytically active Pd(II) intermediate with a bidentately coordinated dianionic amino acid ligand. They have demonstrated[202] that the amino-acid ligand plays multiple roles in the [(chiral mono-*N*-protected amino acid)-Pd(II)]-catalyzed C–H bond activation by acting as: (i) a weakly coordinating ligand to stabilize the Pd(II)-precatalyst; (ii) a soft proton donor (from the N-terminal) and bidentately coordinated dianionic ligand to facilitate the formation of the catalytically active Pd(II) intermediate, and (iii) a proton acceptor from the arene C-H bond via the concerted metalation-deprotonation (CMD) mechanism. It is important to emphasize that the Pd-center, in the course of the reaction, acts as a coordinatively and electronically flexible metal center that holds the substrate and amino acid ligand in close vicinity to promote the chemical transformation. Later, this prediction of computation was experimentally confirmed by detailed kinetic studies.[225,226]
3. Computations revealed[239] a dual role of the CsF base in the Pd(0)/PCy_3-catalyzed *intermolecular* arylation of terminal β-C(sp^3)-H bond of aryl amide: (i) it facilitates deprotonation, subsequently, coordination of the substrate to the Pd-center, and (ii) it forms the *unprecedented "Cs_2-I-F" cluster* in catalysis mixture that significantly reduces the activation barrier in arylation of the terminal β-C(sp^3)-H bond of aryl amide. The *unprecedented "Cs_2-I-F cluster" assisted mechanism* for the Pd(0)/PCy_3-catalyzed *intermolecular* arylation of terminal β-C(sp^3)-H bond of aryl amide has been predicted. The role of CsF base in this reaction is attributed to "cesium effect" in organic synthesis that stems from: (a) better solubility of cesium bases and the generation of highly reactive "naked" anions, (b) large size of Cs, and (c) facile polarizability of Cs.[235-238]

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203. In the presented calculations the $RCOO^-$ molecule was modeled by $HCOO^-$. As a substrate we chose the 2-benzhydrylpyridine. Since benzoquinone (BQ) was previously shown to only improve the yield through promoting reductive elimination after the C-H activation step, and has no effect on enantioselectivity,[51,194] we focused on (aminoacid)-Pd(II)-SM complex, **I**. All calculations were performed using the Gaussian 09

program.[204] The geometries of all reported structures were optimized without any symmetry constraint at the B3LYP level of theory[205-207] in conjunction with Lanl2dz basis set and the corresponding Hay-Wadt effective core potential (ECP) for Pd and standard 6-31G(d,p) basis sets for all remaining atoms.[208-210,] Hessians for all structures, calculated at the B3LYP/[Lanl2dz + 6-31G(d,p)] level of theory, confirmed that all reported transition states have one imaginary frequency corresponding to the reaction coordinates, and all minima have no imaginary frequency. The dielectric effects from the surrounding environment were estimated using the self-consistent reaction field IEF-PCM method[211] at the B3LYP/[Lanl2dz + 6-31G(d,p)] level of theory. These corrections were made only for the most important structures. As in the experiments,[51,194] the THF was used as a solvent. Corrections to the gas phase free energies (ΔG_{gas}) due to solvent effects (ΔG_s) were estimated for the selected structures as single point IEF-PCM calculations done at the gas-phase optimized geometries: $\square G_{gas} + \square G_{solv}$.

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240. Calculations were carried out using the Gaussian 09 suite of programs.[204] Geometry of all reported reactants, intermediates, transition states and products were optimized without symmetry constraints at the M06-L level of density functional theory[241] in conjunction with the Lanl2dz basis set and corresponding Hay-Wadt effective core potential (ECP)[208-210] for Pd, I and Cs. Standard 6-31G(d,p) basis sets were used for all remaining atoms (below we call this approach as M06-L/{Lanl2dz+[6-31G(d,p)]} or M06-L/BS1). Structure and energy of the important $C(sp^3)$-H activation step for both substrate modifications for Ar = C_6H_5 and Ar = C_6F_5 were improved by using larger basis sets with diffuse functions on light atoms, Lanl2dz+[6-31++G(d,p)]. Several other density functionals such as M06, B3LYP and B3LYP+D were also validated. The nature of each stationary point was characterized by the presence of zero or one imaginary frequency for minima and transition states, respectively. Energetics were calculated under standard conditions (1 atm and 298.15 K) and are reported as relative free energies and enthalpies in kcal/mol with the notation of $\Delta G(\Delta H)$. Solvent effects were accounted for in an implicit fashion using the PCM[211] formalism in toluene (ε = 2.38) as in the experiments.[218]
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Versatile Reactivity of Pd-Catalysts: Mechanistic Features of the Mono-N-Protected Amino-Acid Ligand and Cesium-Halide Base in Pd-Catalyzed C-H Bond Functionalization

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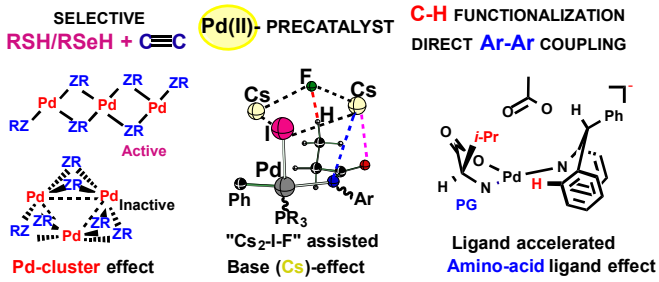
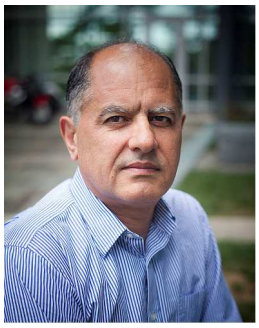


The C-H functionalization strategies, complexity in Pd-catalyzed chemical transformations, unprecedented Pd-clustering, base (Cs-halide) and weakly coordinated amino-acid ligand effects.



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