

The reaction mechanism of the Suzuki-Miyaura cross-coupling reaction. The role of the precatalyst activation

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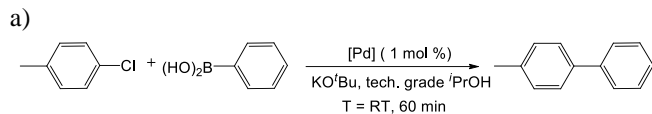
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ABSTRACT: Density functional theory calculations have been used to investigate the activation mechanism for the precatalyst series, **[Pd]-Cl-1-4**, derived from (IPr)Pd(R-allyl)X species by substitutions at the terminal position of the allyl moiety (**[Pd]** = IPr-Pd; R = H (**1**), Me (**2**), *gem*-Me₂ (**3**), Ph (**4**)). Next, we investigated the Suzuki-Miyaura cross-coupling reaction for the active catalyst species **IPr-Pd(0)** using 4-chlorotoluene and phenylboronic acid as the substrates, and isopropyl alcohol as the solvent. Our theoretical findings suggest that the upper barrier trend, corresponding to the activation mechanism for the **[Pd]-Cl-1-4** series, is predicted to be in good agreement with the experiments and indeed provides a quantitative explanation of the low yield (12%) displayed by **[Pd]-Cl-1** species (≈22.0 kcal/mol), while the similar yields (≈90%) observed in case of **[Pd]-Cl-2-4** complexes (≈18.0 kcal/mol). Additionally, the studied Suzuki-Miyaura reaction for **IPr-Pd(0)** species is predicted to be thermodynamically favorable and kinetically easy. Similar investigations for **[Pd]-Br-1-4** series, derived from (IPr)Pd(R-allyl)Br, indicate that **IPr-Pd(0)** mediated catalysis with 4-bromotoluene is kinetically more favorable than with 4-chlorotoluene. Finally, we explored the potential of Ni-based complexes ((IPr)Ni(R-allyl)X) (X = Cl, Br) as Suzuki-Miyaura reaction catalysts. Apart from a less endothermic reaction energy profile for both precatalyst activation and the catalytic cycle, a steep increase in the predicted upper energy barriers (13.0-15.0 kcal/mol) is calculated in the activation mechanism for the **[Ni]-X-1-4** series with respect to the **[Pd]-X-1-4** series. Overall, these results imply that Ni-based catalysts are less catalytically active than the Pd-based catalysts for the studied Suzuki-Miyaura reaction.

Transition-metal-catalyzed C-C Suzuki-Miyaura cross-coupling reactions are among the most useful processes in modern organic synthesis for their wide scope and selectivity under mild conditions.¹ In this context palladium is the most studied metal catalyst, to catalyze the formation of biaryl compounds found in natural products, as well as reagents, phases for chromatography and liquid crystals with chirality.² Among its characteristic qualities, palladium is able to manage perfectly both oxidation states, 0 and 2+, required for the Suzuki-Miyaura reaction, specially stable with just a ligand in its coordination sphere.^{3,4} In recent years, substantial research has been carried out on N-heterocyclic carbene (NHC) ligands,⁵ and the replacement of phosphine^{6,7} by NHC ligands has had notable success in the development of catalysts in the context of palladium chemistry.^{8,9} These two-electron donor ligands combine strong σ -donating properties with a bulky steric pattern which allow stabilization of the metal center and an increase of its catalytic activity. As a consequence, the number of well-defined NHC-bearing palladium(II) complexes is growing up and their use in coupling reactions is witnessing increasing interest. This family of palladium complexes exhibits high stability, allowing an indefinite storage and easy handling. The use of well-defined complexes allows a strict control of the [Pd]/ligand ratio (1:1), keeping away the use of excess of costly ligands. Furthermore, it partially removes the “black box” character often associated with cross coupling chemistry and NHC-[Pd] catalyst formation: a big amount of NHC-[Pd] protocols have been developed for their preparation but many are conducted using an inert atmosphere and often force to use a glove box, significantly limiting the broader application of these techniques.¹⁰

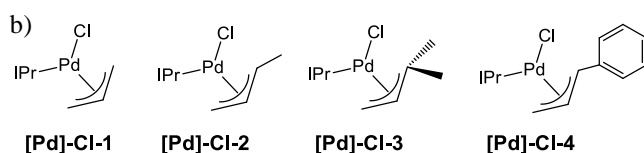
To this end, plenty of studies have been carried out toward the development of an idealized practical protocol which should be efficient at room temperature.¹¹ Complexes of type (NHC)-[Pd](R-allyl)Cl have shown to be really active in the Suzuki-Miyaura coupling reaction.¹² Their good activity results from the fact they offer facile access to the mono-ligated species.¹³ (NHC)-[Pd](R-allyl)Cl catalysts are isolable complexes for which there is a good control over the [Pd]:ligand ratio (1:1). Additionally, these complexes can be synthesized without glove box and after their preparation they are indefinitely air and moisture stable. In 2002, Nolan and co-workers studied the catalytic performance of a precatalyst series **[Pd]-Cl-1-4** (see Scheme 1a), derived from (IPr)Pd(R-allyl)X by substitutions at the terminal position of the allyl moiety (**[Pd]** = IPr-Pd; R = H (**1**), Me (**2**), *gem*-Me₂ (**3**), Ph (**4**)), for Suzuki-Miyaura cross-coupling reaction of 4-chlorotoluene and phenylboronic acid using isopropyl alcohol as solvent at room temperature.¹⁴ They demonstrated that substitution at the terminal position of allyl scaffold results in more facile precatalyst activation, which is then translated into a high catalytic activity. The catalyst preactivation can occur through two possible reaction pathways (see Scheme 2). First, mechanism **A**, which consists of a nucleophilic intermolecular attack of the tert-butoxide (O^tBu) to generate in a single step the precatalyst, KCl and allyl(O^tBu). Second, a two step mechanism with an initial Cl⁻ by O^tBu⁻ substitution, followed by the nucleophilic intramolecular attack of the O^tBu group to the allyl moiety to yield the precatalyst and the allyl(O^tBu) species (mechanism **B**). We believe that understanding the details of the precatalyst activation mechanism proposed by Nolan et al. and the deeper knowledge of the whole

Suzuki-Miyaura reaction mechanism could help the future development of this important reaction.^{15,16}

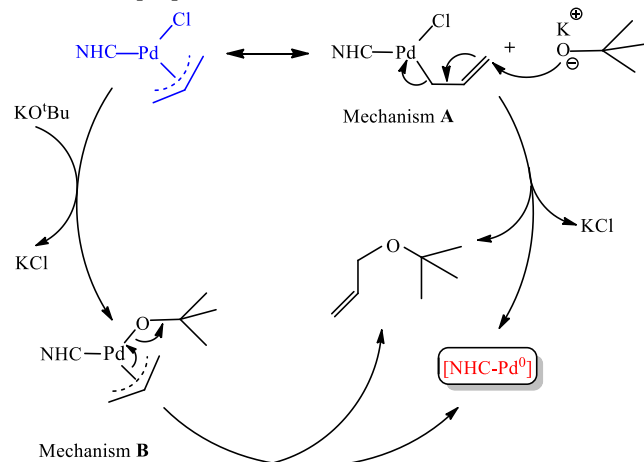


ref ^a	[[Pd]]	Yield (%) ^b
[Pd]-Cl-1	(IPr)[Pd](allyl)Cl	12
[Pd]-Cl-2	(IPr)[Pd](crotyl)Cl	86
[Pd]-Cl-3	(IPr)[Pd](prenyl)Cl	90
[Pd]-Cl-4	(IPr)[Pd](cinnamyl)Cl	90

^a ref is the label used to define each precatalyst in the [Pd]-Cl-1-4 series considered for the present study (IPr is the NHC ligand N,N'-bis-[2,6-(di-iso-propyl)phenyl]imidazol-2-ylidene). ^b Data from ref. 17b.



Scheme 1. a) Effect of substitution at the terminal position of allyl moiety on performance of precatalyst series, [Pd]-Cl-1-4, in the Suzuki-Miyaura cross-coupling reaction with 4-chlorotoluene and phenylboronic acid as the substrates using isopropyl alcohol (ⁱPrOH) solvent, KO^tBu = potassium tert-butoxide; b) chemical structures of [Pd]-Cl-1-4 series.



Scheme 2. The two proposed precatalyst activation mechanisms (A and B) for the considered precatalyst series [Pd]-Cl-1-4.

To sum up, in this current study, we use density functional theory (DFT) calculations to investigate in detail the activation pathway in Scheme 2 for the [Pd]-Cl-1-4 series,¹⁷ followed by a complete description of the Suzuki-Miyaura reaction in Scheme 1a for catalytically active IPr-Pd(0) species. Additionally, to understand the effect of the halogen substituent, we extended the same investigations to [Pd]-Br-1-4 series, derived from (IPr)Pd(R-allyl)Br. Finally, we have explored the role of metal by further extending the similar investigations to Ni-based precatalyst series, [Ni]-X-1-4, derived from (IPr)Ni(R-allyl)X (X=Cl, Br).

Computational Details

All the DFT static calculations have been performed at the GGA level with the Gaussian09 set of programs,¹⁸ using the BP86 functional of Becke and Perdew.¹⁹ The electronic configuration of the molecular systems was described with the standard split-valence basis set with a polarization function of Ahlrichs and co-workers for H, C, B, N, O, Cl, and Br (SVP keyword in Gaussian).²⁰ For Pd and Ni we used the quasi-relativistic Stuttgart/Dresden effective core potential, with an associated valence basis set (standard SDD keywords in Gaussian09).²¹ The geometry optimizations were carried out without symmetry constraints, and the characterization of the located stationary points was performed by analytical frequency calculations. These frequencies were used to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropy effects at 298 K and 1 atm by using the standard statistical-mechanics relationships for an ideal gas. Energies were obtained via single point calculations on the BP86 optimized geometries with triple zeta valence plus polarization (TZVP keyword in Gaussian) using the M06 functional.²² In these single point energy calculations, H, C, B, N, O, Cl, and Br were described using the Def2-TZVP basis set that includes polarization and diffuse functions,²³ while for the metals (Pd, Ni) the SDD basis set has been employed. On top of the M06/Def2-TZVP/BP86/SVP energies we added the ZPEs, thermal corrections obtained at the BP86/SVP level. In addition, to calculate the reported Gibbs energies we included solvent effects of a ⁱPrOH solution estimated with the polarizable continuous solvation model PCM implemented in Gaussian09.²⁴

Results and Discussion

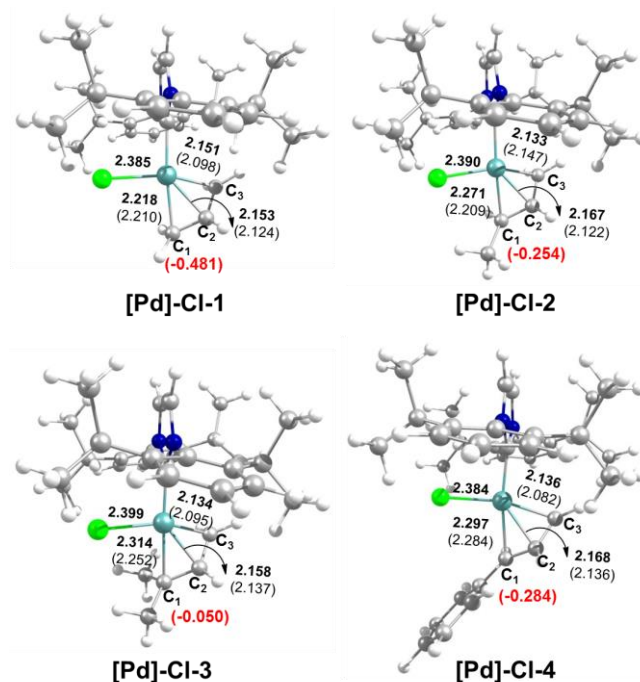


Figure 1. DFT optimized geometries for the [Pd]-Cl-1-4 series along with the key Pd-C distances given in Å, and the corresponding experimental values are given in brackets. NPA charges (e^-) of C1 atom are given in red color.

Geometry optimization of the precatalyst series [Pd]-Cl-1-4 and analysis: The DFT optimized geometries of precatalyst series [Pd]-Cl-1-4 are given in Figure 1. Figure 1 shows some key geometrical parameters, along with the available experimental data, and natural population analysis (NPA) charges for [Pd]-Cl-1-4 series. Overall, the analysis of the computed selected Pd-C distances suggests that the resulting steric hindrance upon the allyl scaffold modification has a non-negligible effect on the ligand bond to the Pd metal center. Going into the details, in agreement with the experiments, Pd-C₃ distances remain fairly constant, while Pd-C₁ distances elongate after the substitution on C₁ of the allyl moiety; with the exception of [Pd]-Cl-4 where the Pd-C₁ distance is slightly lower than [Pd]-Cl-3 (2.297 Å vs. 2.314 Å, respectively). These geometrical differences have significant effect on the Pd-C₁ and Pd-C₃ asymmetry by increasing the difference between Pd-C₁ and Pd-C₃ bond distances in the following trend: [Pd]-Cl-1 < [Pd]-Cl-2 < [Pd]-Cl-3 ≈ [Pd]-Cl-4. Additionally, the Mayer Bond Order (MBO) values^{25,26} (0.577, 0.496, 0.436, and 0.441, respectively) confirm the expected decrease of the Pd-C₁ bond strength in accordance with the computed [Pd]-C₁ bond distances. Finally, NPA charges show that the negative charge on C₁ decreases from [Pd]-Cl-1 to [Pd]-Cl-3, facilitating the nucleophilic attack of the tert-butoxide (O^tBu) in the second step of the reaction that generates the active catalyst.

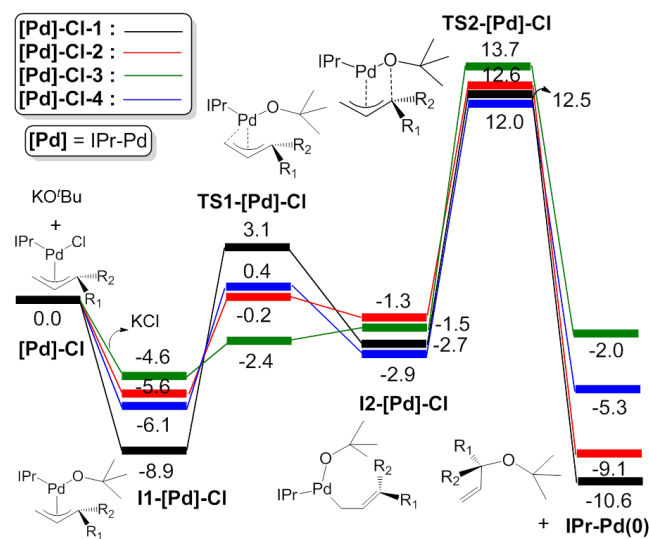


Figure 2. Computed stationary points for the activation mechanism for the studied precatalyst [Pd]-Cl-1-4 series. Gibbs energies are given in kcal/mol.

Precatalyst activation mechanism for the [Pd]-Cl-1-4 series: Figure 2 shows the most stable species and their free energy corresponding to the activation mechanism for the considered [Pd]-Cl-1-4 series. The one-step reaction mechanism (A in Scheme 2) was discarded due to the lack of a concerted transition state for the process. For the two-step reaction mechanism (B in Scheme 2), the reaction starts from the precatalyst species [Pd]-Cl. Substitution of Cl in [Pd]-Cl by a molecule of KO^tBu leads to the formation of intermediate I1-[Pd]-Cl and KCl as the byproduct. This substitution reaction is predicted to be spontaneous for the [Pd]-Cl-1-4 series and the overall thermodynamic stability of I1-[Pd]-Cl intermediates follows the order I1-[Pd]-Cl-3 (4.6 kcal/mol) < I1-[Pd]-Cl-2 (5.6 kcal/mol) < I1-[Pd]-Cl-4 (6.1 kcal/mol) < I1-[Pd]-Cl-1 (8.9 kcal/mol). The exothermic reaction profile can be explained by the fact that the O^tBu⁻ is a better nu-

cleophile than the Cl⁻. Additionally, the presented stability trend for the [Pd]-Cl-1-4 series clearly indicates that the simple modification on the allyl scaffold has a significant effect on the stability of I1-[Pd]-Cl intermediates relative to [Pd]-Cl. For instance, more electron donating R₁ and R₂ substituents destabilize the intermediate I1-[Pd]-Cl. Therefore, intermediate I1-[Pd]-Cl-3 (with two methyl substituents on ¹C) is the less stable, and thus more reactive, than the I1-[Pd]-Cl-2 (with one methyl group), followed by I1-[Pd]-Cl-4 (with a benzyl group) and the more stable I1-[Pd]-Cl-1 (with H atoms). The next step corresponds to the structural rearrangement of allyl scaffold in I1-[Pd]-Cl intermediates leading to the formation of less stable I2-[Pd]-Cl intermediates. The order of thermodynamic stability of I2-[Pd]-Cl from the starting reactants is the following: I2-[Pd]-Cl-2 (-1.3 kcal/mol) < I2-[Pd]-Cl-3 (-1.5 kcal/mol) < I2-[Pd]-Cl-1 (-2.7 kcal/mol) < I2-[Pd]-Cl-4 (-2.9 kcal/mol), thus no trend is observed from these slight energy differences. On the other hand the predicted barrier for this step (TS1-[Pd]-Cl) spans from 2.2 to 12.0 kcal/mol above I1-[Pd]-Cl, with the lowest barrier for [Pd]-Cl-3, while a highest barrier for [Pd]-Cl-1. Not unexpectedly the more stable the I1-[Pd]-Cl intermediate, the higher the barrier for the transformation to the I2-[Pd]-Cl intermediate. A point worth mentioning here that intermediate I2-[Pd]-Cl-3 is 0.9 kcal/mol less stable than its barrier TS1-[Pd]-Cl-3, which indeed reinforces the idea that this step for system [Pd]-Cl-3 is very facile. The final step corresponds to the formation of active catalyst species IPr-Pd(0) by reductive elimination process, through the transition state TS2-[Pd]-Cl. This step is predicted to be the rate determining step of the activation mechanism for the studied precatalyst [Pd]-Cl-1-4 series. Interestingly, the computed barrier TS2-[Pd]-Cl for this step ranges only 1.3 kcal/mol being about 15.0 kcal/mol above I2-[Pd]-Cl, suggesting that the formation of [Pd](0)-Cl species is equally favorable for all the precatalysts in [Pd]-Cl-1-4 series. However, the overall barrier calculated from the most stable intermediate I1-[Pd]-Cl (rate determining intermediate)²⁷ to the highest transition state TS2-[Pd]-Cl (rate determining transition state) for the [Pd]-Cl-1-4 series follows the order [Pd]-Cl-1 (21.4 kcal/mol) > [Pd]-Cl-2 (18.2 kcal/mol) ≈ [Pd]-Cl-3 (18.3 kcal/mol) ≈ [Pd]-Cl-4 (18.1 kcal/mol). This predicted overall barrier trend is in good agreement with the experiments and indeed provides a quantitative explanation of the low yield (12%) displayed by species [Pd]-Cl-1, while the similar yields (≈90%) observed in case of species [Pd]-Cl-2-4.

Suzuki-Miyaura cross-coupling reaction mechanism for IPr-Pd(0) species:

Having completed the description of the mechanism of the activation pathway for the [Pd]-Cl-1-4 series, we here investigate the whole reaction mechanism for IPr-Pd(0) mediated Suzuki-Miyaura reaction shown in Scheme 1a. Figure 3 presents the most stable intermediates and their Gibbs energy for the studied reaction mechanism. On a general note, the reaction mechanism involves a catalytic cycle containing three main steps: oxidative addition, transmetalation and reductive elimination. Going into details, the reaction starts with the coordination of 4-chlorotoluene to Pd metal in IPr-Pd(0), giving intermediate [Pd]-Cl-II, which lies 7.4 kcal/mol below the starting reactants. The next step corresponds to the oxidative addition of C-Cl bond of toluene to Pd metal in [Pd]-Cl-II leads to the formation more stable intermediate [Pd]-Cl-I2, lying 37.7 kcal/mol below [Pd]-Cl-II. This step is predicted to be the rate determining step and proceeds via a three center transition state, [Pd]-Cl-TS1, with an energy barrier of 15.5 kcal/mol above [Pd]-Cl-I2. Then, the coordination of organoborate species via O atom of -OH group to [Pd]-Cl-I2 leads to unstable adduct [Pd]-Cl-I3, which lies 3.8

kcal/mol above **[Pd]-Cl-I2**. Maseras et al. also found that the oxidative addition was the rate determining step in their study of the Suzuki-Miyaura cross-coupling reaction mechanism.¹⁵ This step is followed by the release of Cl atom and the subsequent rearrangement of organoborate species at the metal center leading to intermediate **[Pd]-Cl-I4**. From an energy point of view, **[Pd]-Cl-I4** is 6.6 kcal/mol more stable than the separated **[Pd]-Cl-I2** and organoborate species, and requires overcoming a barrier (**[Pd]-Cl-TS2**) of 11.6 kcal/mol. From **[Pd]-Cl-I4**, the phenyl migration from boron to [Pd] metal occurs via concerted bond cleavage of the C(Ph)-B bond and the formation of the [Pd]-C(Ph) bond, giving intermediate **[Pd]-Cl-I5**, and from which the subsequent release of B(OH)₃ leads to the formation of more stable intermediate **[Pd]-Cl-I6**. This step proceeds through transition state **[Pd]-Cl-TS3** and requires overcoming a barrier of 12.2 kcal/mol above **[Pd]-Cl-I4**.

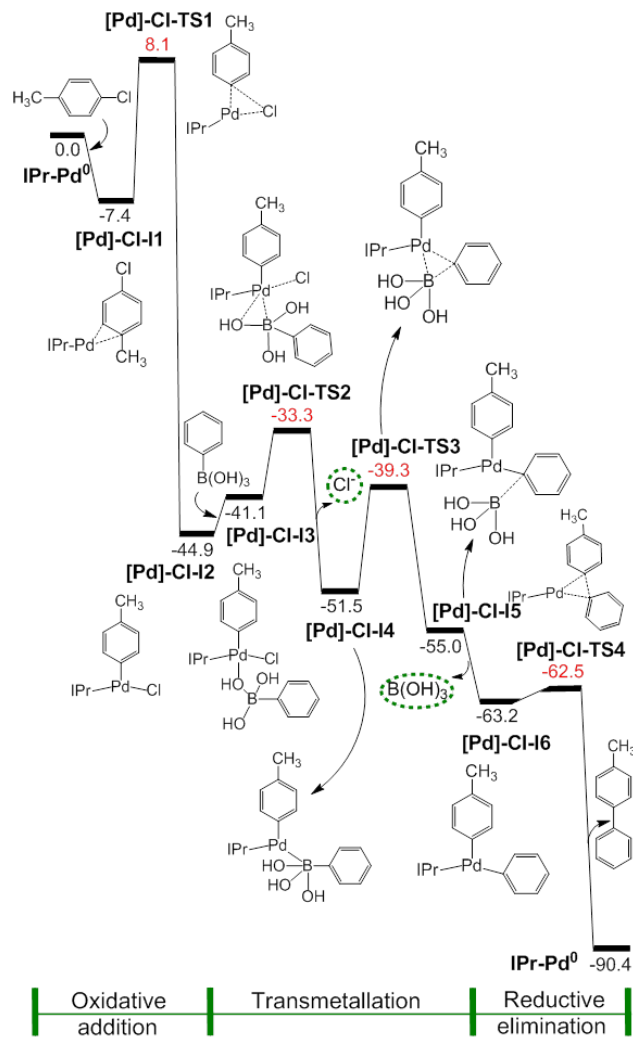


Figure 3. Computed stationary points for the Suzuki-Miyaura cross-coupling reaction pathway for active catalyst **IPr-Pd(0)** species with 4-chlorotoluene and phenylboronic acid as the substrates (Gibbs energies are in kcal/mol).

Overall, the transmetalation process for **IPr-Pd(0)** species is quite smooth, being exothermic by 18.3 kcal/mol with respect to the separated boronic acid and **[Pd]-Cl-I2** reactants. The final step

corresponds to the formation of the C(Ph)-C(Ph) bond by reductive elimination from **[Pd]-Cl-I6**, through transition state **[Pd]-Cl-TS4**. This is a rather low energy step, with a barrier of only 0.7 kcal/mol, that would release the desired biphenyl product, regenerating the catalyst **IPr-Pd(0)** with an energy gain of 27.2 kcal/mol. To summarize, our theoretical findings suggest that the studied Suzuki-Miyaura reaction mechanism for catalyst species **IPr-Pd(0)** is thermodynamically favorable and kinetically easy with the highest barrier of 15.5 kcal/mol, which is quite reasonable considering the fact that the reaction is carried out experimentally at room temperature for 60 min.

Precatalyst activation and Suzuki-Miyaura reaction mechanism for [Pd]-Br-1-4 series: In this section, we investigated the effect of halogen atom, by substituting Cl for Br at the Pd metal center, on the precatalyst activation followed by Suzuki-Miyaura reaction mechanism using 4-bromotoluene substrate. To this end, we considered the precatalyst series **[Pd]-Br-1-4** derived from (IPr)Pd(R-allyl)Br.

A point worth mentioning here about the activation mechanism is that after the substitution of Br by *O*Bu ligand, the energy profile for the **[Pd]-Br-1-4** series coincides with the energy profile for **[Pd]-Cl-1-4** series in Figure 2. Thus, we limit our discussion here to only the first step of the activation mechanism and the corresponding energetics. In the case of **[Pd]-Br-1-4** series, **I1-[Pd]-Br** intermediates (stabilization energies are -7.1, -5.4, -3.7, and -3.5 for **[Pd]-Br-1** to **[Pd]-Br-4**, respectively) are slightly less stable (by 1-2 kcal/mol) when compared with the respective **I1-[Pd]-Cl** intermediates of Figure 2. This observation indicates that the substitution of halogen by a *KO*^tBu might be faster for **[Pd]-Br** system than the **[Pd]-I**, due to the fact that bromide is a better leaving group than chloride.

Next, the calculated reaction energy profile for **IPr-Pd(0)** mediated catalytic cycle with 4-bromotoluene substrate is shown in Figure 4. Similar to the activation mechanism, for the presented catalytic cycle in Figure 4, the steps after the Br⁻ ion dissociation (i.e., intermediate **Pd-Br-I4** and onwards) are identical to that of Figure 3. The main results can be summarized as follows: (i) with respect to separated reactants, intermediate **Pd-Br-I1** is 1.6 kcal/mol less stabilized than **Pd-Cl-I1** of Figure 2; (ii) the barrier for the oxidative addition step (**[Pd]-Br-TS1**) is predicted to be roughly ≈7.0 kcal/mol lower in energy relative to barrier **[Pd]-Cl-TS1** of Figure 3. The easier oxidative addition with 4-bromotoluene can be explained by taking into account that the C-Br bond strength (66.0 kcal/mol), which is 14.8 kcal/mol lower than that of the C-Cl bond strength (80.8 kcal/mol)²⁸; (iii) the transmetalation step (**[Pd]-Br-I4**→**[Pd]-Br-I5**) is predicted to be the rate determining step, requires overcoming a barrier (**[Pd]-Br-TS3**) of 13.2 kcal/mol. Taken together, these observations suggest that the studied Suzuki-Miyaura reaction for **IPr-Pd(0)** species might be slightly faster with 4-bromotoluene than with 4-chlorotoluene, owing to the fact that the predicted barrier for the rate determining transmetalation step for the former is 2.3 kcal/mol lower in energy relative to the rate determining oxidative addition step for the latter species, i.e., **[Pd]-Br-TS3** (13.2 kcal/mol) vs. **[Pd]-Cl-TS1** (15.5 kcal/mol), respectively.

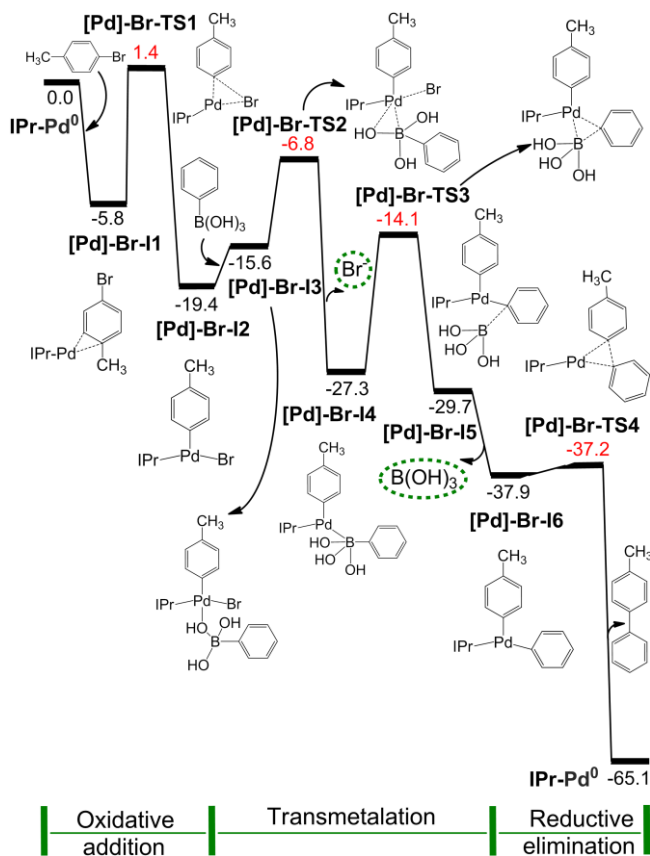


Figure 4. Computed stationary points for the Suzuki-Miyaura cross-coupling reaction pathway for active catalyst **IPr-Pd(0)** species with 4-bromotoluene and phenylboronic acid as the substrates (Gibbs energies are in kcal/mol).

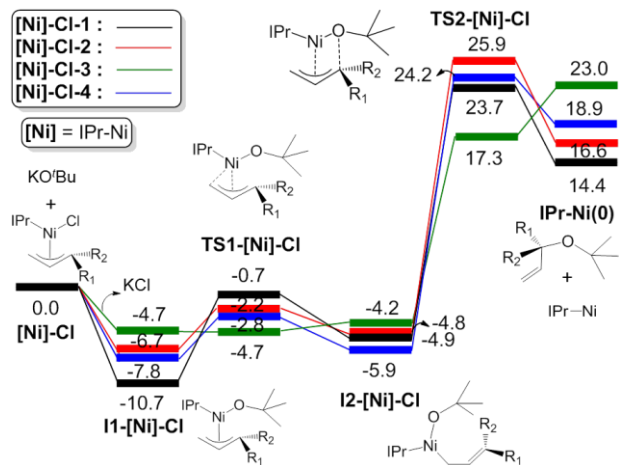


Figure 5. Computed stationary points for the activation mechanism of the studied precatalyst series **[Ni]-Cl-1-4**. Gibbs energies are given in kcal/mol.

Precatalyst activation and cross-coupling reaction mechanism for [Ni]-Cl-1-4 series: Finally, to understand the effect of metal substitution on the studied Suzuki-Miyaura reaction, we here investigated the activation mechanism for nickel precatalyst **[Ni]-Cl-1-4** series, derived from **(IPr)Ni(R-allyl)Cl**, as well as the reaction mechanism for **IPr-Ni(0)** species. The corre-

sponding energy profiles are given in Figure 5 and Figure 6, respectively. Focusing on the activation mechanism, direct comparison of Figures 5 and 2 suggests that **II-[Ni]-Cl** intermediates for the **[Ni]-Cl-1-4** series are either isoenergetic or slightly more stable (by 1-2 kcal/mol) when compared with the respective **II-[Pd]-Cl** intermediates of Figure 2. The thermodynamic stability of **II-[Ni]-Cl** intermediates for **[Ni]-Cl-1-4** series follows the same order as the **[Pd]-Cl-1-4** and **[Pd]-Br-1-4** series, i.e., **II-[Ni]-Cl-3** (-4.7 kcal/mol) < **II-[Ni]-Cl-2** (-6.7 kcal/mol) < **II-[Ni]-Cl-4** (-7.8 kcal/mol) < **II-[Ni]-Cl-1** (-10.7 kcal/mol). Next, the first barrier **TS1-[Ni]-Cl** spans from 0.0–10.0 kcal/mol, with no barrier for **[Ni]-Cl-3**, while a highest barrier of 10.0 kcal/mol for **[Ni]-Cl-1**. This barrier trend for the **[Ni]-Cl-1-4** series is similar to that of **Pd-Cl-1-4** series. However, the barriers for the rate determining reductive elimination step **TS2-[Ni]-Cl**, which generates the active catalyst species **Ni(0)-Cl**, are predicted to be higher in energy (7.0–16.0 kcal/mol) relative to the **TS2-[Pd]-Cl** barrier of Figure 2. Furthermore, for the **[Ni]-Cl-1-4** series, the overall barrier from the most stable intermediate **II-[Ni]-Cl** is predicted to be much higher in energy (13.0–15.0 kcal/mol) than the overall barrier for the **[Pd]-Cl-1-4** series. Finally, the activation mechanism for **[Ni]-Cl-1-4** series is endothermic and in particular, the catalytically active **IPr-Ni(0)** species for **[Ni]-Cl-3** is predicted to be quite endothermic (5.7 kcal/mol above **TS2-[Ni]-Cl-3**), suggesting that the activation mechanism is not favorable for **[Ni]-Cl-3**. Taken together, these observations suggest that the precatalyst activation mechanism for the studied **[Ni]-Cl-1-4** series is energetically more demanding and kinetically more challenging than the activation mechanism for the **[Pd]-Cl-1-4** series. A possible explanation can be given by the fact that the energy of stabilization for Ni to go from **M(II)→M(0)**, which is the negative of the sum of the first and second ionization potential of M, is -595 kcal/mol, while for Pd this value is -640.4 kcal/mol, suggesting that Pd can undergo reduction process much easier than the Ni and thus the predicted barrier for the reductive elimination is lower in the former than the latter.

Focusing on the catalytic cycle in Figure 6, it is evident that the overall reaction energy profile for **IPr-Ni(0)** catalyzed Suzuki-Miyaura reaction is less exothermic in nature when compared with the energy profile for **IPr-Pd(0)** in Figure 3. The main results can be summarized as follows: (i) in the case of **IPr-Ni(0)**, the substrate 4-chlorotoluene bound intermediate **[Ni]-Cl-11** is thermodynamically more stable than the corresponding intermediates **[Pd]-Cl-11** of Figure 3 (11.1 kcal/mol vs. 7.4 kcal/mol, respectively). This extra stability might be due to the η^6 -coordination of the phenyl ring of 4-chlorotoluene to Ni center in **[Ni]-Cl-11** complex, while **[Pd]-Cl-11** intermediate displays an η^2 -coordination; (ii) the oxidative addition step barrier **[Ni]-Cl-TS1** is predicted to be 10.5 kcal/mol lower in energy in comparison to the barrier **[Ni]-Cl-TS1** of Figure 3 (5.0 kcal/mol vs. 15.5 kcal/mol, respectively); (iii) the rate determining step (**[Ni]-Cl-12→[Ni]-Cl-14**), which corresponds to addition of phenylboronic acid during the transmetalation process, requires a barrier of 8.2 kcal/mol. This barrier **[Ni]-Cl-TS2** is predicted to be 2.3 kcal/mol lower in energy than that of the rate determining oxidative addition step through **[Pd]-Cl-TS1** of Figure 3. Taken together, these observations suggest that the nature of metal plays an important role, and that Ni based catalysts are catalytically less efficient than the Pd-based catalysts for the studied Suzuki-Miyaura reaction due to the presented significantly high barrier for the activation mechanism for the **[Ni]-Cl-1-4** series.

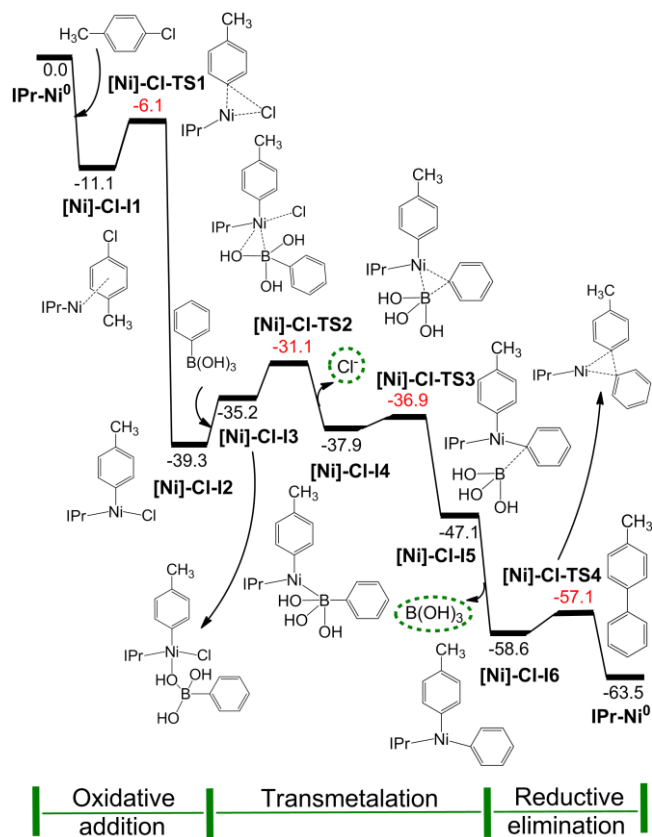


Figure 6. Computed stationary points for the Suzuki-Miyaura cross-coupling reaction pathway for active catalyst **IPr-Ni(0)** species with 4-chlorotoluene and phenylboronic acid as the substrates (energies are in kcal/mol).

Finally, for the sake of comparison, we studied the precatalyst activation for the **[Ni]-Br-1-4** series and Suzuki-Miyaura reaction mechanism for **IPr-Ni(0)** with 4-bromotoluene and phenylboronic acid (see Figure S1 and S2, respectively, in the Supporting Information). Overall, the corresponding energy profiles for **[Ni]-Br-1-4** series are similar to that of **[Ni]-Cl-1-4** series both from a thermodynamic and kinetic perspective.

Conclusions

In summary, using DFT calculations we have reported the precatalyst activation mechanism for the precatalyst series, **[Pd]-Cl-1-4**, derived from **(IPr)Pd(R-allyl)Cl**, followed by the complete description of Suzuki-Miyaura reaction for catalytically active **IPr-Pd(0)** species using 4-chlorobutane and phenylboronic acid as the substrates and isopropyl alcohol as the solvent. Our theoretical results suggest that the upper barrier trend, corresponding to the activation mechanism for the studied **[Pd]-Cl-1-4** series, is predicted to be in good agreement with the experiments, i.e., **[Pd]-Cl-1** being catalytically less active with an upper barrier of ≈ 22.0 kcal/mol, while **[Pd]-Cl-2-4** are equally efficient with an upper barrier of ≈ 18.0 kcal/mol. Additionally, we extended the similar investigations to **[Pd]-Br-1-4** series derived from **(IPr)Pd(R-allyl)Br** species. The main observations are the following: (i) in the activation mechanism, the halogen substitution by *O*Bu ligand is more favorable for the **[Pd]-Br-1-4** series than the **[Pd]-Cl-1-4** series, owing to the fact that bromide is a better leaving group than chloride; (ii) **IPr-Pd(0)** mediated Suzuki-Miyaura reaction

with 4-bromotoluene is kinetically favorable when compared to the reaction with 4-chlorotoluene since the barrier for rate determining transmetalation step with former substrate is 2.3 kcal/mol lower in energy relative to the barrier for rate determining oxidative addition step with the latter substrate, i.e., **[Pd]-Br-TS3** (13.2 kcal/mol) vs. **[Pd]-Cl-TS1** (15.5 kcal/mol), respectively. Finally, for the studied Suzuki-Miyaura reaction, our results indicate that Ni based catalysts **[(IPr)Ni(R-allyl)X]**; X = Cl, Br) are catalytically less active when compared with Pd-based catalysts due to predicted significantly high energy upper barrier (13.0-15.0 kcal/mol higher in energy than the Pd-catalysts) for the activation of precatalyst series **[Ni]-X-1-4** and less exothermic reaction energy profile for **IPr-Ni(0)** mediated catalytic cycle.

ASSOCIATED CONTENT

Suzuki-Miyaura reaction mechanism for **IPr-Ni(0)** species using 4-bromotoluene, cartesian coordinates and absolute energies of all computed species. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

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