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Palladium Catalysis

Is Pd^{II}-Promoted σ-Bond Metathesis Mechanism Operative for the Pd–PEPPSI Complex-Catalyzed Amination of Chlorobenzene with Aniline? Experiment and Theory

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Abstract: Reduction of the Pd–PEPPSI precatalyst to a Pd^0 species is generally thought to be essential to drive Buchwald–Hartwig amination reactions through the well-documented Pd^0/Pd^{II} catalytic cycle and little attention has been paid to other possible mechanisms. Considered here is the Pd–PEPPSI-catalyzed aryl amination of chlorobenzene with aniline. A neat reaction system was used in new experiments, from which the potentially reductive roles of the solvent and labile ligand of the PEPPSI complex in leading to Pd^0 species are ruled out. Computational results demonstrate that anilido-containing Pd^{II} intermediates involving σ-bond metathesis in pathways leading to the diphenylamine product have relatively low barriers. Such pathways are more favorable energetically than the corresponding reductive elimination reactions resulting in Pd^0 species and other putative routes, such as the Pd^{II}/Pd^{IV} mechanism, single electron transfer mechanism, and halide atom transfer mechanism. In some special cases, if reactants/additives are inadequate to reduce a Pd^{II} precatalyst, a Pd^{II}-involved σ-bond metathesis mechanism might be feasible to drive the Buchwald–Hartwig amination reactions.

Introduction

Palladium-catalyzed Buchwald–Hartwig (BH) amination reactions are among the most powerful synthetic methods for the construction of C–N bonds and have been widely employed in both academic research and modern chemical industry.[1] Phosphine-containing Pd catalysts have been extensively studied and optimized to mediate BH amination reactions.[2] However, phosphine-based ligands are toxic, expensive, and air-sensitive. Therefore, development of phosphine-free Pd catalysts would be highly desirable. Over the last two decades, N-heterocyclic carbene (NHC) ligands have attracted tremendous interest because they are more than mimics of phosphine ligands.[3] The unique electronic properties and versatile steric bulk of effective NHC ligands render improved performance in many Pd-catalyzed cross-coupling reactions.[4] In addition, NHC–Pd^{II} complexes are usually stable with respect to air and moisture and relatively easy to synthesize.[4b,d] More attractively, structures of NHC–Pd^{II} complexes are well-defined,[4b–e] a characteristic particularly appealing for mechanistic studies.

The first well-defined NHC–Pd^{II} complexes for catalyzing the BH amination reaction was reported by Nolan and co-workers in 2002 (**1a**, Figure 1).[5] Subsequently, Nolan and co-workers synthesized many other NHC-containing Pd^{II} complexes, such as [NHC–Pd-cycle] (**1b**),[6] [NHC–Pd(acac)Cl] (**1c**),[7] [NHC–Pd(allyl)Cl] (**1d**),[8] and [NHC–Pd(cinnamyl)Cl] (**1e**),[9] all of which are capable of driving BH amination reactions. In 2006, Organ and co-workers developed the Pd–PEPPSI catalyst (PEPPSI is the abbreviation for pyridine-enhanced precatalyst preparation stabilization and initiation).[10] The Pd–PEPPSI catalyst **1f**, for example, is also able to catalyze BH amination reactions.[11a] Subsequently, many other Pd–PEPPSI-like complexes have been reported.[11] Both modification of the NHC moiety and replacement of 3-chloropyridine by other ligands have attracted great interest in order to obtain better catalytic performance.[11]

The commonly proposed reaction mechanism for the NHC–Pd^{II} catalyzed amination reaction[4c,e] is through a Pd^0/Pd^{II} catalytic cycle (Scheme 1). In order to enter the catalytic cycle, a Pd^{II} complex, which is denoted a "precatalyst", is supposed to undergo reduction and ligand dissociation steps to afford the L$_n$-Pd^0 species first. Subsequently, the aryl halide undergoes an oxidative addition (OA) reaction at the activated Pd^0 site to yield a Pd-aryl intermediate (structure **I** in Scheme 1). Next, an amine-Pd-aryl complex (**II**) can be generated via coordination of the amine. Then, deprotonation of the coordinated amine is followed with the assistance of base to yield an aryl-Pd-amido intermediate (**III**). Finally, a reductive elimination (RE) reaction of **III** occurs to afford the cross-coupling product, and the Pd^0 catalyst is regenerated. Computational studies have been

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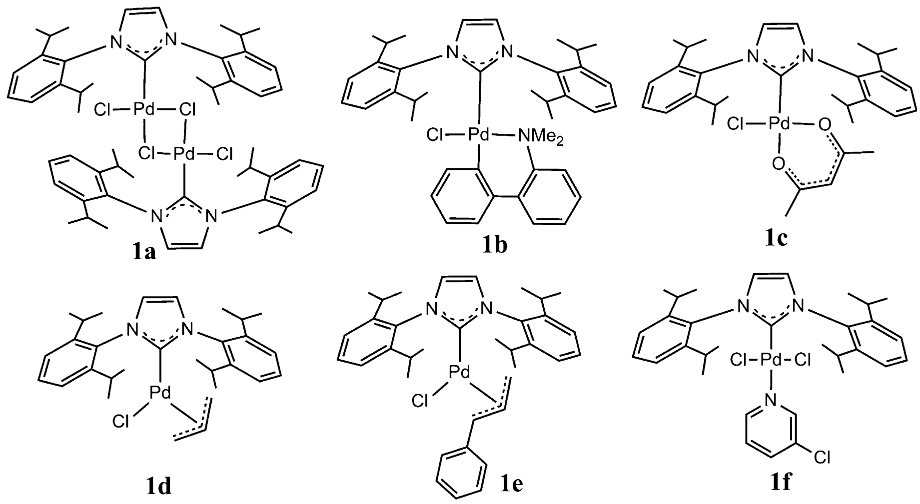
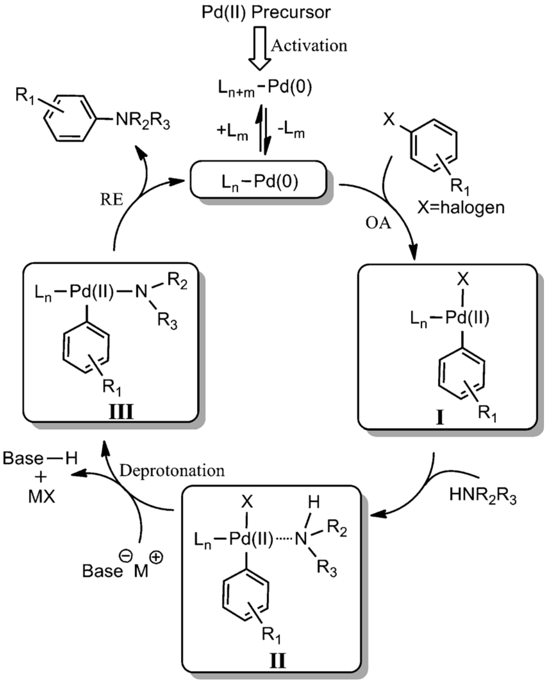


Figure 1. Representative NHC–Pd^{II} complexes serving to catalyze Buchwald–Hartwig (BH) amination reactions.



Scheme 1. Generally proposed Pd^0/Pd^{II} mechanism for Buchwald–Hartwig (BH) amination catalyzed by NHC–Pd^{II} complexes.

carried out to provide an energy profile for the Pd^0/Pd^{II} mechanism.[12]

Some modes for the activation of Pd^{II} complexes to Pd^0 species have been suggested in the literature. Nolan and coworkers proposed that the precatalyst **1b** might be converted to Pd^0 by an attack of alkoxide on Pd to form an [aryl–Pd–alkoxide] complex followed by a RE step.[6a] This pathway can also apply to the activation of **1c** after a rearrangement of the acetylacetonate (acac) moiety from the O,O-bound to the C-bound Pd^{II} tautomer.[7] The reduction of **1d** and **1e** to Pd^0 might be achieved either through a direct nucleophilic attack at the allyl moiety by alkoxide, or through the formation of an [allyl–Pd–alkoxide] complex followed by a RE step.[8,9] It is conceivable that the presence of active transmetalating agents, such as organomagnesium, -zinc, -tin, or -boron reagents, might reduce Pd^{II} species to Pd^0 effectively.[10,13] In addition, the presence of β-H in substrates or additives may convert Pd^{II} to Pd^0 via a β-H elimination followed by RE.[14]

In the **1f**-promoted amination of chlorobenzene with aniline, using KO*t*Bu and 1,4-dioxane as base and solvent, respectively, the product, diphenylamine, can be obtained in excellent yield. However, it seems that the reduction pathways involving the Pd^{II} precatalyst, mentioned in the literature, cannot apply here. The mechanism of the reduction of **1f** to the Pd^0 species, which is essential to start BH amination reactions in the proposed Pd^0/Pd^{II} mechanism, remains elusive. However, with the exception of the Pd^0/Pd^{II} mechanism, no other possible reaction mechanism for the Pd–PEPPSI catalyzed amination reaction has, to our knowledge, been examined, such as a σ-bond metathesis mechanism, Pd^{II}/Pd^{IV} mechanism, single electron transfer (SET) mechanism, or halide atom transfer (HAT) mechanism.

Whether the BH amination reaction could be carried out via another mechanism, in some cases, instead of the well-established Pd^0/Pd^{II} catalytic cycle is an interesting and potentially important question. Herein we propose that a Pd^{II}-promoted σ-bond metathesis mechanism might be feasible in the Pd–PEPPSI-catalyzed amination of chlorobenzene with aniline, in which the Pd^{II} complex has little chance to be reduced to the Pd^0 species.

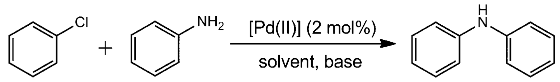
Results and Discussion

Excluding the potentially reductive role of the solvent and labile ligand of the PEPPSI complex: Experimental investigation

We have explored whether an alternative reaction mechanism for the **1f**-catalyzed amination of chlorobenzene with aniline takes place. Instead of the commonly proposed Pd^0/Pd^{II} catalytic cycle, we first ruled out the potential reducing agents, solvents, and labile ligands of the PEPPSI complex, which might be able to reduce Pd^{II} to Pd^0. Our experiments in this context are summarized in Table 1.

In the **1f**-catalyzed amination of chlorobenzene with aniline, using 1,4-dioxane and KO*t*Bu as solvent and base, respectively, diphenylamine can be obtained in excellent yield (Table 1, entry 1). It might be possible that coordination of a 1,4-dioxane to Pd^{II} followed by a β-H elimination could afford a Pd–H

Table 1. Experimental yields when Pd–PEPPSI and its analogs serve effectively to catalyze the amination of chlorobenzene with aniline.



Entry[a]	Catalyst	Solvent	Yield [%][b]
1	**1f**	1,4-dioxane	96
2	**1f**	toluene	95
3	**1f**	aniline	96
4[c]	**1g**	toluene	79
5	**1h**	toluene	89
6	**1h**	aniline	95
7	$PdCl_2$	1,4-dioxane	trace

[a] Reaction conditions: Chlorobenzene (1.0 mmol), aniline (1.1 mmol for solvent ≠ aniline), KO*t*Bu (1.2 mmol), solvent (2 mL), 90 °C, 4 h; [b] yield isolated after two runs; [c] reference [11e].

complex and an oxonium ion intermediate. Next, reduction of the Pd–H complex might lead to Pd^0. To rule out the potentially critical role of the 1,4-dioxane solvent in reducing the Pd^{II} complex, amination reactions in which 1,4-dioxane was replaced by toluene or aniline (Table 1, entries 2 and 3, respectively),[15] were carried out and proceeded with excellent yields of the desired product. Therefore, the solvent, 1,4-dioxane, is not indispensable in the amination reaction.

One might suspect that the "throwaway" ligand of the PEPPSI catalyst could somehow play a role in reducing the Pd^{II} complex. In fact, Shao and co-workers demonstrated that the PEPPSI analog **1g** (Figure 2), in which the 3-chloropyridine ligand was replaced by 1-methylimidazole, can also effectively promote the same reaction.[11e] Moreover, we synthesized another PEPPSI analog, **1h** (Figure 2), in which the labile ligand is replaced by aniline (see the Supporting Information for detailed experimental procedures and characterization). The crystal structure of the new compound **1h** shows that, similar to the complexes of PEPPSI family, the NHC ligand and the labile aniline ligand of **1h** are *trans* to each other. Catalytic studies for **1h** showed that this NHC–Pd^{II} complex can also catalyze the amination reaction remarkably well, using either toluene or aniline as solvent (Table 1, entries 5 and 6). The excellent performance of **1h** can rule out a crucial reductive role of a "throwaway" ligand in forming the Pd^0 species.

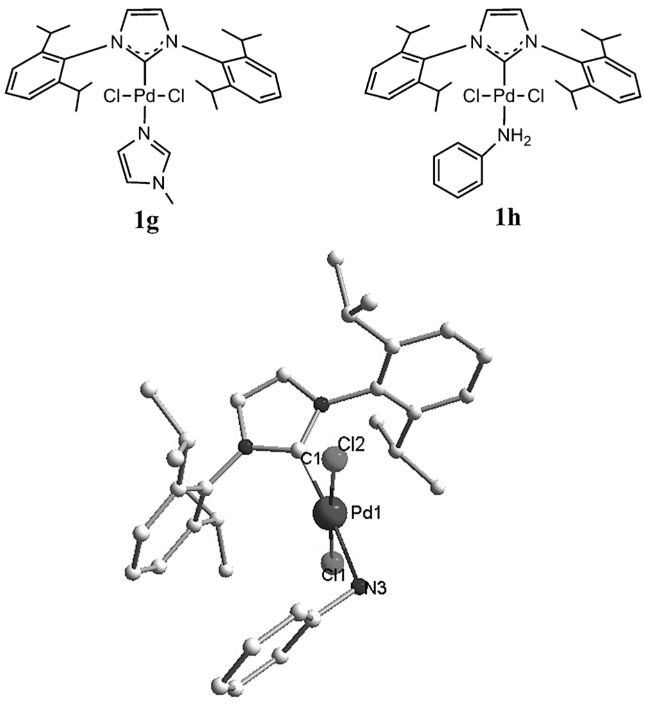
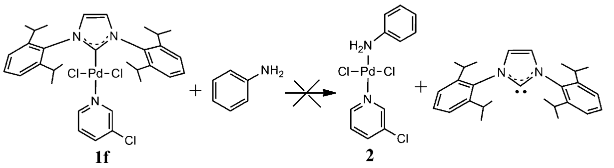


Figure 2. Top) Molecular structures of **1g** and **1h**; bottom) crystal structure of **1h**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1–C1 1.968(2), Pd1–N3 2.1064(17), Pd1–Cl2 2.2970(5), Pd1–Cl1 2.2993(5); C1-Pd1-N3 175.52(8), C1-Pd1-Cl2 90.44(6), N3-Pd1-Cl2 90.52(5), C1-Pd1-Cl1 91.81(6), N3-Pd1-Cl1 87.53(5).

PEPPSI complexes are usually bench-stable, so dissociation of the NHC ligand is very unlikely to occur. This is also supported by computational evidence that ΔG for the ligand exchange is significantly endothermic, by 30 kcal mol^{-1} [Eq. (1); 1 kcal = 4.184 kJ]. The experimental fact that $PdCl_2$ is unable to catalyze the amination reaction also demonstrates the crucial role of the NHC ligand (Table 1, entry 7).



Computational investigation of anilido-containing Pd^{II} intermediates and possible subsequent reactions.

One may suggest that aniline is most likely to function as a potential reducing agent in converting Pd^{II} to the Pd^0 species.[16] Thus, intermediates involving aniline and any possible subsequent reactions were computationally explored.

Anilido-containing Pd^{II} intermediates

For the well-defined complex **1f**, Organ and co-workers proposed that the 3-chloropyridine moiety may be regarded as a "throwaway" ligand.[11a] In the presence of aniline, **1f** can be converted to **1h** via a ligand-exchange step (Figure 3). The present computational study suggests that this step is slightly exothermic in free energy, by 1.2 kcal mol^{-1}. Subsequently, the Pd^{II}–aniline complex formed may undergo a deprotonation step facilitated by the base, KO*t*Bu. This results in the elimination of KCl and *t*BuOH and affords a [(NHC)Pd(Cl)(NHPh)] intermediate (**3**). The latter step is computed to be endothermic by 3.4 kcal mol^{-1}.[17] In addition, the resulting intermediate **3** may undergo an anionic ligand-exchange step with base to generate an intermediate **4**. A very slight exothermicity (0.4 kcal mol^{-1}) is found for this step. Coordination of aniline with **3** and subsequent elimination of KCl and *t*BuOH assisted by KO*t*Bu can afford a [(NHC)Pd(NHPh)$_2$] intermediate (**6**). This step is predicted to be substantially exothermic, by 13.2 kcal mol^{-1} (Figure 3).

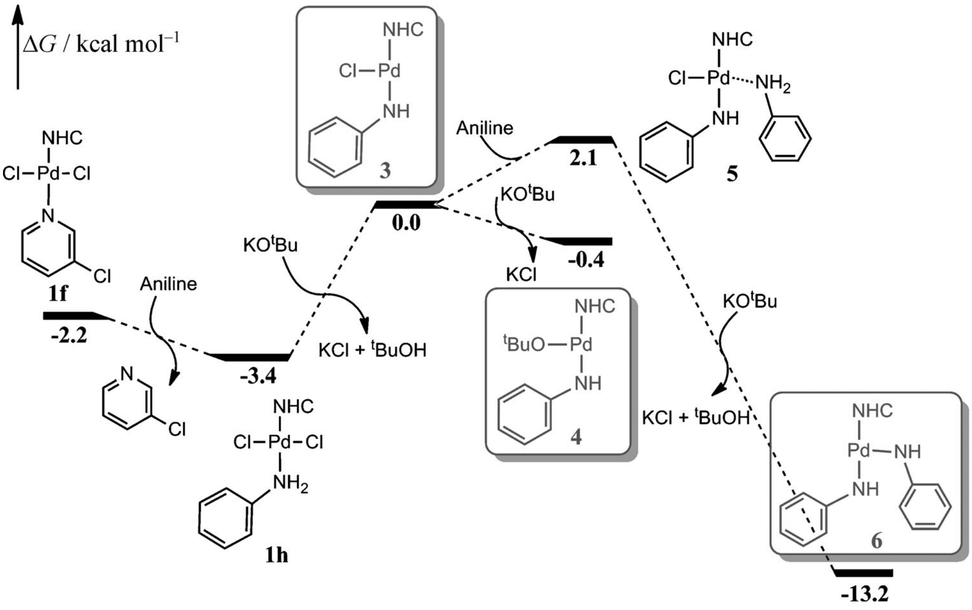
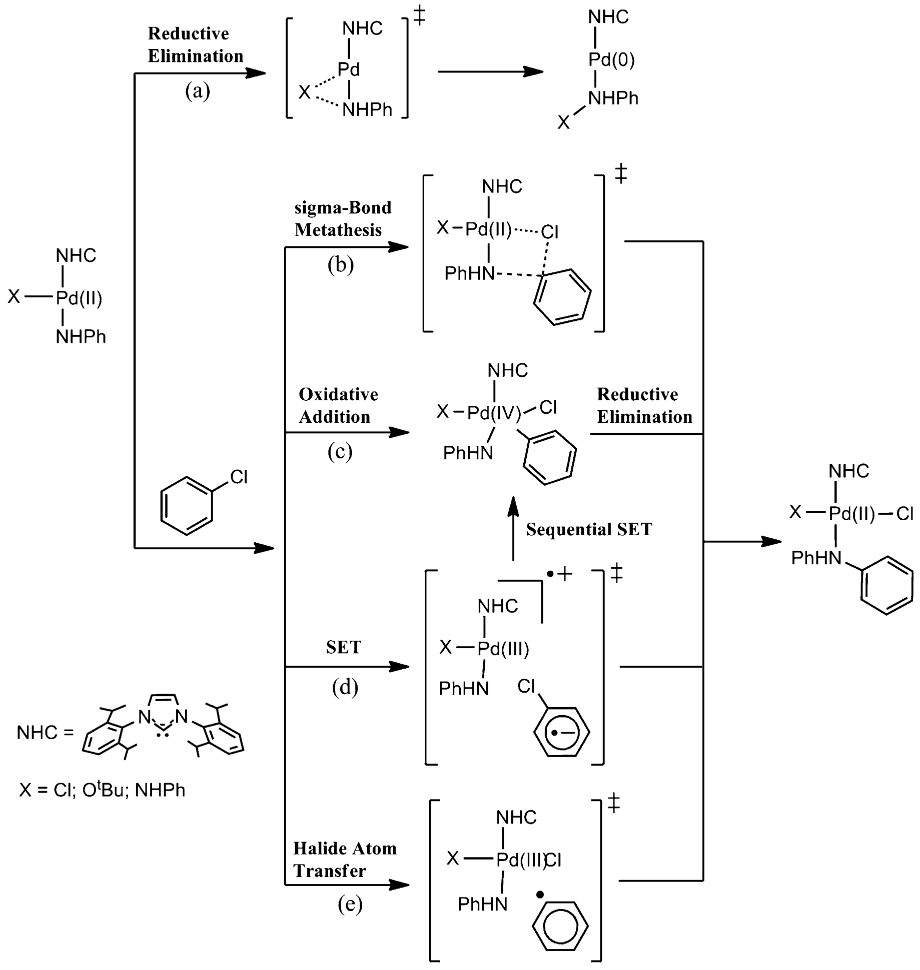


Figure 3. Free-energy profile for the conversion of **1f** to the three anilido-containing Pd^{II} intermediates.

Any or all of the three anilido-containing Pd^{II} intermediates, **3**, **4**, and **6**, might undergo a RE reaction to yield a Pd^{0} species (Scheme 2, path a). Accordingly, the BH reaction could be driven via the well-documented Pd^{0}/Pd^{II} catalytic cycle. Apart from the RE reaction, these three intermediates might utilize a four-centered σ-bond metathesis mechanism in the presence of an aryl halide to produce the desired cross-coupling product in a concerted manner (Scheme 2, path b). The breaking of the C–Cl bond and the formation of the C–N bond occur simultaneously. The oxidation state of Pd is unchanged throughout the catalytic cycle. A mechanism involving a Pd^{II}/Pd^{IV} catalytic cycle is also proposed (Scheme 2, path c). The aryl halide might undergo oxidative addition to an anilido-containing Pd^{II} intermediate, affording a Pd^{IV} intermediate. A subsequent RE step would generate the amination product.

In addition, a Pd^{III}-mediated mechanism[19] has been postulated for the BH amination reaction, regardless of the limited experimental evidence supporting this hypothesis. Single electron transfer (SET) from a Pd^{II} intermediate to an aryl halide can lead to the formation of a Pd^{III} radical cation and a radical anion of the aryl halide (Scheme 2, path d). This radical pair could form the amination product or generate a Pd^{IV} intermediate after a subsequent SET step. An alternative Pd^{III}-mediated mechanism is hypothesized that proceeds via a halide atom transfer (HAT) step, yielding a phenyl radical and a Pd^{III} radical (Scheme 2, path e). The resulting radical pair could recombine to afford the desired product. Both the SET and HAT mechanisms have been proposed for Cu^{I}-catalyzed Ullmann-type reactions.[18] A Pd^{III}-based mechanism was proposed by Ritter and co-workers for the oxidation of Pd^{II} dimer with suitable oxidizing agents[19] and subsequently computationally studied by Schoenebeck and co-workers.[20] To our knowledge, the question of



Scheme 2. Proposed reaction pathways for anilido-containing Pd^{II} intermediates.

whether the Pd^{II}/Pd^{III} catalytic cycle could be operative in the BH reaction has not been evaluated.

Possible reaction routes for the [(NHC)Pd(Cl)(NHPh)] intermediate

Five plausible reaction pathways (Scheme 2) associated with the [(NHC)Pd(Cl)(NHPh)] intermediate **3** were computationally studied (Figure 4). The first is RE of **3** and the others are different reaction routes between **3** and PhCl, leading to the cross-coupling product. The RE of **3** proceeds via a three-membered ring transition state (TS), where the N–Cl bond (2.088 Å) is being formed and the Pd–Cl bond is breaking (3.023 Å) (Figure 5, **TS(3–7)**). The activation barrier for this step is computed to be 42 kcal mol^{-1} and the RE reaction is endothermic by 36 kcal mol^{-1} (Figure 4, path a). The computational results suggest that the RE of **3** is unlikely.

It should be noted that the anilido ligand of **3** (Figure 4) has nucleophilic character. In the presence of PhCl, it is possible to generate the amination product via a σ-bond metathesis step

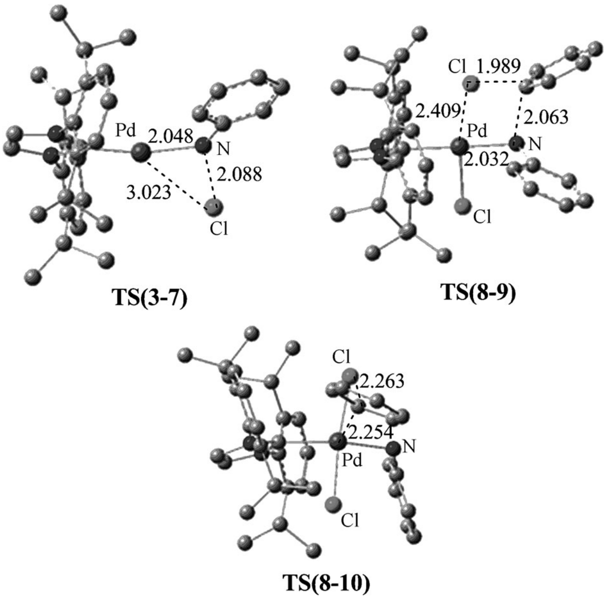


Figure 5. Optimized TS structures pertaining to the reaction routes for RE (**TS(3-7)**), σ-bond metathesis (**TS(8-9)**), and Pd^{II}/Pd^{IV} (**TS(8-10)**) for **3**. Bond lengths are shown in Å. Hydrogen atoms are omitted for clarity.

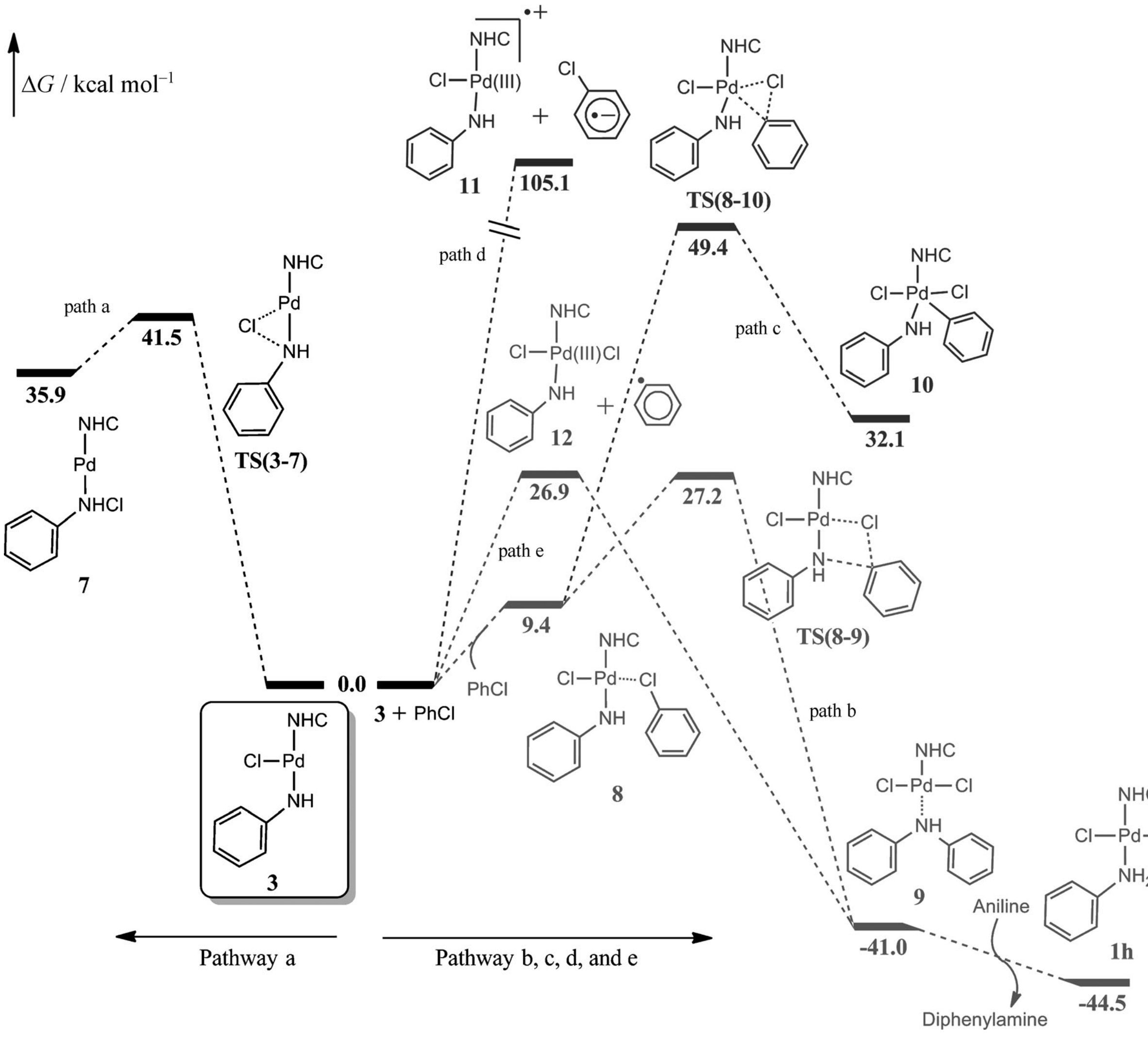


Figure 4. Free-energy profiles of the five reaction pathways examined for **3**.

in a concerted manner. In the structure of **TS(8–9)**, the C–Cl and Pd–N bond lengths are lengthened to 1.989 and 2.032 Å, respectively, whereas the Pd-Cl and C–N bond lengths are shortened to 2.409 and 2.063 Å, respectively (Figure 5). A typical four-center σ-metathesis feature is seen at the TS structure. The predicted free energy barrier for the σ-bond metathesis route is approximately 27 kcal mol^{-1} relative to the separated **3** plus PhCl, which is approximately 14 kcal mol^{-1} lower than that for the reductive elimination of **3**. Formation of the amination product complex is computed to be very exothermic, by 41 kcal mol^{-1} (Figure 4, path b). The complex **1h** can be regenerated after diphenylamine is replaced by aniline. Interestingly, the σ-bond metathesis pathway leading to the Ph_2NH product directly is much more favorable than the generation of Pd^0 via the RE pathway, both kinetically and thermodynamically.

The oxidative addition of PhCl to **3**, forming a Pd^{IV} intermediate, is computed to have a free energy barrier of 49 kcal mol^{-1}. This step results in an endergonic Pd^{IV} intermediate with $\Delta G = 32$ kcal mol^{-1} (Figure 4, path c). The computational results show that the oxidative addition of PhCl to **3** is highly unfavorable.

Intermolecular SET from **3** to PhCl can yield a Pd^{III} radical cation (**11**) and an aryl chloride radical anion. Subsequently, dissociation of the C–Cl bond of the aryl chloride radical anion yields a free aryl radical and a chloride anion. Finally, the free aryl radical reacts with the Pd^{III} radical cation to produce the desired product. However, the theoretical results demonstrate that the free energy barrier of the SET pathway is prohibitively high, suggesting that the SET mechanism is very unlikely to occur (Figure 4, path d).

The chlorine atom transfer pathway involves homolytic cleavage of the C–Cl bond of PhCl and simultaneous formation of the Pd–Cl bond to afford a Pd^{III} radical (**12**) and an aryl radical. The generated aryl radical favors reaction with the anilido ligand of **12** to afford the coupling product, rather than combining with the Pd^{III} radical to form a Pd^{IV} intermediate. This is because the formation of the coupling product is dramatically exothermic, whereas the formation of the Pd^{IV} intermediate is endothermic (Figure 4, path e). Similar to the Cu^{I}-catalyzed Ullmann reactions via the HAT mechanism, the Pd–Cl bond formation can compensate the energy needed to break the C–Cl bond of PhCl.[18] Nevertheless, the predicted energy resulting in formation of **12** and an aryl radical is approximately 27 kcal mol^{-1} higher than the energy of separated **3** and PhCl. Although the TS of the HAT pathway has not been located, the energy barrier height of HAT mechanism must be higher than 27 kcal mol^{-1} and, therefore, higher than that of the σ-bond metathesis mechanism, so the HAT pathway is less feasible than the σ-bond metathesis route.[21]

Possible reaction routes of the [(NHC)Pd(OtBu)(NHPh)] intermediate

Similarly, the five reaction pathways in Scheme 2 can also apply to the [(NHC)Pd(O*t*Bu)(NHPh)] intermediate **4**. Of primary interest is the possibility of the RE of **4** to afford the Pd^0 species (the optimized TS structure of this step, **TS(4–13)**, is shown in Figure S2 in the Supporting Information). The RE reaction of **4** is predicted to have $\Delta G_{RE}{}^{\neq} = 36$ kcal mol^{-1} and to lead to an endergonic Pd^0 product with $\Delta G_{RE} = 8$ kcal mol^{-1} (see the Supporting Information, Figure S1, path a).

As for the σ-bond metathesis mechanism, a four-centered TS structure is located (see the Supporting Information, Figure S2, **TS(14–15)**). Theory shows that the free energy barrier associated with this pathway is 30 kcal mol^{-1} relative to separated **4** and PhCl. The resulting product complex is significantly exothermic, by 31 kcal mol^{-1} (see the Supporting Information, Figure S1, path b). Therefore, the RE pathway of **4** is unfavorable from both kinetic and thermodynamic perspectives compared with the corresponding σ-bond metathesis mechanism. In addition, similar to **3**, the Pd^{II}/Pd^{IV}, SET, and HAT routes of **4** are energetically unfavorable in comparison with the corresponding σ-bond metathesis mechanism (see the Supporting Information for details).

Possible reaction routes of the [(NHC)Pd(NHPh)$_2$] intermediate

For [(NHC)Pd(NHPh)$_2$] intermediate **6**, five possible routes were also investigated. The RE of **6** was computed to have a barrier height of 33 kcal mol^{-1} (the TS structure of this step, **TS(6–19)**, is shown in Figure S4 in the Supporting Information). The generated Pd^0 product complex **19** is endothermic by 3 kcal mol^{-1} (see the Supporting Information, Figure S3, path a). Compared with the RE of intermediates **3** and **4**, the RE of **6** has the lowest energy barrier and the smallest endothermicity.

The σ-bond metathesis pathway for **6** has a computed $\Delta G^{\neq}$ of 24 kcal mol^{-1} relative to separated **6** and PhCl. The four-centered TS results in a product complex, [(NHC)Pd(Cl)(NHPh)(NHPh$_2$)] (**21**), the generation of which is exergonic by 44 kcal mol^{-1} (see the Supporting Information, Figure S3, path b). Similar to **3** and **4**, intermediate **6** also favors the σ-bond metathesis pathway in the presence of PhCl, instead of the corresponding RE route leading to Pd^0. Computational results also suggest that the σ-bond metathesis pathway proceeding through **6** is more favorable than the analogous route via **3** and **4**. The other three routes applied to **6**, Pd^{II}/Pd^{IV}, SET, and HAT, are less competitive than the corresponding σ-bond metathesis mechanism (see the Supporting Information for details).

Overall, the present computational results indicate that the three plausible deprotonated aniline-containing Pd^{II} species may not undergo RE reactions to form Pd^0 easily in the **1f**-catalyzed amination of chlorobenzene with aniline. Instead, the σ-bond metathesis mechanism is more facile for all three intermediates than the corresponding RE reactions, both kinetically and thermodynamically. Other proposed reaction pathways, such as the Pd^{II}/Pd^{IV} mechanism, the SET mechanism, and the HAT mechanism, cannot compete with the σ-bond metathesis mechanism either.

Frontier orbital analysis of the σ-bond metathesis mechanism

A frontier orbital analysis provides more insight into the amination reaction via the σ-bond metathesis mechanism. The

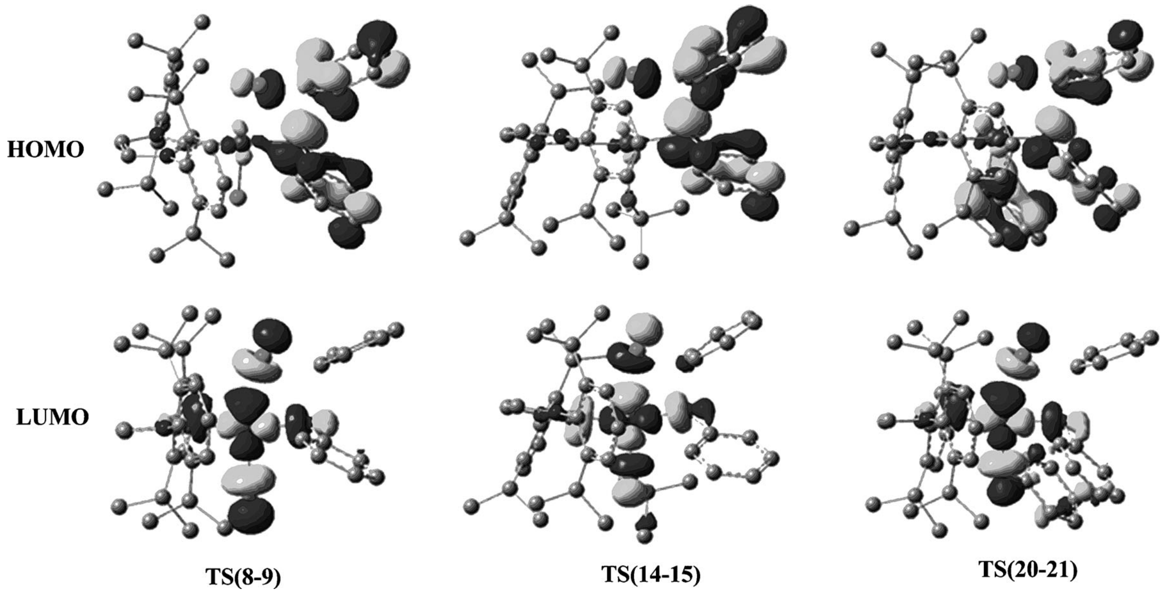


Figure 6. Frontier orbitals for the transition states of the three σ-bond metathesis reactions.

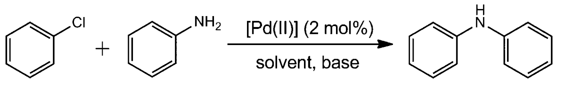
highest occupied molecular orbitals (HOMO) of the transition states for all three σ-bond metathesis reactions qualitatively show a lone pair located on N of the deprotonated aniline ligand, and this lone pair is not employed in bonding to Pd (Figure 6). Thus, the deprotonated aniline moiety can participate in the subsequent nucleophilic substitution reaction. The corresponding lowest unoccupied molecular orbitals (LUMO) display the out-of-phase combinations of the Pd d_σ atomic orbital (AO) and the Cl p_σ AOs (Figure 6). Both the existence of an empty d_σ orbital on Pd^{II} and the presence of a lone pair on the anilido ligand are important for the amination reaction to proceed via σ-bond metathesis mechanism. Such a Pd^{II}-mediated σ-bond metathesis mechanism is consistent with the reaction mechanism of water/alcohol with palladium hydride complexes proposed by Dedieu and co-workers.[22] In addition, it should be noted that the decomposition of all three anilido-containing Pd^{II} intermediates via the RE route is difficult. Thus, the stability of the three intermediates, which cannot undergo RE reactions easily, is also responsible for the viability of subsequent σ-bond metathesis reaction.

Replacement of KO*t*Bu with NaO*t*Bu and KOH in the amination reaction: More experiments

In order to explore whether the counterion of the base used has any effect on the efficiency of the catalytic reaction, the reactions catalyzed by **1f** and **1h** described in Table 1 were performed using NaO*t*Bu in addition to those already described using KO*t*Bu. The yield of the desired product decreased slightly with 1,4-dioxane and aniline as the solvents (see the Supporting Information, Table S2, entries 1, 3, and 5), whereas the yield of diphenylamine diminished significantly when using toluene as the solvent (Table S2, entries 2 and 4). Nevertheless, in the neat reaction system with aniline as the solvent, the studied BH reactions are not very sensitive to the counterion.

One may envision that the base employed, KO*t*Bu, might play a reductive role in converting the Pd^{II} precatalyst to the Pd^{0} species, since KO*t*Bu has been shown to act as a one-electron reducing agent.[23] Therefore, we carried out the amination reaction in the laboratory, replacing KO*t*Bu with KOH. About 20% yield of the diphenylamine product was obtained for both **1f** and **1h** (Table 2, entries 1 and 2). The low efficiency of KOH compared with KO*t*Bu in mediating the amination reaction may be due to the following two factors. One is that KOH is less basic than KO*t*Bu, and hence less effective in assisting the deprotonation of aniline. The other factor may be that KOH is less soluble in aniline than KO*t*Bu. One may envisage that the production of water by the action of KOH on the acidic anilinium proton might have any effect on the catalytic performance. The addition of molecular sieves to sequester water leads to a decrease of the yield of Ph$_2$NH (Table 2, en-

Table 2. Experimental yields for the **1f** and **1h** catalyzed amination of chlorobenzene with aniline using KOH as a base.



Entry[a]	Catalyst	Additive	Yield [%][b]
1	**1f**	–	22
2	**1h**	–	22
3	**1f**	4 Å MS[c]	12
4	**1h**	4 Å MS[c]	11
5	**1f**	water[d]	23
6	**1h**	water[d]	31

[a] Reaction conditions: chlorobenzene (1.0 mmol), aniline (2 mL), KOH (1.2 mmol), 90 °C, 4 h; [b] yield isolated after two runs; [c] 4 Å MS (200 mg); [d] water (1.0 mmol).

tries 3 and 4). The addition of water in stoichiometric amount can slightly increase the yield of Ph_2NH (Table 2, entries 5 and 6). The yielded/added water may increase the solubility of KOH, hence resulting in slightly higher yield of the product. Regardless of the low efficiency of using KOH as a base to drive the amination reaction, KO*t*Bu is not indispensable. If reactants and additives have little chance to reduce the Pd^{II} precatalyst, a Pd^{II}-mediated σ-bond metathesis mechanism might be operative to drive the BH amination reaction.

Conclusions

In summary, it is commonly suggested that the Buchwald–Hartwig (BH) amination reactions promoted by the Pd–PEPPSI catalyst proceed through the well-documented Pd^0/Pd^{II} catalytic cycle. Therefore, the initial reduction of Pd^{II} species to Pd^0 is essential to drive the amination reactions. However, in the special reaction system of **1f**-catalyzed aryl amination of chlorobenzene with aniline, there is no explicit reducing agent. Moreover, a neat reaction system was experimentally created, from which the potentially reductive roles of the solvent and labile ligand of the PEPPSI complex in leading to Pd^0 species were ruled out. Nevertheless, whether the reduction of Pd^{II} species could be realized via plausible anilido-containing Pd^{II} intermediates were computationally evaluated. Computational results suggest that all reductive elimination reactions of the anilido-containing Pd^{II} intermediates have relatively high energy barriers and are thermodynamically disfavored. In contrast, the corresponding Pd^{II}-mediated σ-bond metathesis pathway has a lower energy barrier leading to the C–N cross-coupling product and is much more feasible than the RE route both kinetically and thermodynamically. Other proposed reaction pathways, such as Pd^{II}/Pd^{IV} mechanism, single electron transfer (SET) mechanism, and halide atom transfer (HAT) mechanism, cannot compete with the σ-bond metathesis mechanism either. Therefore, in some special cases, if reactants and additives are insufficient to reduce a Pd^{II} precatalyst, a Pd^{II}-mediated σ-bond metathesis mechanism might be operative to drive the BH amination reaction. The unprecedented mechanism proposed herein is expected to stimulate further mechanistic studies of BH amination reactions.

Computational Methods

The ωB97XD[24] density functional method, which contains both long-range exchange and empirical dispersion corrections, was employed in this work to carry out the computations. This functional has shown good performance in describing processes involving weak interactions and bond breaking/making.[25] The LANL2DZ basis set, in conjunction with the LANL2DZ pseudopotential,[26] was used for the Pd atom, whereas the 6-31G(d) basis set[27] was used for other atoms in the geometry optimizations. Vibrational frequency analyses at the same level of theory were performed on all optimized structures to characterize stationary points as local minima or transition states. Further, intrinsic reaction coordinate (IRC) computations were carried out to confirm that transition states connect appropriate reactants and products. The gas-phase Gibbs free energies for all species were obtained at 298.15 K and 1 atm at their respective optimized structures.

To consider solvation effects, single-point energy computations using the SMD model[28] with toluene as solvent were performed based on the optimized gas-phase geometries of all species. Larger basis sets (LANL2DZ for Pd and 6-311++G(d,p) for other atoms) were utilized for single-point energy calculations on stationary points. The solution-phase Gibbs free energy was determined by adding the solvation single-point energy and the gas-phase thermal correction to the Gibbs free energy obtained from the vibrational frequencies. Unless otherwise specified, the solution-phase Gibbs free energy was used in the present discussions. The Gaussian 09 suite of programs[29] was used throughout.

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Keywords: amination · density functional calculations · palladium · reaction mechanisms · σ-bond metathesis

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FULL PAPER

Palladium Catalysis

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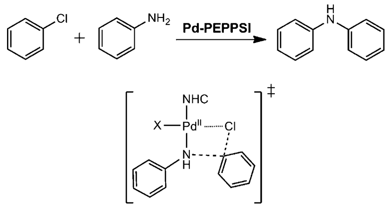
■■ – ■■

Is Pd^{II}-Promoted σ-Bond Metathesis Mechanism Operative for the Pd–PEPPSI Complex-Catalyzed Amination of Chlorobenzene with Aniline? Experiment and Theory



PEPPSI & surely: In some cases, if reactants and/or additives are inadequate to reduce a Pd^{II} precatalyst, a Pd^{II}-mediated σ-bond metathesis mechanism might be feasible to drive the Buchwald–Hartwig amination reaction. Computational study of the Pd–PEPPSI-catalyzed aryl amination of chlorobenzene demonstrates that σ-bond metathesis pathways leading to the diphenylamine have relatively low barriers.