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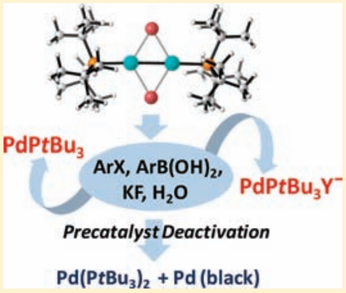
Reactivity and Stability of Dinuclear Pd(I) Complexes: Studies on the Active Catalytic Species, Insights into Precatalyst Activation and Deactivation, and Application in Highly Selective Cross-Coupling Reactions

Fabien Proutiere, Marialuisa Aufiero, and Franziska Schoenebeck*

Laboratory for Organic Chemistry, ETH Zürich, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland

Supporting Information



ABSTRACT: The catalysis derived from the dinuclear Pd(I)−Pd(I) complex, $\{[\mathrm{P}t\mathrm{Bu}_3]\mathrm{PdBr}\}_2$, has been studied with experimental, computational, and spectroscopic techniques. Experimental selectivity studies were performed, and the reactivity was subsequently investigated with density functional theory (B3LYP-D and M06L) to deduce information on the likely active catalytic species. The reactivity with aryl chlorides and bromides was found to be inconsistent with direct catalytic involvement of the Pd(I) dimer but consistent with mononuclear Pd(0) catalysis. Computational studies suggest that precatalyst transformation to the active catalytic species does not proceed via a direct disproportionation mechanism; a reductive pathway is the most likely scenario instead. Through ^{31}P NMR investigations it was identified that the combination of $\mathrm{ArB(OH)}_2$, KF, and water triggers the conversion of the precatalyst to $\mathrm{Pd}(\mathrm{P}t\mathrm{Bu}_3)_2$ and, most likely, Pd-black as a competing side process, explaining the incomplete conversions of aryl chlorides in Suzuki cross-coupling reactions under Pd(I) dimer conditions. New applications in highly regio- and chemoselective transformations in short reaction times at room temperature are also demonstrated.

INTRODUCTION

A number of dinuclear Pd(I)−Pd(I) complexes have been synthesized over the past 70 years, and new reactivities at such multiple palladium sites have been achieved.[1] The di-*tert*-butylphosphane-ligated palladium(I) dimer, $\{[\mathrm{P}t\mathrm{Bu}_3]\mathrm{PdBr}\}_2$, for example, was first synthesized by Mingos, Vilar, and co-workers and was shown to be reactive with a number of small molecules.[2] The catalytic potential was explored by Hartwig and co-workers[3] and Prashad et al.[4,5] The Pd(I) dimer precatalyst gave rise to very high reaction rates, leading to Pd-catalyzed transformations of aryl bromides in as few as 15 min at room temperature in Suzuki and amination reactions.[3,6] With unactivated aryl chlorides, Suzuki cross-coupling reactions were less efficient, and even prolonged reaction times did not give rise to full conversion.[3] Syntheses of structural alternatives of dinuclear Pd(I)−Pd(I) complexes have been reported,[2] and their formation as side products from mononuclear Pd(II) intermediates has been discussed.[7] Related to that, the formation of a dinuclear Pd(I) dimer from a Pd(II)−NHC complex under catalytically relevant conditions has recently been reported also.[8] Further remarkable activity of dinuclear Pd species in different oxidation states, i.e., Pd(III)−Pd(III), has been documented for C−H insertion,[9] and even Pd(I)−Pd(II) dimers have recently been isolated in C−H halogenations.[10] Despite these advances, there is still relatively little understanding of the precise role and mode of action of such multiple Pd sites in catalysis. Nevertheless, the development of Pd−Pd bonds into promising larger sized clusters, i.e., nanoparticles, has progressed significantly in recent years.[11]

This report will focus on the detailed study of the catalysis derived from the Pd(I) dimer, $\{[\mathrm{P}t\mathrm{Bu}_3]\mathrm{PdBr}\}_2$. It has been suggested that the high reactivity of this Pd(I) dimer might be due to the formation of the monoligated 12-electron species, $\mathrm{Pd(0)P}t\mathrm{Bu}_3$, in solution (see Figure 1).[3] This could occur via disproportionation of the Pd(I) dimer into $\mathrm{Pd(0)P}t\mathrm{Bu}_3$ and $\mathrm{Pd(II)(P}t\mathrm{Bu}_3)\mathrm{Br}_2$ species,[2b,3a,5b,6] or by reduction of the Pd(I) dimer to $\mathrm{Pd(0)P}t\mathrm{Bu}_3$ (see Figure 1).[3a,c] Even anionic $[\mathrm{Pd(0)BrP}t\mathrm{Bu}_3]^-$ might be formed.[3a,12] Homolytic scission into Pd(I) radicals, potentially followed by reduction, might also be a possibility.[13] However, other reports favor a direct catalytic involvement of Pd(I) dimers of related structure in catalysis and suggest a catalytic cycle in which the Pd−Pd bond stays intact.[14]

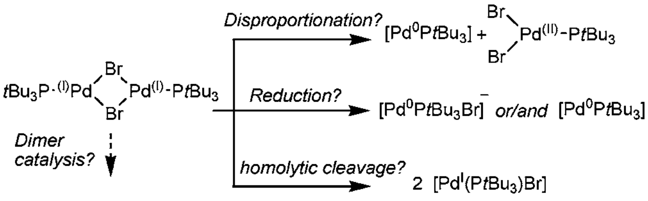


Figure 1. Possible mechanisms of formation of the active species from Pd(I) dimer, or direct involvement in catalysis.

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We herein report our combined experimental and computational efforts to gain detailed mechanistic insights into the catalysis derived from Pd(I) dimers, focusing on $\{[\mathrm{P}t\mathrm{Bu}_3]\mathrm{PdBr}\}_2$ to address the questions of (i) the likely active catalytic species and (ii) precatalyst activation and deactivation. We also (iii) provide an explanation why aryl chlorides react less efficiently under Pd(I) dimer conditions in Suzuki coupling reactions and (iv) present novel applications in highly regioselective cross-coupling reactions in rapid reaction times at room temperature.

■ RESULTS AND DISCUSSION

We have previously shown the usefulness of selectivity studies to gain indirect information on the likely active catalytic species of a given transformation. For this, we had performed a combined computational and experimental study to elucidate the origin of selectivity reversal of a Pd-catalyzed cross-coupling reaction in different solvents (see Figure 2).[15] Fu and coworkers had established that the reaction of $\mathrm{Pd}_2(\mathrm{dba})_3/\mathrm{P}t\mathrm{Bu}_3$ with 4-chlorophenyl triflate (**1**) in THF gives rise to selective C−Cl insertion, consistent with $\mathrm{PdP}t\mathrm{Bu}_3$ as active catalytic species.[16] We discovered that employing the identical conditions in polar solvents, such as MeCN, gives rise to a complete selectivity reversal with exclusive transformation of the C−OTf bond.[15] We also demonstrated this selectivity reversal for intermolecular competition experiments and established that it is general in arylboronic acid.[15] Through detailed computational studies, we were able to show that neither electrostatic stabilization nor coordination by the polar solvent accounts for the selectivity reversal (see Figure 3). Instead, a different active species is likely the cause of selectivity reversal in polar solvent: the reactivity of $\mathrm{Pd}_2(\mathrm{dba})_3/\mathrm{P}t\mathrm{Bu}_3$ in polar solvents was found to be consistent with anionic $[\mathrm{Pd}(0)\mathrm{P}t\mathrm{Bu}_3\mathrm{X}]^-$ as active catalytic species if coordinating additives or cross-coupling partners are present in the mixture, leading to preferential C−OTf addition. In nonpolar solvent, the reactivity is consistent with neutral $[\mathrm{Pd}(0)\mathrm{P}t\mathrm{Bu}_3]$, giving C−Cl addition.

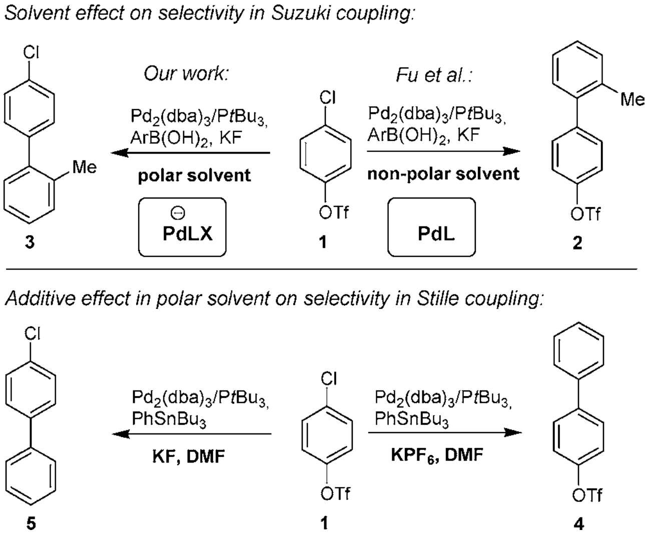


Figure 2. Previous chemoselectivity investigations involving $\mathrm{Pd}_2(\mathrm{dba})_3/\mathrm{P}t\mathrm{Bu}_3$ in Suzuki and Stille cross-coupling reactions with **1** (the formation of the predominant products is illustrated).[15,16]

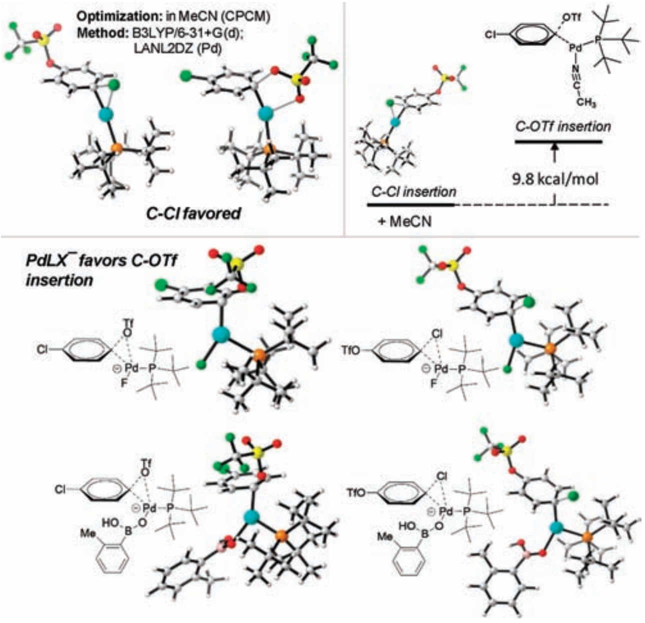


Figure 3. Previous computational investigations on the origin of selectivity reversal in polar solvent: (i) oxidative addition TSs in MeCN (top left), (ii) solvent coordination in TS (top right), and (iii) TSs for oxidative addition by anionic PdLX^- as active species (with X = F or ArB(OH)O).[15]

We also provided experimental support of these conclusions; i.e., we performed cross-coupling reactions in the absence of coordinating additives in polar solvent to disfavor an anionic Pd species (Stille reaction, Figure 2). This gave rise to predominant C−Cl insertion, consistent with $\mathrm{Pd}(0)\mathrm{P}t\mathrm{Bu}_3$ as the active species (Figure 2).[15]

Experimental Selectivity Studies and Reaction Rates under Pd(I) Dimer, $\{[\mathrm{P}t\mathrm{Bu}_3]\mathrm{PdBr}\}_2$, Conditions. The extensive studies performed on the selectivity of substrate **1** led to a reactivity picture that allows us to use it as a mechanistic probe for our current study.[15,16] If, as assumed, $\{[\mathrm{P}t\mathrm{Bu}_3]\mathrm{PdBr}\}_2$ indeed formed $[\mathrm{Pd}(0)\mathrm{P}t\mathrm{Bu}_3]$ in solution, we would expect C−Cl insertion to be favored in reactions of the dimer with substrate **1**. If, on the other hand, anionic $[\mathrm{Pd}(0)(\mathrm{X})\mathrm{P}t\mathrm{Bu}_3]^-$ (with X = Br, F, ArB(OH)O) were to be formed as active species, we would expect triflate insertion (see Figure 2).[15] Thus, we reacted **1** with 1.5 mol % $\{[\mathrm{P}t\mathrm{Bu}_3]\mathrm{PdBr}\}_2$ in the presence of KF and $\mathrm{ArB(OH)}_2$ in MeCN and THF and followed the reactions by calibrated GC-MS analysis.[17] In both reactions, only a single isomer was detected. Selectivity for C−Cl insertion was seen in THF, whereas in MeCN, exclusive addition to C−OTf took place. As such, the identical selectivity is observed under Pd(I) dimer conditions as with the $\mathrm{Pd}_2(\mathrm{dba})_3/\mathrm{P}t\mathrm{Bu}_3$ catalytic system.

Figure 4 gives the conversions of the reactions over time. In both MeCN and THF, the reactions had reached high conversion after 30 min (78% in MeCN and 76% in THF) employing the Pd(I) dimer. Although very similar conversions are reached after 30 min, the initial reaction rate is lower in MeCN, which could be explained by the lower solubility of the Pd(I) dimer in MeCN compared to THF. The analogous reactions involving $\mathrm{Pd}_2(\mathrm{dba})_3/\mathrm{P}t\mathrm{Bu}_3$ in comparison (Figure 5) were much slower and led to only 3−5% conversion after 30 min.[18]

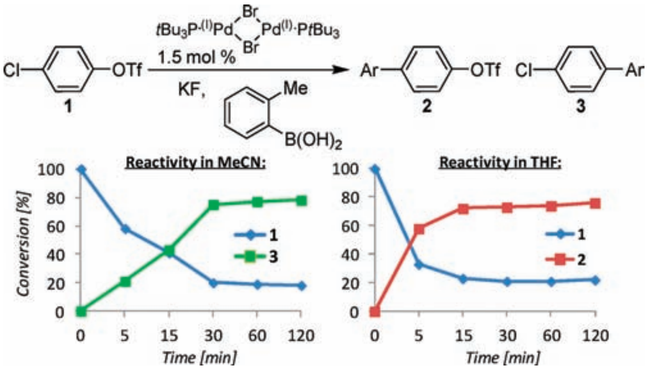


Figure 4. Reactivity of **1** with Pd(I) dimer over time. The reaction was monitored with calibrated GC-MS analysis.

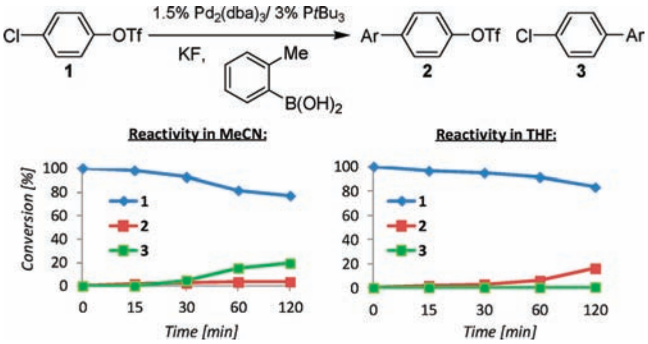


Figure 5. Reactivity of $Pd_2(dba)_3/PtBu_3$ with **1**. The reaction was monitored with calibrated GC-MS analysis.

Using an alternative base, KOH, instead of KF in the Suzuki coupling reaction of 1 under Pd(I) dimer conditions gave very similar results: we obtained 80% yield of **2** in THF and 82% of **3** in MeCN after 30 min reaction time.

At first sight, the selectivities observed in the reactions of the Pd(I) dimer with **1** appear to be consistent with $[Pd(0)PtBu_3]$ as active catalytic species in nonpolar solvents and $[Pd(0)(X)\text{-}PtBu_3]^-$ (with X = Br or F or ArB(OH)O or OH) in polar solvents.[19] As such, the observed selectivity would be consistent with "standard" Pd(0) catalysis. However, an alternative scenario could be the direct involvement of the Pd(I) dimer in catalysis—would this be consistent with the observed reactivity also?

Is Bimetallic Catalysis a Likely Scenario? Recent reports suggested the direct involvement of structurally related dinuclear Pd(I) species in Suzuki cross-coupling reactions with aryl bromides.[14] We therefore set out to explore whether $\{[PtBu_3]PdBr\}_2$ could possibly be the reactive species also in our case, rather than a Pd(0) species derived from it. To test this, we mixed the Pd(I) dimer with 4-chlorophenyl triflate (**1**) in THF in a glovebox and examined the mixture by ^{31}P NMR spectroscopy. Over the course of 30 min, the only peak observed was that corresponding to the dimer itself (87 ppm).[6] We did not detect a species resulting from oxidative addition to **1**.

To test an additional, significantly easier target for oxidative addition,[20] we repeated the study with bromobenzene in place of **1**. Using bromobenzene as the solvent at room temperature, however, also did not give rise to reaction with the Pd(I) dimer. This suggests that the Pd(I) dimer does not react directly with aryl bromides or chlorides. Activation of the dinuclear Pd(I) complex to the active catalytic species therefore needs to take place prior to reaction.

Could a Pd(I) Radical Be Reactive? Such a species could result from homolytic dimer dissociation (see Figure 1). The bond dissociation energy of a related Pd(I)−Pd(I) dimer was previously determined to be between 21 and 29 kcal/mol.[21] Using dispersion-corrected unrestricted density functional theory (DFT-D, see Figure 6),[22] we calculate an energy penalty of 26.1 kcal/mol in the gas phase for the homolytic dimer scission (see Figure 6).[23,24] Calculation at the M06L level of theory[36]—to use an alternative method—and application of solvation correction for THF (using a CPCM model) gives 24.8 kcal/mol as dissociation energy.[25] Thus, homolytic dimer dissociation might potentially be a feasible process.

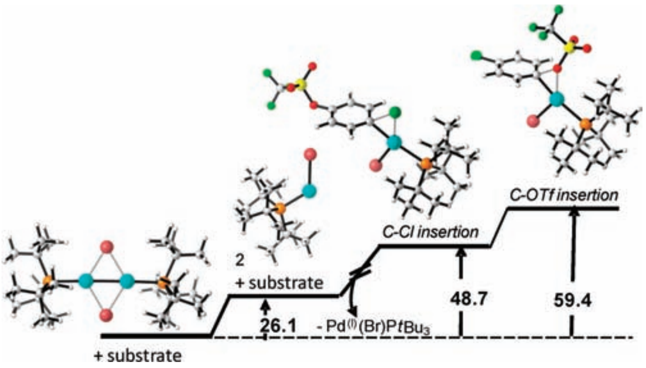


Figure 6. Free energy reaction profile for the oxidative addition of $[Pd(I)Br(PtBu_3)]$ to **1** [at UB3LYP-D/6-31+G(d) and SDD (for Pd)].[29]

However, would the resulting Pd(I) radical species also be reactive? To investigate this, we calculated the transition states for oxidative addition by the Pd(I) radical, $[Pd(I)Br(PtBu_3)]$, using DFT-D.[26,27] The barriers for oxidative addition by Pd(I) are calculated to be rather high: an overall 14 kcal/mol higher energy barrier was calculated for C−Cl insertion compared to the analogous reaction relative to $Pd(PtBu_3)_2$, making this mechanistic possibility therefore unlikely (see Figure 4). Moreover, the Pd(I) radical was calculated to favorably insert into C−Cl in the gas phase, in THF, and in MeCN,[28] and would thus be inconsistent with the opposing selectivities in different media.

The reactivity derived from the dinculear Pd(I) complex, $\{[PtBu_3]PdBr\}_2$, is thus inconsistent with dincuclear and mononuclear Pd(I) catalysis. Instead, the reactivity is consistent with "standard" mononuclear Pd(0) catalysis (giving neutral Pd(0) in THF) or anionic Pd(0) in MeCN as active catalytic species) in Suzuki cross-coupling reactions, completely analogous to the catalytic system involving $Pd_2(dba)_3/PtBu_3$.[15]

Further Applications of Pd(I) Dimer in Regioselective Cross-Coupling Reactions of Dihalogenated Heterocycles. In light of the excellent chemoselectivity achieved with substrate **1**, we were intrigued to further explore the scope of the Pd(I) dimer in regioselective cross-coupling reactions. In particular, functionalization of polyhalogenated heterocycles via regioselective and iterative cross-coupling reactions is a straightforward and attractive route to synthesize important building blocks for pharmaceutical and materials applications.[30,31] To the best of our knowledge, Pd(I)−Pd(I) precatalysts have not been explored for their potential in regioselective cross-coupling reactions. Thus, we selected N- and S-containing five- and six-membered heterocycles (see Table 1) and performed Suzuki cross-coupling reactions with these substrates (Scheme 1) in THF. Brominated thiophenes usually give preferential cross-coupling at the 2-position. However, those couplings are reported to require high reaction temperature (ca. 80−100 °C) for hours.[33] We found that use of the Pd(I) dimer gives highly selective transformation in 30 min at room temperature (see entries 1 and 2). We achieved similar success (82% yield) in the Suzuki coupling of 2,4-dichloropyrimidine applying identical conditions (see entry 3). The rapid and completely selective couplings of 2,4-dibromothiazole (entries 4−6) at room temperature were particularly pleasing, since it has potential in the synthesis of natural products[32] or relevant drugs. We analyzed the reaction mixtures in all cases by GC-MS prior to workup and did not detect the alternative regioisomers for entries 1, 2, and 4−6 (Table 1). For dichloropyrimidine (entry 3), we observed the second isomer in 9% yield.

Scheme 1. Selective Couplings of Dihalogenated Heterocycles

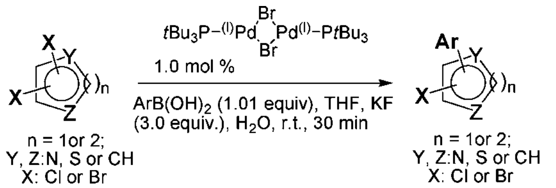
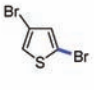
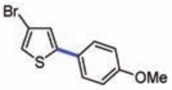
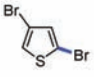
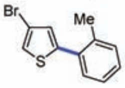
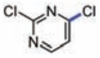
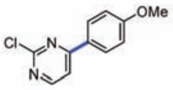
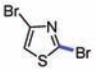
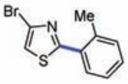
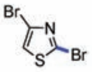
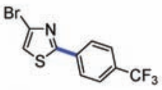
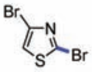
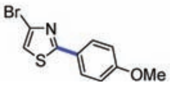


Table 1. Results of Regioselective Couplings (See Scheme 1) and Computed $\Delta\Delta G^\ddagger$ Preference (Calculated with B3LYP-D)[29] for the Illustrated Regioisomer (in kcal/mol)

Entry	Heterocycle / Product		Yield (%)	$\Delta\Delta G^\ddagger$
1			90	3.7
2			92	3.7
3			82*	1.0
4			91	4.5
5			87	4.5
6			94	4.5

[a]9% of the alternative regioisomeric product formed also.

Calculations of the transition states for oxidative addition to C−halogen by $Pd(0)PtBu_3$ predict a clear preference ($\Delta\Delta G^\ddagger$ = 3.7 −4.5 kcal/mol) for the 2-positions for dibromothiophene and -thiazole (see with Table 1). For oxidative addition to 2,4-dichloropyrimidine, the predicted $\Delta\Delta G^\ddagger$ is smallest (1 kcal/mol), which is in line with the observed formation of the second, minor regioisomeric product. Thus, the computationally predicted selectivity is in line with the experimental selectivities. This further supports $Pd(0)PtBu_3$ as the active catalytic species under the conditions applied (i.e., nonpolar solvent THF), consistent with our findings in Figure 4.[34] Moreover, these results reinforce that high selectivities can be achieved without having to sacrifice reaction rates.

Studies on the Precatalyst Activation Mechanism—Computational Studies. In standard Pd(0) catalysis, high reactivities can be achieved through the use of bulky ligands in combination with a Pd(0) precatalyst (e.g., $Pd_2(dba)_3$).[35] Sterically demanding ligands, such as $PtBu_3$, usually give rise to PdL_2 as catalyst resting state (L = phosphine ligand) after displacement of dba. The displacement of dba is rather rapid in THF (e.g., for the reaction shown in Figure 5, we already observed the peak corresponding to PdL_2 as the exclusive P signal in ^{31}P NMR when we examined the mixture after 10 min reaction time).[36] However, overall such catalytic systems are presumed to favor a monoligated Pd as the active catalytic species (in nonpolar solvent, see ref 15 and Figures 2 and 3 above). The PdL_1 species in turn is believed to be the origin of enhanced reactivity.[3c] Although no such monoligated Pd species has ever been spectroscopically indentified nor detected otherwise, experimental and computational data support ligand dissociation to $Pd(0)L_1$ and L prior to oxidative addition.[22b] This initial ligand dissociation step ($PdL_2 \rightarrow PdL + L$) is frequently considered to be a reactivity-limiting step and may occur via direct ligand dissociation or substrate-assisted ligand displacement.[22c,3c] Recent computational studies suggest an energy barrier of ca. 30 kcal/mol for an associated displacement of $PtBu_3$ from PdL_2 (i.e., substitution of one ligand by the substrate takes place prior to oxidative addition).[22b,c]

As the reaction rates under Pd(I) dimer precatalyst conditions are much higher than those under Pd(0) precatalyst conditions (see Figures 4 and 5), it has been suggested that precatalyst activation to form the putative active Pd(0) species might be a very facile process.[2,3,5] Thus, the precatalyst activation should have an activation barrier significantly smaller than 30 kcal/mol.

Considering the possibilities for precatalyst breakdown (e.g., dimer dissociation or disproportionation, see Figure 1), we calculated[37] the energetic penalties for the different possibilities and compared those to the $PdL_2 \rightarrow PdL + L$ dissociation energy. As a first approximation, we studied the direct dissociative pathways. Table 2 summarizes the results. We employed the M06L functional that has been shown to be appropriate for the treatment of metal−ligand binding interaction,[36] and used a CPCM solvation model for THF.

Table 2. Calculated Dissociation Energies for Potential Dimer Dissociations[25,36] (Compare with Figure 1; L = $PtBu_3$)

dissociation	ΔG_{diss} (kcal/mol)[a]
$Pd^{(0)}L_2 \rightarrow Pd^{(0)}L + L$	27.2
$\{Pd^{(I)}BrL\}_2 \rightarrow 2\ Pd^{(I)}LBr$	24.8
$\{Pd^{(I)}BrL\}_2 \rightarrow Pd^{(II)}Br_2L + Pd^{(0)}L$	38.1
$\{Pd^{(I)}BrL\}_2 \rightarrow Pd^{(II)}Br_2 + Pd^{(0)}L_2$	65.4
$\{Pd^{(I)}BrL\}_2 \rightarrow LPd_2Br_2 + L$	36.2

[a]M06L(THF)//B3LYP/6-31+G(d) with SDD (for Pd).

For the "benchmark" dissociation of $PdL_2 \rightarrow PdL + L$, we calculated an energetic penalty of 27.2 kcal/mol (entry 1), which is in the range of the previously calculated 30 kcal/mol for the alternative substrate-assisted displacement mechanism (see above).

For the Pd(I) dimer precatalyst activation, disproportionation has frequently been assumed as the likely mechanism to form Pd(0)L.[2,3,5] However, the calculations suggest that disproportionation of Pd(I) dimer to $\mathrm{PdBr_2P}t\mathrm{Bu_3}$ and $\mathrm{PdP}t\mathrm{Bu_3}$ is too high an energy process (38.1 kcal/mol) and therefore disfavored (see entry 3, Table 2). Thus, the generally assumed facile liberation of highly reactive $\mathrm{Pd(0)P}t\mathrm{Bu_3}$ does not seem to occur in a direct disproportionate manner from the precatalyst. As discussed previously, homolytic dissociation into the Pd(I) radical seems to be feasible (24.8 kcal/mol), and this pathway for precatalyst transformation is of lowest energy, at least among the possibilities that we calculated in Table 2. However, the involvement of Pd(I) radicals in the catalytic cycle was already excluded above (Figure 6). If the precatalyst activation were to occur via homolytic cleavage, reduction of the Pd(I) radical to Pd(0) would need to subsequently take place.

Thus, the most likely scenario for precatalyst activation is via a reductive mechanism.[38]

Stability of the Pd(I) Dimer—Spectroscopic Studies.

To get additional insights into the transformation and stability of the dinuclear Pd(I) complex, we performed ^{31}P NMR investigations on the reaction involving the Pd(I) dimer precatalyst with **1** under Suzuki cross-coupling conditions. We mixed 2-methylphenylboronic acid, substrate **1**, KF, the Pd(I) dimer (under catalytic conditions with 2.5 mol % catalyst loading), and THF in a glovebox (t = 0 s) and subsequently followed the reaction by ^{31}P NMR spectroscopy versus an internal standard (Me_3PO_4). Figure 7 shows the ^{31}P NMR spectra after (i) 5 and (ii) 20 min reaction time, which is the point when the conversion reached a plateau at ca. 80% and did not reach full conversion thereafter. Interestingly, we observed a second peak in the ^{31}P NMR at 85.5 ppm along with the Pd(I) dimer (87 ppm)[6] after 5 min. We identified this peak as $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$, verified through independent mixing of $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$, 2-methylphenylboronic acid, water, KF, and internal standard in THF. After 20 min reaction time, $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ is the only phosphine-containing species present in the mixture.

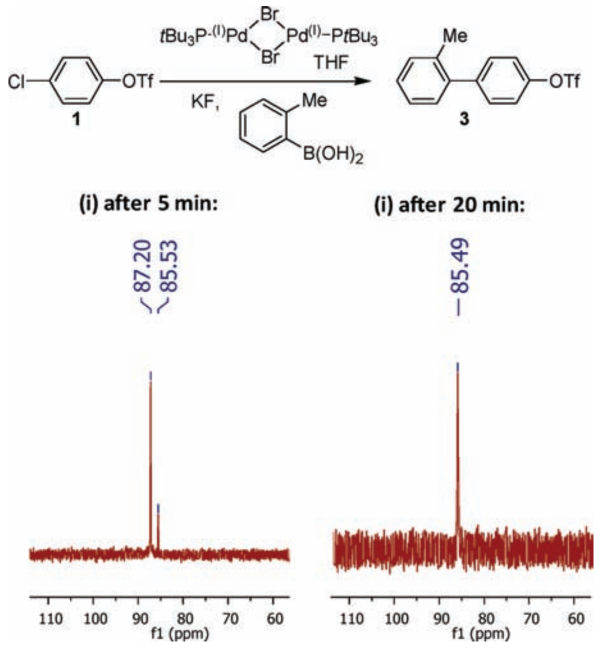


Figure 7. ^{31}P NMR study versus internal standard (Me_3PO_4).

$\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ in turn is the resting state observed in catalysis derived from $\mathrm{Pd_2(dba)_3/P}t\mathrm{Bu_3}$.[16] Under those conditions (and when 1:1 Pd:L ratios are employed), a second, phosphine-free Pd(0) species is presumed to be present in the mixture also.

Does the observation of $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ in the ^{31}P NMR spectrum mean that the Pd(I) dimer reactivity in fact involves the intermediacy of $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$? To examine this, we performed further spectroscopic studies and carried out a stepwise addition sequence of the reagents. We separately mixed the Pd(I) dimer, water,[39] arylboronic acid, and KF along with the internal standard in THF. This led to partial conversion of dimer to $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ (peak at 85.5 ppm,[16] see Figure 8). Through examination of different addition sequences,[40] we found that only the combination of water, arylboronic acid, and KF gives rise to conversion of the Pd(I)—Pd(I) precatalyst to $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$. During this process of Pd(I) dimer transformation to $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$, we also noted a black precipitation from solution, which we presume to be Pd-black. As such, the conversion to $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ is independent of the substrate and the catalytic cycle and constitutes either an activating or deactivating process of the precatalyst.

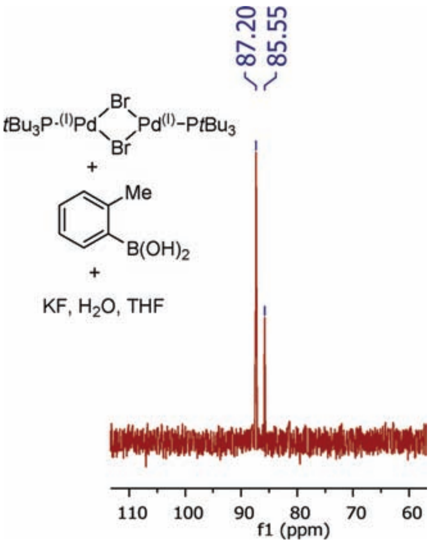
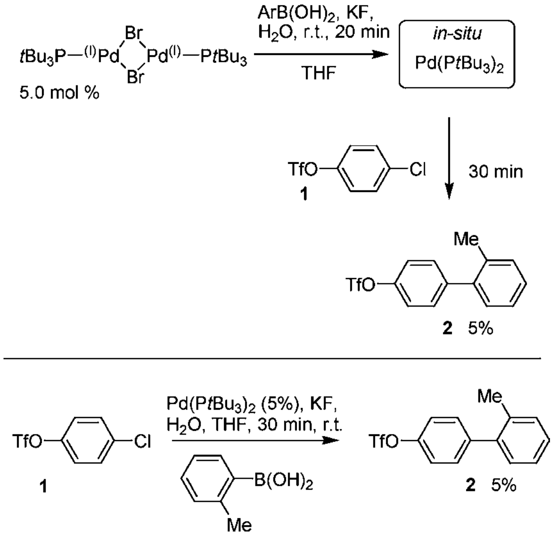


Figure 8. ^{31}P NMR study versus internal standard (Me_3PO_4).

We next set out to test whether the transformation of Pd(I) dimer to $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ is in fact crucial for catalysis. To investigate this, we fully transformed the Pd(I) dimer *in situ* using 2-methylphenylboronic acid, KF, and H_2O in THF (see Scheme 2). Once full conversion to $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ had taken place (as judged by ^{31}P NMR), **1** was added. Thirty minutes later, we examined the reaction mixture by calibrated ^{1}H NMR spectroscopic analysis, which indicated that product **3** had formed in only 5% yield. Using commercially available $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ in a separate experiment gave rise to the same conversion with substrate **1** (see Scheme 2). For comparison, the reaction with Pd(I) dimer with only 1.5 mol % catalyst loading gave 76% yield after the identical reaction time (see Figure 4). The conversion from Pd(I) dimer to $\mathrm{Pd(P}t\mathrm{Bu_3)_2}$ (and Pd-black) must thus be a deactivation pathway of the

Scheme 2. Reactivity of 1 with Pd(P*t*Bu$_3$)$_2$[a]



[a]Conditions: KF (3.0 equiv), ArB(OH)$_2$ (1.01 equiv), H$_2$O (3.0 equiv).

precatalyst. Whether the same process is also responsible for generating the active Pd(0) species can be neither confirmed nor excluded. However, this process could explain why reactions with aryl chlorides do not reach full conversion under Pd(I) dimer conditions, even with greater catalyst loadings or prolonged reaction times.[3] Wheras Pd(P*t*Bu$_3$)$_2$ is also a proficient catalyst for aryl bromides (e.g., under alternative autocatalytic pathways[7b]), it is an inefficient species for the transformation of aryl chlorides. The competing Pd(I) dimer to Pd(P*t*Bu$_3$)$_2$ transformation is thus the likely cause of subquantitative conversions in Suzuki cross-coupling reactions of {[P*t*Bu$_3$]PdBr}$_2$ with aryl chlorides.

■ CONCLUSIONS

In conclusion, through computational, experimental, and NMR studies, we have shown that the reactivity derived from the dinuclear Pd(I)−Pd(I) precatalyst, {[P*t*Bu$_3$]PdBr}$_2$, is consistent with monocuclear Pd(0) catalysis. The Suzuki cross-coupling reactivity observed in nonpolar solvents is consistent with Pd(0)L and with anionic Pd(0)LX$^-$ in polar solvents, completely analogous to reactivity under Pd$_2$(dba)$_3$/P*t*Bu$_3$ conditions. Computational studies suggest that precatalyst transformation to the active catalytic species does not proceed via a direct disproportionation mechanism, and a reductive pathway is likely instead. Through ^{31}P NMR investigations it was identified that the combination of ArB(OH)$_2$, KF, and water triggers the conversion of the precatalyst to Pd(P*t*Bu$_3$)$_2$ and, most likely, Pd-black as a competing side-process, explaining the subquantitative conversions of unactivated aryl chlorides in Suzuki cross-coupling reactions. Highly regio- and chemoselective transformations have also been demonstrated in short reaction times at room temperature employing Pd(I) dimer conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details on experimental procedures, spectroscopic data, computational information, Cartesian coordinates of all calculated species and thermal data, and complete ref 26. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

Schoenebeck@org.chem.ethz.ch

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■ REFERENCES

(1) (a) First preparation of a Pd(I) dimer: Gelman, A. D.; Meilakh, E. *Dokl. Akad. Nauk SSSR* **1942**, *36*, 188. (b) For a review: Murahashi, T.; Kurosawa, H. *Coord. Chem. Rev.* **2002**, *231*, 207. (c) Werner, H. *Adv. Organomet. Chem.* **1981**, *19*, 155.

(2) (a) Vilar, R.; Mingos, D. M. P.; Cardin, C. J. *J. Chem. Soc., Dalton Trans.* **1996**, 4313. (b) Dura-Vila, V.; Mingos, D. M. P.; Vilar, R.; White, A. J. P.; Williams, D. J. *J. Organomet. Chem.* **2000**, *600*, 198. For further studies, see: (c) Christmann, U.; Vilar, R.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **2004**, 1294. (d) Christmann, U.; Pantazis, D. A.; Benet-Buchholz, J.; McGrady, J. E.; Maseras, F.; Vilar, R. *J. Am. Chem. Soc.* **2006**, *128*, 6376.

(3) (a) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746. (b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176. (c) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.

(4) Prashad, M.; Mak, X. Y.; Liu, Y.; Repic, O. *J. Org. Chem.* **2003**, *68*, 1163.

(5) For other transformations using Pd(I) dimers, see: (a) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (b) Hill, L. L.; Crowell, J. L.; Tutwiler, S. L.; Massie, N. L.; Hines, C. C.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. *J. Org. Chem.* **2010**, *75*, 6477. (c) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793. (d) Barder, T. E. *J. Am. Chem. Soc.* **2006**, *128*, 898. (e) Han, X.; Weng, Z.; Hor, T. S. A. *J. Organomet. Chem.* **2007**, *692*, 5690.

(6) Colacot, T. J. *Platinum Metals Rev.* **2009**, *53*, 183.

(7) In efforts to synthesize Pd(II) complexes in the presence of dba, dimer formation was observed: (a) Strambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184. See also: (b) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 5842.

(8) Boyd, P. D. W.; Edwards, A. J.; Gardiner, M. G.; Ho, C. C.; Lemée-Cailleau, M.-H.; McGuinness, D. S.; Riapanitra, A.; Steed, J. W.; Stringer, D. N.; Yates, B. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6315.

(9) (a) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

(10) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524.

(11) *Nanoparticles and Catalysis*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2007.

(12) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(13) The bond dissociation energy of a related Pd(I)−Pd(I) dimer was previously determined to be between 21 and 29 kcal/mol. See: Lee, C. L.; James, B. R.; Nelson, D. A.; Hallen, R. T. *Organometallics* **1984**, *3*, 1360.

(14) (a) Das, R. K.; Saha, B.; Rahaman, S. M. W.; Bera, J. K. *Chem.—Eur. J.* **2010**, *16*, 14459. (b) Murahashi, T.; Takase, K.; Oka, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 14908. For discussion, see also: (c) Han, X.; Weng, Z.; Hor, T. S. A. *J. Organomet. Chem.* **2007**, *692*, 5690. (d) See also ref 8.

(15) Proutiere, F.; Schoenebeck, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8192.

(16) Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(17) The boronic acid used was deoxygenated prior to use. Boronic acid, **1**, KF, and water were dissolved in solvent. The mixture was stirred for 5 min and the catalyst subsequently added (t = 0).

(18) This is in line with previous comparative kinetic studies of various precatalysts with the Pd(I) dimer in amination reactions, see: Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861.

(19) We performed the Pd(I) dimer reactions also in DMF and toluene (under otherwise identical conditions). In DMF, exclusive C−OTf insertion was seen (61% of **3** was formed, and 39% of **1** was recovered). In toluene, exclusive C−Cl insertion was detected (**2** was formed in 75% yield and 22% of **1** was recovered).

(20) *Metal-catalyzed cross-coupling reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(21) Lee, C. L.; James, B. R.; Nelson, D. A.; Hallen, R. T. *Organometallics* **1984**, *3*, 1360.

(22) (a) Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787. For application of DFT-D for the study of organometallic catalysis, see: (b) Kozuch, S.; Martin, J. M. L. *ACS Catal.* **2011**, *1*, 246. (c) McMullin, C. L.; Jover, J.; Harvey, J. N.; Fey, N. *Dalton Trans.* **2010**, *39*, 10833.

(23) Dispersion correction was previously shown to be beneficial in the treatment of dimeric metal complexes, see: Grimme, S.; Djukic, J.-P. *Inorg. Chem.* **2011**, *50*, 2619.

(24) Regarding the appropriateness of DFT for radicals, see: (a) Riley, K. E.; Op't Holt, B. T.; Merz, K. M. *J. Chem. Theory Comput.* **2007**, *3*, 407. (b) Lyaskovskyy, V.; Olivos Suarez, A. I.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011**, *133*, 12264. (c) Valcarcel, A.; Clotet, A.; Ricart, J. M.; Delbecq, F.; Sautet, P. *J. Phys. Chem. B* **2005**, *109*, 14175.

(25) CPCM (THF) M06L/6-31+G(d)//B3LYP/6-31+G(d) with SDD (for Pd) was applied. The standard state was converted to 1 M in solution.

(26) Frisch, M. J.;et al. *Gaussian09*, Revision A.01 [see SI for full reference].

(27) The $\langle S^2 \rangle$ values for the oxidative addition TSs are $\langle S^2 \rangle$ = 0.763 for C−Cl insertion by Pd(I) radical and $\langle S^2 \rangle$ = 0.772 for C−OTf insertion, which do not deviate too much from the expected values for a radical.

(28) The preference for C−Cl insertion is calculated to be $\Delta\Delta G^{\ddagger}$= 8.7 kcal/mol in THF and 8.4 kcal/mol in MeCN. Calculated with CPCM B3LYP-D/6-31+G(d) and SDD (for Pd). See SI for details.

(29) Gas-phase energies are given. See ref 22 for application of D-DFT in Pd catalysis. B3LYP was previously found to be an adequate method to study such transformations: de Jong, G. T.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2006**, *2*, 322.

(30) (a) Pozharskii, A. F.; Soldatenkov, A. T.; Katrizky, A. R. *Heterocycles in Life and Society*; Wiley: New York, 1997. (b) Reynolds, J.; Skotheim, T. A. *Handbook of Conducting Polymers*, 3rd ed.; CRC Press: Boca Raton, FL, 2007. (c) *Electronic Materials: The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, 1998. (d) Sariciftci, N. S.; Smilowitz, L.; Heeger, A. J.; Wudl, F. *Science* **1992**, *258*, 1474.

(31) (a) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537. (b) Strotman, N. A.; Chobanian, H. R.; He, J.; Guo, Y.; Dormer, P. G.; Jones, C. M.; Steves, J. E. *J. Org. Chem.* **2010**, *75*, 1733. (c) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036. (d) For a review, see: Schroter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.

(32) (a) Gallant, M.; Belley, M.; Carriere, M.-C.; Chateauneuf, A.; Denis, D.; Lachance, N.; Lamontagne, S.; Metters, K. M.; Sawyer, N.; Slipetz, D.; Truchon, J. F.; Labelle, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3813. (b) Samantha, V.; Handy, S. T. *Synthesis* **2009**, *1*, 138.

(33) (a) Müller, H. M.; Delgado, O.; Bach, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4771. (b) Delgado, O.; Müller, H. M.; Bach, T. *Chem.—Eur. J.* **2008**, *14*, 2322.

(34) We also investigated the regioselectivities under $Pd_2(dba)_3$ (2.5 mol%)/PtBu$_3$ (5 mol %) conditions: reaction of dichloropyrimidine with 4-methoxyphenylboronic acid gave similar selectivity as entry 3, Table 1, but lower conversion after 30 min at room temperature (31%, 9:1 selectivity). Reaction of dibromothiazole with 4-methoxyphenylboronic acid gave 91% of the product arising from coupling in the 2-position as the exclusive product.

(35) (a) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (b) See also ref 3c.

(36) In THF, previous studies suggest an equilibration time of 5 min to form Pd(PtBu$_3$)$_2$. See ref 18.

(37) For appropriateness of M06L to calculate binding energies, see: (a) Sieffert, N.; Bühl, M. *Inorg. Chem.* **2009**, *48*, 4622. (b) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364. (c) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101. (d) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2006**, *110*, 13126.

(38) The mechanism of this reductive process is the topic of future work.

(39) (a) On the importance of water in the transmetallation, see: Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. Butters, M.; Harvey, J.; Jover, J.; Lennox, A.; Lloyd-Jones, G.; Murray, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156. (b) On the importance of water in precatalyst activation in amination reactions, see: Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505. (c) Lou, S.; Fu, G. C. *Adv. Synth. Catal.* **2010**, *352*, 2081. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(40) We examined mixing of (i) dimer + boronic acid + water, then KF; (ii) dimer + KF + water, then boronic acid; and (iii) dimer + boronic acid + KF, then H_2O.