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Mechanistic Study of the Role of Substrate Steric Effects and Aniline Inhibition on the Bis(trineopentylphosphine)palladium(0)-Catalyzed Arylation of Aniline Derivatives

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Abstract: The mechanism of the bis(trineopentylphosphine)palladium(0) ($Pd(PNp_3)_2$)-catalyzed coupling of aryl halides and aniline derivatives was studied in an effort to understand the role of substrate steric effects on the reaction. Prior studies had shown that the rate of Pd/PNp_3-catalyzed coupling of aryl bromides and aniline derivatives was largely unaffected by substrate steric demand. The oxidative addition of aryl bromides to $Pd(PNp_3)_2$ is found to follow first order kinetics with a rate that is independent of both ligand and aryl halide concentration. Thus, the rate limiting step for oxidative addition of aryl bromides is irreversible ligand dissociation. In the case of aryl chlorides, the oxidative addition rate has a first order dependence on [ArCl] and an inverse dependence on [PNp_3] indicating a mechanism involving reversible dissociation of ligand followed by rate limiting oxidative addition. This difference in aryl halide effect was also

found for the catalytic coupling reaction. Aryl bromide steric demand does not affect the coupling rate with hindered anilines, whereas the coupling rate of aryl chlorides is negatively affected by substrate steric demand. These results suggest that oxidative addition is rate limiting in the catalytic reaction for aryl chlorides, but that oxidative addition is not rate limiting for aryl bromides. Aniline was found to give significantly slower coupling rates than 2,6-diisopropylaniline for both aryl bromides and chlorides. Aniline promotes the decomposition of the $[(PNp_3)Pd(Ar)(\mu\text{-}X)]_2$ catalytic intermediate to a catalytically inactive palladacycle ($[(\kappa^2\text{-}P,C\text{-}Np_2PCH_2C(Me_2)CH_2)Pd(\mu\text{-}X)]_2$) through C-H activation of a neopentyl group and elimination of arene. These studies show that the ability of the Pd/PNp_3 catalyst system to tolerate steric demand in aryl bromides stems from the fact that the rate limiting step of the catalytic cycle is independent of the concentration and steric demand of aryl bromides. A catalyst deactivation pathway involving ligand metallation has been identified that is promoted by unhindered aniline derivatives.

KEYWORDS: amination, oxidative addition, kinetics, mechanistic study, palladium, palladacycle, phosphine

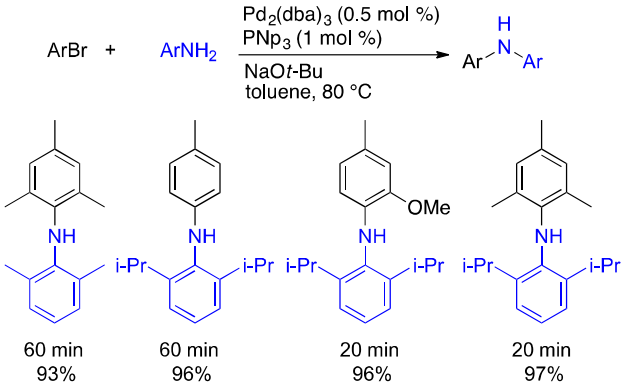
Introduction

Aryl amines are common motifs in pharmaceuticals, agricultural chemicals, and electronic materials. Metal-catalyzed amine arylations have become widely used synthetic methods in both academic and industrial labs. These methods date back over 100 years to Ullman's[1] initial report of the coupling of aryl halides with amines mediated by copper. Copper-catalyzed methods continue to be widely used for C–N bond formation.[2] Beginning with the seminal work of Buchwald and Hartwig,[3] palladium-catalyzed amine arylation has been developed into a

powerful method for the synthesis of carbon-nitrogen bonds.[4] Much of the development of these catalyst systems has focused on the identification of more effective ligands to promote the catalytic process. Current classes of privileged ligands include sterically demanding trialkylphosphines,[5] 2-biarylphosphines,[6] *N*-heterocyclic carbenes,[7] and chelating alkylphosphines.[8]

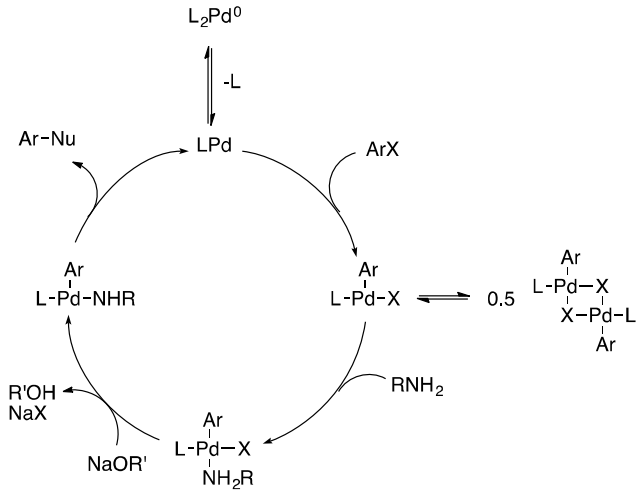
Our group has shown that neopentylphosphines, such as di(*tert*-butyl)-neopentylphosphine ((*t*-Bu)$_2$PNp) and trineopentylphosphine (PNp$_3$) afford effective catalysts for a variety of C–C and C–N coupling reactions.[9] The neopentyl substituent provides additional conformational flexibility compared to other sterically demanding substituents, such as *t*-butyl or 1-adamantyl. Depending on the conformation, the neopentyl group can have a relatively large or small steric impact. Conformationally flexible ligands have shown promise for coupling of challenging sterically demanding substrates.[10] The catalyst derived from Pd$_2$(dba)$_3$ and trineopentylphosphine displays high catalytic efficiency for the coupling of a wide scope of sterically demanding aryl bromides and chlorides with sterically hindered aniline derivatives.[9f] In contrast, the catalysts derived from the more rigid (*t*-Bu)$_2$PNp or P(*t*-Bu)$_3$ are much less active for the coupling of di-*ortho*-substituted aryl halides with hindered aryl amines. More interestingly, the Pd$_2$(dba)$_3$/PNp$_3$ system showed limited sensitivity to the steric demand of the substrates based on both isolated yields and reaction rate. In some cases, more sterically hindered substrates gave faster reaction rates than less hindered examples (Scheme 1).

Scheme 1. Pd$_2$(dba)$_3$/PNp$_3$-catalyzed coupling of aryl bromides and aniline derivatives.



In order to better understand the effect of sterically demanding substrates on the Pd/PNp$_3$ catalyst system, we sought to explore the mechanism in more detail. Mechanistic studies of B-H amination systems have generally supported a mechanism involving formation of a coordinatively unsaturated active species followed by a sequence of oxidative addition, replacement of the halide with the amide nucleophile, and reductive elimination (Scheme 2). In the case of sterically demanding, monodentate ligands, the active species is proposed to be a monoligated complex (LPd(0)). The oxidative addition product may form an off cycle halide-bridged dimer with these ligands.

Scheme 2. General mechanism for palladium-catalyzed amination



Detailed mechanistic studies have been performed on several B-H catalyst systems. The Hartwig, Blackmond, and Buchwald groups carefully studied the Pd/BINAP catalyst system.[11] The consensus mechanism involves reversible ligand dissociation from $Pd(BINAP)_2$ to provide the coordinatively unsaturated Pd(BINAP) species that undergoes rate limiting oxidative addition of the aryl bromide (Scheme 2, L = BINAP). Reaction with amine and base affords a palladium amide species, which undergoes reductive elimination to provide the product and regenerate the active Pd(BINAP) species.

The Buchwald group has performed computational and experimental studies on palladium/2-biphenylphosphine catalyst systems.[12] Based on these studies, a similar mechanism beginning with a monophosphine-palladium complex was proposed. The reaction is proposed to involve rotation of the palladium from interacting with the ligand arene group to orienting away from the arene upon amine coordination. Reaction progress kinetic analysis (RPKA) of the coupling of aryl halides with sterically demanding primary amines catalyzed by CPhos (2-((2',6'-bis(dimethylamino)biphenyl)diphenylphosphine) gave different rate limiting steps depending on

the aryl halide substrates.[13] For aryl chlorides, oxidative addition appears to be rate limiting, whereas for aryl bromides the reductive elimination is the likely rate limiting step.

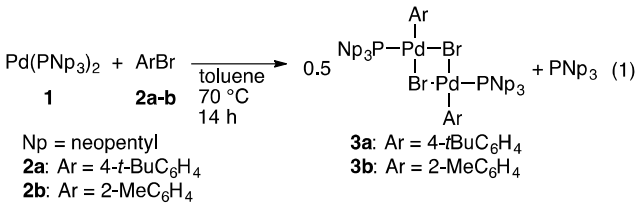
Organ has studied the mechanism of amination using PEPPSI precatalysts and weak bases, such as Cs_2CO_3. In the case of alkyl amines, deprotonation of the palladium-bound amine by the heterogeneous weak base is the rate determining step.[10c,14] This step is sensitive to the electronic nature of the aryl halide and aryl amine, both of which affect the pK_a of the palladium-bound amine. With more acidic aniline complexes, deprotonation is faster and reductive elimination is thought to be rate determining.[15]

Mechanistic studies of trialkylphosphine catalyst systems are most relevant to the trineopentylphosphine system. The oxidative addition of aryl halides to PdL_2 complexes (L = P(*t*-Bu)$_3$, (1-Ad)P(*t*-Bu)$_2$, CyP(*t*-Bu)$_2$, and PCy$_3$) was found to depend on the nature of the ligand and the halide leaving group.[16] For aryl bromides, the mechanism appears to involve two competing rate limiting ligand displacement steps prior to oxidative addition: irreversible ligand dissociation and irreversible associative displacement of the ligand by the aryl bromide. The associative mechanism is the major pathway with the less hindered tricyclohexylphosphine ligand, whereas the dissociative pathway becomes competitive with more hindered ligands. The participation of an associative pathway is supported by computational studies showing this as an energetically favorable pathway.[17] In contrast, oxidative addition of aryl chlorides involves reversible dissociation of a ligand followed by rate limiting oxidative addition with no evidence of a competing associative pathway. Analysis of the full catalytic mechanism using Pd(P(*t*-Bu)$_3$)$_2$ showed that the reaction rate depended on base identity, but not the amine.[18] Hartwig proposed competing mechanisms involving rate limiting oxidative addition to both Pd(P(*t*-Bu)$_3$) and [((*t*-Bu)$_3$P)Pd(OR)]$^-$ species.

The majority of these experimental and computational studies have focused on simple aryl halides. Organ has explored the effect of substrate electronic properties,[10c,14-15] but there has been limited work on the mechanistic impact of substrate steric properties. In light of the steric tolerance seen in the $Pd_2(dba)_3/PNp_3$ catalyst system,[9f] we were interested to explore the mechanism of this reaction in more detail. We hypothesized that the conformational flexibility of trineopentylphosphine was responsible for the tolerance of steric bulk in these reactions. Trineopentylphosphine is capable of adopting very sterically demanding conformations with significantly larger cone angles than $P(t\text{-Bu})_3$.[9b] Unlike, $P(t\text{-Bu})_3$, PNp_3 exhibits significant conformational flexibility allowing it to facilitate the coupling of sterically demanding substrates. We sought to better understand the mechanism for this system and how substrate steric demand affects the reaction.

Results

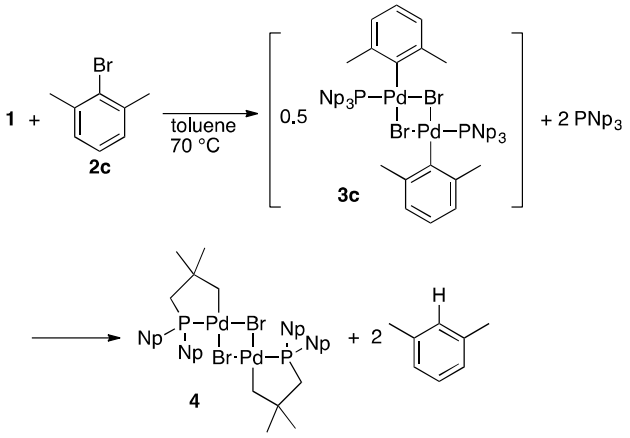
Oxidative addition of aryl halides to $Pd(PNp_3)_2$. In our report of the Pd/PNp_3-catalyzed amination reaction, the catalyst was generated in situ from $Pd_2(dba)_3$ and PNp_3. Given the complexity of the $Pd_2(dba)_3$ system, we chose to use the well defined $Pd(PNp_3)_2$ complex (**1**) to study of the mechanism of the oxidative addition reaction. We have previously reported that $Pd(PNp_3)_2$ reacts cleanly with unhindered or mono-*ortho*-substituted aryl bromides to cleanly afford halide-bridged $[(Np_3P)Pd(Ar)(\mu\text{-Br})]_2$ complexes **3a** and **3b** (eq 1).[9f]



In the case of 2-bromo-*m*-xylene (**2c**), the oxidative addition occurs to afford **3c** as observed by ^{31}P NMR spectroscopy, but the product undergoes decomposition by C-H activation of the ligand

to afford palladacycle **4** and arene (Scheme 3). Our group has recently reported the synthesis of palladacycles derived from (*t*-Bu)$_2$PNp ([(κ^2-*P,C*-*t*-Bu$_2$PCH$_2$C(Me$_2$)CH$_2$)Pd(μ-Br)]$_2$ and [(κ^2-*P,C*-*t*-Bu$_2$PCH$_2$C(Me$_2$)CH$_2$)Pt(μ-OAc)]$_2$, but the complexes were not structurally characterized.[19] The acetate bridged dimer is an active catalyst for the cross-coupling of aryl acetylenes with propargyl alcohols. Metallacyclic complexes of platinum ([(κ^2-*P,C*-*t*-Bu$_2$PCH$_2$C(Me$_2$)CH$_2$)Pt(μ-Cl)]$_2$)[20] and iridium ((κ^2-*P,C*-*t*-Bu$_2$PCH$_2$C(Me$_2$)CH$_2$)IrCl(P(*t*-Bu)$_2$Np)[21] derived from (*t*-Bu)$_2$PNp have been structurally characterized. Dahlenburg reported a PNp$_3$-derived iridium metallacycle, but the complex was not structurally characterized.[22]

Scheme 3. Attempted oxidative addition of 2-bromo-*m*-xylene to Pd(PNp$_3$)$_2$



Complex **4** was isolated and X-ray quality crystals were obtained by recrystallization from pentane (Figure 1). The complex adopts a butterfly structure with a 126° angle between the two palladium square planes. The palladacycle has a constrained P-Pd-C angle (82.7°, 82.8°). This value is similar to other reported five-membered ring palladacycles derived from alkylphosphines.[23] Due to the steric strain, the P-C-C angles of the neopentyl groups are large (123.8–125.0°). The neopentyl substituents are positioned above and below the palladium square planes with relatively small Pd-P-C-C dihedral angles (28.4–53.9°).

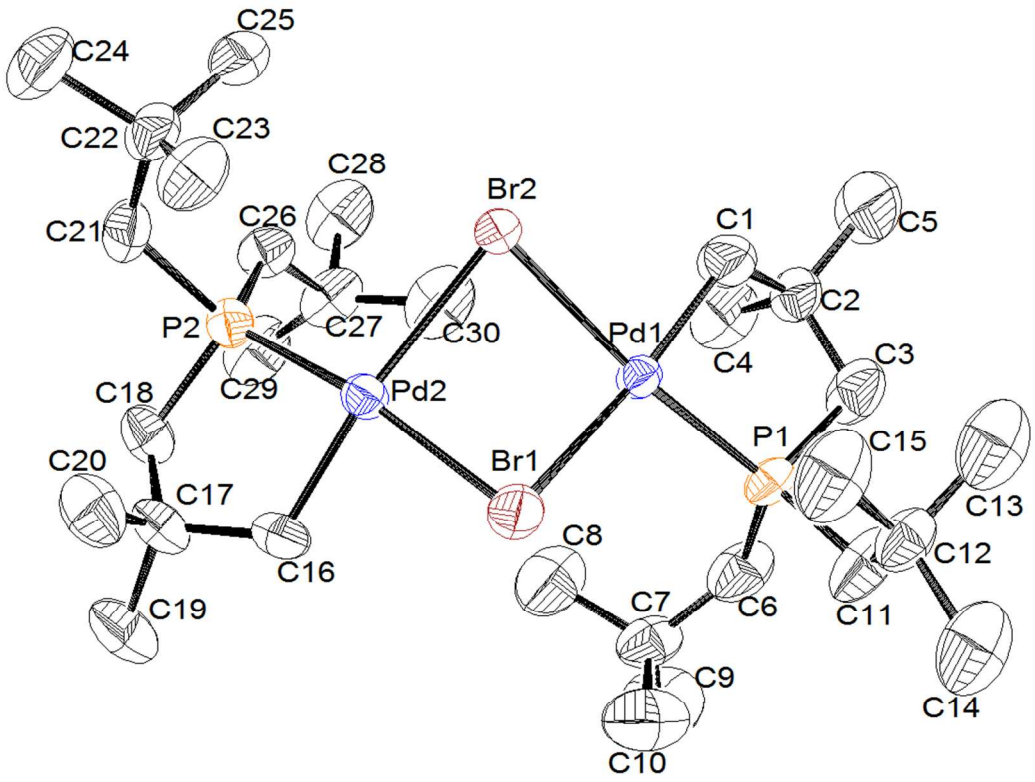
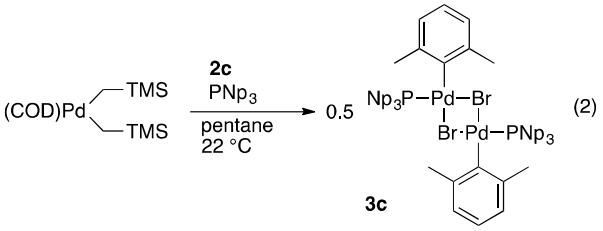


Figure 1. ORTEP diagram of complex **4** (ellipsoids drawn at the 50% probability level). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Pd1-Br1, 2.5914(5); Pd1-P1, 2.240(1); Pd1-Br2, 2.5357(5); Pd1-C1, 2.033(4); Pd2-Br1, 2.5268(5); Pd2-Br2, 2.5952(5); Pd2-P2, 2.234(1); Pd2-C16, 2.046(4); P1-C3, 1.822(4). Selected bond angles (deg): Br1-Pd1-Br2, 85.14(2); Br1-Pd2-Br2, 85.24(2); C1-Pd1-P1, 82.7(1); Br1-Pd1-P1, 103.91(3); Br2-Pd1-C1, 88.4(1); Pd1-C1-C2, 118.3(3); C1-C2-C3, 108.6(4); P1-C2-C3, 109.4(3); Pd1-P1-C3, 104.9(2); P1-C6-C7, 124.8(4) P1-C11-C12, 125.0(3); Pd1-P1-C6-C7, -45.4(5); Pd1-P1-C11-C12, -28.4(5); Pd2-P2-C21-C22, 45.0(4); Pd2-P2-C26-C27, 53.9(4).

The observation of **3c** during the oxidative addition to $Pd(PNp_3)_2$ suggested the compound could be formed, but that it was not thermally stable. Complex **3c** can be prepared by the

reaction of 2-bromo-*m*-xylene (**2c**) with (COD)Pd($CH_2TMS)_2$ and PNp_3 in pentane at room temperature (eq 2).[24] Under these conditions, complex **3c** is stable and can be isolated. X-ray quality crystals of **3c** were obtained by recrystallization from pentane. Complex **3c** adopts a similar structure to previously reported complexes **3a** and **3b** (Figure 2).



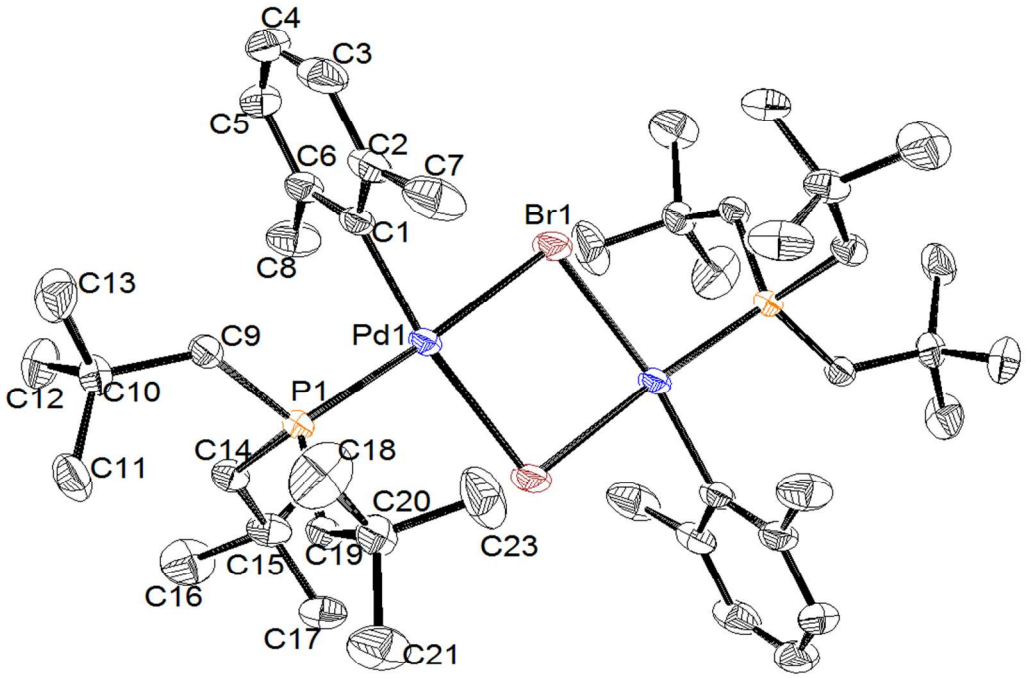
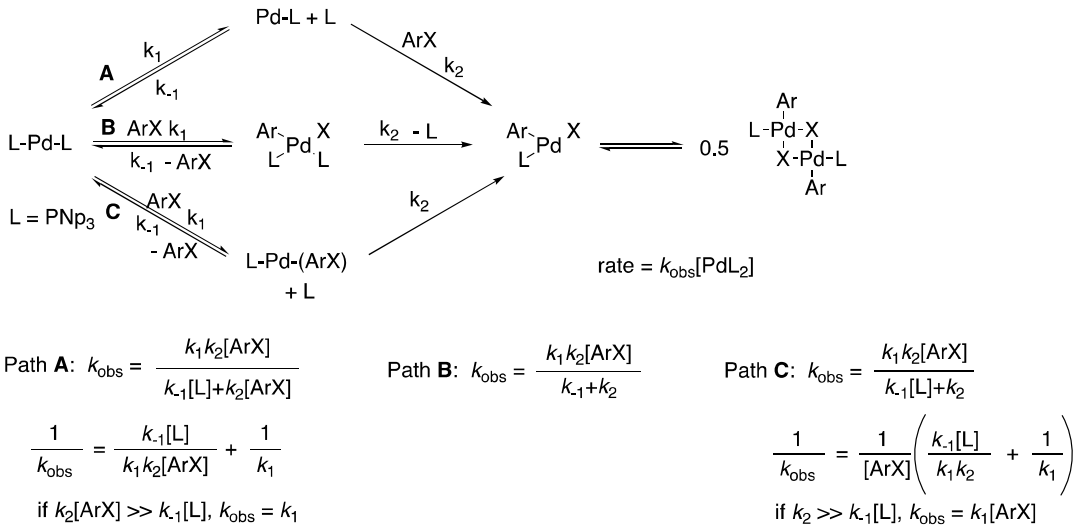


Figure 2. ORTEP diagram of complex **3c** (ellipsoids drawn at the 50% probability level). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Br1-Pd1, 2.5814(4); Br1-Pd1, 2.5060(3); Pd1-P1, 2.2710(3); Pd1-C1 2.009(1); Br1-Pd1-Br1, 85.68(1). Selected bond

angles (deg): Br1-Pd1-P1, 97.49(1); P1-Pd1-C1, 91.31(4); C1-Pd1-Br1, 85.52(4); Pd1-P1-C9, 112.80(4); Pd1-P1-C19, 115.11(4); Pd1-P1-C14, 115.71(4); Pd1-Br1-Pd1, 94.32(1); C10-C9-P1, 128.7(1); C20-C19-P1, 125.57(9); C15-C14-P1, 126.5(1); Pd1-P1-C9-C10, 163.9(1); Pd1-P1-C14-C15, 49.9(1); Pd1-P1-C19-C20, 60.9(1).

Oxidative addition of aryl halides to PdL_2 can be envisioned to proceed by three main mechanisms: dissociative ligand loss followed by oxidative addition (path A), direct oxidative addition to the L_2Pd species (path B), or associative displacement of the ligand by aryl halide followed by oxidative addition (Scheme 4).[16a] Prior experimental and computational studies have shown that path B is unlikely with sterically demanding ligands,[16a,17a] although it may be possible in the case of PCy_3.[16c] Both paths A and C have a potentially reversible ligand displacement followed by the oxidative addition step. In path A, a reversible ligand dissociation followed by rate limiting oxidative addition would result in a rate expression with an inverse dependence on ligand concentration and a non-linear dependence on aryl halide. The inverse of this rate expression would depend linearly on [L] and inversely on [ArX] with the same non-zero y-intercept if $1/k_{obs}$ is plotted versus 1/[ArX] or [L]. If ligand dissociation is rate limiting and irreversible, then the rate expression would be a simple first order dependence on $[PdL_2]$ with no dependence on [L] or [ArX]. The associative pathway (path C) requires a first order dependence on [ArX] in all cases. If oxidative addition were rate limiting, there would be an inverse dependence on [L]. Conversely, if associative ligand substitution were rate limiting, there would be no ligand concentration dependence. Thus the mechanism can be ascertained by analysis of the effect of aryl halide and ligand concentration on the rate of the reaction.

Scheme 4. Possible Mechanism for the Oxidative Addition of ArX to $Pd(PNp_3)_2$.



Path **A**: $k_{obs} = \frac{k_1 k_2[ArX]}{k_{-1}[L]+k_2[ArX]}$ Path **B**: $k_{obs} = \frac{k_1 k_2[ArX]}{k_{-1}+k_2}$ Path **C**: $k_{obs} = \frac{k_1 k_2[ArX]}{k_{-1}[L]+k_2}$

$\frac{1}{k_{obs}} = \frac{k_{-1}[L]}{k_1 k_2[ArX]} + \frac{1}{k_1}$

if $k_2[ArX] >> k_{-1}[L]$, $k_{obs} = k_1$

$\frac{1}{k_{obs}} = \frac{1}{[ArX]}\left(\frac{k_{-1}[L]}{k_1 k_2} + \frac{1}{k_1}\right)$

if $k_2 >> k_{-1}[L]$, $k_{obs} = k_1[ArX]$

The rate of the reaction of $Pd(PNp_3)_2$ (7.9 mM) with aryl bromides **2a**, **2b**, and **2c** was determined under pseudo-first order conditions over the aryl bromide concentration range of 150 to 310 mM in toluene at 60 °C. Reaction progress was followed by ^{31}P NMR spectroscopy by observing the decrease in the concentration of $Pd(PNp_3)_2$. $Pd(PNp_3)_2$, dimeric complexes **3a-b**, and free PNp_3 were the only phosphorus containing products observable for **2a** and **2b** (Figure S59, Supporting Information). In the case of **2c**, the oxidative addition product is converted to palladacycle **4** after formation (Scheme 3). Formation of complex **4** is irreversible under these conditions. In addition, complex **4** does not react with aryl halides. Therefore, conversion of **3c** to **4** does not affect the rate of $Pd(PNp_3)_2$ consumption in the reaction with **2c**. Oxidative addition products **3a-c** give broad spectra at the reaction temperature due to isomerization between stereoisomeric forms, which makes accurate integration difficult. Therefore, the decrease in the concentration of $Pd(PNp_3)_2$ was used to determine the reaction rate. Plotting $\ln[Pd(PNp_3)_2]$ versus time afforded linear plots indicating that the reactions were first order in palladium (see Supporting Information). At 0.15 mM 1-bromo-4-*tert*-butylbenzene (**2a**), the observed rate

constant was 1.11 x 10^{-4} s^{-1}. Changing the concentration of **2a** over a factor of 2 had no effect on the reaction rate (Figure 3, Table S2, Supporting Information) indicating a zero order dependence on [ArBr]. Oxidative addition of **2b** and **2c** to $Pd(PNp_3)_2$ were also zero order in [ArBr] and gave a similar rate constant (1.05 ± 0.07 x 10^{-4} s^{-1}) to that observed with **2a**. The lack of dependence of the reaction rate on the concentration and identity of the aryl bromide shows that the aryl bromide is not involved in the rate determining step of the oxidative addition reaction.

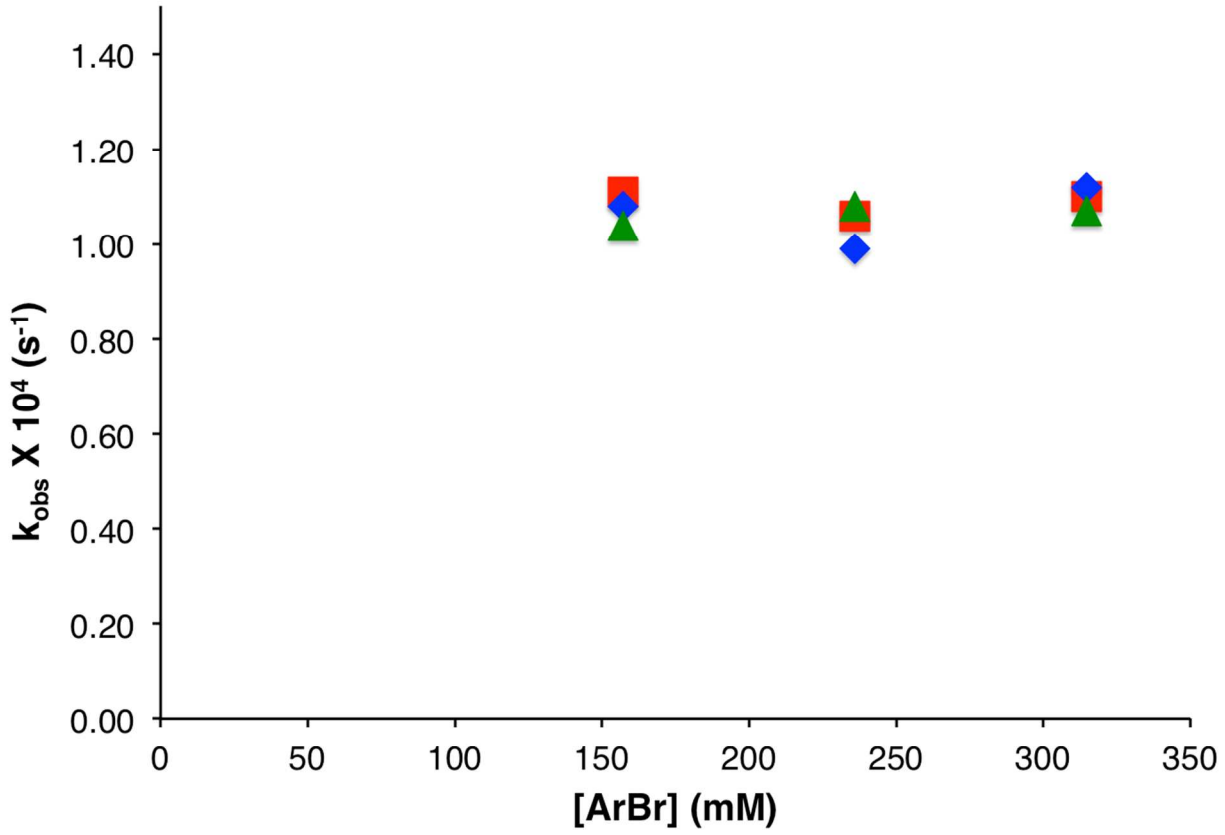


Figure 3. Plot of aryl bromide concentration vs. first order rate constant for the oxidative addition of **2a** (red square), **2b** (blue diamond), and **2c** (green triangle) to **1**.

The effect of added ligand on the oxidative addition was then studied. The oxidative addition of **2a** (80 mM) to $Pd(PNp_3)_2$ (7.9 mM) was carried out in the presence of 2, 4, 6, and 10 equivalents of PNp_3 (16 to 79 mM) at 60 °C. The reactions in the presence of additional PNp_3 proceeded in the same fashion as those run in the absence of added ligand. The decay of $Pd(PNp_3)_2$ was linear with no evidence of an induction period. At all concentrations of excess PNp_3 tested, the observed rate constant was the same within experimental error (0.86 ± 0.02 X 10^{-4} s^{-1}, Figure 4). Thus, the reaction is also zero order in $[PNp_3]$.

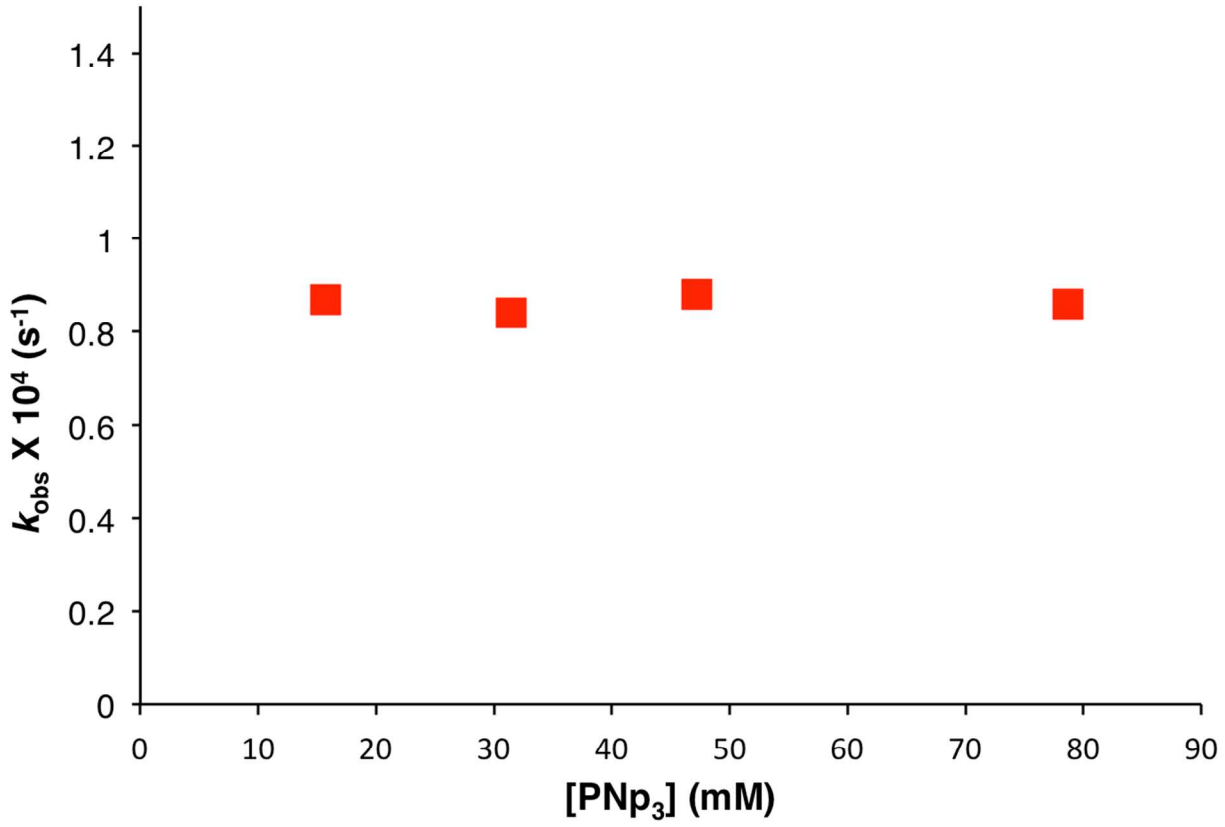
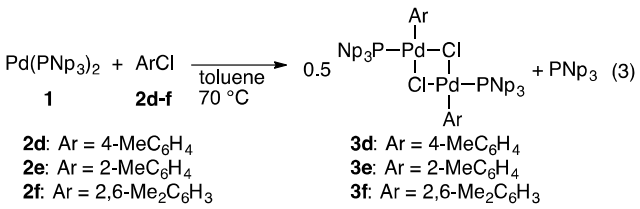


Figure 4. Plot of excess PNp_3 concentration vs. first order rate constant for the oxidative addition of **2a** (10 mM) to **1**.

The zero order dependence of both [ArBr] and [PNp_3] on the rate of the oxidative addition reaction is only consistent with a mechanism involving rate limiting irreversible ligand dissociation followed by oxidative addition (Path A, Scheme 4). Therefore, the observed rate constant 1.0 ± 0.15 X 10^{-4} s^{-1} corresponds to k_1, the ligand dissociation rate constant. Other sterically demanding trialkylphosphines, such as P(*t*-Bu)$_3$, (1-Ad)P(*t*-Bu)$_2$, CyP(*t*-Bu)$_2$, and PCy_3 all undergo oxidative addition by mechanisms that involve reaction of the aryl halide directly with PdL_2 as a competitive mechanistic pathway.[16a,16c] Of the systems studied to date, only Q-phos-tol (1-di(*tert*-butyl)phosphino-1',2',3',4',5'-penta(4-tolyl)ferrocene) undergoes oxidative addition by rate limiting irreversible ligand dissociation.[16b] Trineopentylphosphine has a smaller dissociation rate constant than that reported for Q-phos-tol (6 X 10^{-4} s^{-1} at 50 °C).[16b]

Similar kinetic studies were conducted on the oxidative addition of aryl chlorides to $Pd(PNp_3)_2$. In the absence of excess PNp_3, 4-chlorotoluene (**2d**), 2-chlorotoluene (**2e**), and 2-chloro-*m*-xylene (**2f)** were reacted with $Pd(PNp_3)_2$ under pseudo-first order conditions at 70 °C (eq 3). The plot of ln[$Pd(PNp_3)_2$] vs. time gave a linear relationship indicating these reactions were first order in palladium (see Supporting Information). Plotting k_{obs} vs. [ArCl] showed that the reaction rate had a positive, but non-linear, dependence on [ArCl] (Figure 5). In addition, the rate of the reaction depended on the identity of the aryl chloride with the reaction occurring faster with less hindered aryl chlorides (**2d** > **2e** > **2f**). The oxidative addition of 4-chlorotoluene (**2d**) was then performed in the presence of excess PNp_3. Plotting k_{obs} vs. [PNp_3] provides a negative dependence of the rate on [PNp_3] (Figure 6).



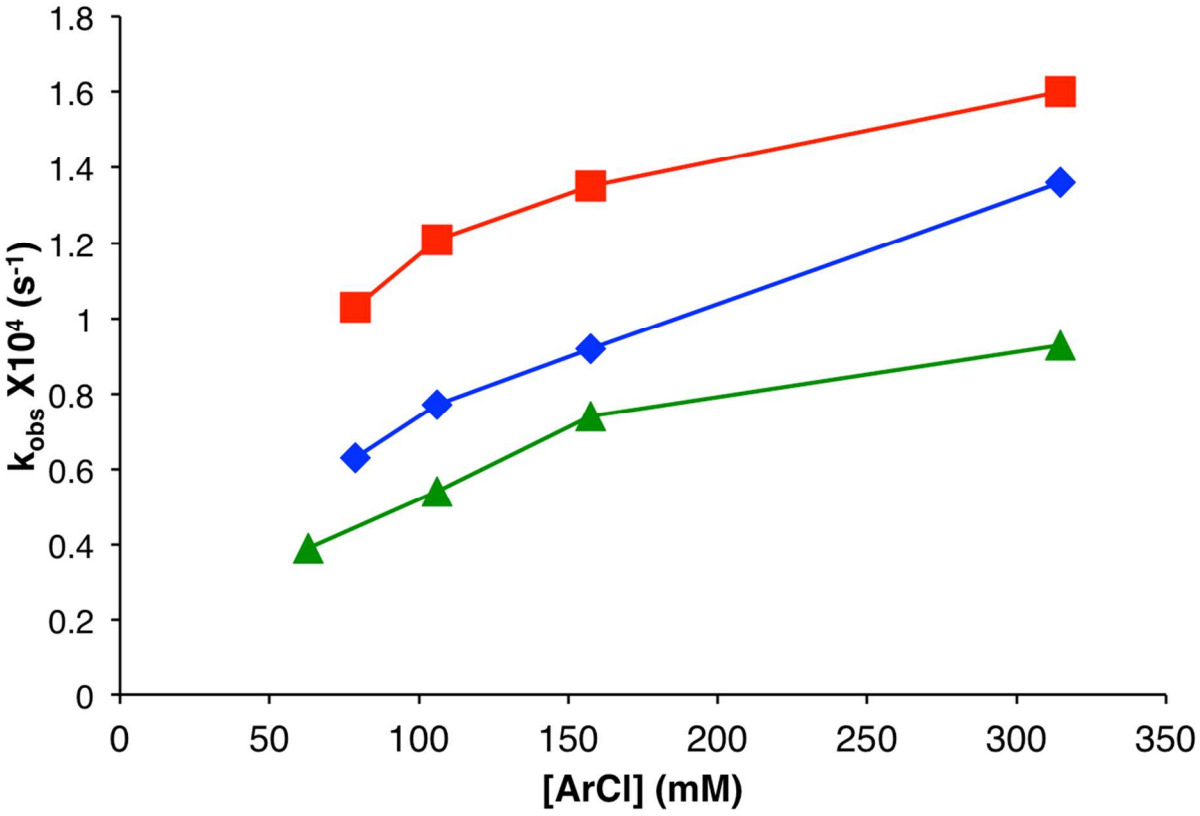


Figure 5. Plot of aryl chloride concentration vs. first order rate constant for the oxidative addition of **2d** (red square), **2e** (blue diamond), and **2f** (green triangle) to **1**.

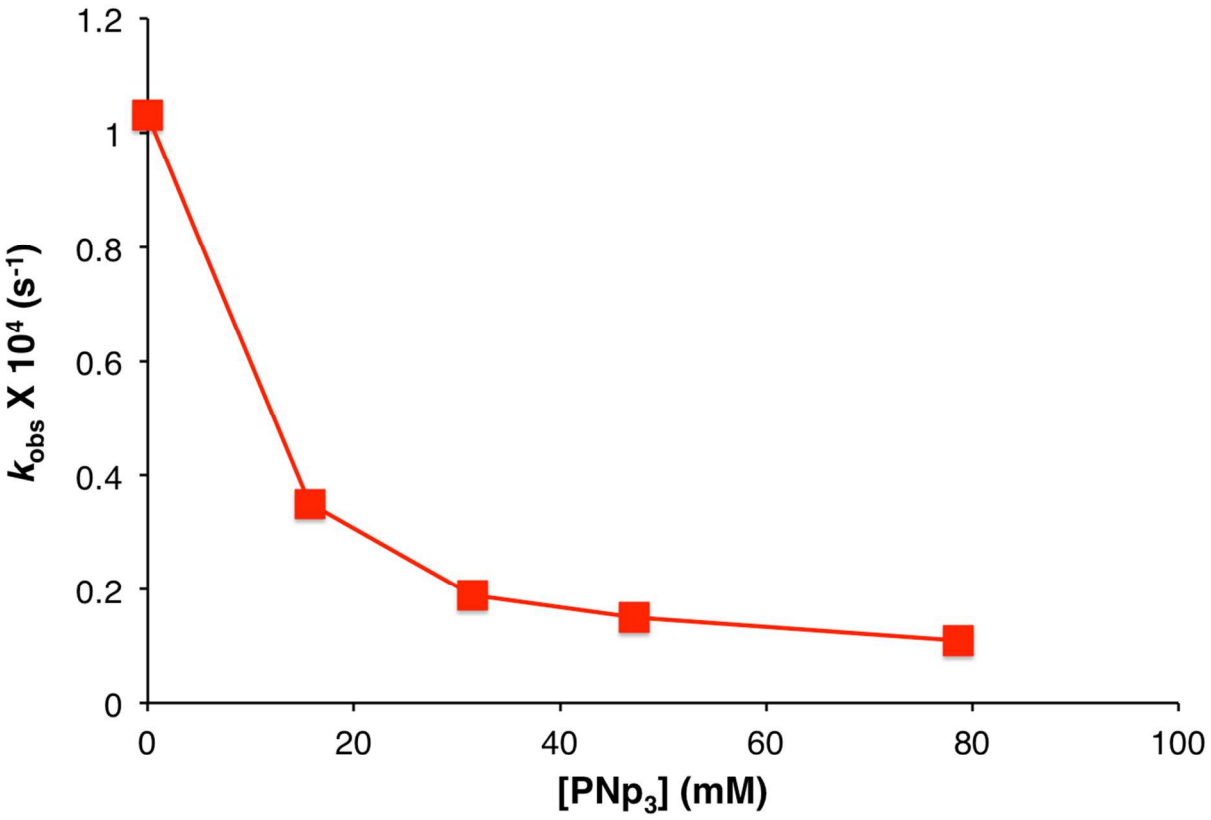


Figure 6. Plot of excess PNp_3 concentration vs. first order rate constant for the oxidative addition of **2d** (10 mM) to **1**.

The results in Figures 5 and 6 show that aryl chlorides react by a different mechanism than is observed for aryl bromides. The inverse ligand dependence is consistent with a reversible ligand loss, as opposed to the irreversible ligand dissociation seen for aryl bromides. Both the reversible dissociative displacement mechanism (path A) and reversible associative ligand substitution (path C) are consistent with a positive dependence on [ArCl] and a negative dependence on [PNp_3]. Path C would be expected to have a linear dependence on [ArCl], however. Plotting $1/k_{obs}$ vs. 1/[ArCl] and [PNp_3] allows the two mechanisms to be further distinguished (Scheme 4). The reversible associative displacement mechanism (path A) should provide linear plots for both $1/k_{obs}$ vs. 1/[ArCl] and $1/k_{obs}$ vs. [L] with both plots giving the same non-zero *y*-intercept.

The dissociative mechanism (path C) would also give linear plots for $1/k_{obs}$ vs. 1/[ArCl] and $1/k_{obs}$ vs. [L]. In this case, the $1/k_{obs}$ vs. 1/[ArCl] plot would have a *y*-intercept of zero, whereas the $1/k_{obs}$ vs. [L] plot would have a non-zero *y*-intercept.

A plot of $1/k_{obs}$ and 1/[ArCl] provides a linear plot for **2d**, **2e**, and **2f** with a non-zero *y*-intercept (Figure 7). The *y*-intercepts for **2d** and **2e** are identical (4,800 s), whereas a higher value (6,600 s) is obtained with **2f**. The non-zero *y*-intercept is consistent with reversible ligand dissociation prior to rate limiting oxidative addition as the major pathway. A plot of $1/k_{obs}$ vs. [PNp_3] shows a positive correlation that appears to deviate from linearity at higher ligand concentration ($R^2 = 0.977$, Figure 8). Linear regression provides a *y*-intercept of 13,800 s, which is a factor of 2-3 larger than those obtained from the aryl chloride plots.

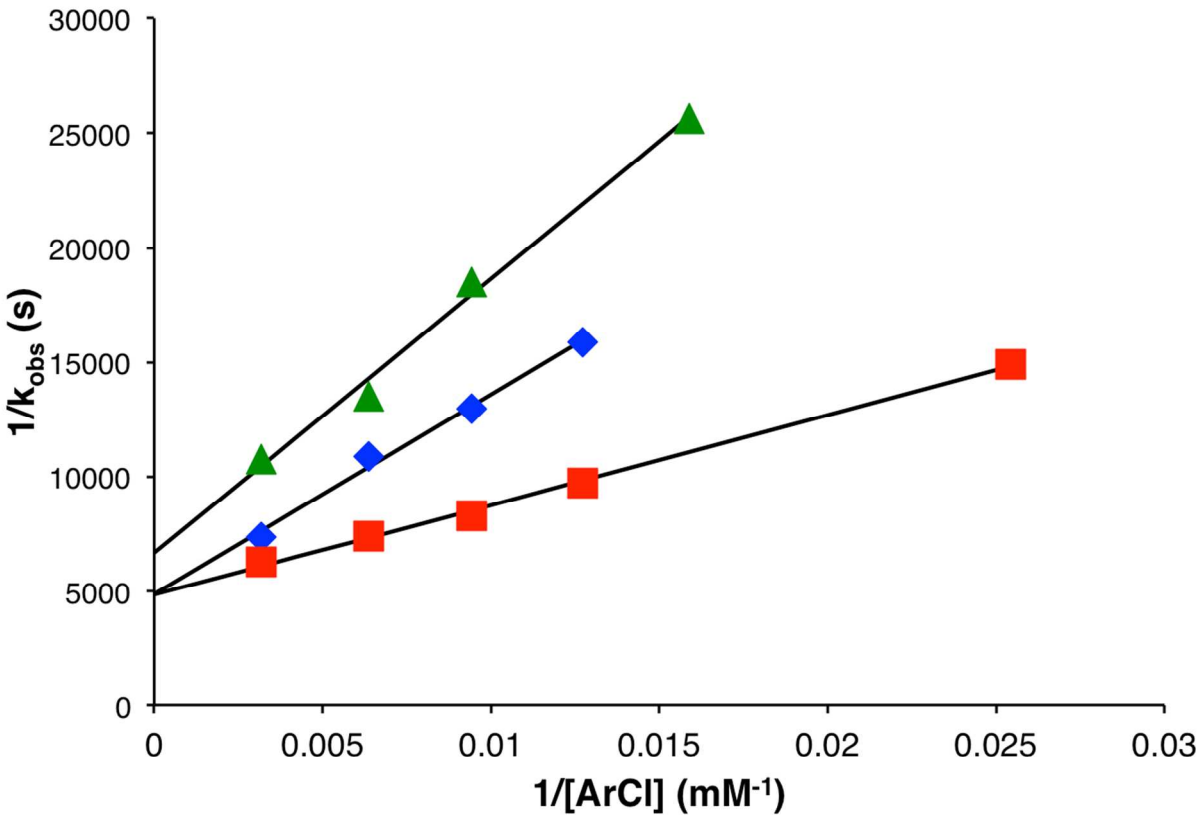


Figure 7. Plot of $[ArCl]^{-1}$ concentration vs. k_{obs}^{-1} for the oxidative addition of **2d** (red square), **2e** (blue diamond), and **2f** (green triangle) to **1**. Black lines show linear regression ($R^2 > 0.99$)

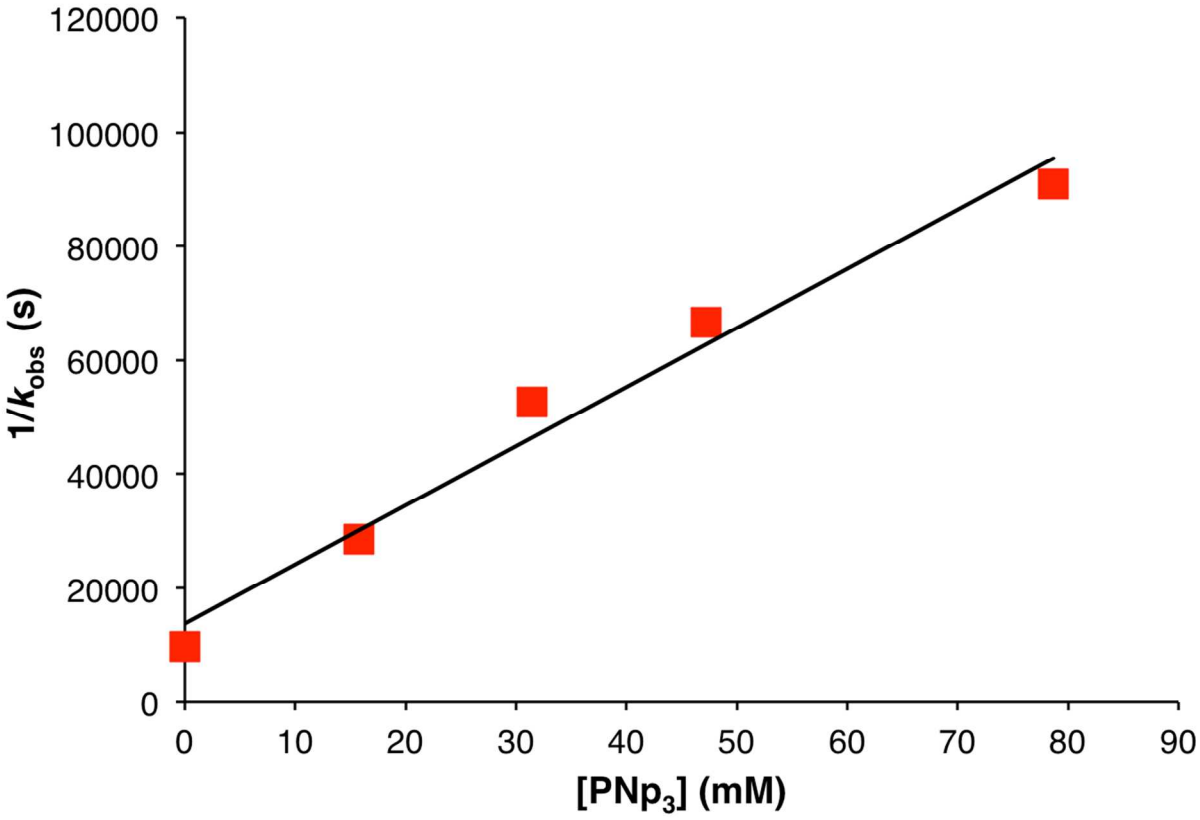


Figure 8. Correlation of the Inverse of Observed Rate Constant ($1/k_{obs}$) and the Concentration of PNp_3 Ligand in Excess of 4-Chlorotoluene ($[Pd(PNp_3)_2]$: [4-Chlorotoluene] = 1: 10). (linear fit: $y = 1.04*10^3x + 1.39*10^4$, $R^2 = 0.977$)

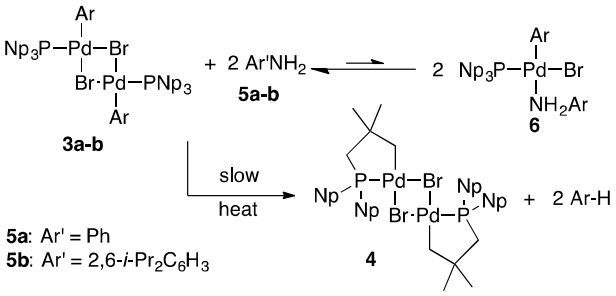
Although the *y*-intercept of the plots obtained in these experiments are not identical, they fall within a relatively narrow range. Significantly, the plot of $1/k_{obs}$ vs. 1/[ArCl] has a non-zero *y*-intercept, which would exclude the associative pathway (Path C). The average *y*-intercept values for the three aryl chlorides (Figure 7) provides a ligand dissociation rate constant (k_1, Scheme 4)

of 1.8 X 10^{-4} s^{-1} at 70 °C. This values is approximately twice that obtained for k_1 from the oxidative addition of aryl bromides at 60 °C (1 X 10^{-4} s^{-1}), which is consistent with the higher temperature. The fact that the values for the ligand dissociation rate constants (k_1) obtained with aryl bromides and chlorides are comparable provides strong support for both processes involving ligand dissociation as a first step. The rate of this step should be independent of the aryl halide, whereas an associative ligand substitution would be dependent on the nature of the aryl halide. The evidence indicates that oxidative addition of aryl chlorides proceeds by a reversible dissociation of ligand followed by rate limiting oxidative addition (Path A, Scheme 4). This is the same mechanism seen for the oxidative addition of aryl chlorides with other bulky trialkylphosphines.[16a,16b] The reaction of aryl bromides and chlorides both involve dissociative loss of PNp_3. In the case of the more reactive aryl bromide, oxidative addition occurs rapidly and the ligand dissociation is rate limiting. With the less reactive aryl chloride, the oxidative addition is rate limiting and ligand dissociation is reversible.

Reaction of aryl halide complexes with aniline. The next step in the standard mechanism is the coordination of the amine nucleophile to the arylpalladium complex (Scheme 2). The four-coordinate amine complex has been characterized for complexes of tri-(*o*-tolylphosphine),[25] SPhos, and XPhos.[12b,12c] Analogous complexes of sterically demanding trialkylphosphines have not been reported. Dimeric aryl halide complexes **3a** and **3b** were reacted with aniline and 2,6-diisopropylaniline in an effort to generate the amine adducts (**6**, Scheme 5). Treatment of **3a** or **3b** with 20 equivalents of aniline or 2,6-diisopropylaniline resulted in no change in the ^{31}P NMR spectrum at room temperature after 20 minutes. Heating of the reaction at 60 °C resulted in slow formation of palladacycle **4** and loss of arene. Coordination of aniline is not thermodynamically favored for dimeric complexes **3a** and **3b**. Aniline complexation to $[(SPhos)PdPh(\mu\text{-}Cl)]_2$ has

been observed spectroscopically.[12c] The relative binding constant for aniline is three orders of magnitude less than that of morpholine, however.

Scheme 5. Reaction of aniline derivatives with Pd(II)-aryl complexes **3a-b**

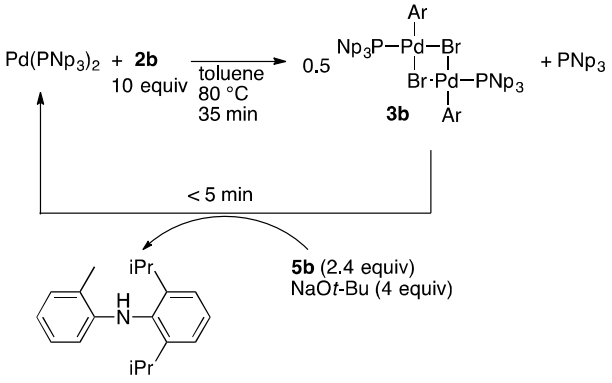


We hypothesized that aniline coordinates in an unfavorable equilibrium with the arylpalladium complex (**3**) followed by a thermodynamically favored deprotonation to give the palladium amide intermediate that undergoes irreversible reductive elimination. Deprotonation of the relatively acidic palladium bound amine by the strong base should be strongly favored thermodynamically and would likely occur with a high rate. Buchwald observed that the competitive reaction of (S-phos)Pd(Ph)Cl with dibutylamine and aniline resulted in no observable binding of aniline.[12c] Upon introduction of base, only diphenylamine was formed, however. These results suggest that the aniline complex is formed as a minor component at equilibrium, but undergoes conversion to product much faster than the more abundant dibutylamine complex.

To test this hypothesis, a solution of complex **3b** was generated by reacting $Pd(PNp_3)_2$ (7.7 mM) with 2-bromotoluene (77 mM) in toluene at 80 °C (Scheme 6). The reaction was followed by ^{31}P NMR spectroscopy and reached completion after 35 minutes. After the consumption of $Pd(PNp_3)_2$ was complete, 2,6-diisopropylaniline (**5b**, 18.5 mM) and NaO-*t*-Bu (30.8 mM) were

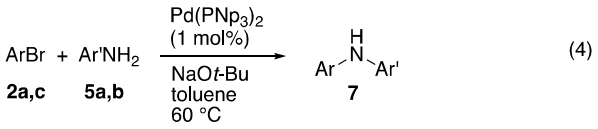
added to the NMR tube and the reaction was monitored by ^{31}P NMR spectroscopy. In less than five minutes, complex **3b** and the free PNp_3 were completely converted to $Pd(PNp_3)_2$ with formation of the diaryl amine product (Scheme 6). Individually, aniline shows no observable reaction with **3a** and NaO*t*-Bu decomposes complex **3**. In combination, aniline and NaO*t*-Bu cleanly react with **3b** to give $Pd(PNp_3)_2$ and the diaryl amine product. This process happens significantly faster than the formation of aryl palladium dimer **3b** from **1**.

Scheme 6. Reaction of arylpalladium complex **3b** with aniline and NaO*t*-Bu



The possibility of alkoxide coordination to palladium prior to amine coordination has been proposed for some systems.[18] To explore this possibility, complex **3a** was reacted with an excess NaO-*t*-Bu (10 equivalents). The reaction resulted in consumption of **3a** and formation of multiple uncharacterized, non-palladacycle phosphorus-containing products in the NMR spectrum. In the presence of both aniline and base, complex **3b** cleanly turns over the catalytic cycle to give $Pd(PNp_3)_2$ (Scheme 6). This result suggests that the reaction of aniline and base with the arylpalladium intermediate to turn over the catalytic cycle is much faster than the decomposition of **3b** by *tert*-butoxide.

Full Catalytic Reaction Profile. The reaction profile for the full catalytic reaction was analyzed for the coupling of aryl bromides and aryl chlorides with anilines catalyzed by $Pd(PNp_3)_2$ (eq 4). The reaction of 1-bromo-4-*tert*-butylbenzene (**2a**) or 2-bromo-*m*-xylene (**2c**) with 2,6-diisopropylaniline (**5b**) occurred at nearly identical rates to give complete conversion in approximately 50 minutes at 60 °C (Figure 9). Aniline (**5a**) gives significantly slower conversion rates than 2,6-diisopropylaniline, however. In addition, **2a** reacted faster with aniline than the more hindered **2c**. Only 50% conversion was observed after six hours when aniline was reacted with **2c**, compared to complete conversion of **2a** in less than 4 hours. All aryl bromide and aniline combinations show an induction period early in the reaction prior to achieving maximum conversion rate.



(4)

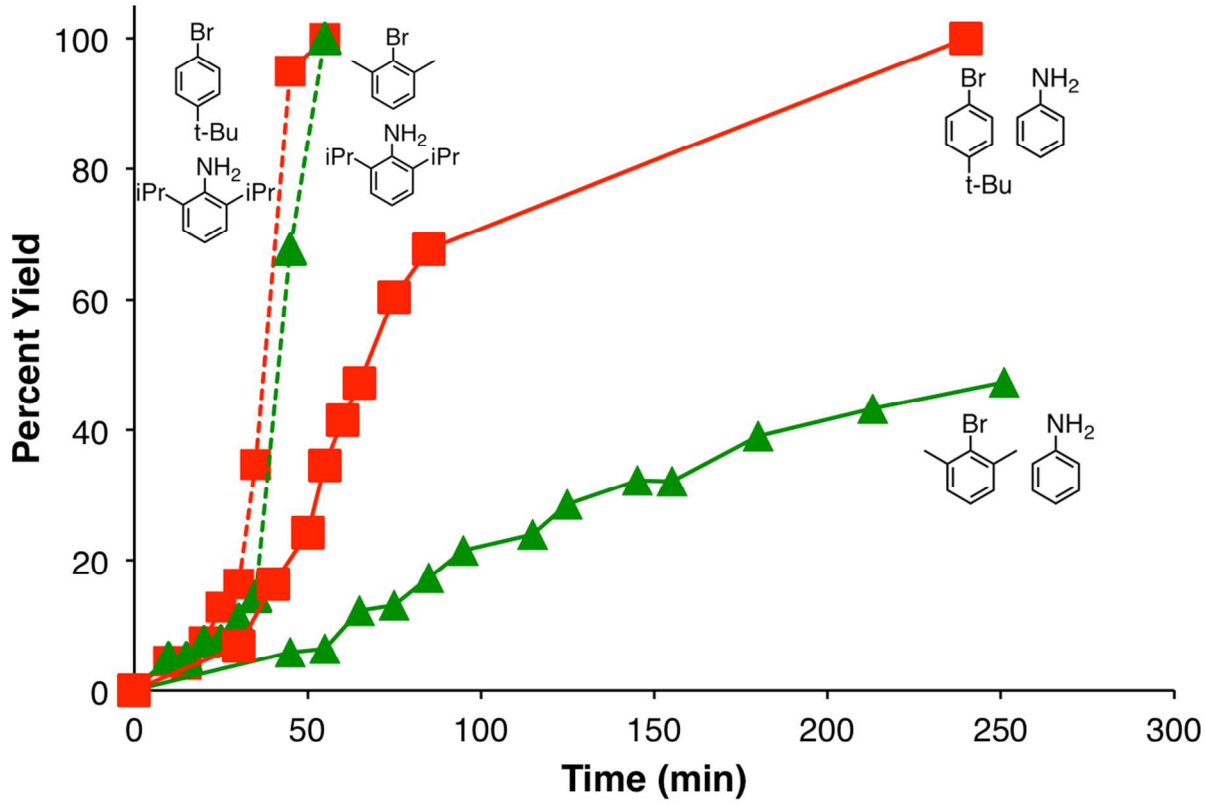
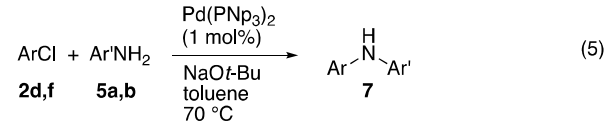


Figure 9. Reaction profile for the $Pd(PNp_3)_2$-catalyzed coupling of **2a** and **5a** (red square, solid line), **2a** and **5b** (red square, dotted line), **2c** and **5a** (green triangle, solid line), and **2c** and **5b** (green triangle, dotted line). Product yields determined by GC.

The same analysis was done on the coupling of 4-chlorotoluene (**2d**) and 2-chloro-*m*-xylene (**2f**) with aniline (**5a**) and 2,6-diisopropylaniline (**5b**) at 70 °C (eq 5). The amination occurred at a higher rate with 4-chorotoluene than 2-chloro-*m*-xylene whether the aryl amine was aniline or 2,6-diisopropylaniline (Figure 10). Similar to the reaction with aryl bromides, aniline was arylated at a much slower rate than the more sterically demanding 2,6-diisopropylaniline. In contrast to aryl bromides, no induction period is observed for the coupling of aryl chlorides with aniline derivatives.



(5)

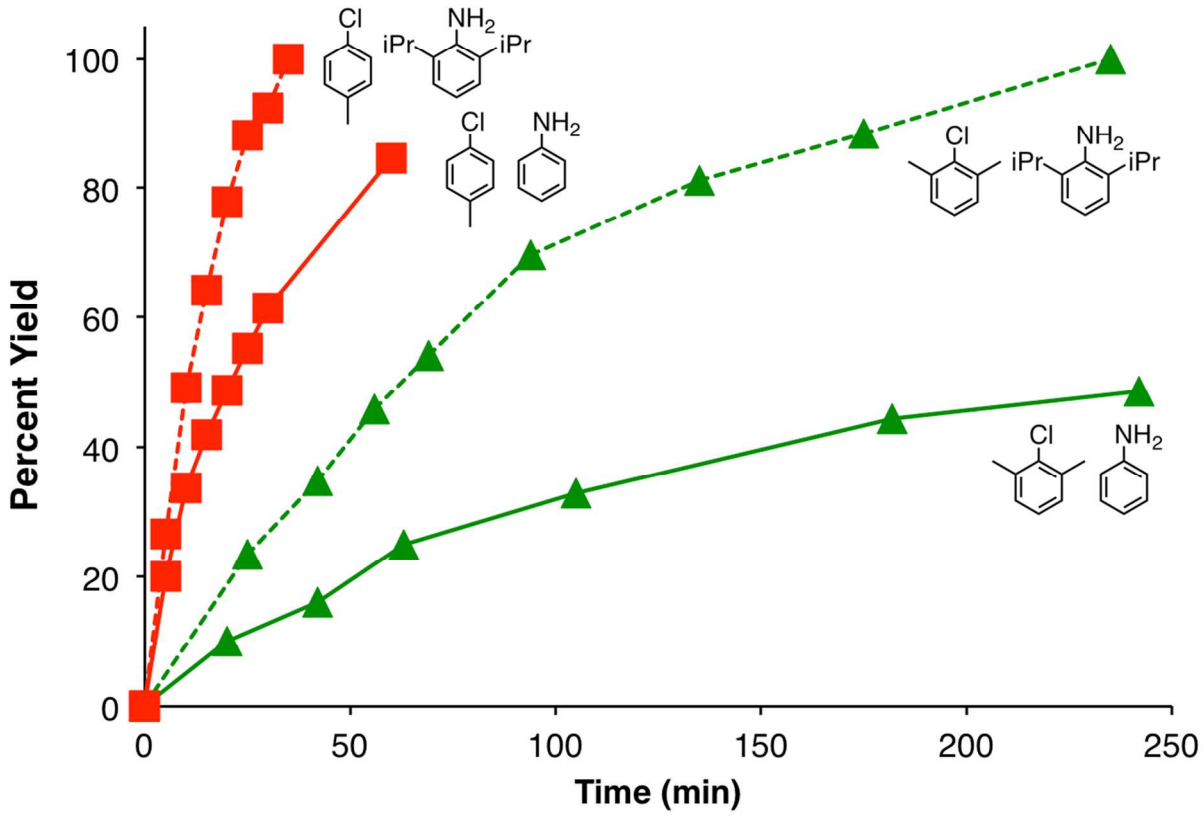
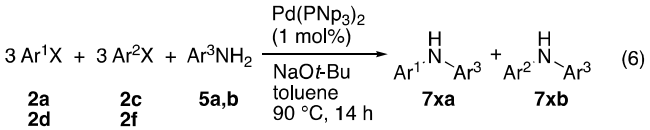


Figure 10. Reaction profile for the $Pd(PNp_3)_2$-catalyzed coupling of **2d** and **5a** (red square, solid line), **2d** and **5b** (red square, dotted line), **2f** and **5a** (green triangle, solid line), and **2f** and **5b** (green triangle, dotted line). Product yields determined by GC.

With the hindered 2,6-diisopropylaniline (**5b**), the results are consistent with the oxidative addition studies. Aryl bromides have little effect on the rate of the catalytic reaction, whereas more hindered aryl chlorides are coupled at slower rates than unhindered aryl chlorides. These results are consistent with the fact that rate of oxidative addition is independent of the aryl bromide, but depends on the aryl chloride. In contrast, the rate of coupling of both aryl bromides

and chlorides with aniline is strongly dependent on the steric demand of the aryl halide. In addition, aniline (**5a**) causes a significant inhibition of the coupling reaction. Another noteworthy point is that an induction period is observed in the coupling of aryl bromides. No induction period is seen in the oxidative addition of aryl bromides, however.

Substrate competition studies. In order to gain more insight into the effect of substrate steric hindrance on the coupling reaction, competition experiments in which two aryl halides were coupled in the same reaction were performed. Competition studies were performed by reacting aniline or 2,6-diisopropylaniline (1 equiv) with a mixture of aryl halides (3 equiv each) in the presence of $Pd(PNp_3)_2$ (0.01 equiv) and NaO*t*-Bu (1.5 equiv) in toluene at 90 °C (eq 6). The reactions were analyzed by GC, which allowed the quantity of both residual aryl halides and both diaryl amine products to be determined (Table 1). In the coupling of 1-bromo-4-*tert*-butylbenzene (**2a**) and 2-bromo-*m*-xylene (**2c**) with aniline (**5a**), the aniline was completely consumed to give a 64:36 ratio of products **7aa** and **7ca** favoring coupling of the less hindered aryl bromides (**2a**). The preference for **2a** is slightly stronger in the case of the more hindered aniline (**5b**, 68:32 **7ab**:**7cb**). Independent rate measurements of **2a** and **2c** reacting with **5b** show little difference in rate, presumably because the oxidative addition step is not rate determining. When the two aryl bromides are both present, the relative reaction rates for the oxidative addition **2a** and **2c** to $Pd(PNp_3)$ can be observed. As expected, the less hindered aryl bromide reacts faster in the oxidative addition step.



(6)

7aa: Ar^1 = 4-*t*-BuC_6H_4, Ar^3 = Ph
7ab: Ar^1 = 4-*t*-BuC_6H_4, Ar^3 = 2,6-*i*-$Pr_2C_6H_3$
7ca: Ar^2 = 2,6-$Me_2C_6H_3$, Ar^3 = Ph
7cb: Ar^2 = 2,6-$Me_2C_6H_3$, Ar^3 = 2,6-*i*-$Pr_2C_6H_3$
7da: Ar^1 = 4-MeC_6H_4, Ar^3 = Ph
7db: Ar^1 = 4-MeC_6H_4, Ar^3 = 2,6-*i*-$Pr_2C_6H_3$

Table 1. Product ratios for competitive coupling of aryl halide mixtures with aniline derivatives.

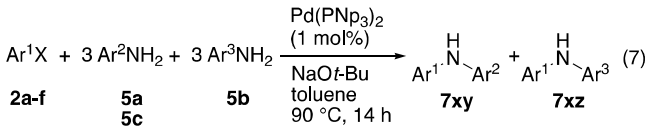
Ar^1X/Ar^2X	Ar^3NH_2	Ar^1NHAr^3 yield (%)[a]	Ar^2NHAr^3 yield (%)[a]
2a/**2c**	**5a**	64 (**7aa**)	36 (**7ca**)
2a/**2c**	**5b**	68 (**7ab**)	32 (**7cb**)
2d/**2f**	**5a**	68 (**7da**)	32 (**7ca**)
2d/**2f**	**5b**	72 (**7db**)	37 (**7cb**)

[a]Product yields determined by GC analysis

The coupling of an excess of aryl chlorides (**2d** and **2f**) with a limiting amount of aniline or 2,6-diisopropyl aniline at 90 °C resulted in complete consumption of aniline to give a mixture of diaryl products (Table 1). The product ratio for the mixture of 4-chlorotoluene (**2d**) and 2-chloro-*m*-xylene (**2f**) favored the **2d**-derived product by a slightly higher ratio (68:32 **7da**:**7ca**) than was seen with aryl bromides. As was seen with the aryl bromides, the less hindered aryl chloride was favored by a slightly higher ratio with the more hindered aniline **5b** (73:27 **7db**:**7cb**). The product selectivity appears to be primarily determined by the preference for the $Pd(PNp_3)$ active species to oxidatively add the less hindered aryl halide. This preference is not strongly affected by the halide identity.

Because of the fast rate of the reaction of aniline and base with aryl halide dimers, the kinetics of this portion of the catalytic cycle could not be studied independently. To probe this portion of the mechanism, we performed a competition experiment using a limiting amount of an aryl halide (**2a-f**) with an excess of a mixture of aniline (**5a**) and 2,6-diisopropyl aniline (**5b**) or 2-toluidine (**5c**) and **5b** (eq 7). The resulting products were analyzed by GC and reported in Table 2. In each case, only the secondary amines derived from the less-hindered aniline (**5a** or **5c**) were

detected at the end of the reactions with no products derived from **5b** observed. These results contrast with the rate profiles for individual aniline derivatives, which show that aniline **5a** gives much slower rates than does the more hindered **5b** (Figures 9 and 10). Another observation from these studies was that the 2,6-disubstituted aryl halides (**2c** and **2f**) gave incomplete conversion in the presence of aniline (**2a**), whereas the less hindered aryl halides were completely consumed. Complete conversion is seen for the coupling of **2c** and **2f** with the mixture of more hindered aryl amines (**5c** and **5b**).



5c: Ar^2 = 2-MeC_6H_4

7ac: Ar^1 = 4-*t*-BuC_6H_4, Ar^2 = 2-MeC_6H_4
7ba: Ar^1 = 2-MeC_6H_4, Ar^2 = Ph
7bb: Ar^1 = 2-MeC_6H_4, Ar^3 = 2,6-*i*-$Pr_2C_6H_3$
7bc: Ar^1 = 2-MeC_6H_4, Ar^2 = 2-MeC_6H_4
7cc: Ar^1 = 2,6-$Me_2C_6H_3$, Ar^2 = 2-MeC_6H_4
7dc: Ar^1 = 4-MeC_6H_4, Ar^2 = 2-MeC_6H_4

Table 2. Product ratios for competitive coupling of aryl halides with aniline mixtures.

Ar^1X	Ar^2NH_2/Ar^3NH_2	Ar^1NHAr^2 yield (%)[a]	Ar^1NHAr^3 yield (%)[a]
2a	**5a/5b**	100 (**7aa**)	0 (**7ab**)
2b	**5a/5b**	100 (**7ba**)	0 (**7bb**)
2c	**5a/5b**	49 (**7ca**)	0 (**7cb**)
2a	**5c/5b**	100 (**7ac**)	0 (**7ab**)
2b	**5c/5b**	100 (**7bc**)	0 (**7bb**)
2c	**5c/5b**	100 (**7cc**)	0 (**7cb**)
2d	**5a/5b**	100 (**7da**)	0 (**7db**)
2e	**5a/5b**	100 (**7ea**)	0 (**7eb**)
2f	**5a/5b**	52 (**7ca**)	0 (**7cb**)
2d	**5c/5b**	100 (**7dc**)	0 (**7db**)

2e	**5c/5b**	100 (**7bc)**	0 (**7bb)**
2f	**5c/5b**	100 (**7cc)**	0 (**7cb)**

[a]Product yields determined by GC analysis

4. Aniline inhibition

The nature of the inhibitory effect of aniline on these reactions was not immediately apparent. Stoichiometric studies showed that the reaction of the oxidative addition product **3** with aniline in the presence of base is fast relative to oxidative addition. Thus, it is not clear what kinetic role aniline would play in the catalytic cycle. We first considered whether aniline has an effect on the rate of oxidative addition, perhaps by coordinating to the $Pd(PNp_3)$ species and inhibiting the oxidative addition step. The oxidative addition of **2a** (20 equiv) to $Pd(PNp_3)_2$ was carried out in the presence of aniline or 2,6-diisopropylaniline (30 equiv) at 60 °C for 6 hours (eq 8). The rate of consumption of $Pd(PNp_3)_2$ was observed to be slightly faster in the presence of anilines **5a** or **5b** than in their absence (Table 3). Palladacycle **4** was formed in the presence of **5a** or **5b** with a corresponding decrease in the oxidative addition yield, however. Palladacycle **4** does not form in the absence of aryl amine under these conditions. Complex **4** was formed in larger amounts in the presence of aniline (**5a**) than with the more hindered **5b**.

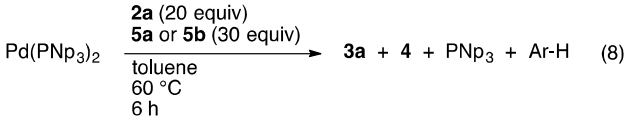


Table 3. Product distribution for oxidative addition of **2a** to $Pd(PNp_3)_2$ in the presence of aniline

aniline	**1** (%)[a]	**3a** (%)[a]	**4** (%)[a]
none	14	86	0

5a	6	83	11
5b	9	87	4

[a]Product distributions determined by ^{31}P NMR spectroscopy relative to an internal standard (trimethylphosphate).

At higher temperatures, arylpalladium complexes **3a-c** undergo direct conversion to palladacycle **4** in the absence of aniline. The rate of palladacycle formation is dependent on the aryl substituent. At 85 °C, hindered complex **3c** is completely converted to palladacycle **4** after 100 minutes. Complex **3a** with a sterically undemanding aryl substituent requires 500 minutes to be completely converted to the palladacycle under the same conditions. With 10 equivalents of aniline (**5a**) present, the decomposition time for complex **3a** was reduced to 160 minutes.

Palladacycle formation by activation of alkylphosphine substituents has been observed previously with P(*t*-Bu)$_3$, where the resulting palladacycle was either a catalyst resting state[26] or a catalytically active species.[27] To test the potential ability of palladacycle **4** to reenter the catalyst cycle, it was tested as a precatalyst. Complex **3c** was heated at 85 °C for 100 minutes in toluene to afford a solution containing palladacycle **4** as the only phosphorus-containing species observable by ^{31}P NMR spectroscopy. Sodium *tert*-butoxide (30 equiv relative to Pd), 2-bromo-*m*-xylene (**2c**, 20 equiv)) and 2,6 diisopropylaniline (**5b**, 22 equiv) were added and the reaction was heated at 80 °C. After stirring for 24 hours, GC analysis showed 36% conversion of **2c** to diaryl amine **7cb**. In contrast, the same reaction catalyzed by Pd(PNp$_3$)$_2$ reached completion in 55 minutes. The reaction was repeated with *t*-butanol added to determine if the alcohol opens the palladacycle to regenerate the active catalyst. In the presence of *t*-butanol, 32% conversion to product **7cb** was obtained.

The inhibitory effect of aniline appears to be due to diversion of the arylpalladium intermediate to palladacycle **4**. Using the palladacycle as the precatalyst results in very slow conversion, suggesting that **4** does not readily reenter the catalytic cycle. Aniline promotes the formation of **4** at a faster rate than the more hindered 2,6-diisopropylaniline (**5b**), resulting in lower catalyst productivity in couplings with aniline. This decomposition process is more favored with more sterically demanding aryl groups on palladium, which accounts for the incomplete conversion of 2,6-disubstituted aryl halides **2c** and **2f** in the presence of excess aniline (Table 2).

5. Analysis of the Induction Period of Amination of ArBr and $ArNH_2$.

An induction period is observed in the reaction of aryl bromides (Figure 9), but not with aryl chlorides (Figure 10). Because ligand dissociation is rate limiting for the stoichiometric aryl bromide oxidative addition, the induction period with aryl bromides could be due to slow formation of the active $Pd(PNp_3)$ complex relative to the catalytic turnover rate. To test this hypothesis, dimers **3a** and **3c**, were used as the precatalysts (0.5 mol% **3a** or **3b**, 1 mol% Pd) in the coupling reaction of **2a** or **2c** with aniline **5b**. These complexes rapidly react with aniline and base to generate the active species (Scheme 6). The reaction catalyzed by complexes **2a** and **2c** both finished within 10 minutes (Figure 11) with no observable induction period. In contrast, the reactions catalyzed by $Pd(PNp_3)_2$ reached only 3% conversion after 5 minutes and required over 20 minutes before the reaction began to proceed at a rate comparable to those catalyzed by **3a** or **3c**. Another interesting observation is that the coupling of **2c** using precatalyst **3c** occurred at a slightly faster rate than the coupling of **2a** with precatalyst **3a**.

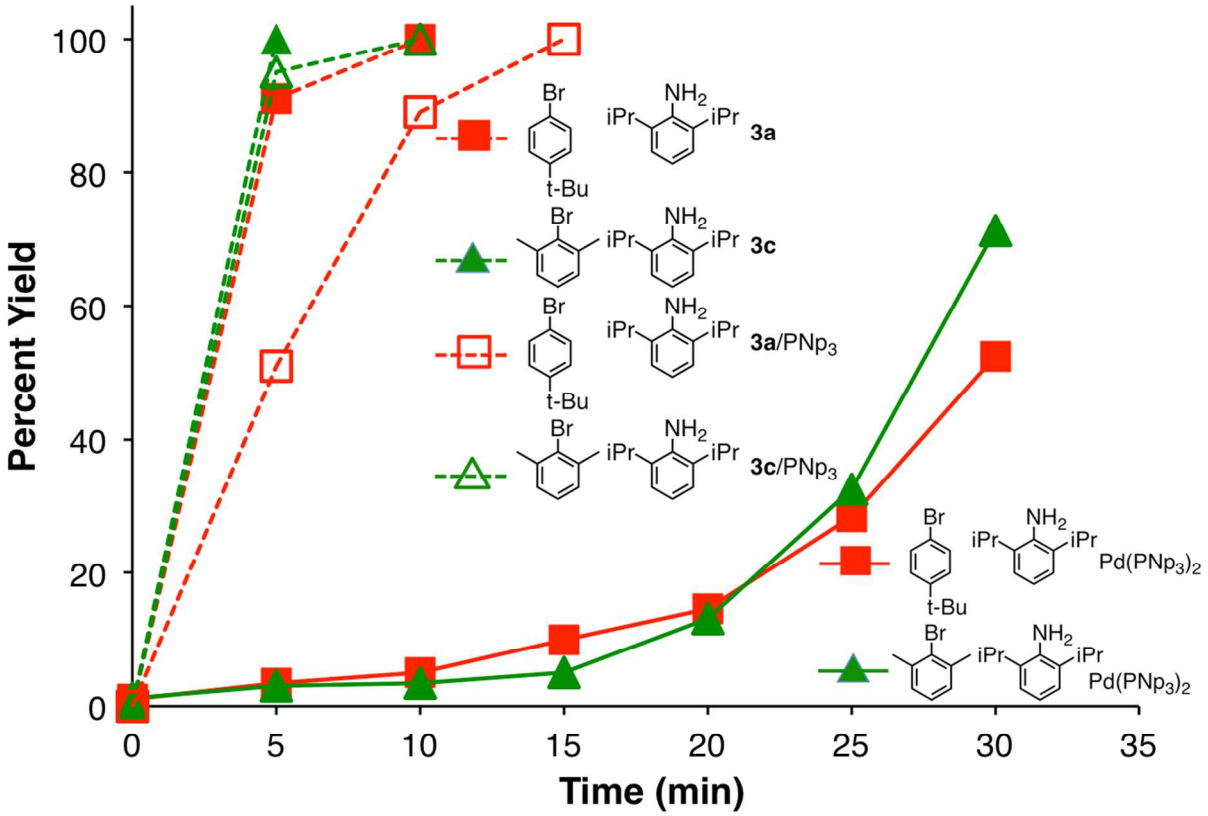


Figure 11. Reaction profile for the coupling of aryl bromides with **5b** using different precatalysts: **2a** with $Pd(PNp_3)_2$ precatalyst (1 mol %, solid red squares, solid line), **2c** with $Pd(PNp_3)_2$ precatalyst (1 mol %, solid green triangles, solid line), **2a** with **3a** precatalyst (0.5 mol %, solid red squares, dotted line), **2c** with **3c** precatalyst (0.5 mol %, solid green triangles, dotted line), **2a** with **3a** precatalyst (0.5 mol %) and PNp_3 (1 mol %, open red squares, dotted line), **2c** with **3c** precatalyst (0.5 mol %) and PNp_3 (1 mol %, open green triangles, dotted line)

The significantly higher conversion rate observed with precatalysts **3a** and **3c** compared to $Pd(PNp_3)_2$ could be attributed to two potential factors. Kinetic studies of the oxidative addition of aryl bromides to $Pd(PNp_3)_2$ showed that initial ligand dissociation is rate limiting. Thus, formation of the reactive $Pd(PNp_3)$ complex is slow relative to the overall catalytic cycle and

could account for the induction period. An alternative possibility is that the higher ligand:Pd ratio of the $Pd(PNp_3)_2$ precatalyst (2:1) compared to **3a** and **3c** (1:1) inhibits catalyst activity. A 1:1 ligand:Pd ratio is often optimal for palladium/bulky alkylphosphine systems.[28]

To test this latter possibility, the reactions catalyzed by **3a** and **3c** were repeated in the presence of one equivalent of PNp_3 relative to palladium (Figure 11). The additional PNp_3 provides the same phosphine concentration as reactions catalyzed by $Pd(PNp_3)_2$. In the presence of excess phosphine, the reaction rates were decreased slightly, but the reactions using precatalysts **3a** and **3c** were still significantly faster than when $Pd(PNp_3)_2$ was used as the precatalyst and did not exhibit an induction period. The coupling of **2a** using precatalyst **3a** was again slower than the coupling of **2c** with precatalyst **3c**.

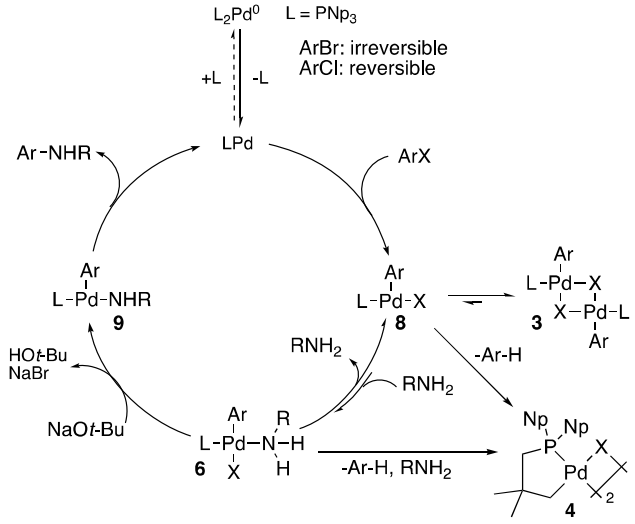
These results suggest that the induction period observed in the coupling of aryl bromides with anilines using precatalyst $Pd(PNp_3)_2$ is due the slow initial ligand dissociation to give the active $Pd(PNp_3)$ complex. This dissociation appears to be largely irreversible under the catalytic conditions, which is consistent with the mechanism determined for the oxidative addition process. The minimal inhibition of reactions performed with precatalysts **3a** and **3c** in the presence of excess PNp_3 suggests that $Pd(PNp_3)$ reacts faster with the aryl bromide than it coordinates with PNp_3 to reform the $Pd(PNp_3)_2$ resting state.

Discussion

Based on the data obtained the catalytic mechanism shown in Scheme 7 can be proposed. The general sequence of steps in the catalytic cycle: 1) ligand dissociation from an L_2Pd resting state; 2) oxidative addition; 3) amine coordination; 4) deprotonation of the coordinated amine; and 5)

reductive elimination are similar to mechanisms elucidated for related systems. Our results allow additional details regarding the $Pd(PNp_3)_2$ system to be clarified.

Scheme 7. Proposed mechanism for $Pd(PNp_3)_2$-catalyzed arylation of aniline derivatives.



The mechanism for oxidative addition of aryl halides to $Pd(PNp_3)_2$ proceeds by ligand dissociation followed by oxidative addition. For aryl bromides, ligand dissociation is rate limiting and oxidative addition is much faster than recoordination of the ligand. For aryl chlorides, the slower oxidative addition rate results in ligand dissociation being reversible and oxidative addition being rate limiting. Oxidative addition of aryl bromides to L_2Pd complexes of other sterically demanding trialkylphosphines, such as P(*t*-Bu)$_3$, (1-Ad)P(*t*-Bu)$_2$, CyP(*t*-Bu)$_2$, proceed at least partially through an associative displacement of ligand by the aryl bromide. The lack of an associative pathway could reflect a faster rate of phosphine dissociation and/or a slower rate of arene coordination to $Pd(PNp_3)_2$. The calculated ligand dissociation energy for $Pd(PNp_3)_2$ (33.7 kcal/mol) is less than that of $Pd(P(t\text{-}Bu)_3)_2$ (37.3 kcal/mol), which suggests a faster ligand dissociation for PNp_3, which may account for the preferred dissociative pathway.[9b] In addition, the solid state structure of $Pd(PNp_3)_2$ shows that the neopentyl substituents

significantly shield the palladium center, which may inhibit arene coordination as part of an associative pathway.[9f]

Based on stoichiometric studies, the reaction of the oxidative addition products (**3a-c**) with aniline and base occurs much faster than oxidative addition for both aryl bromides and chlorides. In the case of aryl chlorides, the oxidative addition step is the rate limiting step for oxidative addition. Therefore, oxidative addition is the rate limiting step for the catalytic cycle as well. This conclusion is consistent with the fact that the rate of the coupling reaction depends on the identity of the aryl chloride (**2d** vs. **2f**).

In the case of aryl bromides, the stoichiometric studies show that ligand dissociation prior to oxidative addition is rate limiting for the process of going from $Pd(PNp_3)_2$ through the full reaction cycle (Scheme 6). The PdL_2 species is proposed to be an off cycle resting state in other similar systems.[12a,12b,18] Experimental evidence supports this conclusion for the trineopentylphosphine system. Reaction profiles for coupling of aryl bromides show an induction period early in the reaction. We hypothesize that this induction period is due to the slow dissociation of PNp_3 from $Pd(PNp_3)_2$ to generate the catalytically active $Pd(PNp_3)$, which was shown to be slower than oxidative addition of aryl bromides. In the case of aryl chlorides, no induction period is seen, which is consistent with aryl chloride oxidative addition being slower than ligand dissociation.

The induction period can be eliminated by using an arylpalladium(II) precatalyst (**3a** or **3c**) that can rapidly enter the catalytic cycle. Complexes **3a** and **3c** can directly enter the catalytic cycle by reaction with base and aniline to form the product and generate the $Pd(PNp_3)$ active species. We have demonstrated that this process is very fast compared to ligand dissociation from $Pd(PNp_3)_2$ (Scheme 6). Addition of excess PNp_3 to reactions catalyzed by **3a** or **3c** causes a

slight decrease in conversion rate, but the reactions still proceeds much faster than those catalyzed by $Pd(PNp_3)_2$. Thus, once the $Pd(PNp_3)$ active species is generated, catalyst turnover is much faster than trapping by ligand. This conclusion is consistent with the rate limiting irreversible ligand dissociation mechanism determined for aryl bromide oxidative addition.

We are unable to definitely identify the rate limiting step on the catalytic cycle for the coupling of aryl bromides, but the results suggest that the RDS is not oxidative addition. The coupling of 1-bromo-4-*tert*-butylbenzene (**2a**) with 2,6-diisopropylaniline (**5b**) occurs at a comparable rate to the coupling of 2-bromo-*m*-xylene (**2c**) and **5b**. Reactions using precatalysts **3a** or **3b** also give similar rates for the coupling of **2a** and **2c** with **5b**. In this case, the more hindered **2c** is coupled at a slightly higher rate. In contrast, when the coupling is carried out with a mixture of **2a** and **2c**, the product derived from **2a** is formed approximately twice as fast as that from **2c**. These results show that $Pd(PNp_3)$ oxidatively adds **2a** faster than **2c**. The kinetic preference for **2a** over **2c** is similar to that seen in the corresponding aryl chlorides (**2d** and **2f**). If oxidative addition were rate limiting in the catalytic cycle, this rate difference should be seen in the independent coupling rates. The fact that this kinetic preference is not seen in the independent coupling rates suggests that oxidative addition is not rate limiting for the coupling of aryl bromides.

Upon generation of the oxidative addition product (**3**/**8**), the next necessary step is thought to be amine coordination. Coordination of anilines to dimer **3b** is an unfavorable equilibrium ($K < 1$ X 10^{-4}). The possibility of direct reaction of complex **3** with *tert*-butoxide was considered, but this stoichiometric reaction leads to decomposition. Therefore, we conclude that complex **6** is formed in equilibrium with **3**, or **8**. Complex **6** is then deprotonated to afford amide complex **9**, which then undergoes reductive elimination to form the product and regenerate the $Pd(PNp_3)$ active species. Having excluded aryl bromide oxidative addition, the catalytic rate determining

step presumably lies in this sequence of steps. With a strong base and relatively acidic aniline substrate, deprotonation is likely not rate limiting. The fact that amine coordination to dimer **3** is unfavorable might suggest that this is the rate limiting process. Alternatively, it may be the reductive elimination process as has been proposed for other systems.[13,15]

The other interesting observation from these experiments is the impact of the aniline structure on the reaction efficiency. Arylation of hindered aniline **5b** occurs at high rate and with complete conversion (Figures 9 and 10). In contrast, reactions in the presence of aniline (**5a**) are slower and show signs of catalyst deactivation, particularly with the more hindered aryl halides **2c** and **2f**. Competition studies show that aniline is arylated at a much faster rate than the more hindered aniline **5b** (Table 2). Therefore, the inhibition effect does not appear to be due to aniline reacting at a slower rate than **5b** in the catalytic cycle.

We propose that aniline inhibits the reaction by promoting the conversion of active palladium species to an inactive palladacycle (**4**). Performing the oxidative addition of aryl halides to $Pd(PNp_3)_2$ in the presence of aniline results in the competitive formation of palladacycle **4**. The more hindered **5b** results in less palladacycle formation than aniline (**5a**). Reaction of complexes **3a** and **3b** with aniline in the absence of base also results in slow conversion to **4**. We propose that this reaction occurs from amine complex **6**, but it could also occur directly from complex **8**. One possible role for aniline is to serve as an internal or external base to promote the C–H activation. Alternatively, aniline coordination could sterically promote C–H activation of the ligand with the aryl substituent acting as an internal base. The inhibitory effect of aniline is most pronounced with the more hindered aryl halides (**2c** and **2f**). This observation is consistent with the decreased stability of complex **3c** compared to complexes **3a** and **3b**. The thermal decomposition of complex **3a-c** in the absence of aniline likely proceeds directly from the three-

coordinate species **8**. In the catalytic reaction, this decomposition process consumes the active catalyst resulting in decreased reaction rates and in some cases incomplete consumption of the substrates.

Despite the inhibiting effect of aniline on the catalytic reaction, competition studies show that aniline is arylated at a much higher rate than di-*ortho*-substituted aniline derivative **5b** (Table 2) when both are present. The strong preference to arylate anilines **5a** and **5c** over the more hindered **5b** appears to be at odds with the observation that aniline gives slower coupling rates than **5b**. We hypothesize that the less hindered aniline coordinates more readily to the aryl halide complex (**3**) than does **5b** or **5c**. As a result, there is a much higher equilibrium concentration of aniline bound complex **6**, which results in a strong preference to produce products derived from aniline. The same trend is seen with the mono-*ortho*-substituted **5c**, which is also exclusively coupled in the presence of **5b**. Although less hindered anilines are favored in the competitive coupling reaction, the inhibiting effect of **5a** can be seen in the incomplete conversion seen with less reactive aryl halides.

Conclusions

In summary, we sought to develop an understanding of the Pd/PNp_3-catalyzed coupling of aryl halides and aniline derivatives. In particular, we wanted to explore the effect of substrate steric demand on the reaction. The results suggest that for the coupling of aryl bromides, the oxidative addition step is not rate limiting. As a result, the steric demand of the aryl bromide does not significantly affect the catalytic reaction rate when coupling with hindered aniline derivatives. This insensitivity to steric demand is an attractive feature that allows highly sterically congested diaryl amines to be prepared. In the case of aryl chlorides, oxidative addition is rate limiting and less hindered aryl chlorides react faster than more hindered analogs. The mechanistic studies also

showed that the neopentyl substituent provides an undesirable pathway to catalyst deactivation through formation of a κ^2-*P,C*-palladacycle. Unhindered aniline derivatives promote this deactivation pathway at a rate competitive with cross-coupling, which results in slower reaction rates and in some cases incomplete conversion. This study shows the impact that subtle differences in catalyst structure can have on the mechanism of catalytic processes, and the importance of careful mechanistic studies to inform further catalyst development.

ASSOCIATED CONTENT

Supporting Information. Supporting Information Available:

Full experimental procedures and characterization data, kinetic rate plots, and ^{1}H, ^{13}C, and ^{31}P NMR spectra for complexes **3c** and **4**, X-ray structure refinement tables for compounds **3c** and **4**. (PDF)

Crystallographic data for **3c** (cif)

Crystallographic data for **4** (cif)

This material is available free of charge via the Internet at http://pubs.acs.org.

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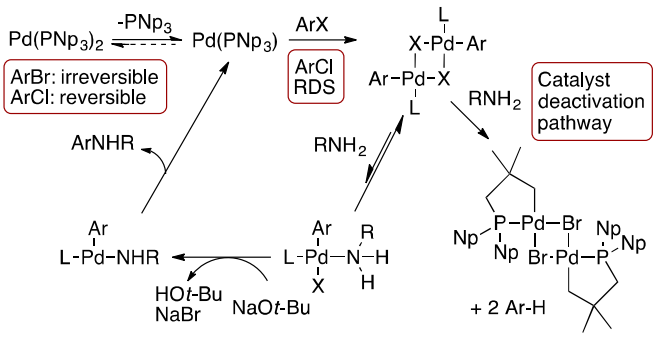
TOC Graphic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Pd(PNp3)
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