Catalysis with Platinum-Group Alkylamido Complexes. The Active Palladium Amide in Catalytic Aryl Halide Aminations As Deduced from Kinetic Data and Independent Generation

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Mechanistic studies of the palladium-catalyzed coupling between aryl bromides and tin amides were conducted as a means to evaluate the pathway of this reaction as well as the general potential of low valent amido complexes to be reactive intermediates in catalysis. The specific systems involved reactions between Bu_3SnNMe_2 and aryl halides catalyzed by {Pd[P(*o*-Tol)$_3$]$_2$} (**1**), {Pd[P(*o*-Tol)$_3$](*p*-MeC$_6$H$_4$)(Br)}$_2$ (**2a**), and {Pd[P(*o*-Tol)$_3$](NHMe$_2$)(*p*-MeC$_6$H$_4$)(Br)} (**3a**). A combination of kinetic studies and independent synthesis of reaction intermediates indicated that the three-coordinate platinum-group amido complex {Pd[P(*o*-Tol)$_3$](Ar)(NMe$_2$)} was an intermediate in these reactions. Thus, these aryl halide aminations are rare examples of catalysis with a platinum-group amido complex. Kinetic data were obtained by ^{1}H NMR spectroscopy, and the rate behavior was determined to be zero order in added phosphine, zero order in aryl halide, and first order in tin amide under conditions of equal or greater concentrations of aryl bromide compared to tin amide. Reactions catalyzed by **3a** were first order in the palladium complex. Reaction rates were inhibited by added tin bromide, but not by the arylamine product. The inhibition by tin bromide showed that reversible transmetalation between an aryl halide complex and the tin reagent was occurring. Subsequent to reversible transmetalation, a rate-determining reductive elimination of arylamine occurred. Under conditions with a 10-fold excess of tin amide and high phosphine concentrations, the rate-determining-step became oxidative addition of aryl bromide, and reactions became first order, rather than zero order, in aryl bromide. The amido intermediate deduced from kinetic studies appeared to be generated by reacting {Pd[P(*o*-Tol)$_3$](*p*-BuC$_6$H$_4$)(Br)}$_2$ (**2b**) with lithium arylamides or by deprotonating {Pd[P(*o*-Tol)$_3$](NHEt$_2$)(*p*-BuC$_6$H$_4$)(Br)} (**3b**) with MN(SiMe$_3$)$_2$ (M = K, Li). Both reactions gave yields of arylamine that were comparable to those of catalytic reactions. Competition and relative rate studies revealed an equilibrium between aryl halide complexes **2a**−**c** and a tin amide adduct of it. In competition studies involving an *in situ* selectivity for reaction of Bu_3SnNMe_2 or Bu_3SnNEt_2 with *p*-*t*-BuC$_6$H$_4$Br catalyzed by **1**, the ratio of *N*,*N*-dimethylaniline to *N*,*N*-diethylaniline was 2.9. However, kinetic measurements of individual reactions showed that Bu_3SnNMe_2 reacted only 1.4 times faster than Bu_3SnNEt_2, consistent with a reversible equilibrium involving tin amide binding to the catalyst, similar to that resulting from substrate binding preëquilibria in enzyme systems.

Introduction

A principal goal of organometallic chemistry is the catalytic production of organic molecules by exploiting the distinct reaction chemistry of organic ligands covalently bound to transition metals. Most organometallic chemistry has focused on complexes with covalent metal−carbon or metal−hydrogen bonds. The platinum group transition metals, in particular palladium and rhodium, have been workhorse elements in many commercialized catalytic processes that include hydrogenations, hydroformylations, acetic acid production, and other C−C and C−H bond forming processes.[1] Although carbon−oxygen, carbon−nitrogen, or carbon−sulfur bonds are found in the majority of important organic molecules, catalytic organometallic reaction chemistry that leads to the formation of carbon−heteroatom bonds is less common than that forming carbon−carbon and carbon−hydrogen bonds. Moreover, the construction of C−N bonds in amines is particularly rare.[2−11] In large part, routes to the necessary reactive intermediates for such catalysis and the fundamental

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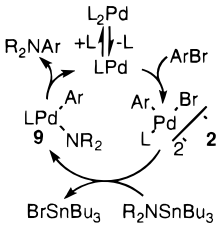
Scheme 1



reactions required of such intermediates are poorly developed. Specifically, synthetic routes to reactive amido (M−NRR′) and alkoxo (M−OR) complexes have attracted significant attention only recently, and late transition metal amido and alkoxo complexes with β-hydrogens typically decompose rapidly to metal hydrides.[12,13] As a result, no dialkylamido complexes of platinum-group metals have been isolated or even observed,[14] and only a few monoalkyl complexes[15−19] have been isolated despite the generality of the amido group.

The addition of tin amides to aryl halides in the presence of a hindered Pd(0) catalyst forms arylamines and tin halides by a process that is general for a variety of dialkyl or aryl amides and aryl halides (Scheme 1).[20−26] Turnover numbers can be greater than 100, and selectivity for arylamines can exceed 95%. This "hetero-cross-coupling" chemistry is a heteroatom analog of Stille couplings that form C−C bonds from aryl, vinyl, or acetylenic tin reagents and sp^2-hybridized organic halides.[27,28] The use of the Stille reaction is widespread in the preparation of natural products and novel organic materials.

Formation of arylamines from aryl halides has been a difficult transformation. Ullman chemistry, the reaction of copper amides with aryl halides, has been used for this transformation in the past, but yields are variable, high temperatures are necessary, inconvenient and toxic solvents are required, and the active copper reagents are ill-defined.[29,30] Further, the copper mediated processes have eluded any clear mechanistic conclusions.[30] Although Kosugi reported over 10 years ago a palladium-catalyzed amination of aryl halides, the reaction is relatively unexplored both mechanistically and synthetically. Recently our group[15,23,25,31−33] and Buchwald's group[22,26] have been working to determine the synthetic scope of the palladium-catalyzed formation of arylamines from aryl halides, to develop the simplest coupling procedures, and to characterize intermediates in the coupling reaction. It seemed likely to us that the palladium chemistry would be more receptive than the copper chemistry to mechanistic analysis and that a well-understood coupling process would allow for rational modification of reaction conditions, development of new catalysts, and design of substrates that would participate in the aryl halide aminations. The tin amide chemistry seemed likely to be most receptive to mechanistic analysis, and the mild tin reagents present some synthetic advantages, particularly with base-sensitive systems. Perhaps most important from a mechanistic standpoint, it seemed likely that a palladium amido complex was the key intermediate on the reaction pathway. If this proved to be the case, then its reactivity would help clear a path for further catalytic applications of late metal amides and alkoxides.

The accepted mechanism for Stille carbon−carbon bond-forming coupling reactions involves oxidative addition of an organic halide to a Pd(0) complex, followed by transfer of a group from an organotin reagent to the palladium aryl halide complex and reductive elimination of the organic product to regenerate Pd(0).[27,28] Kinetic studies and stoichiometric chemistry of organopalladium complexes have led to the acceptance of these general mechanistic features.[34]

A rough mechanism for the formation of arylamines (Scheme 1) that would parallel the accepted mechanism for Stille couplings requires an amido intermediate and a catalytic cycle that would be comprised of a number of unusual features and reactions that are rare or unprecedented in stoichiometric chemistry. For example, an amido intermediate would have to undergo reductive elimination of arylamine, a reaction with little precedent, faster than β-hydrogen elimination to yield imine, a reaction which has been thought to be rapid for alkylamido complexes with β-hydrogens.[12,35] Further, formation of a transition metal amide from a tin amide is unknown and has been shown by our group to be unfavorable thermodynamically.[15]

We have employed a combination of kinetic studies, stoichiometric reactivity, and independent synthesis of reaction intermediates to demonstrate that the novel organometallic chemistry outlined roughly in Scheme 1 does occur. Herein, we identify specifically the complexes that lie on the catalytic pathway, the primary reactions that are kinetically important, the steps that are reversible, and the steps that form product irreversibly. All of our data indicates that a three-coordinate

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Pd(II) amido complex is formed by transmetalation between an aryl halide complex and a tin amide and that this intermediate forms the amine C−N bond by carbon−heteroatom bond-forming reductive elimination. These data provide the first firm identification of a catalytically active, platinum-group alkylamido complex and reveal its unprecedented selectivity for carbon−heteroatom bond formation. As a result of this selectivity, this chemistry produces arylamines during a practical catalytic nucleophilic aromatic substitution reaction.

Results

Our initial mechanistic studies of the catalytic process involved determination of the reaction order in aryl halide, tin amide, and palladium catalyst. We conducted our reactions such that turnover numbers were limited to five. These conditions prevented measurable catalyst decomposition, as determined by integration of a ^{31}P NMR spectrum of the reaction solution vs a phosphine standard contained in a capillary. Reactions were monitored by the decay of tin amide reagent whose concentration was conveniently determined by ^{1}H NMR spectroscopy while heating the sample in the probe. Quantities of the other reagents were chosen such that the concentrations of all reagents except that of the tin amide remained virtually constant. A typical catalytic solution for kinetic analysis contained 3−5 equiv of tributyltin dimethylamide, 5−10 equiv of tributyltin bromide, 10−30 equiv of *p*-*t*-BuC_6H_4Br, and at least 5 equiv of added phosphine for every 1 equiv of catalyst. Catalyst concentrations were on the order of 0.01 M, and reaction temperatures ranged from 60 to 85 °C depending on the catalyst used (see Experimental Section for details).

Three palladium catalysts were employed for our mechanistic studies. One complex was the Pd(0) species {Pd[P(*o*-Tol)$_3$]$_2$} (**1**), whose synthesis, spectroscopic characterization, and X-ray structure has been reported by our group previously.[33] A second complex we employed was the dimeric {Pd[P(*o*-Tol)$_3$](*p*-MeC_6H_4)(Br)}$_2$ (**2a**), resulting from aryl bromide oxidative addition reactions to **1** (eq 1). Compound **2a** also catalyzes the amination

$$\underset{\mathbf{1}}{\mathrm{Pd[P}(o\text{-Tol})_3]_2} \xrightarrow[\mathrm{ArBr}]{} \{\mathrm{Pd[P}(o\text{-Tol})_3](\mathrm{Ar})(\mathrm{Br})\}_2 \quad (1)$$

2a Ar = *p*-$CH_3C_6H_4$
2b Ar = *p*-*t*-BuC_6H_4
2c Ar = *p*-BuC_6H_4

reaction, and its synthesis, spectroscopic characterization, and X-ray structure have also been reported by our group.[33] This aryl halide complex undergoes reversible dimer cleavage before reaction with conventional aryltin reagents such as phenyl trimethyltin.[32] Additionally, this dimeric species reacts with primary and secondary amines as in eq 2 to yield monometallic amine

$$\underset{\mathbf{2a,c}}{\{\mathrm{Pd[P}(o\text{-Tol})_3](\mathrm{Ar})(\mathrm{Br})\}_2} \xrightarrow[\mathrm{HNR_2}]{} \{\mathrm{Pd[P}(o\text{-Tol})_3](\mathrm{Ar})(\mathrm{Br})(\mathrm{NHR_2})\} \quad (2)$$

3a Ar = *p*-$CH_3C_6H_4$, R = Me
3b Ar = *p*-BuC_6H_4, R = Et

complexes, {Pd[P(*o*-Tol)$_3$](NHR_2)(Ar)(Br)} (**3a**, Ar = *p*-MeC_6H_4, R = Me; **3b**, Ar = *p*-BuC_6H_4, R = Et).[33] These amine complexes also catalyze the coupling between aryl halides and tin amides and were the third type of complex used in the catalytic studies. We have employed these three types of compounds rather than {Pd[P(*o*-Tol)$_3$]$_2$Cl$_2$} (**4**), the catalyst originally reported by Kosugi, since reduction of these Pd(II) complexes occurs on a time scale similar to the actual catalytic amination.

Simple ^{31}P NMR spectroscopic monitoring of reactions catalyzed by amine complexes **3a** or by **1** or **2a** in the presence of amine showed that complex **3a** was the resting state of the palladium. The clear identification of this species as the resting state led us to conduct detailed kinetic studies with this catalyst. Potential Pd(0) intermediates or Pd(II) amido complexes were not observed in the reaction medium by spectroscopic techniques. Amine complexes related to **3a** have previously been characterized fully by spectroscopic and microanalytical techniques.[33] Both ^{1}H and ^{31}P NMR spectra of reaction solutions showed **3a** to be the only palladium complex present in observable quantities. We have reported in stoichiometric studies that this amine complex reacts with tin amides to give Pd(0) and arylamines.[32] The bulky tin amide did not displace the secondary amine of catalyst **3a** to give a tin amide complex as an observable species, although such a displacement may be part of the reaction pathway. Identification of the resting state of reactions catalyzed by **1** or **2a** was more complicated. ^{31}P NMR spectra of the reaction solutions showed a broad resonance at 29 ppm similar to that of isolated **2b**. However, as will be described below, further studies showed the resting state to be an equilibrium mixture of **2b** and a tin amide adduct of it, which presumably has a structure similar to amine complex **3a**.

Kinetic Evidence for a Palladium−Amido Intermediate. A mechanism involving rate determining reaction of **3a** and the tin reagent would provide first-order rate behavior in tin amide, zero-order behavior in phosphine, zero-order behavior in aryl halide, first-order behavior in palladium catalyst, and inverse first-order behavior in amine. Similar rate behavior would be expected for reactions catalyzed by **2a**, except that half-order behavior in the palladium catalyst would be observed if the tin amide reacted with the resulting monomeric aryl halide complex formed from reversible cleavage of dimeric **2a**. Reactions catalyzed by **1** would show the same characteristics as those catalyzed by **2a**, since oxidative addition of aryl bromides to **1** is rapid, relative to subsequent steps, under normal conditions. Importantly, rate-determining transmetalation would prevent our spectroscopic *or* kinetic detection of the amido intermediate in the catalytic system.

It was expected, but important to confirm, that the overall process was irreversible. Catalytic reactions between Bu_3SnNEt_2 and *t*-BuC_6H_4Br in the presence of excess *N*,*N*′-dimethylaniline showed no formation of *p*-*t*-Bu$C_6H_4NMe_2$. Moreover, reactions between Bu_3SnNMe_2 and *p*-$CH_3C_6H_4$Br monitored in the presence and absence of added *N*,*N*′-dimethyltoluidine product showed the same conversions at various reaction times.

Although the overall reaction was irreversible, the portion of the catalytic cycle that formed tin bromide as product proved to be reversible. In contrast to addition of the arylamine product to reaction solutions, addition of >4 equiv of tributyltin bromide to the reaction solution led to a dramatic decrease in reaction rates. In fact, as can be seen by comparing A and B of Figure 1, addition of an excess of tin bromide to initial reaction solutions provided linear first-order plots. As presented in the Discussion, the curvature of the plot in Figure 1A is due to product inhibition. The

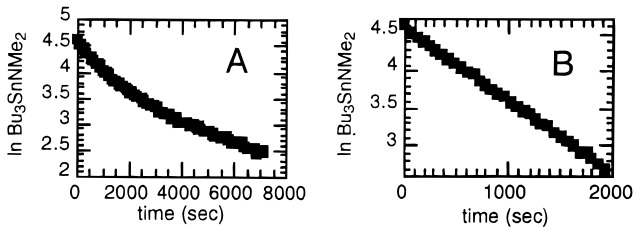


Figure 1. Results of monitoring the decay of tin amide during reaction of Bu_3SnNMe_2 with *p*-$CH_3C_6H_4Br$ catalyzed by **3a** at 75 °C (graph A) or identical reaction conditions, but containing 4 equiv of added Bu_3SnBr and conducted at 85 °C (graph B).

addition of excess tin bromide to the reaction solutions ensures little change in tin bromide concentrations throughout the reactions, and first-order decay of tin amide is observed.

The dramatic rate decrease in the presence of tin bromide was not due to catalyst decomposition, as initial rates also showed a strong inhibition upon addition of tin bromide. Further, reaction mixtures containing small concentrations of added tin bromide did not show catalyst decomposition for up to 12 h at room temperature or a rate of catalyst decomposition that significantly exceeded that of reactions containing no added tin bromide. As suggested by these results, added tin bromide did not affect yields of the oxidative addition of *p*-$CH_3C_6H_4Br$ by **1**. For example, compound **1** reacted with *p*-$CH_3C_6H_4Br$ to form **2a** in 85−90% yield in the presence of 5 equiv of tin bromide. It should be noted, however, that large concentrations of tin bromide did lead to slow decomposition of the catalyst, and tributyltin bromide reacted at 70 °C with aryl halide complex **2a** to give a black Pd precipitate in the absence of added aryl bromide. This slow tin bromide induced decomposition of catalyst led to low arylamine yields at artificially high concentrations of tin bromide and, thus, prevented our determining an accurate reaction order in tin bromide. At low concentrations of tin bromide (0.050−0.15 M), however, reactions did show a rough inverse first-order behavior in added tin bromide, although the lower concentrations in this range did not provide strictly pseudo-first-order reaction conditions preventing quantitative information.

As a result of this rate inhibition by tin bromide and the need for excess tin bromide to obtain linear first-order plots, quantitative rate measurements were conducted in the presence of 5 equiv of added tin bromide per 1 equiv of tin amide. Under these conditions, reactions between *p*-$CH_3C_6H_4Br$ and Bu_3SnNMe_2 in the presence of catalytic amounts of **3a** stabilized by added P(*o*-Tol)$_3$ were zero order in free aryl bromide from 0.21 to 1.01 M. Reaction rates were also independent of the phosphine concentration from 0.11 to 0.57 M. Varying the concentrations of these reagents provided first order rate constants that were all within 10% of 2.0×10^{-4} s^{-1}. Figure 2 shows the results of varying the catalyst concentration from 0.006 to 0.030 M. Catalysis involving a dimeric palladium complex would show second-order behavior in **3a**; our results indicate first-order, rather than second-order, behavior in catalyst and show that the catalysis involves monomeric palladium complexes. Rate constants for reactions catalyzed by **3a** were measured in the presence of 0.051 and 0.27 M of added $HNMe_2$, and an inverse first-order dependence of rate on amine concentration was observed as shown in Figure 3.

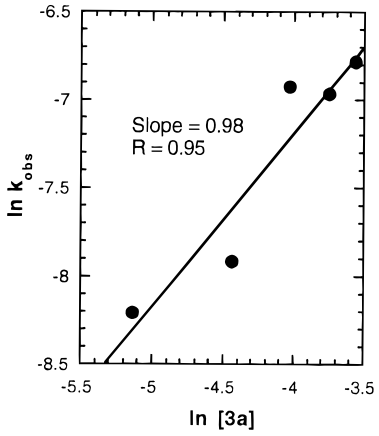


Figure 2. Determination of the order in **3a** for the reaction of *p*-MeC_6H_4Br with Bu_3SnNMe_2 catalyzed by **3a**.

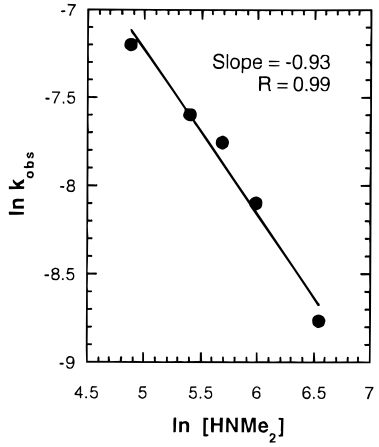


Figure 3. Determination of the order in $HNMe_2$ for the reaction of *p*-MeC_6H_4Br with Bu_3SnNMe_2 catalyzed by **3a**.

A complete kinetic analysis of reactions between *p*-*t*-BuC_6H_4Br and Bu_3SnNMe_2 catalyzed by **1** or **2a** was not conducted in the presence of added tin bromide. However, qualitative data obtained in the absence of added tin bromide by comparing conversions at a series of reaction times over at least 3 half-lives showed that these reactions had the same overall features as those catalyzed by **3a**—first order in tin amide, zero order in aryl bromide, and zero order in added phosphine. Reaction rates were unaffected by free aryl bromide concentration (0.10−0.40 M) and were independent of the concentration of added phosphine (0.05−0.21 M). Again, adding tin bromide led to inhibition of the reactions. Monitoring the decay of tin amide during experiments that were conducted with added tin bromide gave linear first-order plots, confirming the first-order behavior in tin amide. It was experimentally difficult to distinguish half from first-order behavior in palladium catalyst when starting from the dimer **2a**. However, as presented in the Discussion, the clear presence of a three-coordinate, monomeric intermediate in the reactions of **3a** strongly suggests that the catalytically active form of **2a** is mononuclear.

Electronic Effects. In order to probe for direct attack of the tin amide at the palladium-bound aryl group, we conducted the catalytic reactions with several aryl bromides possessing different para substituents. Rate constants were compared for reactions of Bu_3SnNMe_2 and *p*-XC_6H_4Br (X = *t*-Bu, CF_3, F, NMe_2, OMe) catalyzed by **1**. Our results given in Table 1 showed that the rates were slightly faster as the electron density

Table 1. Rate Constants for Coupling Reactions with Different Aryl Bromides *p*-R-C_6H_4Br

R	σ	rate const ($s^{-1} \times 10^{-4}$)	relative rates
CF_3	0.54	9.0	3.8
F	0.06	6.5	2.7
t-Bu	−0.19	4.8	2.2
MeO	−0.28	2.9	1.2
Me_2N	−0.83	2.4	1.0

at the aryl ring was decreased. However, reaction rates for the two extreme cases, *p*-CF_3- and *p*-NMe_2-substituted aryl halides, were different by a factor of only 3.8.

Effect of High Concentrations of Phosphine. Reactions conducted with high concentrations of tin amide and phosphine showed a different resting state than those with low concentrations (below 40 mM) of added phosphine and similar amounts of tin amide to aryl halide. Specifically, reactions conducted with either **1** or **2a**, a 10:1 ratio of tin amide to aryl bromide, and concentrations of free phosphine near 100 mM showed only resonances for free phosphine (−29 ppm) and L_2Pd^0 complex **1** (−6 ppm). Moreover, linear first-order plots for the decay of aryl bromide were obtained, contrasting the zero-order behavior observed at lower concentrations of phosphine and tin amide. Clearly the rate-determining-step of the catalytic cycle was shifted from a combination of transmetalation and reductive elimination to aryl halide oxidative addition.

Reactions run without added phosphine gave lower yields of arylamine than those run in the presence of added phosphine, and formation of black palladium(0) precipitate was observed. Addition of 5 equiv of P(*o*-Tol)$_3$ per 1 equiv of catalyst kept reaction mixtures homogeneous, thereby increasing turnover numbers and product yields. Increasing the phosphine concentration from 5−15 equiv induced a slight increase in the rate, due to further prevention of catalyst decomposition, particularly when conducting reactions with Pd(0) complex **1** or the dihalo complexes $Pd[P(o\text{-Tol})_3]_2Br_2$ (**5**) and **4**. However, addition of 20 equiv of phosphine led to a measurable decrease in rate. Under these conditions, a ^{31}P NMR signal was observed at −6 ppm and first-order rate behavior in aryl bromide and palladium catalyst were obtained, consistent with rate-determining oxidative addition and a change in resting state to **1**.

Formation of a Tin Amide Adduct. Determination of the resting state of the palladium for reactions catalyzed by **1** or **2b** did not prove to be as straightforward as identifying the resting state for reactions catalyzed by **3a**. A broad resonance at 29 ppm was observed that could be attributed to the dimeric aryl halide complexes. It should be noted that both aryl halide complex **2a** and its amine adducts **3a** and **3b** have essentially identical ^{31}P NMR chemical shifts.[33] In stoichiometric studies, addition of tin amide to the dimeric aryl halide complexes led to little change in the ^{31}P NMR chemical shift, but ^1H NMR spectra showed distinct differences indicating that reaction had occurred. For example, upon addition of 10 equiv of Bu_3SnNMe_2 to the *p*-*t*-BuC_6H_4 derivative of **2a** (**2b**, {Pd[P(*o*-Tol)$_3$](*p*-*t*-BuC_6H_4)(Br)}$_2$) a new, broad *tert*-butyl resonance was observed slightly downfield of that for **2b**.[36] No tin bromide was formed, demonstrating that simple substitution of amide for halide and generation of a palladium amide had not occurred. Addition of 1 equiv of tin amide left a large, sharp *tert*-butyl resonance for **2b**, but also formed a small, broad resonance at the same chemical shift as the resonance observed upon addition of 10 equiv of tin amide. Unfortunately, accurate integrations could not be obtained, due to large nearby butyl resonances of the tin amide. Incrementally increasing amounts of tin amide, however, did lead to a clear increase in the broad adduct resonance and a disappearance of the sharp *tert*-butyl resonance of the aryl halide complex **2b**. Cooling of the samples below room temperature led to complex ^1H and ^{31}P NMR spectra, as expected, since even spectra for analytically pure dimeric aryl halides are extremely complex at low temperatures.[33] Unfortunately, one cannot draw firm conclusions from ^{31}P NMR spectra of samples containing **2b** and Bu_3SnNMe_2 at ambient temperatures, since only slight differences in line shape were observed. Although the spectroscopic data is not straightforward, it is clear that **2a** and **2b** reversibly react with tin amide without forming tin bromide. The simplest explanation for this reversible reactivity is shown in eq 3 and involves the

$$\underset{\textbf{2a-b}}{\{Pd[P(o\text{-Tol})_3](Ar)(Br)\}_2} \underset{Bu_3SnNR_2}{\rightleftharpoons} \underset{\textbf{8}}{\{Pd[P(o\text{-Tol})_3](Ar)(Br)(NR_2SnBu_3)\}} \quad (3)$$

formation of **8**, a tin amide adduct of **2a** and **2b** that would have a structure similar to those of amine complexes **3**. The similarity of the ^{31}P NMR chemical shifts to those of amine complexes **3** are consistent with this conclusion.

Reactions involving reversible formation of a complex between substrate and catalyst often provide product ratios from reactions containing more than one substrate that are different from the ratio of rate constants obtained from two reactions, each involving one of the substrates. This situation is common for enzyme systems and is termed competitive inhibition.[37] In our case, the apparent equilibrium between free and substrate-bound catalyst would suggest that competitive inhibition is likely to be observed and that different relative rates would be obtained from competition experiments and from individual rate measurements. Quantitative rate measurements for reactions of tin amides catalyzed by **1** showed that rate constants for Bu_3SnNMe_2 were 1.4 ± 0.1 times faster than those of Bu_3SnNEt_2. However, the selectivity for reactions of *p*-BuC_6H_4Br with a mixture of these two reagents was 2.9 ± 0.4.[38] The differences between these values suggest that reversible binding of substrate occurs and is consistent with the apparent equilibrium between free dimeric **2** and a tin amide-bound species.

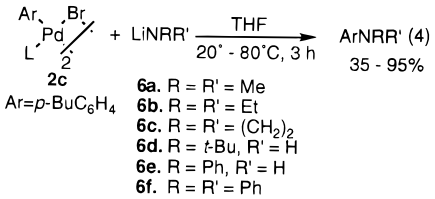
Independent Generation of the Amido Complex. Reaction of {Pd[P(o-tolyl)$_3$](p-BuC_6H_4)(Br)}$_2$ (2c) with Lithium Amides. We sought to support our kinetic studies by synthetic studies aimed at independently generating the tri-*o*-tolylphosphine-ligated palladium amido complexes. Initially, we reacted aryl

(36) ^1H NMR spectra were different from the amine complex, ruling out formation of **3** by an amine impurity in the tin amide.

(37) Segel, I. H. In *Enzyme Kinetics*; John Wiley and Sons, Inc.: New York, 1975; pp 113−118.

(38) Buchwald and Guram reported a 2:1 selectivity for formation of *N*,*N*-dimethylanilines over *N*,*N*-diethylanilines as a competition study. Their reactions were run in the presence of 1.4 equiv of both the diethyl- and dimethylamido tin reagents per equivalent of aryl bromide. In order to obtain the accurate value that our comparison requires, a constant concentration of the two tin amides must be ensured. With the 10-fold excess of each tin amide in our experiments, a 3:1 selectivity was observed.

halide complex **2c** with lithium amides, as shown in eq 4. Addition of lithium amides to a slurry of **2c** in THF



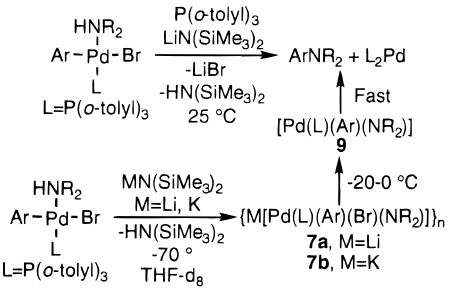
solvent caused dissolution of the aryl bromide complex and produced an orange or red solution accompanied by a black palladium precipitate. As determined by a combination of ^{31}P NMR spectroscopy and GC, the solution contained L_2Pd complex **1**, free phosphine, and arylamine. However, the formation of arylamine occurred in yields varying from only 35% to 85% as determined by GC analysis against a naphthalene internal standard. These yields were well below those observed during catalytic experiments employing tin amides.

Control reactions demonstrated that lithium amides reacted to a small extent with *p*-BuC_6H_4Br under the same conditions, giving two isomeric arylamines in 22% and 17% yields as well as arene in 23% yield. These product ratios were different from those obtained from the more selective reaction with **2c**. Most importantly, only one arylamine isomer was formed from addition of lithium amides to **2c**.

Variation of the lithium amide concentration, reaction temperature, or added phosphine concentration had either a detrimental effect or only a small positive effect on the yields of the reactions of **2c** with lithium amides. However, the identity of the amide had a measurable influence. Higher yields were observed with lithium diethylamide, **6b**, than lithium dimethylamide, **6a**, under the same conditions. Surprisingly, the most dramatic difference was observed with arylamides. Addition of lithium anilide, **6e**, or lithium diphenylamide, **6f**, led to yields of diaryl- or triarylamines that were competitive or exceeded catalytic reactions (66−95%) with tin amides. Since the yields of these stoichiometric additions of arylamides were similar to those observed during catalysis, we concluded that the lower yields with the less soluble lithium dialkylamides resulted either from a detrimental effect of the excess amounts of these highly reducing reagents on the chemistry of the resulting amido complex or from a low yield in the generation of the expected amido intermediate. We, therefore, sought an alternative and milder method for the independent generation of the dialkylamido intermediate.

Deprotonation of the Amine Complex {Pd[P(o-Tol)$_3$](p-BuC_6H_4)(Br)(HNEt$_2$)} (3b). Our methods for successful independent generation of alkylamido intermediates are shown in Scheme 2. The N−H bonds in metal amine complexes are more acidic than those in free amines and are deprotonated irreversibly by lithium amides.[39−41] As shown in Scheme 2, reaction of the soluble, hindered amide $LiN(SiMe_3)_2$ with amine complex **3b** in the presence of phosphine led to formation

Scheme 2



of arylamine and $[P(o\text{-Tol})_3]_2Pd^0$ products in greater than 90% yield and regenerated Pd(0). As communicated earlier, this reaction became the basis for the catalytic amination of aryl halides in the absence of tin.[25]

Addition of the lithium silylamide at low temperature allowed spectroscopic detection of the anionic amido complex, M{Pd[P(*o*-Tol)$_3$](*p*-BuC_6H_4)(Br)(NEt$_2$)} (M = Li, K) (**7**). The starting amine complex, which displayed a singlet ^{31}P NMR spectroscopic resonance at δ 29 was converted at −70 °C to a new species displaying a resonance at δ 25. No N−H resonance for a coordinated amine was observed in the low temperature ^{1}H NMR spectra obtained after addition of the silylamide, and $HN(SiMe_3)_2$ was observed. These results imply that a palladium amido complex was formed by the low temperature deprotonation.

However, further experiments showed that this amido complex was not a neutral species. The use of $KN(SiMe_3)_2$, rather than the lithium reagent, led to conversion of the amine complex to a set of compounds displaying resonances between δ 20 and δ 24 at −70 °C, rather than the single resonance at δ 25. The presence of several resonances was not simply due to the irreversible formation of multiple reaction products, as these compounds underwent interconversion on the NMR time scale. The set of signals observed at −70 °C coalesced at -40 °C to a single peak at δ 22. Warming of this complex to −20 °C led to formation of arylamine and **1** after 20 min. The analogous complex formed by deprotonation by $LiN(SiMe_3)_2$ was stable at −20 °C for at least 1 h, but slowly formed arylamine and L_2Pd^0 product **1** at 0 °C.

The differences in spectral features and reaction rates for the amido complexes formed from $LiN(SiMe_3)_2$ and $KN(SiMe_3)_2$ strongly suggested that the amido complexes formed at low temperatures are anionic species **7** with interconverting geometries and aggregation numbers. Warming these complexes led to loss of the alkali metal bromide, along with formation of arylamine and Pd(0) without direct detection of a neutral amido species. However, the formation of a neutral amido complex by loss of lithium or potassium bromide is the most reasonable pathway for reaction of **7**, as argued in the discussion.

Salt Effects. Due to low solubility in aromatic solvents, added lithium and potassium salts had no influence on the catalytic reaction. However, added salts did have an effect on reactions conducted in THF solvent. Amination reactions catalyzed by **1** in the presence of LiBr or LiCl resulted in less than 100% conversion of aryl halide (88%) to give arylamine (53%) and arene products including various biphenyls.[42−46] LiBr changed the color of homogeneous reaction mixtures from yellow to orange.

(39) Park, S.; Roundhill, D. M.; Rheingold, A. L. *Inorg. Chem.* **1987**, *26*, 3972−3974.
(40) Park, S.; Rheingold, A. L.; Roundhill, D. M. *Organometallics* **1991**, *10*, 615−623.
(41) Joslin, F. L.; Johnson, M. P.; Mague, J. T.; Roundhill, D. M. *Organometallics* **1991**, *10*, 2781−2794.

The presence of dissolved KF gave much lower yields of arylamines and slightly higher yields of hydrogenolysis product. Only 35% arylamine product was produced when using $[P(o\text{-tolyl})_3]_2PdBr_2$ (**5**), and conversion of aryl halide was not complete (61%). Conversely, a 1.5 h reaction run with **1** in THF gave full conversion of the aryl bromide. Yet, only 68% arylamine was produced. All reactions conducted in the presence of KF involved either catalyst **5** or **1**, and both formed a black Pd(0) precipitate. Thus, added halide salts generally had little effect on reactions run in aromatic solvents but had a detrimental effect on reactions in THF, especially when the Pd(II) precursor **5** was employed.

Copper halides had a far more detrimental effect on the amination chemistry than lithium chloride or potassium flouride. CuCl, CuBr, and CuI all promoted the formation of black Pd(0) precipitates in either THF or toluene. Although conversion of the aryl halide in THF was complete in the presence of CuCl and CuBr, the 2 h reaction at 75 °C gave only 5−7% arylamine product. Arene was the major organic product in this case. Similarly, 92−98% conversion of aryl halide occurred in the presence of CuCl or CuBr in toluene solvent, but yielded only 3−12% arylamine. Addition of CuI led to low turnover numbers in either solvent. Only 2−3 equiv of aryl halide per equivalent of catalyst reacted in THF solvent and only 10−15 equiv of aryl halide reacted in toluene. Some conversion of the tin amide to the corresponding tin halide occurred in a separate reaction between Bu_3SnNMe_2 with CuCl and CuI as determined by GC/MS analysis of the reaction solution.

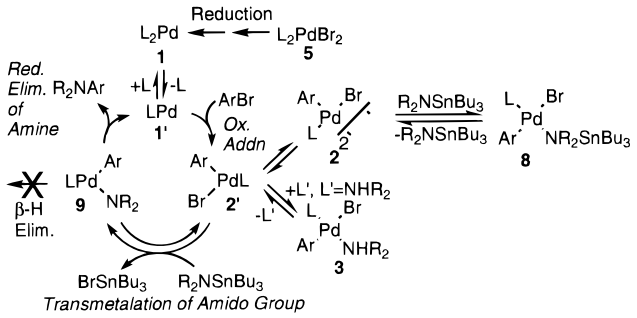
Solvent Effects. A comparison of rates measured in THF and toluene solvents showed subtle differences between the conditions employing high aryl halide concentrations and conditions employing high tin amide concentrations. Conversion of the aryl halide was complete and gave yields greater than 85% in both solvents. However, qualitative comparison of reaction rates showed rates in THF solvent that were roughly twice as fast as the same reactions conducted in toluene. These qualitative data were obtained by measuring tin amide conversions at various times during reactions catalyzed by **1** and containing excess aryl halide.

In contrast, reactions with high tin amide concentrations and limiting aryl halide concentrations conducted in THF were slower than those in toluene by a factor of three. Yields of arylamine (93%) were again similar. On the other hand, more polar solvents such as $PhNO_2$, NMP, and CH_3CN apparently led to catalyst decomposition before complete conversion of aryl bromide. Thus, dramatically lower yields (10−17%) of arylamine product were obtained in these media, low conversions were observed, and reaction rates were greatly reduced.

Discussion

All of our data are consistent with a mechanism for the coupling chemistry that involves a three-coordinate palladium amido complex $\{Pd[P(o\text{-Tol})_3](Ar)(NR_2)\}$ (**9**). A general mechanism involving oxidative addition, transmetalation, and reductive elimination appears to be followed, but we have now obtained a variety of kinetic and synthetic data that clearly identify complexes lying on the reaction pathway and delineate the relative rates of the individual steps and the reversiblity or irreversiblity of them. These important modifications of Scheme 1 are included in Scheme 3.

Scheme 3



Resting State of the Catalyst. Reactions Catalyzed by Amine Complexes. Monitoring catalytic reactions by ^{31}P and ^{1}H NMR spectroscopy showed that the resting state was clearly the amine complex **3a**. A combination of ^{1}H and ^{31}P NMR spectroscopy conclusively showed that the tin amides did not compete with amine for a coordination site.

Reactions Catalyzed by 1 or 2. It was obvious from ^{31}P NMR spectroscopy of reaction solutions involving **1** or complexes **2** as catalyst that their resting state was not L_2Pd^0 under conditions where the tin amide and aryl halide complexes were present in equal concentrations or when the aryl halide substrate was present in excess. Initially, it appeared that the resting state of the catalyst was simply the dimeric aryl halide complexes **2**. However, ^{1}H NMR spectroscopy suggested that these aryl halide complexes equilibrated with a tin amide adduct **8**. This conclusion was supported by conversion of the sharp *tert*-butyl resonance of **2b** to a separate broad resonance at high concentrations of tin amide, the observation of both signals at room temperature when a 1:1 ratio of **2b** and tin amide was present, and the lack of formation of tributyl tin bromide during these observations. Thus, we tentatively concluded that the dimeric aryl halide complexes were reversibly cleaved during the catalytic reactions and formed complexes with monometallic structures similar to those of the isolated and fully characterized amine adducts **3**.

Conclusions from spectroscopic data were tentative because clear spectroscopic data is difficult to obtain on these tri-*o*-tolylphosphine complexes. However, independent evidence for reversible formation of a catalyst−substrate complex was obtained by a comparison of relative rate data under different conditions. Specifically, a 2.9:1 ratio of two arylamine products was observed during competition studies, and this selectivity contrasted the 1.4:1 ratio of rate constants obtained from individual reactions with only one of the two tin amides. Such differences in relative rates are signatures of competitive inhibition and signal reversible binding of substrate to catalyst.

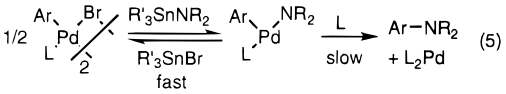
Effect of Phosphine Concentration and Substrate Ratios on the Resting State. Not only do the tin amide adducts such as **8** lie close in energy to free tin amide and dimeric complexes **2** but activation energies for oxidative addition of aryl bromide and reductive elimination of arylamine are close enough that

(42) A variety of biaryls are formed under these conditions, presumably by exchange of palladium- and phosphorus-bound aryl groups similar to that in the following four leading references.
(43) Barañano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937.
(44) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576.
(45) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.
(46) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313.

different concentrations of reagents can change the rate-determining-step. Under typical conditions of a synthetic catalytic experiment with this system, a combination of transmetalation and reductive elimination of arylamine determined the rates of reactions. However, at high phosphine concentrations and in the presence of excess tin amide, the resting state of the palladium clearly became L_2Pd complex **1** rather than the dimeric complexes **2** and their tin amide adducts. Under these conditions, oxidative addition rather than reductive elimination was rate limiting, and first-order behavior in aryl halide was observed. We have previously demonstrated that the oxidative addition of aryl halides to **1** has an inverse first-order dependence on phosphine concentration, indicating that phosphine dissociation precedes irreversible carbon−halogen bond cleavage.[31] As a result of this oxidative addition mechanism, high concentrations of phosphine retard the step of the catalysis involving free aryl halide. If the phosphine concentration is high and the ratio of aryl bromide concentration to tin amide concentration is low, then the oxidative addition step becomes slower than the transmetalation step. Small amounts of added phosphine, however, assist in inhibiting irreversible catalyst decomposition.

Kinetic Evidence for an Amido Intermediate: Reversible Transmetalation and Electronic Effects. Reversible Transmetalation. The combination of phosphine dissociation and organic group transfer is typically the rate-determining-step of C−C bond-forming Stille coupling reactions, and we have shown that dimer cleavage and aryl group transfer is the rate-determining-step in reactions of dimeric complexes **2** with aryltin reagents.[32] Thus, it seemed likely that an analogous amido group transfer to a three-coordinate aryl halide complex formed by either amine dissociation from **3** or dimer cleavage of **2** would be rate determining. Our observation of **2b** and its apparent tin amide adduct as the resting state was initially consistent with this expectation. However, nonlinear first-order plots obtained from monitoring the decay of tin amide during both catalytic and stoichiometric reactions run without added tin bromide implied our initial mechanistic hypothesis was too simplistic.

During recent experiments with triphenylphosphine-ligated palladium amido complexes, we determined that transfer of an amido group from palladium to tin had a negative free energy.[15] Therefore, transmetalation of an amido group from tin to tri-*o*-tolylphosphine-ligated palladium almost certainly has a positive free energy. This information led us to hypothesize that the curvature of the first order plots in Figure 1A resulted from rate inhibition by tin bromide. Since transfer of the amido group is thermodynamically disfavored, it would be reversible if reductive elimination were slower than reversion to the aryl bromide complex (eq 5). In this



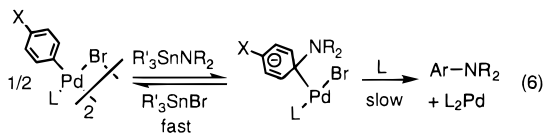
(5)

case, C−N bond-forming reductive elimination would be the irreversible step in our modified mechanism involving a palladium amide. Increasing amounts of tin bromide product would displace the preëquilibrium in eq 5 toward the starting aryl bromide complex and would inhibit the overall reaction rate.

Indeed, added tin bromide did inhibit reaction rates. This inhibition was clearly observed when qualitatively monitoring reaction rates and was also assessed quantitatively. For example, a rough inverse first-order behavior was observed at low concentrations of tin bromide, comparable to concentrations generated during catalysis. Perhaps most convincing, the curvature of first-order plots conducted in the absence of added tin bromide was not observed in the presence of added tin bromide as shown in Figure 1. This effect is consistent with curvature due to product inhibition. The curvature is eliminated by creating conditions under which the product concentration remains constant.

One must also consider whether the added tin bromide leads to a change in the identity of the catalyst or leads to decomposition of the catalyst. Although we did observe that decomposition of catalyst occurred in competition with the production of arylamine in the presence of a 20−30-fold excess of tin bromide for each tin amide (100−150 times the catalyst concentration), several pieces of data besides the changes in tin amide decay curve shape in the presence and absence of tin amide (Figure 1) are not consistent with decreasing catalyst concentration leading to the mechanistically important inhibitory effect at lower concentrations of added tin bromide. First, the initial rates were slower in the presence of even low concentrations of tin bromide. Second, quantitative studies of the stoichiometric reactions of monometallic amine complex **3** with tin amides showed inhibition by tin bromide.[32] Finally, reaction mixtures containing small quantities of tin bromide did not show significant catalyst decomposition, as determined by ^{31}P NMR spectroscopy involving a PPh_3 standard contained in a capillary tube, even though much slower reaction rates were observed. The absence of significant catalyst decomposition at low concentrations of tin bromide is consistent with the slow reactivity of complexes **2** with tributyltin bromide and the selective reaction of **1** with aryl bromides rather than tributyltin bromide presented in the Results.

Electronic Effects: Initial Reaction of Tin Amide at the Palladium Center Rather Than at the Aryl Group. Although these kinetic experiments demonstrated the presence of an intermediate after reaction of aryl bromide complexes **2b** or amine complex **3a** with tin amide that could be **9**, they provided no structural basis for identifying the proposed amido complex as the intermediate formed. Specifically, it was possible that the reversibly formed intermediate was a species that resulted from attack of the tin amide directly on the palladium-bound aryl ring as presented in eq 6. This



(6)

mechanism would account for the reaction orders we observed since uncatalyzed nucleophilic aromatic substitution reactions involve analogous disruption of the aromatic π-system.[47] However, catalytic reactions run with several aryl bromides possessing different *p*-substituents suggested otherwise. Direct addition of nucleophiles to aryl systems substituted with strong electron donors such as $-NMe_2$ are known to react

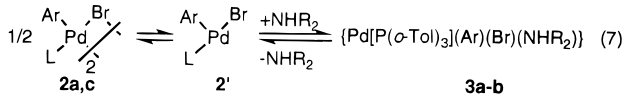
(47) March, J. *Advanced Organic Chemistry;* 3rd ed.; John Wiley and Sons: New York, 1985.

several orders of magnitude slower than those substituted with strong electron acceptors.[48] We found that rates for aryl halides substituted with $-CF_3$ and $-NMe_2$ groups were different by a factor of only 3.8. Such small rate differences are inconsistent with transfer of the amide group from the tin to the aromatic system. Instead, these data support transfer of the amido group from the tin reagent to the metal center, creating a neutral palladium−amido intermediate that would undergo irreversible reductive elimination. The small acceleration by electron-withdrawing groups is consistent with the electronic effects of sulfide elimination, another type of carbon−heteroatom bond forming reductive elimination that we have reported.[43]

Reaction Orders with Catalyst 3a and Their Relationship to Catalysis with 1 or 2b. The use of catalyst **3a** in the kinetic studies allowed for clear determination of the nuclearity and coordination number of the complex that is involved in the irreversible step of the catalysis. The first-order rate behavior in the concentration of **3a** shows that the transition state of the irreversible step involves a mononuclear species. Further, the lack of dependence on phosphine concentration and inverse first-order dependence on amine concentration show that the complex contains phosphine as the only dative ligand. The clear identification of the resting state as an amine-ligated aryl halide complex shows that the covalent ligands include an aryl group and either a halide or an amide. The electronic properties of the reaction show that the tin amide transfers its amido group to palladium, rather than the aryl ring, and forms an amido complex. The reversibility of the transmetalation step shows that the amido species is involved in the kinetically important, irreversible step of the catalysis. The first-order dependence of the reaction rate on Bu_3SnNMe_2 shows that the amido complex is not coordinated to tin amide during its irreversible reaction. Further, the inhibition of the reaction rate by free tin bromide shows that the amido complex is not coordinated to tin bromide during its irreversible reaction. Thus, the kinetically important, irreversible step involves the Pd(II) complex {Pd[P(*o*-tolyl)$_3$](Ar)(NR$_2$)} (**9**), an amido complex that contains one phosphine and one aryl group.

It is not required that the reversible transmetalation step involve amine dissociation. However, transfer of carbon and sulfur nucleophiles from tin to palladium involves three-coordinate monophosphine intermediates.[32] The transfer of amides is, therefore, likely to involve a similar three-coordinate monophosphine intermediate that would form by amine dissociation from amine complexes such as **3a**.

Since reactions catalyzed by Pd(0) complex **1** or aryl halide complexes **2** show reaction orders in aryl halide, tin amide, added tin bromide, and added phosphine that are analogous to those observed for reactions catalyzed by amine complex **3a**, it is most reasonable that reactions involving **1**, **2b**, and **3a** follow similar pathways. As shown in eq 7, dissociation of amine from



(7)

3a gives rise to the same three-coordinate monomeric palladium complex as would be formed from cleavage of dimer **2b**. The inverse first-order behavior in amine concentration and the first order rate behavior in palladium for reactions catalyzed by **3a**, along with the parallels between the kinetics in the presence and absence of amine, imply that reactions of dimeric **2b** in the absence of amine involve a mononuclear species in the kinetically important irreversible step. Thus, reactions catalyzed by **1** and **2b** most likely involve irreversible arylamine reductive elimination from the same three-coordinate amido complex **9** that forms during reactions of **3a**.

The most concise mechanism for formation of **9** during reactions involving **1** or **2** is loss of tin bromide from the tin amide adduct **8**. Further, the first-order, rather than second-order, rate behavior in tin amide for reactions catalyzed by **3a** make it unlikely that free Bu_3SnNMe_2 reacts with tin amide adduct **8** to generate an amido complex. It is not, however, rigorously ruled out that more than one tin amide is involved in the formation of **9**. The irreversible reaction must involve a single amido group, however, since reactions involving **3a** as resting state are first order in tin amide.

Independent Generation of the Amido Intermediate. Stoichiometric, synthetic studies allowed for independent generation of the proposed amido intermediate and demonstrated the chemical competence of such a species for arylamine formation. Although the neutral amido intermediate on the catalytic cycle is too reactive to observe, the independent synthetic route allowed us to observe an anionic palladium dialkylamido complex by low temperature NMR spectroscopy. This anionic amido complex most reasonably leads to the same neutral amido intermediate **9**, which was deduced from our kinetic studies. Thus, these synthetic experiments allowed us to evaluate the reaction chemistry of monomeric palladium dialkylamido reactive intermediates by generating them through a pathway that is separate from the catalytic process with tin amides.

The stoichiometric reactions of silylamide base with amine complexes **3** were likely to be initiated by deprotonation of the coordinated amine, and consistent with this expectation the silylamine $HN(SiMe_3)_2$ was formed. Subsequent loss of LiBr or KBr would then give rise to the same three-coordinate amide **9**, whose presence in the catalytic chemistry was deduced from kinetic studies (Schemes 2 and 3). The differences in spectroscopic characteristics and the different rates of reactivity between compounds generated from potassium and lithium silylamides demonstrated that LiBr and KBr were maintained in the palladium coordination sphere of the observed compound. We propose that the amido complexes observed at low temperatures are the anionic amido species **7** drawn in Scheme 2 and isomeric or oligomeric forms of it, and that these compounds are stable to reductive elimination as a result of their electron rich character. Loss of LiBr at 0 °C or KBr at −20 °C would then form the neutral amido intermediate that would undergo rapid reductive elimination of amine and form [P(*o*-Tol)$_3$]$_2$Pd^0.

An alternative pathway could involve reductive elimination of amine from the anionic amido complex and subsequent extrusion of LiBr or KBr from the Pd(0) product. However, this alternative pathway would involve an unusual reductive elimination from a particularly electron-rich anionic palladium complex. Further, this pathway would involve faster reductive elimi-

(48) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273−412.

nation from the more ionic potassium palladate than from the lithium palladate. In other words, the more electron-rich palladium center would undergo reductive elimination faster than the more electron-poor one. Thus, initial formation of neutral amido complex **9** that undergoes reductive elimination is a more reasonable pathway, albeit not the only possible one.

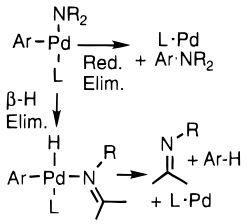
Salt and Solvent Effects. Carbon−carbon bond-forming coupling reactions are significantly influenced by the presence of anions capable of acting as covalent ligands and by solvents with high polarity and Lewis base character. The beneficial effect of chloride in the coupling reactions involving organic triflates is, presumably, due to the creation of a palladium halide intermediate that is more stable than the corresponding triflate.[27,49,50] However, the beneficial effect of copper halides has been shown to result from their ability to coordinate phosphine and thereby effectively lower the free phosphine concentration.[51] These added salts are beneficial in polar coordinating solvents which not only solubilize the added salt but also can act as good ligands to further stablilize unsaturated intermediates.[52] The amination chemistry showed no beneficial effects of added halides. No salt effects from added lithium chloride or potassium fluoride were observed in benzene, presumably due to the insolubility of them, but some detrimental effects were observed in THF. Copper halides radically reduced the production of arylamines in both THF and toluene.

The effect of employing THF vs toluene solvent depended on the catalyst resting state. Under normal catalytic conditions where tin amide concentrations were greater than or comparable to aryl halide concentrations, transmetalation and reductive elimination are rate determining. Polar and donating solvents are known to enhance the rate of transmetalation involving tetraalkyltin reagents,[53] and consistent with these data, reaction rates were slightly faster in THF. However, solvents that are more polar and coordinating than THF led to catalyst decomposition. Apparently, intermediates in the coupling with tin amides decompose more rapidly in polar solvents than intermediates in C−C bond-forming Stille chemistry.

Conversely, reactions rates in THF were slower than those in toluene by a factor of 3 when aryl halide concentrations were low relative to tin amide and phosphine concentrations and aryl halide oxidative addition was rate determining. Aryl halide oxidative additions to $(PPh_3)_4Pd^0$ are known to be slightly slower in THF solvent than in aromatic solvents.[54] Thus, the slower rates in THF are consistent with the previous data concerning solvent effects on aryl halide oxidative addition to Pd(0).

***β*-Hydrogen Elimination vs Reductive Elimination.** The selectivity of the amido intermediate shown in Scheme 4 for the unusual C−N bond-forming reductive elimination reaction rather than common *β*-hydrogen elimination is striking. In the chemistry of late metal amido complexes, the kinetic selectivity of the tri-*o*-tolylphosphine palladium system for reductive elimination over *β*-hydrogen elimination is unparalleled. Imine hydrogenations[56] involve imine insertion into a hydride rather than *β*-hydrogen elimination, but the preference for insertion is likely to be dictated by thermodynamic, rather than kinetic, effects. In any case, the factors that control relative rates for *β*-hydrogen vs reductive elimination are clearly important for catalysis with amido compounds. Some of the factors that control the relative rates for these two processes have been recently reported.[55]

Scheme 4



Conclusions. In addition to defining the principal reactions comprising palladium-catalyzed aromatic aminations, this mechanistic study clearly illustrates that catalytic organometallic chemistry of the platinum-group metals involving complexes with metal−carbon and metal−hydrogen bonds can be extended to similar catalysis involving platinum-group amides. Although transition metal alkylamido complexes of low valent metal centers are rare, they can exist as reactive intermediates which produce synthetically useful transformations when bound to the proper metal and surrounded by the proper ligand set.[3]

It is often the case that the complexes lying directly on a catalytic pathway cannot be isolated or observed.[57] In the case of this study, all of the species lying on the catalytic cycle not only are too reactive to isolate but are too reactive to even observe by NMR spectroscopic techniques. The Pd(0) complex on the reaction pathway is highly unsaturated and contains only one phosphine ligand. The aryl halide complex in the catalytic cycle is not the dimeric or amine-ligated complexes that have been isolated, but is likely to be a monomeric, three-coordinate aryl halide species. Further, the unusual amido complex is most likely a neutral, three-coordinate dialkylamido species that lies uphill from the combination of aryl halide complex and tin amide and whose barrier for reaction is lower than that for simple loss of KBr or LiBr from the observed anionic amido complex. Thus, the general difficulty in isolating neutral alkyl or dialkylamido complexes with *β*-hydrogens to date should not imply that these complexes cannot act as important reactive intermediates in catalytic chemistry. Instead, this high reactivity may make them more prone to participate in catalysis than late metal amido complexes that have been susceptible to characterization by conventional spectroscopic techniques.

Experimental Section

General Data. Unless otherwise specified, all reagents were purchased from commercial suppliers and were used

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(56) Imine hydrogenation catalyzed by rhodium and iridium complexes would be expected to occur through an amide complex. However, mechanistic data is scarce. A direct observation of imine insertion that produces an amide complex potentially similar to those in catalytic systems is the following: Fryzuk, M. D.; Piers, W. E. *Organometallics* **1990**, *9*, 986−98.
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without further purification. Pentane, benzene, toluene, ether, and THF were distilled under nitrogen over sodium and benzophenone. Deuterated solvents for use in NMR experiments were dried as their protiated analogs, but were vacuum transferred from their drying agents. LiCl and LiBr were heated under vacuum for 1 h prior to use. KF was purchased in an anhydrous form and was stored and transferred under nitrogen. Anhydrous NMP solvent was purchased from Aldrich. $PhNO_2$ and CH_3CN were distilled from CaH_2. {Pd[P(*o*-Tol)$_3$](Ar)(Br)}$_2$,[23,33] {Pd[P(*o*-Tol)$_3$](Ar)(Br)(NHR$_2$)},[33] P(*o*-Tol)$_3$,[58] Bu_3SnNMe_2,[59] and Bu_3SnNEt_2[59] were synthesized following reported procedures.

Unless otherwise noted, all manipulations were carried out in an inert atmosphere glovebox or by using standard Schlenk or vacuum line techniques. ^{1}H NMR spectra were obtained on a GE QE 300 MHz or an Ω 300 Fourier transform spectrometer. ^{31}P NMR spectra were obtained on the Ω 300 at 121.6 MHz. ^{1}H NMR chemical shifts are reported in units of parts per million relative to tetramethylsilane and were referenced to residual protiated solvent. ^{31}P{^{1}H} chemical shifts are reported in units of parts per million relative to 85% H_3PO_4. Infrared spectra were recorded on a MIDAC Fourier transform spectrometer. Samples for elemental analysis were submitted to Atlantic Microlab, Inc. GC analyses were performed on a Hewlett-Packard Series 800 gas chromatograph, equipped with a 60 m methylsilicone capillary column. GC/MS analyses were also conducted on a HP series 800 Gas Chromatograph, equipped with a 10 m SE 30 column. Quantitative analyses were obtained integrating peak areas versus 1,3,5-tri-*tert*-butylbenzene or naphthalene internal standard. Response factors relative to the internal standard were determined by coinjection of known quantities of authentic product samples with the internal standards.

{Pd[P(*o*-Tol)$_3$](HNMe$_2$)(Br)(*p*-CH$_3$C$_6$H$_4$)} (3a). A suspension of 112.4 mg (0.193 mmol) of **2a** in toluene (10 mL) was degasssed, and an excess (ca. 50 equiv) of $HNMe_2$ was added to the suspension. In minutes, the sparingly soluble yellow aryl halide complex dissolved to give a pale yellow solution of **3a**. After being stirred for 30 min, the solution was filtered through Celite to remove any traces of precipitate, and the resulting solution was concentrated. A pale yellow precipitate formed upon concentration and this pure **3a** (108.0 mg, 89.2%) was isolated by filtration. Alternatively, crystalline samples of **3a** were obtained by slow diffusion of pentane into a concentrated toluene solution at room temperature. IR (KBr): 3282 (m), 3244 (w), 3052 (m), 2995 (m), 2963 (m), 2920 (s), 2865 (w), 1589 (s), 1562 (m), 1443 (vs), 1384 (s), 1281 (s), 1199 (m), 1165 (w), 1130 (s), 1070 (m), 1053 (m), 1008 (vs), 895 (m), 795 (vs), 748 (vs), 714 (s), 674 (s), 560 (s), 535 (s), 465 (s) cm^{-1}. ^{1}H NMR (C_7D_8, 80 °C): δ 7.94 (broad s, 2H), 6.80−7.17 (m, 12H), 6.51 (d, J = 7.8 Hz, 2H), 3.45 (broad s, 1H), 2.29 (broad s, 9H), 2.20 (broad s, 6H), 2.02 (s, 3H). ^{31}P{^{1}H} NMR (C_7H_8, 80 °C): δ 28.6 (s). ^{31}P{^{1}H} NMR (C_7H_8, 20 °C): δ 28.7 (s). Anal. Calcd for $C_{30}H_{35}NPdPBr$: C, 57.48; H, 5.63; N, 2.23. Found: C, 57.58; H, 5.70; N, 2.31.

Kinetic Studies. Most of the samples for kinetic experiments were prepared in a similar fashion to each other. Deviations from normal setup procedures are noted. The procedure used for obtaining the reaction order in palladium catalyst concentration in the reaction of *p*-$CH_3C_6H_4Br$ with Bu_3SnNMe_2 catalyzed by **3a** will be used as the example. Concentrations, reaction temperatures, and rate constants for subsequent runs are provided after the detailed description of this procedure.

Kinetic Measurements of Reaction between *p*-CH$_3$C$_6$H$_4$Br and Bu$_3$SnNMe$_2$ Catalyzed by Amine Complex 3a. Order in Palladium Catalyst. Into a 3.0 mL volumetric flask were added 82.3 mg (0.270 mmol) of P(*o*-Tol)$_3$, 98.2 μL (0.355 mmol) of Bu_3SnBr, 33.0 μL (0.110 mmol) of Bu_3SnNMe_2, and 121.2 mg (0.709 mmol) of *p*-$CH_3C_6H_4Br$ and the volume was made up to 3.0 mL with toluene-d_8. Samples for each rate measurement were prepared by weighing the appropriate amount of **3a** into a vial and adding 0.54 mL of the 3.0 mL stock solution. The resulting homogeneous solution was transferred to a screw top NMR tube equipped with a Teflon septum. Reaction rates were measured by ^{1}H NMR spectroscopy at 85 °C. Sample tubes were shimmed at room temperature and removed, and the probe was warmed to 85 °C. The sample was placed into the probe, quickly reshimmed, and an automated program was initiated that collected single-pulse experiments with at least 1 min between data collections. The Bu_3SnNMe_2 methyl resonance at 2.804 ppm was integrated over the course of at least 3 half-lives. The following pseudo-first-order rate constants were obtained at different concentrations of **3a** (k, [**3a**]): 2.7×10^{-4} s^{-1}, 0.0059 M; 3.3×10^{-4} s^{-1}, 0.012 M; 9.8×10^{-4} s^{-1}, 0.018 M; 9.4×10^{-4} s^{-1}, 0.024 M; 1.1×10^{-3} s^{-1}, 0.029 M.

Order in HNMe$_2$. Five samples were prepared by placing into an NMR sample tube 0.50 mL of a stock solution made from 24.0 mg (0.0383 mmol) of **3a**, 105.9 mg (0.348 mmol) of P(*o*-Tol)$_3$, 80.0 μL (0.650 mmol) of *p*-$CH_3C_6H_4Br$, 53.0 μL (0.192 mmol) of Bu_3SnBr, and 35.0 μL (0.116 mmol) of Bu_3SnNMe_2 dissolved in 3.0 mL of toluene-d_8. Varying amounts of $HNMe_2$ were injected into each sample with a gas tight syringe. Reactions were monitored at 95 °C. The following pseudo-first-order rate constants were obtained at different concentrations of $HNMe_2$ (k, [$HNMe_2$]): 7.5×10^{-4} s^{-1}, 0.051 M; 5.0×10^{-4} s^{-1}, 0.086 M; 4.3×10^{-4} s^{-1}, 0.11 M; 3.0×10^{-4} s^{-1}, 0.15 M; 1.6×10^{-4} s^{-1}, 0.27 M.

Order in P(*o*-Tol)$_3$ and *p*-CH$_3$C$_6$H$_4$Br. Three samples were prepared by placing into an NMR sample tube 0.50 mL of a stock solution made from 24.4 mg (0.0389 mmol) of **3a**, 96.3 mg (0.316 mmol) of P(*o*-Tol)$_3$, 107.6 mg (0.629 mmol) of *p*-$CH_3C_6H_4Br$, 53.0 μL (0.192 mmol) of Bu_3SnBr, and 35.0 μL (0.116 mmol) of Bu_3SnNMe_2 dissolved in 3.0 mL of toluene-d_8. To one sample was added an additional 67.9 mg (0.223 mmol) of P(*o*-Tol)$_3$. To another sample was added an additional 68.1 mg (0.398 mmol) of *p*-$CH_3C_6H_4Br$. Reactions were monitored at 80 °C. The following pseudo-first-order rate constants were obtained: (k, [P(*o*-Tol)$_3$], [*p*-$CH_3C_6H_4Br$]): 2.0×10^{-4} s^{-1}, 0.11 M, 0.21 M; 2.1×10^{-4} s^{-1}, 0.57 M, 0.21 M; 2.2×10^{-4} s^{-1}, 0.11 M, 1.0 M.

Variation of Aryl Bromide Concentrations in the Reaction of *p*-*t*-BuC$_6$H$_4$Br with Bu$_3$SnNMe$_2$ Catalyzed by 1. Three samples were prepared by placing into an NMR sample tube 0.70 mL of a stock solution made from 13.5 mg (0.0189 mmol) of **1**, 49.3 μL (0.280 mmol) of *p*-*t*-BuC_6H_4Br, and 57.5 mg (0.189 mmol) of P(*o*-Tol)$_3$ dissolved in 2.1 mL of benzene-d_6. To one sample was added an additional 16.4 μL (0.0940 mmol) of *p*-*t*-BuC_6H_4Br. To another sample was added an additional 32.9 μL (0.190 mmol) *p*-*t*-BuC_6H_4Br. Bu_3SnNMe_2 (10.5 μL, 0.0349 mmol) were injected into the samples immediately before data collection at 60 °C. Reactions were monitored to 90% completion. Although first-order plots were slightly curved due to the absence of added tin bromide, inspection of concentrations of the tin amide at different time points during these reactions showed essentially identical conversions at each time point.

Variation of P(*o*-Tol)$_3$ Concentrations in the Reaction of *p*-*t*-BuC$_6$H$_4$Br with Bu$_3$SnNMe$_2$ Catalyzed by 1. Three 0.70 mL samples were prepared that each contained 4.5 mg (0.0063 mmol) of **1**, 21.0 μL (0.120 mmol) *p*-*t*-BuC_6H_4Br, and 60.1 μL (0.200 mmol) of Bu_3SnNMe_2 in toluene-d_8. Then 11.0 mg (0.0361 mmol), 22.0 mg (0.0723 mmol), and 44.0 mg (0.145 mmol) of P(*o*-Tol)$_3$ were added to individual samples. Reactions were monitored at 75 °C.

Reaction of 1 with *p*-BuC$_6$H$_4$Br in the Presence of Bu$_3$SnBr. First, 5.0 mg (0.0070 mmol) of **1**, 11.9 mg (0.0391 mmol) of P(*o*-Tol)$_3$, and 2.6 mg (0.016 mmol) of 1,3,5-trimethoxybenzene were dissolved in 0.5 mL of benzene-d_6. A ^{1}H NMR spectrum was obtained and the quantity of **1** vs 1,3,5-trimethoxybenzene internal standard was determined by integration. A mixture of 20.2 μL (0.121 mmol) of *p*-BuC_6H_4-

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Br and 8.0 μL (0.029 mmol) of Bu_3SnBr was added. The reaction was heated at 60 °C, and integration of a second ^1H NMR spectrum obtained at this time showed that formation of **2c** had occurred in 88% yield.

Reaction Rate in the Presence of *N,N′*-Dimethylaniline Product. A sample containing 4.4 mg (0.0062 mmol) of **1**, 19.5 mg (0.0637 mmol) of P(*o*-Tol)$_3$, 49.2 μL (0.280 mmol) of *p*-*t*-BuC_6H_4Br, and 8.0 μL of freshly distilled *N,N′*-dimethylaniline in 0.70 mL benzene-d_6 was prepared. Reaction with 10.2 μL (0.0339 mmol) of Bu_3SnNMe_2 at 60 °C gave an observed rate constant of 4.8×10^{-4} s^{-1}.

Reaction Rate in Polar Solvents. A sample containing 0.98 mg (0.0014 mmol) of **1**, 2.3 mg (0.0075 mmol) of P(*o*-Tol)$_3$, 18.8 μL (0.0537 mmol) of Bu_3SnNEt_2, 5.0 μL (0.028 mmol) of *p*-BuC_6H_4Br, and 3.5 mg (0.027 mmol) of naphthalene was prepared in 0.5 mL of THF. A similar sample containing 1.0 mg (0.0014 mmol) of **1**, 2.1 mg (0.0070 mmol) of P(*o*-Tol)$_3$, 18.8 μL (0.0559 mmol) of Bu_3SnNEt_2, 5.0 μL (0.028 mmol) of *p*-BuC_6H_4Br, and 4.4 mg (0.028 mmol) of naphthalene was prepared in 0.5 mL of toluene. These samples were also used as controls for the effect of copper additives (*vide infra*). Conversion of aryl halide to arylamine was monitored by GC at 75 °C at different reaction times over the course of 2−5 h.

A sample containing 3.1 mg (0.0043 mmol) of **1**, 20.0 mg (0.0657 mmol) of P(*o*-Tol)$_3$, and 3.9 μL (0.022 mmol) of *p*-*t*-BuC_6H_4Br in 0.50 mL of THF-d_8 was prepared. Reaction with 37.5 μL (0.125 mmol) of Bu_3SnNMe_2 at 60 °C gave an observed rate constant of 3.0×10^{-4} s^{-1}. Reactions were similarly set up in $PhNO_2$, NMP, and CH_3CN solvents although no rate constants were obtained.

Relative Rate Study with Substituted Aryl Bromides. Samples were prepared containing 4.5 mg (0.0063 mmol) of **1**, 0.284 mmol of the ArBr, and 19.5 mg (0.0641 mmol) of P(*o*-Tol)$_3$ in 0.70 mL of benzene-d_6. Bu_3SnNMe_2 (5.3 μL, 0.018 mmol) was injected into each tube prior to data collection. The following observed rate constants (k) were obtained at 60 °C for various substituted aryl bromides: ArBr, 2.4×10^{-4} s^{-1}, *p*-$Me_2NC_6H_4Br$; 9.0×10^{-4} s^{-1}, *p*-$CF_3C_6H_4Br$; 2.9×10^{-4} s^{-1}, *p*-$MeOC_6H_4Br$; 6.5×10^{-4} s^{-1}, *p*-FC_6H_4Br.

Quantitative Relative Rates for Reaction of Bu_3SnNMe_2 and Bu_3SnNEt_2. To 0.50 mL of a 1.2 mL stock solution containing 9.2 mg (0.013 mmol) of **1**, 16.5 mg (0.0542 mmol) of P(*o*-Tol)$_3$, 35.2 mg (0.206 mmol) of *p*-$CH_3C_6H_4Br$, and 15.0 μL (0.0543 mmol) of Bu_3SnBr in toluene-d_8 was added either 12.0 μL (0.0399 mmol) Bu_3SnNMe_2 or 13.0 μL (0.0388 mmol) Bu_3SnNEt_2. In one case, the disappearance of Bu_3SnNMe_2 was monitored and in the other, the appearance of *p*-$CH_3C_6H_4NEt_2$ was monitored, both at 75 °C over 3 half-lives. Pseudo-first-order rate constants of 6.6×10^{-4} s^{-1} and 4.9×10^{-4} s^{-1} were obtained for the reactions with Bu_3SnNMe_2 and Bu_3SnNEt_2, respectively, giving a relative ratio of 1.4.

Competition Study between Bu_3SnNMe_2 and Bu_3SnNEt_2. Into a screw top vial equipped with septum were added 1.2 mg (0.0017 mmol) of **1**, 2.3 mg (0.0076 mmol) of P(*o*-Tol)$_3$, 5.0 μL (0.028 mmol) of *p*-BuC_6H_4Br and between 1.0 and 3.0 mL of toluene. Bu_3SnNMe_2 (70.0 μL, 0.233 mmol) and Bu_3SnNEt_2 (80.0 μL, 0.239 mmol) were syringed into the medium. The vial was sealed and warmed to 70 °C for 2 h. The ratio of arylamine products was analyzed by GC. The average of two runs was found to be 2.9 ± 0.4.

Independent Synthesis. Amine complex **3b** {[P(*o*-Tol)$_3$](NHEt$_2$)Pd[*p*-BuC_6H_4](Br)} was used for synthetic studies at low temperatures because its ^{31}P NMR spectrum displays one dominant resonance in THF solvent.

Low Temperature Additions. Complex **3b** (6.0 mg, 0.0086 mmol) was dissolved in 0.5 mL of THF or THF-d_8 and placed into a screw-topped NMR sample tube equipped with a Teflon lined septum. Then 2 equiv of either $LiN(SiMe_3)_2$ or $KN(SiMe_3)_2$ was dissolved into 0.2 mL of THF or THF-d_8 and placed into an airtight syringe. The NMR sample tube was placed into an NMR probe at −70 °C before addition of silylamide and ^{31}P and ^1H NMR spectra were obtained. The sample was removed and placed into a −78 °C bath. The silylamide base was then added by syringe, and the sample was shaken before replacing it in the NMR probe. ^1H and ^{31}P NMR spectra were recorded at −70 °C and the sample was monitored by increasing the temperature by 10 °C intervals until formation of arylamine and L_2Pd^0 had occurred.

Room Temperature Additions. Reaction of 2c with Lithium Amides. Into a screw top vial equipped with a Teflon lined septum was added 11.2 mg (0.0183 mmol) of **2c**. This complex was dissolved in 0.5 mL of THF in the presence of 24.3 mg (0.0798 mmol) of P(*o*-Tol)$_3$ by gentle warming. Then 50.0 μL of a solution or slurry of LiNRR′ that would be 0.70 M if fully dissolved (NMe_2, NEt_2, NH-*t*-Bu, NHPh, or NPh_2) was injected after the solution cooled to room temperature. Reaction mixtures turned from yellow to red. After 20 min at ambient temperatures, 10 μL of solution containing an internal standard (0.016 M naphthalene or 1,3,5-tri-*tert*-butylbenzene in toluene) was added to the sample. Reactions were analyzed for arylamine formation by GC and GC/MS.

Salt Effects. Catalytic reactions with various salt additives were prepared in a similar manner to the procedure described for competition reactions. Each reaction contained 13.5 mg (0.0444 mmol) of P(*o*-Tol)$_3$, 22.3 mg (0.0910 mmol) of 1,3,5-tri-*tert*-butylbenzene, 85.0 μL (0.253 mmol) of Bu_3SnNEt_2, and 35.0 μL (0.198 mmol) of *p*-BuC_6H_4Br in 2 mL of toluene or THF solvent. All possible pairs of the following Pd catalysts and salts were combined with the above mixtures and reacted at 75 °C for 12 h: 6.2 mg (0.0087 mmol) of **1**; 7.6 mg (0.0087 mmol) of Pd[P(*o*-Tol)$_3$]$_2$Br$_2$; 11.5 mg (0.198 mmol) of KF; 8.0 mg (0.20 mmol) of LiCl; 7.6 mg (0.088 mmol) of LiBr. Reactions were monitored by GC.

Copper Additives. A stock solution containing 3.9 mg (0.0054 mmol) of **1**, 9.1 mg (0.030 mmol) of P(*o*-Tol)$_3$, 75.0 μL (0.224 mmol) of Bu_3SnNEt_2, 20.0 μL (0.113 mmol) of *p*-BuC_6H_4Br, and 13.9 mg (0.108 mmol) of naphthalene was prepared in 2 mL of THF. A 0.50 mL amount of the stock solution was added to the following quantities of individual copper reagents: 3.7 mg (0.037 mmol) of CuCl, 4.4 mg (0.031 mmol) of CuBr, and 6.3 mg (0.033 mmol) of CuI. Reactions were heated to 75 °C for 4 h and monitored by GC. The remaining 0.5 mL stock solution was heated simultaneously with the copper reactions as a control experiment and used to compare solvent effects (*vide supra*).

Another stock solution containing 4.1 mg (0.0057 mmol) of **1**, 8.5 mg (0.028 mmol) of P(*o*-Tol)$_3$, 75.0 μL (0.224 mmol) of Bu_3SnNEt_2, 20.0 μL (0.131 mmol) of *p*-BuC_6H_4Br, and 14.1 mg (0.110 mmol) of naphthalene was prepared in 2 mL of toluene. A 0.5 mL amount of the stock solution was added to 4.0 mg (0.040 mmol) of CuCl, 4.4 mg (0.031 mmol) of CuBr, or 6.3 mg (0.033 mmol) of CuI. Reactions were heated to 75 °C for 4 h and monitored by GC. The remaining 0.5 mL stock solution was heated simultaneously as a control experiment and used to compare solvent effects (*vide supra*).

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