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Slow Reductive Elimination from Arylpalladium Parent Amido Complexes

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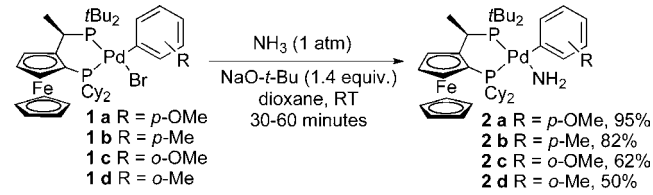
Abstract: We report reductive eliminations of primary arylamines from a series of bisphosphine-ligated arylpalladium(II) parent amido complexes that counter several established trends. In contrast to arylamido and alkylamido complexes of the aromatic bisphosphines DPPF and BINAP, parent amido complexes of these ligands do not form or undergo reductive elimination of monoarylamines. However, arylpalladium parent amido complexes ligated by the alkylbisphosphine CyPF-*t*-Bu do form in good yield and undergo reductive elimination. Despite the basicity of the parent amido ligand and the typically faster reductive elimination from complexes containing more basic amido ligands, the CyPF-*t*-Bu-ligated arylpalladium parent amido complexes undergo reductive elimination much more slowly than the analogous complexes containing arylamido or alkylamido ligands. Moreover, the parent amido complexes form more rapidly and are more stable thermodynamically in a series of exchange processes than the arylamido complexes. Computational studies support the overriding influence of steric effects on the stability and reactivity of the parent amido complex. The slow rate of reductive elimination causes the arylpalladium amido complex to be the resting state of the coupling of aryl halides with ammonia catalyzed by CyPF-*t*-Bu-ligated palladium, and this resting state contrasts the Pd(0) or arylpalladium(II) resting states of reactions of aryl halides with amines catalyzed by most palladium complexes.

Parent amido complexes of the late transition metals are rare, and few classes of catalytic or stoichiometric reactions have been discovered that occur through such species. The existing stoichiometric reactions demonstrate that this class of compound is highly basic at nitrogen,[1−3] but studies of reaction chemistry have been limited to proton exchanges with weak acids,[1−6] insertions of CO into the N−H bond,[7] and reductive eliminations of ammonia.[8] The recently discovered palladium-catalyzed coupling of aryl halides with ammonia is likely to occur through parent amido complexes,[9−13] but only one potential amido intermediate in this process has been generated, and it was investigated briefly.[5a] Thus, no study reveals the relative thermodynamic stability and reactivity of parent amido complexes versus the analogous alkyl- and arylamido complexes containing the same ancillary ligands.

We report results from studies of a series of arylpalladium amido complexes containing bisphosphine ligands that contradict several established trends. The parent amido complexes we generate are more stable thermodynamically than amides derived from more acidic amines, undergo reductive elimination when ligated by only a select set of bisphosphines, and reductively eliminate more slowly than complexes containing less basic arylamido and more basic alkylamido ligands. They are sufficiently stable that the arylpalladium amido complex is even the resting state of the catalyst bound by a hindered alkylbisphosphine ligand.

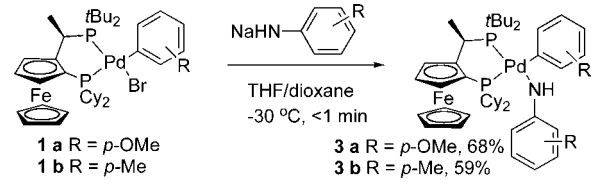
Our synthesis of arylpalladium parent amido complexes **2a**−**2d** containing the Josiphos ligand CyPF-*t*-Bu is summarized in Scheme 1. These complexes were generated by combining arylpalladium bromide precursors, (CyPF-*t*-Bu)Pd(Ar)(Br) (Ar = *p*-tolyl, *p*-anisyl, *o*-tolyl, *o*-anisyl), 1 atm of ammonia, and 1.4 equiv of NaO-*t*-Bu base. Conversion of **1a**−**1d** to the amido complexes occurred in less than 1 h at 25 °C. These complexes were found to be stable enough at −30 °C to be characterized in solution by low temperature ^{1}H and ^{31}P NMR spectroscopy and infrared spectroscopy, including data on ^{15}N-labeled analogs.

Scheme 1. *In Situ* Generation of Parent Amido Complexes **2a**−**d**



Arylpalladium arylamido and alkylamido complexes containing CyPF-*t*-Bu as ligand were also generated to compare their reactivity to that of complexes **2a**−**2d**. Arylamido complexes **3a** and **3b** formed in ∼70 and 60% yield, respectively, as shown in Scheme 2 and were characterized by NMR spectroscopy at −30 °C. Although we were able to characterize arylpalladium parent amido complexes containing *ortho* substituents on the palladium bound aryl group, arylpalladium anilido complexes containing *ortho* substituents did not form at room temperature. The slow formation of such *ortho*-substituted arylpalladium arylamido complexes is consistent with selective formation of primary vs secondary arylamines from the coupling of ammonia with *ortho*-substituted aryl halides. Reaction of complex **1a** with *iso*-butylamine and NaO-*t*-Bu at −30 °C did not lead to observable quantities of an alkylamido complex; instead, the *N*-alkyl aniline product (>90%) and (CyPF-*t*Bu)Pd(PPh_3) (>98%), which would form by reductive elimination from the arylpalladium *iso*-butylamido complex in the presence of PPh_3, were the only species observed.

Scheme 2. Generation of Arylpalladium Arylamido Complexes **3a**−**b**



Reductive eliminations of arylamines from arylamido and alkylamido complexes ligated by DPPF have been reported previously,[14−16] and similar reactions of arylpalladium amido complexes ligated by BINAP certainly occur during reactions catalyzed by palladium complexes of this ligand.[17] In contrast to these systems containing alkyl- and arylamido ligands, DPPF- and

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BINAP-ligated arylpalladium parent amido complexes did not undergo reductive elimination of arylamines. Reaction of (L)Pd(Ar)(Br) (L = DPPF, BINAP, Ar = C_6H_4-*p*-OMe, Ph) with ammonia and NaO-*t*-Bu did not lead to (L)Pd(Ar)(NH_2) or primary arylamines; these reactions led to homocoupling of the aryl ligand and unidentified Pd side products. The alternative route to a BINAP-ligated parent amido complex involving deprotonation of [(BINAP)Pd(Ph)(NH_3)](OTf)[18] led to a new species by ^{31}P NMR that formed biphenyl products, free PPh_3, and less than 5% of diphenylamine. Consistent with these results, the combination of a Pd(0) precatalyst and DPPF or BINAP does not catalyze the monoarylation of ammonia under the previously described conditions for reactions catalyzed by CyPF-*t*-Bu-ligated palladium.[5a] These data with two common arylphosphines imply that arylpalladium parent amido complexes undergo reductive elimination more slowly than arylpalladium alkylamido and arylamido complexes, are more open to competing side reactions, or both.

In contrast, both parent amido complexes and arylamido complexes ligated by CyPF-*t*-Bu undergo reductive elimination, as shown in Scheme 3. In the presence of 2 equiv of PPh_3 to trap the Pd(0) product, the complexes ligated by CyPF-*t*-Bu formed the primary arylamines in 50−86% yield for the two-step sequence at room temperature; the reductive elimination step formed the arylamine in 60−90% yield and the Pd(0) species in 55−85% yield. The aniline products formed in higher yields when they were allowed to undergo reductive elimination at elevated temperatures, the largest difference being observed for the reductive elimination of *p*-toluidine from **2b**.

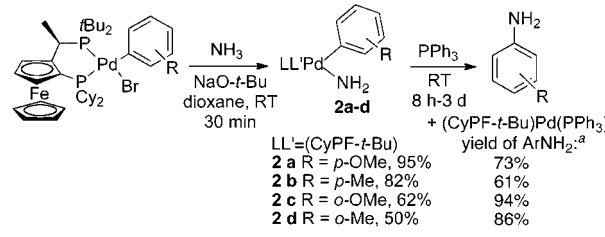
Reactions of the arylpalladium anilides **3a** and **3b** occurred rapidly at room temperature to form diarylamine products in 36−53% yield for the two-step sequence and 60−70% for the reductive elimination step. This fast reductive elimination from the arylamido complex at room temperature, along with the fast formation of the *N*-alkyl arylamine from reaction of **1a** with *iso*-butylamine and NaO-*t*-Bu, shows qualitatively that reductive elimination from the parent amido complex is slower than from both more electron-poor arylamido complexes and more electron-rich alkylamido complexes.

Rate constants for reductive eliminations from the parent amido and arylamido complexes in the presence of 2 equiv of PPh_3 determined by ^{31}P NMR spectroscopy at room temperature are shown in Scheme 3.[19] Reactions conducted with 2, 4, and 8 equiv of added PPh_3 occurred with indistinguishable rate constants, indicating that the reductive elimination is zero-order in added phosphine and occurs directly from the arylpalladium amide.

The data in Scheme 3 reveal large differences in the rates for reductive elimination from the various arylpalladium parent amido complexes. The rate constant for reductive elimination from the *para*-anisylpalladium complex **2a** was an order of magnitude smaller than that from the less electron-rich *para*-tolyl complex **2b**. Complexes **2c** and **2d** containing an *ortho* substituent on the aryl group underwent reductive elimination nearly 50 times faster than those containing *para* substituents.

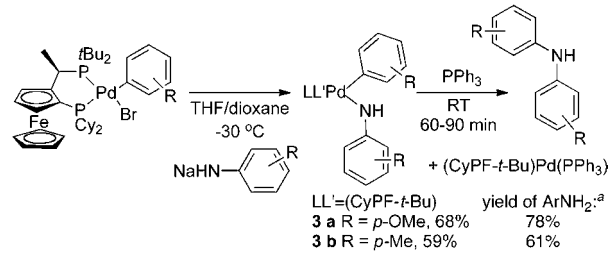
A quantitative assessment of the relative rates for reductive elimination from complexes containing different types of amido groups is also contained in Scheme 3. The *para*-anisylamido complex **3a** reacted 100 times faster than the corresponding parent amido complex **2a**, and the *para*-tolylamido complex **3b** reacted 150 times faster than the corresponding parent amido complex **2b**, the half-life for reaction of **3b** being less than a minute. Because we have shown previously that amido complexes containing more basic nitrogen atoms undergo faster reductive eliminations than those with less basic nitrogen atoms,[15] and terminal amido

Scheme 3. Reductive Elimination of Arylamines from Parent Amido Complexes **2a**−**d** and Arylamido Complexes **3a**−**b**



LL'=(CyPF-*t*-Bu)	yield of $ArNH_2$:[a]
2 a R = *p*-OMe, 95%	73%
2 b R = *p*-Me, 82%	61%
2 c R = *o*-OMe, 62%	94%
2 d R = *o*-Me, 50%	86%

Complex	Solvent	k (s^{-1})[b,c,e]
2a, R=*p*-OMe	Dioxane	7.5 x 10^{-6}
2b, R=*p*-Me	Dioxane	5±1 x 10^{-5}
2c, R=*o*-OMe	Dioxane	4.2 x 10^{-5}
2d, R=*o*-Me	Dioxane	3.0 x 10^{-4}
2b, R = *p*-Me	Dioxane	3.6 x 10^{-5} [e]
2b, R = *p*-Me	Dioxane	4.0 x 10^{-5} [f]



LL'=(CyPF-*t*-Bu)	yield of $ArNH_2$:[a]
3 a R = *p*-OMe, 68%	78%
3 b R = *p*-Me, 59%	61%

Complex	Solvent	k (s^{-1})[b,c]
3a, R=*p*-OMe	THF:dioxane[d]	8.7 x 10^{-4}
3b, R=*p*-Me	THF:dioxane[d]	7±2 x 10^{-3}

[a] GC yield of monoarylamine or diarylamine at 20 °C for the reductive elimination step. [b] At 20 °C. [c] Determined by monitoring the decay of the amido or arylamido complex by ^{31}P NMR spectroscopy. [d] THF/dioxane mixture of 3:2. [e] Average of 2−4 runs. A standard deviation is provided for the cases that are run more than twice and have the largest errors; the rate constants for cases run twice are within 5% of each other. [f] Amido complex generated with KO-*t*-Bu as the base. [g] Amido complex generated with LiO-*t*-Bu as the base.

complexes are known to be highly basic,[1−3] the smaller size of the parent amido ligand is, most likely, responsible for the large differences in the rates of reductive elimination.

To understand the thermodynamic properties of the different amido complexes and origins of the relative rates for reductive elimination, we assessed the different thermodynamic stabilities of the parent amido and arylamido complexes, relative to the free amines, by both computational and experimental methods, and we computed the barriers to reductive elimination from a series of arylpalladium amido complexes. To distinguish between steric and electronic effects on the stability and reactivity of the complexes containing the different amido groups, we assessed by DFT calculations the thermodynamic properties and barriers for reductive eliminations involving complexes in which steric effects should have less of an influence on the relative thermodynamic stability of the complexes and rates for reductive elimination than they do in the experimental system.

The stability of the amido complexes, transition states for C−N reductive elimination, and overall free energies for formation of the amine product in dioxane solvent were calculated for a series of *cis*-bis(trimethylphosphine)-ligated phenylpalladium amido complexes, and the results of this analysis are shown in Figure 1. As expected from the greater acidity of aniline,[11] the equilibrium between the combination of the arylamido complex and ammonia and the combination of the parent amido complex and aniline favored the arylamido complex by a free energy of 1.9 kcal/mol.

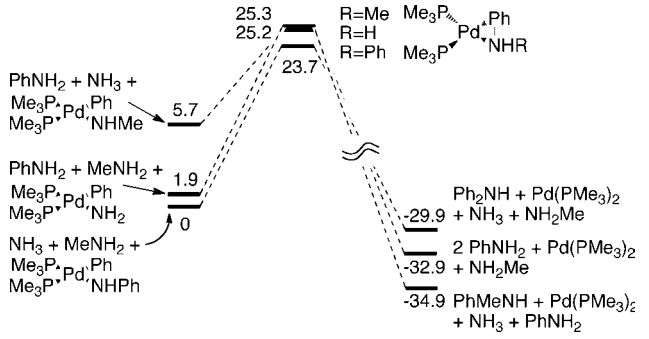
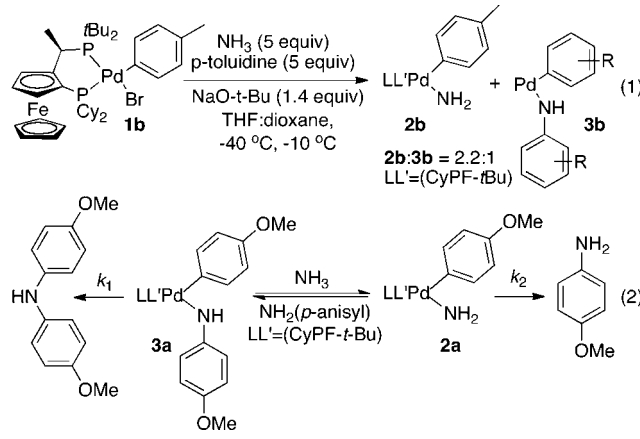


Figure 1. Relative ground state and transition state free energies in kcal/mol for PMe_3-ligated phenylpalladium parent amido, arylamido, and methylamido complexes undergoing C−N reductive elimination.

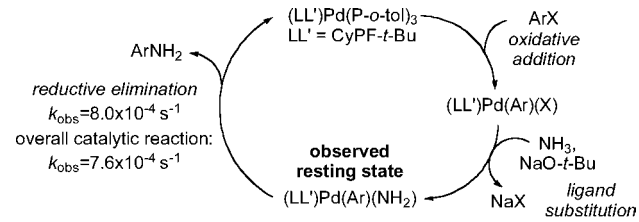
The free energy barrier for reductive elimination of diphenylamine from the anilide complex was calculated to be higher than that for reductive elimination of aniline from the parent amido complex by just 0.3 kcal/mol. The reductive elimination of aniline was more downhill than the reductive elimination of diphenylamine by 3.0 kcal/mol in free energy. The *N*-methylamido complex was calculated to be significantly less stable than either the parent amido or arylamido complex in the exchange equilibria, but the barrier for reductive elimination from the methylamido complex was calculated to be more than 4 kcal/mol lower than that for reductive elimination from either the parent amido or arylamido complexes.

The calculated thermodynamic values can then be compared to experimental results with the arylpalladium amido complexes ligated by more sterically encumbered CyPF-*t*-Bu. In contrast to the typical trend of the base of a more acidic molecule being the preferred ligand among an analogous series of acid−base pairs[20] (as underscored by the computed equilibria for the PMe_3 complexes), the palladium center ligated by CyPF-*t*-Bu favored binding of the parent amido group. Although competitive reductive elimination from the arylpalladium arylamido complexes prevented our obtaining quantitative K_{eq} values for the proton transfer equilibria, reaction of complex **1b** with ammonia and *p*-toluidine in the presence of 1.4 equiv of NaO-*t*-Bu generated a mixture containing a higher population of parent amide **2b** than of the arylamide **3b** (eq 1). Moreover, treatment of arylamide **3a** generated in situ with 5 equiv of ammonia began to form **2a** (1:2.5 ratio of **2a** to **3a** after 20 min at −40 °C), but treatment of **2a** with 5 equiv of *p*-anisidine at −40 °C gave little arylamide **3a** (ratio of **2a** to **3a** was >20:1 after 20 min). When the latter sample was warmed to room temperature and allowed to equilibrate for an additional 20 min, parent amide **2a** was favored over arylamide **3a** by a ratio of 3:1 (eq 2). Thus, the faster generation of the parent amide **2a** and greater thermodynamic stability of **2a** lead to selective formation of the primary arylamine, not faster reductive elimination from the parent amido complexes due to the strong basicity of the parent amido group.[1,2,21] At the same time, the strong basicity of the primary alkylamido complexes does appear to affect the rates of reductive elimination. The low barrier computed for reductive elimination from the methylamido complex agrees with the fast reductive elimination observed from the CyPF-*t*Bu-ligated isobutylamido complex generated *in situ*.

Finally, we studied the identity of the palladium complex in the coupling of aryl halides with ammonia catalyzed by the combination of $Pd[P(o\text{-tol})_3]_2$ and CyPF-*t*-Bu. The mechanism for this reaction is shown below in Scheme 4. Like many common C−N cross-coupling reactions, the process occurs by initial oxidative addition of an aryl halide to the Pd(0) precursor (CyPF-*t*-Bu)Pd(P-*o*-tol_3). Conversion of the arylpalladium halide complex to the arylpalladium amide by ammonia and NaO-*t*-Bu leads to the arylpalladium parent amido complex. Reductive elimination from this species forms the monoarylamine. Monitoring of the reaction of 4-bromotoluene with ammonia in dioxane by ^{31}P NMR spectroscopy at 80 °C with 11 mol % of the catalyst showed that the parent amido complex was the major species present in the reaction solution. This amide resting state contrasts with the Pd(0) resting state in reactions of amines with aryl halides catalyzed by complexes of DPPF and BINAP.[17,22] Consistent with the parent amido complex as the resting state, the rate constant for the catalytic coupling at 50 °C with 5 mol % of the preformed arylpalladium halide complex **1b** was similar (8.0×10^{-4} vs 7.6×10^{-4} s^{-1}) to that for the stoichiometric reaction of the arylpalladium parent amido complex at the same temperature, after correcting for the catalyst concentration (Scheme 4).



Scheme 4. Mechanism of Pd-Catalyzed Amination with Ammonia and Observed Arylpalladium Parent Amido Resting State



In summary, the chemistry of the parent amido complexes [Pd(CyPF-*t*-Bu)(Ar)(NH_2)], as well as analogs containing aromatic bisphosphine ligands, is distinct from that of the alkyl- and arylamido analogs. The parent amido complexes ligated by CyPF-*t*-Bu are more stable thermodynamically and undergo reductive elimination more slowly than the alkylamido and arylamido analogs. This difference from the usual trends in stability and reactivity that result from electronic effects is likely due to the hindered ligand environment of CyPF-*t*-Bu. This hindered environment disfavors formation of complexes of the larger amides and reduces the energies for reductive elimination from complexes of the bulkier aryl- and alkyl-substituted amides. Finally, parent amido complexes containing common aromatic bisphosphine ligands do not form or undergo reductive elimination of arylamines in high yields.

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Supporting Information Available: All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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