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Authors
Wang, Justin Y
Strom, Alexandra E
Hartwig, John F

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Mechanistic Studies of Palladium-Catalyzed Aminocarbonylation of Aryl Chlorides with Carbon Monoxide and Ammonia

Justin Y. Wang[†], **Alexandra E. Strom**[†], **John F. Hartwig**[*,†,‡]

[†]Department of Chemistry, University of California, Berkeley, California 94720, United States

[‡]Chemical Sciences Division, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, California 94720, United States

Abstract

Mechanistic information on a reliable, palladium-catalyzed aminocarbonylation of aryl chlorides with ammonia is reported. The reaction occurs with ethylene complex **1** as catalyst, and mechanistic information was gained by isolation of catalytic intermediates and kinetic measurements, including the first mechanistic data on the oxidative addition of aryl chloride to a palladium(0) complex in the presence of CO. Arylpalladium and phenacylpalladium halide intermediates were synthesized, and kinetic measurements of the formation and reactions of these intermediates were undertaken to determine the mechanism of the oxidative addition of aryl bromides and chlorides to a Pd(0) dicarbonyl compound in the presence of CO and the mechanism of the reaction of ammonia with a Pd(II) phenacyl complex to form benzamide. The oxidative addition of aryl chlorides and aryl bromides was determined to occur with rate-limiting reaction of the haloarene with a three-coordinate Pd(0) species bearing a bidentate phosphine and one CO ligand. A primary ^{13}C kinetic isotope effect suggested that this step involves cleavage of the carbon–halogen bond. Our data show that the formation of benzamide from the reaction of phenacylpalladium halide complexes with ammonia occurs by a pathway involving reversible displacement of chloride from a phenacylpalladium chloride complex by ammonia, deprotonation of the bound ammonia to form a phenacylpalladium amido complex, and reductive elimination to form the C–N bond. Consistent with this mechanism, the reaction of an aryl palladium amido complex with CO formed the corresponding primary benzamide. A catalyst deactivation pathway involving the formation of a Pd(I) dimer also was elucidated.

Graphical Abstract

[*]**Corresponding Author:** jhartwig@berkeley.edu.

The authors declare no competing financial interest.

Supporting Information

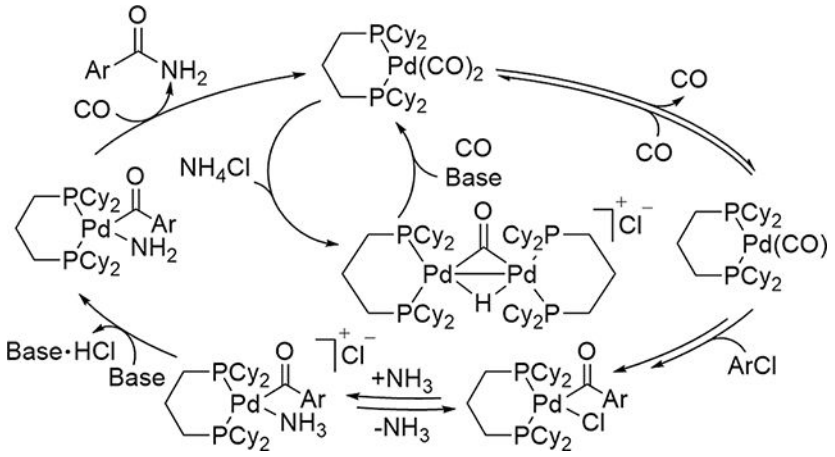
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04073.

X-ray crystallographic data for **1** (CIF)

X-ray crystallographic data for **4** (CIF)

X-ray crystallographic data for **8b** (CIF)

Experimental procedures, characterization, X-ray data, and computational details (PDF)



INTRODUCTION

Palladium-catalyzed carbonylation reactions of aryl halides and pseudohalides furnish aromatic ketones,[1] aldehydes,[2] amides,[3] esters,[4] and other carboxylic acid derivatives.[5] These processes have been used in industry to create pharmaceuticals, agrochemicals, and dyes.[6] For example, lazabemide, a monoamine oxidase B inhibitor, was prepared in one step by the palladium-catalyzed aminocarbonylation of 2,5-dichloropyridine.[7] An intermediate in the synthesis of a GPIIb/IIa receptor antagonist also was synthesized by palladium-catalyzed aminocarbonylation of a highly functionalized aryl iodide on a 40 kg scale.[8] Finally, the reductive carbonylation of aryl halides with a palladium catalyst has been conducted on a >100 kg scale.[9]

Despite the broad scope and utility of palladium-catalyzed carbonylations of aryl halides, most of the steps of these reactions are poorly defined (Figure 1).[10] The migratory insertion of CO into square planar arylpalladium halide complexes is fast and has been proposed to occur via a five-coordinate intermediate,[11] but few studies on the mechanism of oxidative addition of aryl halides in the presence of CO have been reported,[10b] few studies on the reactions of amines with acylpalladium complexes have been published,[12] and no examples of the reactions of ammonia with acylpalladium complexes have been described. Pd(0) carbonyl complexes have been proposed as intermediates when reactions are conducted in the presence of carbon monoxide, but often, such compounds containing ligands used for these carbonylation reactions have not been isolated, and examples of the reactions of Pd(0) carbonyl complexes with aryl halides are limited.[13,14] The mechanism of oxidative addition of aryl halides in the presence of CO has been proposed to be distinct from the mechanism of oxidative addition of the same aryl halide during palladium-catalyzed coupling in the absence of CO. This difference results from the unproductive equilibria between active Pd(0) complexes lacking CO and inactive Pd(0) carbonyl adducts or clusters.[10a,13a] Although bidentate phosphines often have been used as ancillary ligands to discourage aggregation of Pd(0) compounds, monomeric Pd(0) complexes of these ligands in the presence of CO can contain one or two CO ligands, and they can associate to form bimetallic dimers containing a bridging CO moiety.[15] It is unclear which of these compounds undergo oxidative addition of the aryl halide. In one of the few studies on the oxidative additions of aryl halides

to Pd(0)-carbonyl complexes, Grushin conducted the oxidative addition of aryl iodides to (Xantphos)$Pd(CO)_2$[10b] to form a phenacyl Pd(II) iodide complex. However, experimental studies to reveal the Pd(0) species that reacts with the aryl halide were not reported; the mechanism of this oxidative addition was only explored computationally.

Data on the mechanism of the catalytic carbonylation of aryl chlorides and data on the oxidative addition of aryl chlorides to Pd(0) in the presence of CO are particularly scarce.[6a] Catalytic carbonylations of aryl chlorides are attractive because aryl chlorides are more commercially available and less expensive than other aryl halides.[16] However, the oxidative addition of aryl chlorides to Pd(0) in the presence of CO and the overall carbonylation of aryl chlorides are likely to be slow because the oxidative addition of aryl chlorides occurs most rapidly with low-coordinate, electron-rich Pd(0) species and the binding of CO makes the electron density lower and the coordination number higher than those in homoleptic Pd(0) phosphine complexes.[6a,17] Indeed, many methods for the carbonylation of aryl or heteroaryl chlorides require high temperatures (≥100 °C),[13a,18] presumably to cause dissociation of CO from Pd(0) or separation of Pd(0) carbonyl clusters. Thus, an improved understanding of the identity of the palladium complex that reacts with the aryl chloride could enable the discovery of new carbonylations and catalysts that induce milder carbonylations of aryl chlorides.

In addition to the ambiguity about the mechanism of the oxidative addition of aryl halides to Pd(0) in the presence of CO, the mechanism of the reaction of acylpalladium complexes with nucleophiles is unclear. The mechanism of the reaction of phenacylpalladium complexes with alcohols to generate phenyl esters has been examined,[19] but few studies of the analogous reactions with amines have been conducted.[12,13b] Alcohols are typically more acidic than amines; therefore, alkoxides can be generated *in situ* during catalysis under basic conditions, and either the alcohol or the alkoxide could serve as coupling partners. In contrast, anionic amides are unlikely to be generated. Moreover, the coordinating ability and nucleophilicity of alcohols and alkoxides is much different from that of amines, leading to differences between the mechanism for the reaction of acyl complexes with oxygen-based nucleophiles and the mechanism for reactions with nitrogen-based nucleophiles. For example, the formation of phenyl esters from *trans*-$(PPh_3)_2Pd(COPh)I$ was suggested by Yamamoto to involve displacement of PPh_3 by an alcohol.[20] Upon deprotonation of the bound alcohol and extrusion of iodide, $(PPh_3)Pd(COPh)$-(OR) underwent reductive elimination of an ester. In contrast, the formation of benzamide was proposed to occur by substitution of iodide from *trans*-$(PPh_2Me)_2$ Pd(Ar)I by CO to generate a cationic Pd(II) carbonyl species, nucleophilic attack of amine on the bound CO, deprotonation of the ammonium nitrogen to form an arylpalladium carbamoyl complex, and reductive elimination of benzamide by formation of a carbon–carbon bond.[13b] The difference between the mechanisms proposed to be followed with an alcohol and amine and the required displacement of phosphine and iodide for these paths make it even less clear how the aminocarbonylation of an aryl chloride with a catalyst containing a bidentate ligand and ammonia as nucleophile would occur (Figure 1).

The synthesis of primary benzamides by palladium-catalyzed carbonylation of aryl halides with ammonia is one of the least explored versions of carbonylative couplings.[18e,21]

Palladium-catalyzed carbonylation reactions to form primary benzamides are typically conducted with ammonia surrogates, followed by deprotection.[22] While procedures involving ammonia or ammonium salts to generate primary benzamides exist, they are limited in number.[23] Reactions to form primary amides with ammonia may be particularly difficult to achieve, due to the low nucleophilicity of ammonia,[24] the slow reductive elimination from Pd(II) complexes containing unsubstituted amido groups (i.e., $–NH_2$),[25] and the tendency of ammonia to poison transition metal catalysts.[26] Thus, the challenge of achieving the aminocarbonylation of aryl halides directly with ammonia prompted us to identify a system that catalyzes the aminocarbonylation of aryl halides with ammonia as the nucleophile.

Herein, we report the aminocarbonylation of aryl chlorides with ammonia to form primary benzamides catalyzed by a Pd(0) complex of 1,3-(dicyclohexylphosphino)propane (DCPP) and describe detailed mechanistic studies of the reaction. A series of intermediates in the catalytic cycle were prepared independently and demonstrated to be competent reaction intermediates. Aryl chlorides and bromides were shown to react with a three-coordinate Pd(0) complex bearing a bidentate phosphine and a carbonyl ligand generated by dissociation of CO from the more stable dicarbonyl complex. A primary ^{13}C kinetic isotope effect and a Hammett analysis of the effect of the electronic properties of aryl chlorides showed that the reaction of the chloroarene with the palladium complex is irreversible, involves cleavage of the carbon–halogen bond, and occurs by the same concerted, non-ionic C–Cl cleavage as the oxidative addition of aryl halides to lower-coordinate Pd(0) species. Our data show that benzamide forms from the resulting phenacylpalladium chloride intermediate by an inner-sphere pathway during which ammonia displaces chloride from a phenacylpalladium chloride complex to generate a cationic Pd(II) ammine complex. This ammine complex undergoes deprotonation to furnish a phenacyl Pd(II) amido complex, which reductively eliminates benzamide. Overall, the rate-limiting step of the aminocarbonylation of aryl chlorides with ammonia was found to be the oxidative addition of an aryl chloride to Pd(0). Finally, a catalyst deactivation pathway involving the protonation of a dicarbonyl Pd(0) complex ligated by DCPP with NH_4Cl to produce a cationic, dimeric Pd(I) complex was revealed. Thus, our studies provide a rare experimental foundation for deducing the full mechanism of a palladium-catalyzed carbonylation process and provide data on the individual steps of valuable carbonylations of aryl chlorides with ammonia.

RESULTS AND DISCUSSION

Identification of a Reaction System for Studies on the Mechanism of Aminocarbonylation of Aryl Chlorides with Ammonia.

We chose to study the mechanism of palladium-catalyzed carbonylative couplings of chloroarenes with ammonia as the nucleophile because of the simplicity of these reagents and the synthetic value of the formation of primary benzamides. However, identifying a suitable system for mechanistic studies was not straightforward. Buchwald published aminocarbonylations of aryl halides with primary and secondary amines catalyzed by $Pd(OAc)_2$ and DCPP, but they showed that these reactions occur by phenoxy-carbonylation

of the aryl halide with the phenoxide base to form phenyl esters, which subsequently react with amines to form amides.[3c] Thus, the catalytic process was not an aminocarbonylation, and the insolubility of the phenoxide base would complicate mechanistic studies. Beller published the aminocarbonylations of aryl bromides with ammonia, but the analogous reactions of aryl chlorides, particularly those of electron-neutral aryl chlorides, occurred in low yield.[18e,21] Barnard published the most striking system for the aminocarbonylation of chloroarenes with ammonium chloride in a review. The reaction was reported to occur with 1 bar of CO at 100–120 °C with a catalyst generated from $Pd(OAc)_2$ and DCPP.[23a] The scope of the reaction in the review was limited to two examples of aryl chlorides, but the work by Buchwald suggested that (DCPP)Pd(0) complexes could catalyze the carbonylation of electron-rich and electron-poor aryl chlorides in the presence of 1 atm of CO.[3c] DCPP is similar to the 1,3-bis(diisopropylphosphino)propane ligand in some of the earliest publications by Milstein on palladium-catalyzed alkoxy-and aminocarbonylations of aryl chlorides with CO.[13a]

Thus, we conducted studies to assess the scope of the aminocarbonylation of chloroarenes with ammonia catalyzed by DCPP complexes of palladium. We conducted initial studies on the reaction of *p*-chlorotoluene in the presence of ammonia or ammonium salts and low pressures of CO (Table 1) published by Barnard. The conditions for reactions of ammonium chloride did not form *p*-toluamide (Table 1, entry 1) in our hands, but reactions with gaseous ammonia afforded a measurable yield of the benzamide (entry 2). Reactions with a catalyst generated from the free base of DCPP (entry 3) formed *p*-toluamide in higher yields than those initiated with the HBF_4 salt of DCPP (entry 2). Ultimately, we found that reactions catalyzed by the ethylene complex **1** shown in Scheme 1 occurred in a high 91% yield (entry 4), even at 110 °C instead of 120 °C, with 450 Torr of CO.

Ethylene complex **1** was synthesized by bubbling ethylene through a solution of $Pd[P(^tBu_3)]_2$ and DCPP. Complex **1** was characterized by NMR spectroscopy, elemental analysis, and X-ray crystallography (see Supporting Information). We used complex **1** as a catalyst precursor because Bunel and Pörschke previously showed that the addition of CO to structurally analogous Pd ethylene complexes bearing bidentate phosphines rapidly formed (bisphosphine)$Pd(CO)_2$ complexes.[27] By starting with the ethylene complex, the carbonylation reactions would occur without induction periods that could result from reduction of Pd(II) to Pd(0).

A summary of our assessment of the scope of the aminocarbonylation is shown in Table 2. With 2.5 mol% of ethylene complex **1** as a precatalyst, 450 Torr of CO, and 4 equiv of ammonia, chlorobenzene (**2a**) was converted to benzamide (**3a**) in 83% yield. Electronically deactivated aryl chlorides **2b–d** underwent the aminocarbonylation process in good yields (75–89%). The sterically hindered and electron-rich aryl chloride **2e** underwent carbonylation, in a lower, but acceptable, yield of 62%. Reactions with electron-poor aryl chlorides **2f–j** afforded the corresponding benzamides **3f–j** in 60–100% yields, showing the compatibility of the reaction with a bulky ester (**2h**), cyano group (**2i**), and extended π systems (**2j**). Reactions with the heteroaryl chlorides 3-chloropyridine (**2k**) and 2-chlorothiophene (**2i**) generated the corresponding heteroaromatic amides **3k** and **3l** in 77% yield and 69% yield, respectively. Thus, complex **1** catalyzes the aminocarbonylation of a

broad set of aryl chlorides with ammonia, and mechanistic studies on this system, therefore, would involve a system that is synthetically valuable.

Identification of Pd(0) Carbonyl Adducts.

To initiate our studies on the mechanism of the aminocarbonylation of chloroarenes with ammonia, we prepared the Pd(0) carbonyl compound ligated by DCPP. The stable carbonyl complex that would be present in the catalytic system was generated by the addition of 1000 Torr of CO to ethylene complex **1**. The dicarbonyl compound (DCPP)Pd$(CO)_2$ (**4**) was generated within 5 min in 98% yield (Scheme 2). The ^{31}P NMR spectrum consisted of a singlet resonance at 20.8 ppm, and the ^{13}C NMR spectrum consisted of a broad resonance at 196.7 ppm for a carbonyl ligand. To determine the number and bonding mode of CO ligands bound to **4** under conditions relevant to the catalytic process, we measured solution-phase IR spectra of the (DCPP)Pd(0) carbonyl compound generated from **1** under 760 Torr of CO in a mixture of DMSO and toluene (1:1 v/v).[28] Two C–O stretches were observed at 1993 and 1949 cm^{-1} (see Supporting Information), which is consistent with the formulation of the Pd(0) species as a tetrahedral complex with C_{2v} symmetry containing two terminal carbonyl ligands. The solid-state structure of Pd(0) complex **4** was determined by X-ray crystallography (Figure 2). In the solid state, this complex displays a distorted tetrahedral geometry in which the propyl backbone of DCPP constrains the P1–Pd1–P2 angle to 98.84(3)° and the C1–Pd1–C2 angle is 110.98(6)°. The C1–O1 and C2–O2 bond distances (1.132(5) and 1.147(5) Å, respectively) are indicative of metal-to-ligand π-backbonding and are similar to those of other previously reported mononuclear Pd(0) complexes containing terminal CO ligands.[10b,27a,29] Dicarbonyl compound **4**, as a solid or in solution, is only briefly stable in the absence of CO.

To evaluate if dicarbonyl **4** remains intact at elevated temperatures, solution-IR spectra were obtained at 75 °C under 760 Torr of CO in a variable temperature IR cell. Two stretches at 1993 and 1949 cm^{-1} were detected, indicating that the Pd(0) complex retains both carbonyl ligands at elevated temperatures. To determine if the speciation of (DCPP)Pd(0) carbonyl compounds is dependent on CO pressure, the headspace of a solution of **4** was briefly flushed with nitrogen. The IR spectrum of an aliquot of this solution contained the same two C–O stretches at 1993 and 1949 cm^{-1} at room temperature and stretches at 1994 and 1948 cm^{-1} at 75 °C (see Supporting Information). Thus, at both **1** atm of CO and low pressures of CO, dicarbonyl compound **4** was the sole carbonyl compound observed.

To complement the IR spectral data, NMR spectra of dicarbonyl compound **4** were obtained with 600 Torr of ^{13}CO in toluene-d_8 (Figure 3). Unfortunately, ^{31}P–^{13}C coupling between bound ^{13}CO and DCPP was not detected in either ^{13}C or ^{31}P NMR spectra; thus, the number of carbonyl ligands bound to **4** could not be determined from the multiplicity of the resonances observed in the ^{13}C or ^{31}P NMR spectra.[30] A broad resonance at 197 ppm was observed in the ^{13}C NMR spectrum of (DCPP)Pd$(CO)_2$ in toluene-d_8 at room temperature, and the resonance for unbound ^{13}CO was absent, indicating rapid exchange between bound and unbound ^{13}CO. The ^{13}C NMR spectrum at −40 °C contained a sharper resonance at 197 ppm, and a signal consistent with unbound ^{13}CO was observed at 184 ppm at −80 °C. Even at these temperatures, ^{31}P–^{13}C coupling was not observed in either the ^{l3}C or

^{31}P NMR spectra. Due to the absence of phosphorus–carbon coupling, the number of CO ligands bound to **4** was determined by quantitative ^{13}C NMR spectroscopy with ^{13}CO and an internal ^{13}C-enriched integration standard, 4-phenyl-anisole. At −40 °C with 1000 Torr of ^{13}CO, the number of CO ligands per palladium was determined to be 2.0. This value is consistent with the structure of dicarbonyl complex **4**.[31,32]

Thus, IR and NMR spectroscopy along with X-ray crystallography showed that ethylene complex **1** is converted quantitatively to dicarbonyl complex **4** in the presence of CO. These methods also showed that complex **4** retains both CO ligands at elevated temperatures and under reduced pressures of CO. Therefore, we employed (DCPP)Pd(C_2H_4) (**1**) as a precursor to (DCPP)Pd$(CO)_2$ (**4**) for kinetic studies (*vide infra*).

Synthesis and Reactivity of Pd(II) Intermediates.

To determine if Pd(II) aryl and phenacyl halide complexes bearing DCPP were catalytic intermediates, we synthesized (DCPP)Pd(II) aryl halide complexes **5a–j** and (DCPP)Pd(II) phenacyl halide complexes **6a–j**. Pd(II) aryl halide complexes (**5a–j**) ligated by DCPP were synthesized by the reaction of Pd(P^tBu_3)$_2$ and an aryl halide in the presence of DCPP (Scheme 3). Phenacylpalladium chloride complexes **6a,b** and **6e,f** were obtained from the reaction of Pd$(PPh_3)_4$ with an acid chloride and subsequent ligand exchange with DCPP (Scheme 4a), whereas phenacylpalladium halide complexes **6c,d** (Scheme 4b) were generated by carbonylation of (DCPP)Pd(II) aryl halide complexes. Phenacylpalladium halide complexes (**6g–i**) were also obtained by the reaction of dicarbonyl complex **4** (generated *in situ* from **1** and CO) with an aryl chloride or bromide in the presence of CO (Scheme 4c), demonstrating that **4** or compounds generated from **4** are capable of oxidative addition of aryl chlorides and bromides. Pd(II) phenacyl complexes **6a–i** are stable in solution and as solids and in the presence or absence of CO; they also do not undergo decarbonylation under vacuum at room temperature.

In contrast to complexes **6a–i**, phenacyl Pd(II) compound **6j** is only stable in solution in the presence of a CO atmosphere. Our attempts to isolate this compound resulted in the formation of decarbonylation product **5j**. Thus, characterization of **6j** was performed *in situ* by NMR spectroscopy under CO. After warming a solution of ethylene compound **1** and 1.5 equiv of 2-methoxy-4-fluoro-bromobenzene to 80 °C under 800 Torr of CO for 2.5 h, phenacylpalladium complex **6j** formed in 53% yield, and arylpalladium complex **5j** formed in 8% yield (Scheme 5). Reaction for an additional 24 h at room temperature did not fully convert **5j** to **6j**.

The reaction of phenacyl complex **6a** with excess ammonia in the presence of a soluble and hindered base, DBU, formed the corresponding primary benzamide in high yield (Scheme 6), indicating that these acyl complexes are chemically competent to be intermediates in the palladium-catalyzed aminocarbonylation reactions. Thus, by studying a series of stoichiometric reactions of palladium complexes, we have provided strong evidence that compounds **5a–j** and **6a–j** are catalytic intermediates in palladium-catalyzed aminocarbonylation of aryl chlorides with ammonia.

Mechanism of Oxidative Addition of Aryl Chlorides to (DCPP)Pd(CO)$_2$.

The rate constants for the oxidative addition of 3,5-difluorochlorobenzene to (DCPP)Pd(CO)$_2$ (**4**) were measured by monitoring the appearance of the sum of the concentrations of arylpalladium halide complex **5e** and phenacylpalladium halide complex **6e** under pseudo-first-order conditions of excess haloarene at 100 °C in a mixture of DMSO and toluene (1:1 v/v) (Scheme 7). Because dicarbonyl compound **4** is stable for only short times in the absence of CO, complex **4** was generated *in situ* from ethylene complex **1** prior to rate measurements.[33] The dependence of the rate of oxidative addition on CO pressure was determined to be inverse first order, based on the linear relationship between $\mathbf{1}/k_{obs}$ and CO pressure (Figure 4a). The dependence of the rate on the concentration of 3,5-difluorochlorobenzene was determined to be first order based on the linear relationship between $1/k_{obs}$ and 1/[ArCl] (Figure 4b).

The observation of a first-order dependence on the concentration of aryl chloride and an inverse first-order dependence on the pressure of CO is consistent with the mechanisms of oxidative addition depicted in Figure 5. Path A involves reaction of the arene with the neutral, three-coordinate species to cleave the carbon–halogen bond and form a five-coordinate intermediate that undergoes rapid insertion of CO into the metal–aryl bond. This mechanism would be the simplest one that is consistent with our data. However, two alternative pathways are also consistent with the reaction orders. Path B involves the reaction of an aryl chloride with (κ^1-DCPP)Pd(CO) after dissociation of one of the phosphino groups of the DCPP ligand in (κ^2-DCPP)Pd(CO) to form (κ^1-DCPP)Pd(CO), followed by oxidative addition. Path C involves rate-limiting displacement of the CO ligand in (κ^2-DCPP)Pd(CO) by the haloarene to form (κ^2-DCPP)Pd(ArX). Carbon–halogen bond cleavage would then occur in this arene complex to form a four-coordinate, arylpalladium halide complex that would insert CO to form the phenacylpalladium halide species. Paths B and C occur without formation of a five-coordinate addition product from a neutral, three-coordinate Pd(0) complex.

We differentiated between these oxidative addition pathways for reactions of aryl chlorides to (DCPP)Pd(CO) by a combination of ^{13}C kinetic isotope effects (*vide infra*) and calculations by DFT (see Supporting Information). Our computational studies strongly suggested that the reaction did not occur by Path B involving partial dissociation of the bisphosphine ligand. The overall barrier for the oxidative addition of an aryl chloride to (κ^1-DCPP)Pd(CO) was computed to be 15 kcal/mol higher than the experimental barrier at standard state conditions, and it was calculated to be 12 kcal/mol higher than the experimental barrier at the temperature and concentrations of the reaction.[34] This high barrier for reaction by path B is consistent with the importance of chelating ligands to observe the carbonylation of aryl chlorides.[3c,13a,18b,c] In contrast, the difference in energy between the highest-energy transition state—the transition state for oxidative addition of an aryl chloride—via path A and the computed energy of the experimentally determined resting state (DCPP)Pd(CO)$_2$ at concentrations close to those of the catalytic reaction was higher than the experimentally measured barrier by only 4 kcal/mol. The computed barrier for reaction by path C is ambiguous because we were unable to locate a transition state for the ligand substitution process, but this computed barrier is likely several kcal/mol

lower than the experimental barrier based on the ground-state energies and transition state for oxidative addition to the (DCPP)Pd fragment. Although the transition state for carbon–chlorine bond cleavage was located for path C, this bond cleavage event cannot be rate limiting because our kinetic data show an inverse first-order dependence on pressure of CO. Thus, computation did not clearly show whether the reaction occurs by path A or C.

Instead, reaction by path A or C was distinguished by measuring the ^{13}C kinetic isotope effect (KIE) of the reaction of an aryl chloride with the Pd(0) dicarbonyl complex **4**. Path A involves irreversible reaction of the haloarene, followed by carbon–halogen bond cleavage. This addition could occur with or without initial, reversible formation of an arene complex, but cleavage of the carbon–halogen bond would occur in the irreversible step. Therefore, this pathway would be expected to occur with a primary kinetic isotope effect at the carbon *ipso* to chlorine. In contrast, reaction by pathway C involves irreversible displacement of CO to form an arene complex; because the irreversible step of the arene does not involve cleavage of the carbon–chlorine bond, this pathway would not give rise to a primary ^{13}C KIE at the carbon ipso to chlorine. Thus, the presence or absence of a primary ^{13}C KIE at the carbon *ipso* to chlorine would distinguish between these pathways.

Measurement of a ^{13}C KIE for the Oxidative Addition of 4-Chloro-*N*-methylbenzamide to (DCPP)Pd(CO)$_2$.

The ^{13}C KIE for the oxidative addition reaction of an aryl chloride to dicarbonyl **4** was obtained by the NMR spectroscopic method pioneered by Singleton.[35] A primary ^{13}C KIE of 1.013(6) was measured at the carbon ipso to chlorine for the oxidative addition of 4-chloro-*N*-methylbenzamide to complex **4** (Scheme 8). The ^{13}C KIEs at the carbonyl carbon was 0.993(8) and for the carbon atoms *ortho*, *meta*, and *para* to chlorine were 0.994(5), 0.998(5), and 0.992(8), respectively. 4-Chloro-*N*-methylbenzamide was chosen as the substrate in this study for its ease of isolation and the carbon of the *N*-methyl group was used at the standard. This ^{13}C KIE indicates that C–Cl bond cleavage is irreversible. Thus, our data are inconsistent with reaction by path C and are consistent with oxidative addition of the aryl chloride to a three-coordinate Pd(0) complex (path A, Figure 5).[36] Oxidative addition of an aryl chloride to a neutral, three-coordinate Pd(0) complex has not been documented previously. It is possible that the transition state for this oxidative addition reaction could involve concomitant dissociation of CO from (DCPP)Pd(CO) and cleavage of a C–Cl bond to avoid formation of a five-coordinate product.

Hammett Analysis of the Oxidative Addition of Aryl Chlorides to (DCPP)Pd(CO)$_2$.

Because our data indicate that the oxidative addition of aryl chlorides to dicarbonyl **4** may occur via a three-coordinate Pd(0) center bearing a bidentate ligand, we investigated whether this unusual oxidative addition of an aryl chloride proceeds by a concerted cleavage of the C–Cl bond or by a stepwise S_NAr-type mechanism. The oxidative addition of aryl halides to Pd(0) compounds bearing bidentate ligands has been proposed in prior publications to occur by an S_NAr-type process on the basis of computational findings and a Hammett analysis of the electronic effects of aryl halides on oxidative addition to $L_2Pd(0)$ species.[37] In contrast, the accepted mechanism for oxidative addition of aryl halides to Pd(0) complexes containing

one or two dative ligands is a concerted cleavage of the carbon–halogen bond of the aryl halide.[38]

To gain additional insight into the oxidative addition of aryl chlorides to dicarbonyl complex **4**, the electronic effects of the aryl group on the rate of the reaction were measured. A linear correlation between the σ parameter and the rate of oxidative addition was observed with a ρ value of 1.74 (Figure 6).[39] This ρ value indicates negative charge build-up at the carbon *ipso* to chlorine during the transition state of oxidative addition of aryl chlorides to **4**. A similar ρ value of 1.7 was measured by Yamamoto in the double carbonylation of aryl bromides with $Pd(PPh_2Me)_2Cl_2$.[13b] In addition, the ρ value of 1.74 obtained from our Hammett analysis is comparable to ρ values of oxidative addition of aryl iodides ($\rho = 2$) and triflates ($\rho = 2.55$) to $Pd(PPh_3)_4$, which are proposed to occur via concerted cleavage of the carbon–halogen or carbon–triflate bond.[38] Conversely, the oxidative addition of 2-bromo- and 2-chloropyridines with substituents in the 5 position to $Pd(PPh_3)_4$ exhibit larger ρ values (4.4 and 4.3, respectively), and the oxidative addition of these heteroaryl halides has been proposed to occur by an S_NAr-type process.[40] Thus, on the basis of our Hammett analysis, a ρ value of 1.74 is inconsistent with oxidative addition by an S_NAr mechanism.

In addition, the ^{13}C KIE measured for the oxidative addition of an aryl chloride to dicarbonyl **4** is distinct from ^{13}C KIE values reported for S_NAr reactions. The ^{13}C KIE values for the S_NAr reaction of the chlorine in atrazine with hydroxide are between 1.03 and 1.04.[41] Thus, based on our ^{13}C KIE measurements, kinetic studies, and a Hammett analysis, we conclude that the C–Cl bond cleavage by reaction with (DCPP)Pd(CO) occurs by a concerted process, not by an S_NAr-type reaction.

Mechanism of Oxidative Addition of Aryl Bromides to (DCPP)Pd(CO)$_2$.

Because the carbonylative functionalization of aryl chlorides by Pd(0) in the presence of CO is less common than the analogous functionalization of aryl bromides and iodides, we performed mechanistic studies on the oxidative addition of aryl bromides to $(DCPP)Pd(CO)_2$. This study would reveal whether the mechanism of oxidative addition of aryl bromides to **4** differs from the mechanism of the reaction of aryl chlorides. The dependence of the rate of oxidative addition on the concentration of aryl bromide and on the pressure of CO was determined for reactions in a mixture of DMSO and toluene (1:1 v/v) under pseudo-first-order conditions. Ethylene complex **1** served as a precursor to dicarbonyl compound **4**, and the sterically hindered and electronically deactivated aryl bromide 2-methoxy-4-fluorobromobenzene was selected for this study because oxidative addition of this substrate occurs at elevated temperatures with rates that are convenient to measure (Scheme 9). The observed rate exhibited an inverse first-order dependence on the pressure of CO (Figure 7a) and a first-order dependence on the concentration of aryl bromide (Figure 7b). As such, these experiments suggest that aryl bromides and aryl chlorides react by similar pathways under these reaction conditions, wherein the haloarene reacts irreversibly with (DCPP)Pd(CO) to cleave the carbon–halogen bond. These results also agree with the computational studies performed by Grushin on the oxidative addition of aryl iodides to $(Xantphos)Pd(CO)_2$ discussed in the introduction.

Potential Mechanisms for the Formation of Benzamide from a Phenacylpalladium Chloride Intermediate.

The formation of benzamide from phenacylpalladium chloride complexes ligated by DCPP could occur by reductive elimination of benzoyl chloride, followed by reaction of this acid chloride with ammonia and base, or it could occur by direct reaction of ammonia and base with the phenacylpalladium chloride complex. Although most mechanisms proposed for carbonylative couplings of aryl halides involve reaction of the nucleophile with an acylpalladium halide complex, phenacylpalladium chloride complexes have been reported recently to undergo reductive elimination to generate benzoyl chloride as part of a catalytic synthesis of benzoyl chlorides from aryl halides, CO and chloride salts.[5c,10c,42] This synthesis of benzoyl chlorides occurs with palladium catalysts containing bulky, monophosphine ligands, not bidentate phosphines like those in our current study. Nevertheless, we conducted experiments to test whether this reductive elimination occurs in the catalytic aminocarbonylation. To do so, DCPP-ligated phenacyl complex **6a** was heated at 80 °C for 2.5 h in the presence of 20 equiv of 4-iodobenzotrifluoride and 760 Torr of CO (Scheme 10). This temperature and time corresponds to those at which **6a** reacts with ammonia and DBU to form 4-fluorobenzamide (Scheme 6). If **6a** reductively eliminated 4-fluorobenzoyl chloride, the iodoarene would trap the Pd(0) resulting from the reductive elimination. Under these conditions, 4-fluorobenzoyl chloride was not detected by ^{19}F NMR spectroscopy. Thus, we conclude that the reductive elimination of benzoyl chloride is not a likely pathway in the formation of benzamide from DCPP-ligated phenacyl complexes, and we conducted detailed studies to distinguish between pathways for the formation of benzamide by reaction of ammonia and base with the phenacylpalladium complex (Figure 8).

Four potential pathways for formation of benzamide from phenacyl compound **6a** are shown in Figure 8. Path A occurs by reversible exchange of chloride by ammonia, deprotonation of the coordinated amine to form a Pd(II) acyl amido species, and reductive elimination to generate a primary benzamide. The exchange of amine for chloride could occur by any of the known pathways for ligand substitution on square-planar compounds. Path A is reminiscent of the inner-sphere reductive elimination of esters from acyl Pd(II) aryloxy complexes or the reaction of cationic acyl palladium(II) complexes with alcohols.[19] Path B involves an outer-sphere attack of ammonia at the carbonyl group of compound **6a**, followed by deprotonation of the resulting intermediate. Subsequent collapse of the anionic intermediate and loss of chloride produces the products of reductive elimination. Such pathways involving outer-sphere attack on an acyl group have been discussed for palladium-catalyzed alkoxycarbonylation reactions under basic conditions.[4b,43] Paths C and D involve displacement of chloride by either DMSO or CO to generate a cationic Pd(II) species. This cationic Pd(II) species could be more prone to nucleophilic attack by ammonia than a neutral compound. Path C involves displacement of chloride by DMSO or CO and subsequent displacement of the bound DMSO or CO by ammonia. The reductive elimination products would then be generated by deprotonation and reductive elimination. Path C is equivalent to path A if the first two steps are fully reversible before deprotonation of the bound amine. Path D is the outer-sphere variant of path C, in which ammonia would attack the acyl carbonyl group of a cationic Pd(II)–DMSO or Pd(II)–CO complex.

After deprotonation and collapse of the resulting anionic intermediate, Pd(0) and a primary benzamide would be generated.

Paths A, C, and D can be differentiated from path B by the order in chloride. Paths A, C, and D would be inverse first order in chloride, whereas path B would be zero order in chloride. The order of the reaction in chloride and ammonia for path A would be the same as that for paths C and D, except that reaction by path D would be first order in DMSO or CO and reaction by path C would be first order in DMSO and CO at low amounts of DMSO or CO and zero order at high amounts of DMSO or CO. To elucidate the mechanism by which the phenacyl complex reacts with ammonia, we measured the dependence of the rate of formation of benzamide from acyl complex **6a** on the concentrations of ammonia, chloride, base, and DMSO and the pressure of CO (Scheme 11).

Determination of the Mechanism for the Formation of Benzamide.

The rate of formation of benzamide from compound **6a** was determined by obtaining pseudo-first-order rate constants from the decay of **6a** by ^{31}P NMR spectroscopy (Scheme 11) with 10–30 equiv of ammonia. All experiments were performed under 750 Torr of CO to capture the Pd(0) generated from reductive elimination as (DCPP)Pd(CO)$_2$ and were conducted with DBU as base. DBU was chosen as a substitute for K_2CO_3 to create homogeneous reaction conditions. Because DBU is a hindered base, it does not act as a nucleophile and generate side products.

The rate of formation of benzamide was determined to be first order in ammonia (Figure 9a) and inverse first order in N(*n*-butyl)$_4$Cl (Figure 9b, black trace). The inverse first-order dependence on the concentration of N(*n*-butyl)$_4$Cl, a soluble source of chloride, is consistent with reaction by paths A, C, and D. The reaction of **6a** with ammonia was approximately zero order in N(*n*-butyl)$_4$PF$_6$ (Figure 9b, red trace), indicating that the inverse first-order dependence on added chloride did not result from a salt effect or increase of solvent polarity from the salt.[44]

The dependence of the reaction rate on the concentration of DBU was found to be first order at low concentrations of DBU and zero order at high concentrations of DBU. When initial rates were measured with 1–5 equiv of DBU (0.0342 M to 0.171 M), the rate of formation of benzamide was first order in DBU (Figure 10a). The reaction of **6a** with ammonia and 10–30 equiv (0.342–1.03 M) of DBU occurred with an approximately zero-order dependence on the concentration of DBU (Figure 10b). These results indicate that deprotonation is the rate limiting step at low concentrations of base and that attack of **6a** by ammonia is rate limiting at high concentrations of base. To explore the effects of base on reaction rate further, we determined the order of the reaction in base in the presence of 10 equiv of N(*n*-butyl)$_4$Cl (0.342 M). A first-order dependence of the rate on base was observed under these conditions (Figure 10c).

The first-order behavior in DBU at low concentrations of DBU and zero order behavior in DBU at high concentrations of DBU is consistent with paths A, C, and D. Therefore, to differentiate between paths A, C, and D, the effect of the concentration of DMSO (0.0–1.0 M, 0–30 equiv) and the pressure of CO (250–1000 Torr) on the rate of formation of

benzamide was measured in 1,2-difluorobenzene, a polar but non-coordinating solvent.[45] A positive, fractional order in DMSO was observed (Figure 11a). This non-integer order in DMSO is likely due to an increase in polarity of the reaction mixture at higher concentrations of DMSO, which would lead to a higher concentration of ammonia. At the same time, the formation of benzamide occurs in the absence of added DMSO (Figure 11a), and the addition of DMSO does not significantly alter the rate of formation of benzamide. Thus, it is unlikely that DMSO additive or solvent assists the exchange of ammonia for chloride. This lack of a clear first-order dependence on the concentration of DMSO is inconsistent with path D and is consistent with path A or path C with the first two steps fully reversible. A zero-order dependence of k_{obs} on the pressure of CO also was observed (Figure 11b). This absence of a first-order dependence on the pressure of CO is inconsistent with path D and also is consistent with path A or path C with the first two steps fully reversible. It is unlikely that CO assists in the exchange of ammonia, given that the lack of dependence of the rate of benzamide formation on high concentrations of DMSO, which is more nucleophilic than CO. In addition, the relatively hard property of cationic Pd(II), the known direct substitution of chloride by nitrogen Lewis bases,[46] and lack of dependence of the rate of benzamide formation on CO makes the inclusion of CO in the mechanism of benzamide formation unlikely. Thus, we favor the reaction by path A in the presence or absence of DMSO or CO in the system. Our kinetic data on the formation of benzamide from **6a** are all consistent with ligand substitution of chloride by ammonia, most likely by associative ligand substitution, followed by deprotonation of coordinated ammonia and reductive elimination from the resulting phenacylpalladium(II) amido species to obtain Pd(0) and a primary benzamide.

Formation of Benzamide from an Aryl Pd(II) Amido Complex.

Decarbonylation of phenacyl Pd(II) halide species to the corresponding arylpalladium(II) halide species can occur during the catalytic process.[47] Such arylpalladium(II) halide intermediates were observed during our mechanistic studies of the oxidative addition of electron-poor aryl halides and of ortho-substituted aryl halides in the presence of CO. These complexes could result from reversible migratory insertion or slow migratory insertion of CO. Thus, ammonia could react with an arylpalladium(II) halide complex to form an arylpalladium(II) amido complex prior to migratory insertion of CO, to form aniline by reductive elimination as a side product, or to form a phenacylpalladium amido or arylpalladium carbamoyl complex by insertion of CO into the palladium–aryl or palladium–amido bond and subsequent formation of the organic amide.[48]

To explore the potential intermediacy of arylpalladium amido complexes, arylpalladium amido complex **7** was synthesized as shown in Scheme 12. Abstraction of chloride from **5a** with AgOTf in the presence of ammonia and subsequent deprotonation with KHMDS formed 7. $^{1}H–^{15}N$ HSQC and ^{15}N DEPT experiments confirmed the presence of a mononuclear Pd–NH_2 amido species (see Supporting Information). Amido complex 7 slowly degrades in THF at room temperature. The onset of this decomposition can be detected by ^{31}P NMR spectroscopy after approximately 1.5 h at room temperature, and attempts to isolate 7 as a solid by crystallization led to decomposition. Thus, compound 7 was prepared *in situ* and was allowed to react with 1000 Torr of CO at 80 °C. After 1 h,

p-fluorobenzamide formed in 99% yield, and compound 7 was fully consumed. The sole compound observed by ^{31}P NMR spectroscopy was dicarbonyl complex **4** (Scheme 12). *p*-Fluoroaniline was not observed by ^{19}F NMR spectroscopy. These data imply that reductive elimination from a phenacyl Pd(II) amido complex or an aryl Pd(II) carbamoyl complex to generate the corresponding primary benzamide is faster than reductive elimination from an aryl Pd(II) amido complex to form aniline.

Identification of the Catalyst Resting State.

To identify the major palladium complex in the catalytic reaction, the aminocarbonylation of 4-chlorofluorobenzene was monitored by ^{31}P NMR spectroscopy (Figure 12). Because dicarbonyl **4** is poorly soluble in DMSO alone, leading to weak signals, the catalytic reaction was monitored in a mixture of DMSO and toluene (1:1 v/v) to maintain the solubility of the palladium complexes. After **14** h at 100 °C, at which point 54% conversion of starting material occurred, the ^{31}P NMR spectrum consisted of a singlet at 20.3 ppm, which corresponds to dicarbonyl **4**, along with a second resonance at 15.6 ppm (Figure 12a). After **14** h at the lower temperature of 80 °C, at which point 10% conversion of starting material occurred, the ^{31}P NMR spectrum contained only the resonance at 20.3 ppm for **4** (Figure 12b).

The second compound corresponding to the resonance at 15.6 ppm in Figure 12a is the dinuclear hydride complex **8a** in Scheme 13. This complex was prepared independently in 32% isolated yield by the addition of ammonium chloride to complex **4** at 100 °C for 45 min in the presence of CO. The ^{31}P NMR spectrum of **8a** at room temperature consists of a singlet at 15.6 ppm (Figure 12c), and the ^{1}H NMR spectrum contains a quintet at −5.28 ppm for the bridging hydride. Similar cationic Pd(I) dimers have been synthesized previously and proposed to be resting states in palladium-catalyzed alkoxycarbonylation reactions or have been isolated as byproducts of palladium-catalyzed synthesis of hydrogen peroxide from carbon monoxide, oxygen, and water.[49] We hypothesized that this hydride complex forms in the catalytic cycle by protonation of dicarbonyl complex **4**.

Single crystals of **8b**, an analogue of **8a** containing a tetrafluoroborate counterion, were obtained by addition of HBF_4 etherate to $(DCPP)Pd(CO)_2$, which was generated *in situ* from **4** and CO, and crystallization from a solution of THF and toluene (1.5:1 v/v). (Scheme 13). The ^{1}H and ^{31}P NMR spectrum of **8b** is identical to that of compound **8a**. The solid-state structure of complex **8b** consists of a dinuclear core with two palladium centers that adopt distorted square-planar geometries. This geometry has been observed for other crystallographically characterized Pd(I) dimers bearing two bidentate ligands and a bridging carbonyl and hydride ligand.[49a,50] The Pd–Pd distance is 2.749(1) Å, which is consistent with a metal–metal bond (Figure 13). In this structure, the two phosphorus atoms on each palladium are inequivalent, but a single ^{31}P NMR resonance is observed in solution at room temperature.

This equivalence of the phosphines in solution arises from a rapid, dynamic process, rather than a different structure in the solid state and in solution. Cooling **8b** to −99 °C in THF-d_8 caused the quintet of the bridging hydride in the ^{1}H NMR spectrum to partially coalesce

to become a more complex, broad multiplet. Similarly, the ^{31}P NMR resonance of **8b** at −99 °C in THF-d_8 broadens and exhibits a multiplicity that is more complex than a singlet (see Supporting Information). The NMR spectra recorded of **8b** at −99 °C indicate that a dynamic process approaches but is not slower than the NMR time scale at −99 °C. In addition, due to the complexity of the spectra of **8b** at −99 °C, we were unable to determine the nature of the dynamic process leading to the equivalence of the phosphorus atoms of **8b** in solution at room temperature. This equivalence of the two phosphorus atoms has been previously reported for structurally analogous cationic Pd(I) dimers.[49c,51] A rapid dissociation and association of either the bridging carbonyl or bridging hydride from one of the Pd atoms has been proposed as the cause for the equivalence of the phosphorus atoms at room temperature.[51]

The reactivity of Pd(I) dimer **8a** was studied to assess its relevance to the mechanism of the catalytic aminocarbonylation. Compound **8a** was treated with an excess of DBU in the presence of 760 Torr of CO in DMSO at 100 °C. Over the course of 16 h, complex **8a** slowly reduced to dicarbonyl compound **4**. After this time, only 56% of **8a** converted to **4**, which precipitated as colorless crystals, along with Pd black (Scheme 14). Because the generation of **4** from **8a** is slower than the catalytic process, the formation of **8a** is a catalyst deactivation pathway, and we propose that **4** is the catalyst resting state.

Identification of the Rate-Limiting Step of the Catalytic Reaction.

Based on our kinetic studies and identification of the major palladium complexes present in the catalytic reaction, the rate-limiting step of the catalytic cycle is the oxidative addition of an aryl chloride to dicarbonyl compound **4**. In addition, the rate of the reduction of dimer **8a** to dicarbonyl **4** will affect the observed rate of the catalytic process. To identify the rate-determining step of the catalytic cycle, a time course of the reaction was measured with varying amounts of CO and ammonia (Figure 14). Qualitatively, the rate of the reaction conducted with 900 Torr of CO was less than the reaction conducted with 450 Torr of CO. This smaller rate is consistent with rate-limiting oxidative addition because dissociation of CO from compound **4** occurs prior to oxidative addition. The decrease in rate at higher concentrations of CO is inconsistent with rate-limiting reduction of **8a** to **4**, which would be expected to exhibit either zero or positive orders in CO pressure. Although doubling the amount of ammonia from 3 to 6 equiv increases the reaction rate slightly, the small size of that effect is inconsistent with rate-limiting formation of benzamide from reaction of the phenacyl complex with ammonia. We attribute this slight enhancement in rate to an increase in overall basicity of the reaction medium, which inhibits the formation of the inactive dimer **8a**. Thus, these data are consistent with oxidative addition as the rate-limiting step in the catalytic aminocarbonylation of aryl chlorides, as predicted from studies of the individual steps.

CONCLUSION

The lack of studies on the oxidative addition and the formation of benzamide during the palladium-catalyzed aminocarbonylation of aryl chlorides has made the catalytic cycle of this process ambiguous. Our kinetic studies of the oxidative addition of the

aryl halide and the formation of benzamide from a phenacylpalladium complex during the palladium-catalyzed aminocarbonylation of aryl chlorides with ammonia, as well as determination of the catalyst resting state and deactivation pathways, establish an experimental basis for the elementary steps that constitute the catalytic cycle of palladium-catalyzed aminocarbonylation. Our results indicate that the aminocarbonylation of aryl chlorides catalyzed by DCPP-ligated Pd(0) occurs by the mechanism summarized in Figure 15.

The oxidative addition of a chloroarene and bromoarene to (DCPP)Pd$(CO)_2$ (**4**) was first-order in the concentration of aryl halide and inverse first-order in the pressure of CO, indicating that the haloarene reacts with a three-coordinate Pd complex bearing DCPP and one CO ligand (Figure 5, Path A). A primary ^{13}C KIE of 1.013(6) was measured for the carbon *ipso* to chlorine for the oxidative addition of 4-chloro-*N*-methylbenzamide to **4**, and a ρ value of 1.74 was obtained from a Hammett analysis of the effect of the electronic properties of the arene on the rate of oxidative addition. Together, these data are consistent with irreversible C–Cl bond cleavage during the reaction of the Pd(0) species with the haloarene by a concerted pathway, rather than an S_NAr type pathway. In addition, our ^{13}C KIE study discounts the possibility of irreversible ligand substitution of CO from (DCPP)Pd(CO) with an aryl chloride, wherein oxidative addition occurs at a two-coordinate (DCPP)Pd(0) complex, and implies that the oxidative addition of an aryl chloride occurs at a Pd(0) complex bearing DCPP and one CO ligand. Thus, we propose that the oxidative addition of aryl chlorides occurs at (DCPP)Pd(CO) by a concerted C–Cl bond cleavage event.

The rate of formation of benzamide from Pd(II) phenacyl compound **8a** was first order in ammonia and inverse order in chloride. A non-integer, positive order in the concentration of DMSO and pressure of CO was observed when the reaction was conducted in a non-coordinating solvent. These data are consistent with a mechanism for reaction of phenacyl compound **6a** with ammonia that involves an inner-sphere displacement of chloride by ammonia to form a cationic Pd(II) ammine complex as an intermediate (Figure 8, Path A). The rate of formation of benzamide was zero order in base at high concentrations of base and first order in base at low concentrations of base. These reaction orders imply that the rate-limiting step of benzamide formation is deprotonation at low concentrations of base and formation of an ammine complex at high concentrations of base. Moreover, the formation of benzamide does not occur directly from a cationic ammine intermediate. Instead, deprotonation generates an acyl Pd(II) amido species, which reductively eliminates to generate benzamide.

The rate-limiting step of the overall catalytic reaction with an aryl chloride was determined by studying the dependence of the rate of the catalytic reaction on the pressure of ammonia and CO. Changes to the pressure of ammonia did not affect the rate of the reaction significantly, whereas reactions at higher pressures of CO were slower than those at lower pressures of CO. Because the oxidative addition of an aryl chloride to **4** is inverse order in CO, the rate-limiting step of the catalytic reaction is oxidative addition. The resting state of the catalytic reaction was determined to be dicarbonyl compound **4**, which is consistent with the observed dependence of the rate on CO pressure. A Pd(I) hydride dimer **8a** was

also present in the catalytic system. This complex slowly reduces to dicarbonyl **4** in the presence of CO and base, and this slow rate of reentry into the catalytic cycle leads to the partial accumulation of this complex and reduction of the rate of the reaction. Future efforts in this area will be directed toward the development of palladium-catalyzed carbonylations that occur with additional classes of organic electrophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(30). Bunel also observed the absence of $^{31}P–^{13}C$ coupling in (DIPP)Pd(^{13}CO) (DIPP = 1,3-bis(diisopropylphosphino) propane) under ^{13}CO, which was attributed to rapid exchange between bound and unbound ^{13}CO. See ref 27b.

(31). At this temperature and pressure of CO, a resonance at the chemical shift of free CO was observed, suggesting that exchange between bound and unbound CO was no longer present at the NMR time scale.

(32). Even with 1000 Torr of ^{13}CO at −40 °C, phosphorus–carbon coupling was still not detected.

(33). We monitored this reaction by ^{19}F NMR spectroscopy because the concentration of **4** could not be determined accurately by ^{31}P NMR spectroscopy at low pressures of CO (<500 Torr) and elevated temperatures due to broad resonances.

(34). The 12 kcal/mol barrier is given as the difference in energy between the transition state for oxidative addition and the computed energy of the experimentally determined resting state.

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(36). It should be noted that the y-intercept of the fitof1/k_{obs} versus pressure of CO and the fit of 1/k_{obs} versus 1/[ArCl] (Figure 4b) correspond to 1/k_1 in the equation given for Path A in Figure 5. However, the values of this intercept were too close to zero to deduce an accurate value. This small value of the y-intercept reflects rapid exchange of unbound CO with the CO bound to dicarbonyl **4** and fits with the rapid exchange observed at room temperature by ^{13}C NMR spectroscopy (*vide supra*).

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(44). The small increase in rate with increasing N(*n*-butyl)$_4$PF$_6$ suggests that the reaction of **6a** with ammonia depends slightly on the polarity of the solvent.

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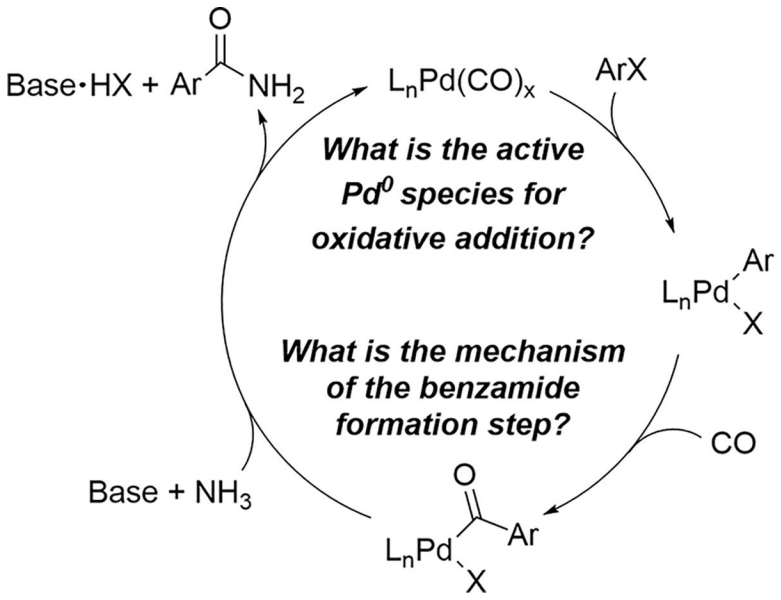


Figure 1.
Simplified catalytic cycle for the aminocarbonylation of aryl halides with Pd and ammonia.

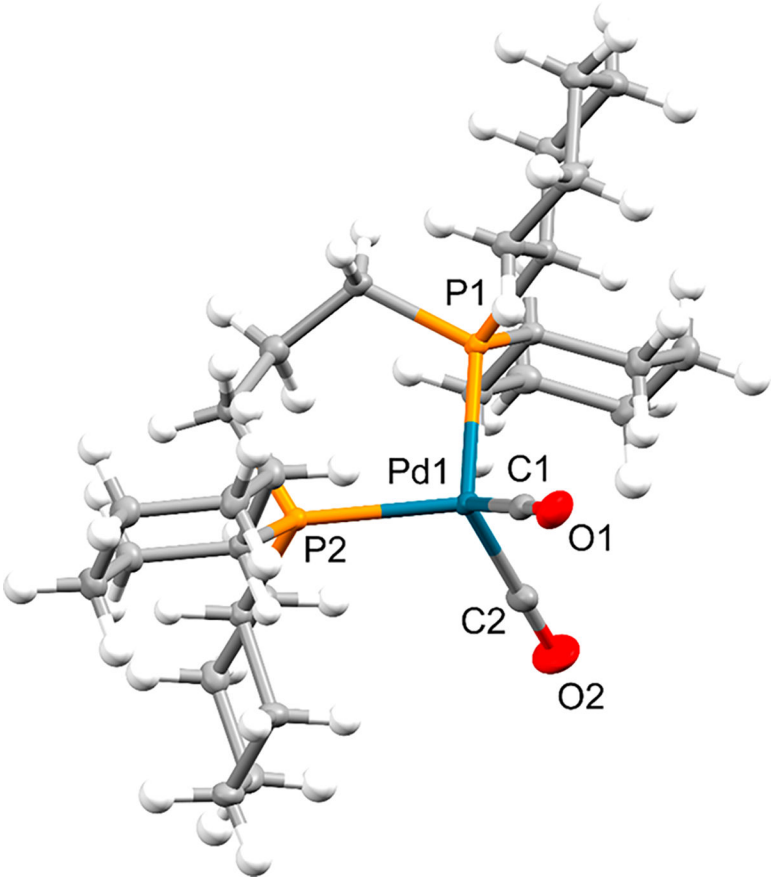


Figure 2.

Solid-state structure of (DCPP)Pd(CO)$_2$ (**4**) with ellipsoids set at 1:1. Selected bond lengths (Å): P1–Pd1 2.3799(6), Pd1–C1 1.961(4), Pd1–C2 1.944(4), C1–O1 1.132(5), C2–O2 1.147(5). Selected bond angles (deg): P1–Pd–P2 98.84(3), C1–Pd1–P1 110.98(6), C1–Pd1–P2 110.98(6), C1–Pd1–C2 113.83(16).

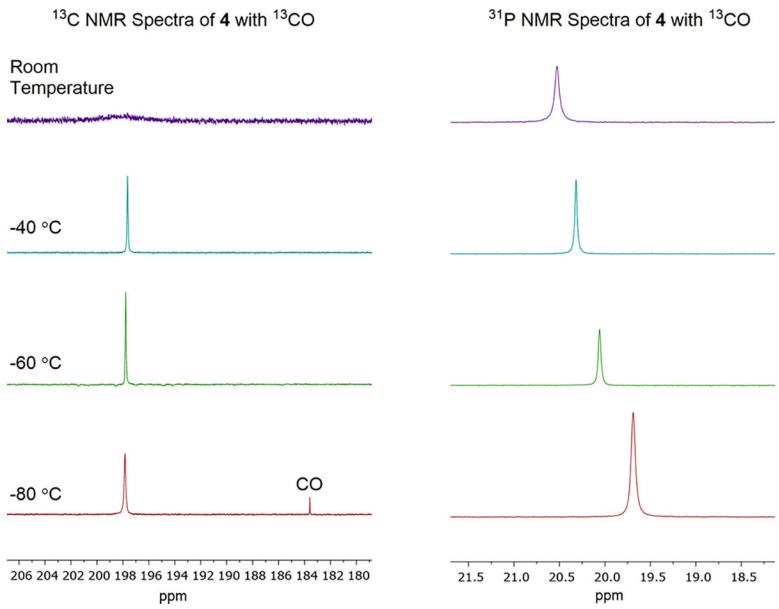


Figure 3.

Variable-temperature ^{13}C and ^{31}P NMR spectra of **4** under 600 Torr of ^{13}CO in toluene-d_8.

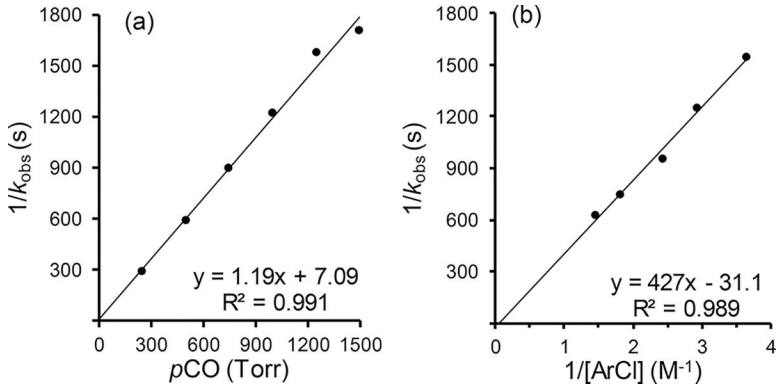


Figure 4.

Dependence of the observed rate constant (k_{obs}) on (a) the pressure of CO (250–1500 Torr) with ArCl = 0.27 M and (b) the concentration ArCl (0.27–0.68 M) with *p*CO = 1000 Torr for the oxidative addition of 3,5-difluorochlorobenzene to (DCPP)Pd$(CO)_2$ (28 mM) in 1:1 v/v DMSO and toluene at 85 °C.

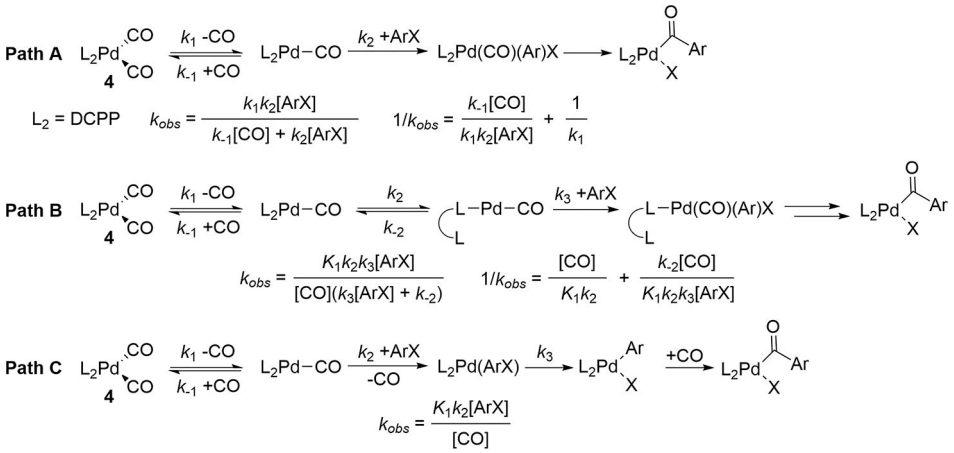


Figure 5.

Proposed oxidative addition mechanisms of aryl halides to dicarbonyl compound **4**.

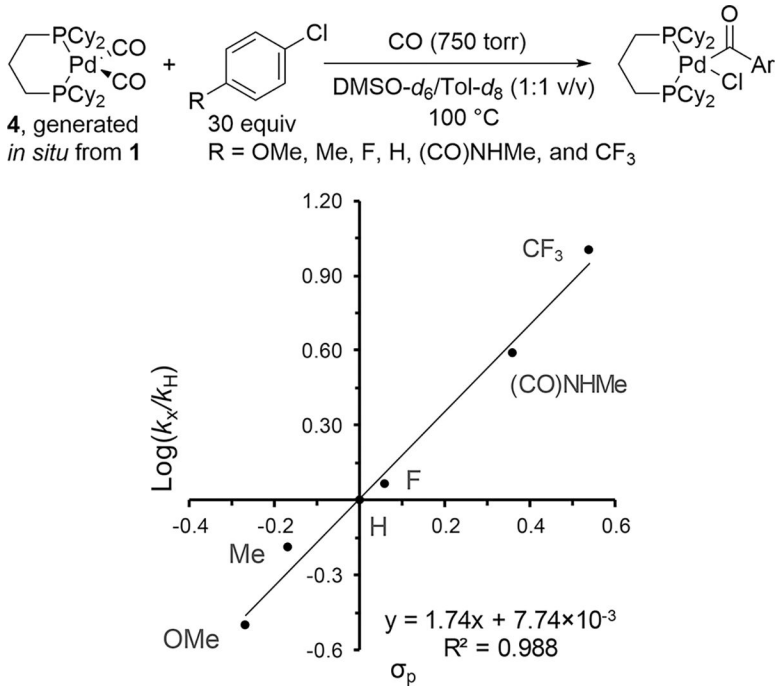


Figure 6.

Hammett plot of the oxidative addition of *para*-substituted aryl chlorides (0.56 M) to (DCPP)Pd(CO)$_2$ (28 mM) with *p*CO = 750 Torr in DMSO-d_6/toluene-d_8 (1:1 v/v) at 100 °C.

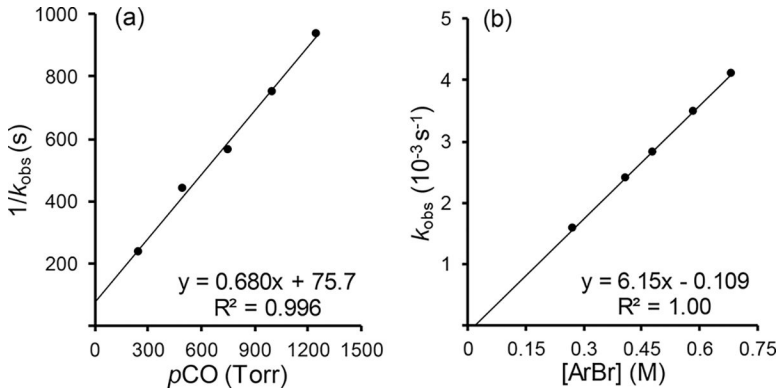


Figure 7.

Dependence of the observed rate constant (k_{obs}) on (a) the pressure of CO (250–1500 Torr) with ArBr = 0.27 M at 75 °C and (b) the concentration of ArBr (0.27–0.68 M) with pCO = 1000 Torr at 70 °C for the oxidative addition of 2-methoxy-4-fluoro-bromobenzene to (DCPP)Pd$(CO)_2$ (28 mM) in DMSO and toluene (1:1 v/v).

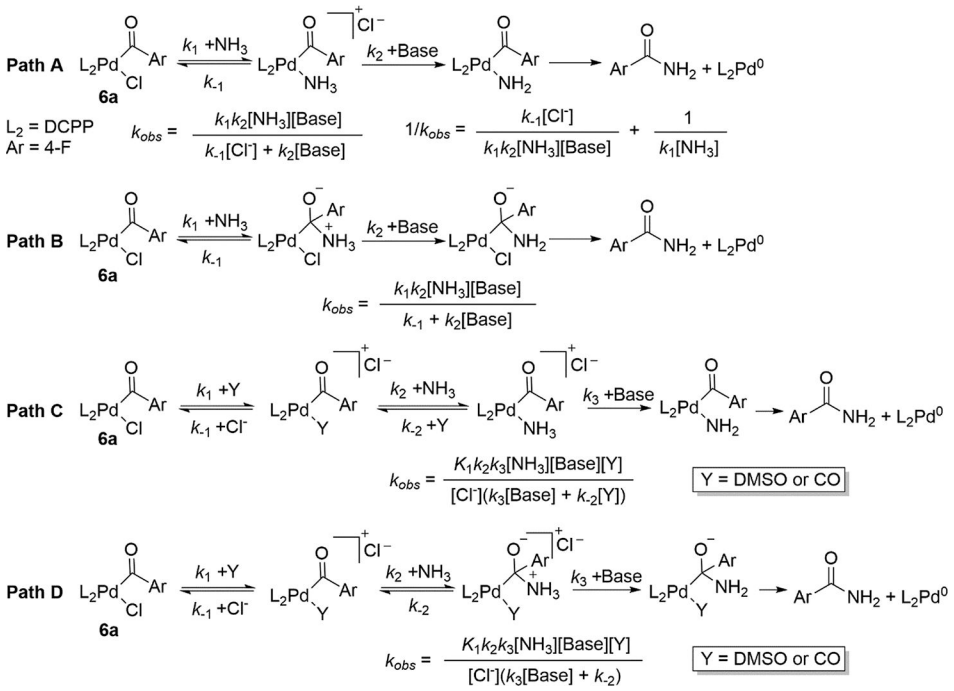


Figure 8.

Proposed mechanisms for the formation of benzamide from (DCPP)Pd(II) phenacyl chloride complexes with ammonia and base.

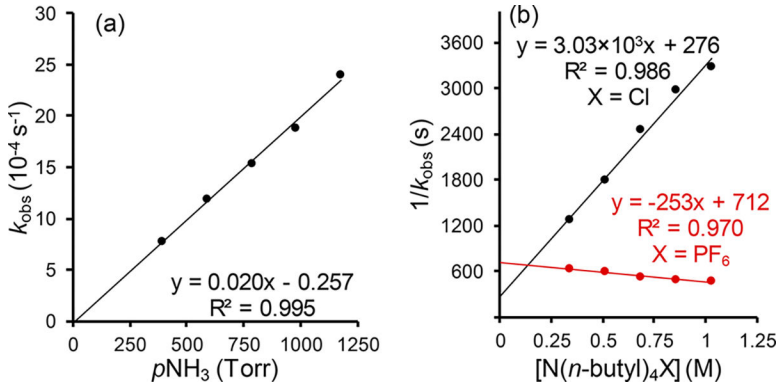


Figure 9.

Dependence of the observed rate constant (k_{obs}) on (a) pNH$_3$ (392–1177 Torr, 10–30 equiv) with pCO = 750 Torr and [DBU] = 0.34 M and on (b) [N(n-butyl)$_4$Cl] (0.34–1.0 M, black trace) or [N(n-butyl)$_4$PF$_6$] (0.34–1.0 M, red trace) with pCO = 750 Torr, [DBU] = 0.34 M, and pNH$_3$ = 785 Torr (20 equiv) for the rate of formation of 4-fluorobenzamide from **6a** (34 mM) in 1:1 v/v DMSO and toluene at 35 °C. The pressure of CO is the pressure added to a J. Young tube at −196 °C.

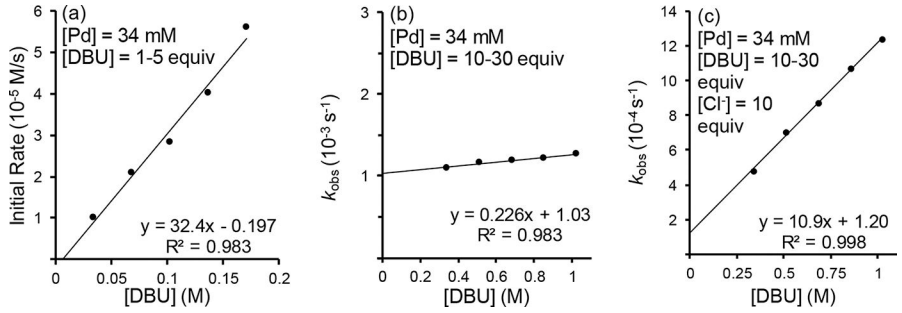


Figure 10.

Dependence of the initial rate on (a) [DBU] (0.034–0.17 M) with *p*CO = 750 Torr and *p*NH_3 = 588 Torr (15 equiv) at 60 °C for the rate of formation of 4-fluorobenzamide from **6a** (34 mM) in DMSO and toluene (1:1 v/v). Dependence of the observed rate constant (k_{obs}) on (b) [DBU] (0.34–1.0 M) with *p*CO = 750 Torr and *p*NH_3 = 392 Torr (10 equiv) at 35 °C for the rate of formation of 4-fluorobenzamide from **6a** (34 mM) in DMSO and toluene (1:1 v/v). Dependence of the observed rate constant (k_{obs}) on (c) [DBU] (0.34–1.0 M) with *p*CO = 750 Torr, *p*NH_3 = 392 Torr (10 equiv), and [N(*n*-butyl)$_4$Cl] = 0.34 M at 35 °C for the formation of *p*-fluorobenzamide from **6a** (34 mM) in DMSO and toluene (1:1 v/v). The pressure of CO is the pressure added to a J. Young tube at −196 °C.

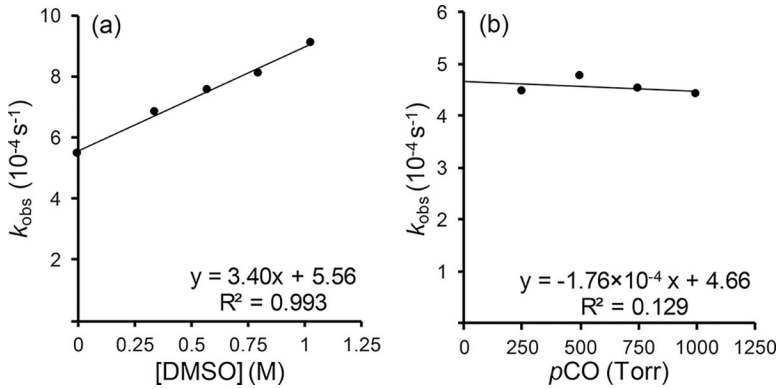


Figure 11.

Dependence of the observed rate constant (k_{obs}) on (a) the concentration of DMSO (0.0–1.0 M) with pCO = 750 Torr, [DBU] = 0.34 M, and pNH$_3$ = 785 Torr (20 equiv) at 65 °C and (b) the pressure of CO (250–1000 Torr) with [DBU] = 0.34 M and pNH$_3$ = 785 Torr (20 equiv) at 65 °C for the rate of formation of *p*-fluorobenzamide from **6a** (34 mM) in 1,2-difluorobenzene. The pressure of CO is the pressure added to a J. Young tube at −196 °C or at −95 °C.

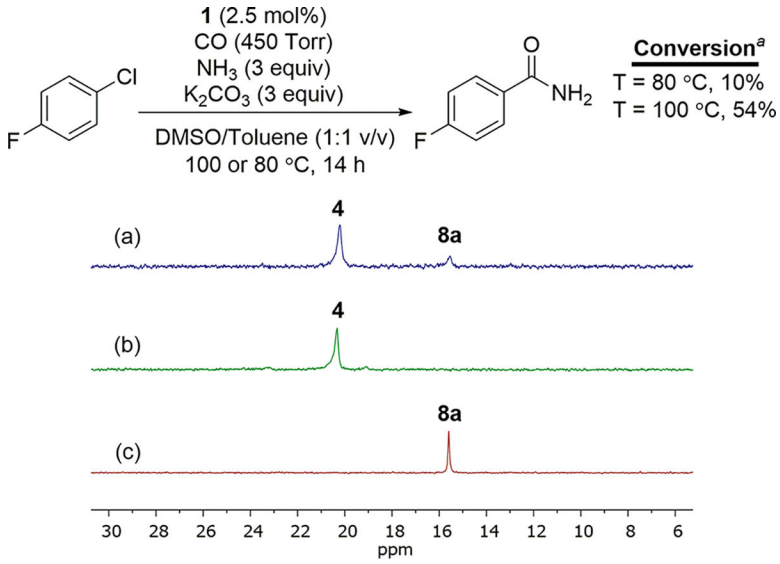


Figure 12.

Room-temperature ^{31}P NMR spectra of a catalytic reaction at partial conversion conducted at 100 (a) and 80 °C (b) after 14 h in DMSO and toluene (1:1 v/v) and of Pd(I) dimer **8a** in $CDCl_3$ at room temperature (c). [a]Conversion was determined with ^{19}F NMR spectroscopy with 4-fluorotoluene as an internal standard.

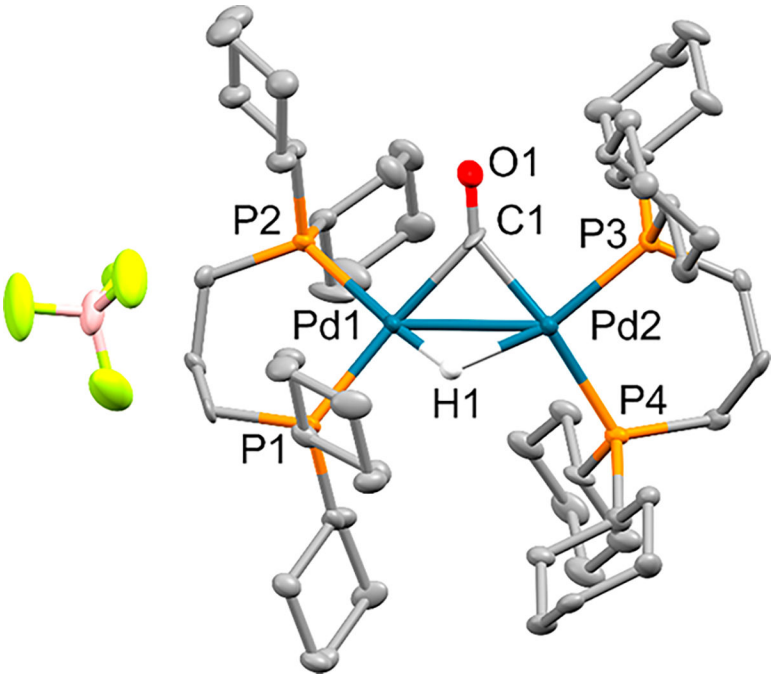


Figure 13.

Solid-state structure of Pd(I) dimer **8b** with ellipsoids set at 30% and selected hydrogen atoms omitted for clarity. Selected bond lengths (Å): Pd1–Pd2 2.749(1), Pd1–C1 2.09(1), Pd2–C1 2.02(2), C1–O1 1.15(2). Selected bond angles (deg): P2–Pd1–P1 97.74(13), Pd1–C1–Pd2 83.9(6), P3–Pd2–P4 98.09(13).

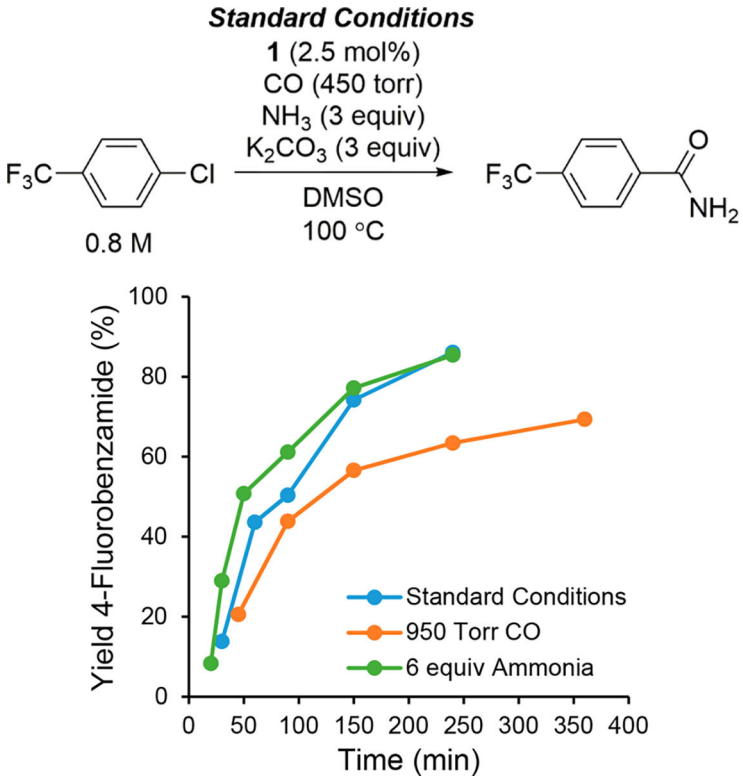


Figure 14.

Time course of the palladium-catalyzed aminocarbonylation of 4-chlorobenzotrifluoride with varying amounts of CO and ammonia. Yields were determined by GC.

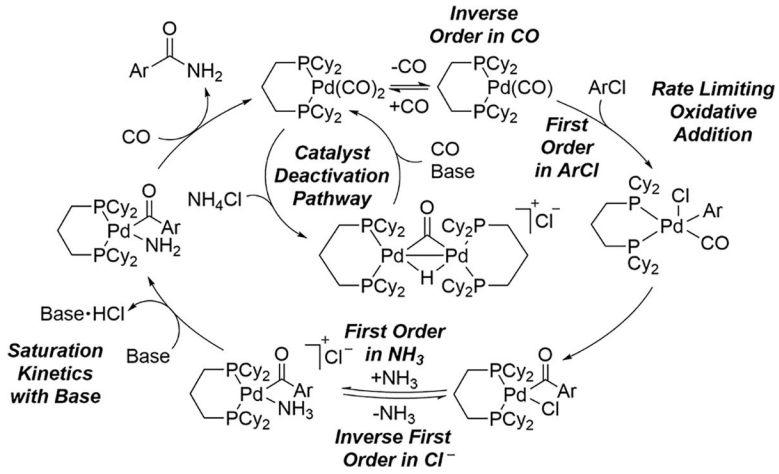
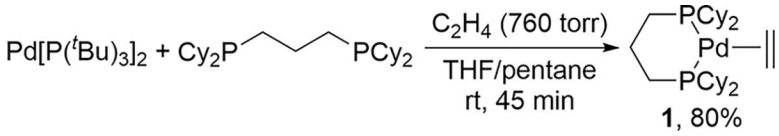
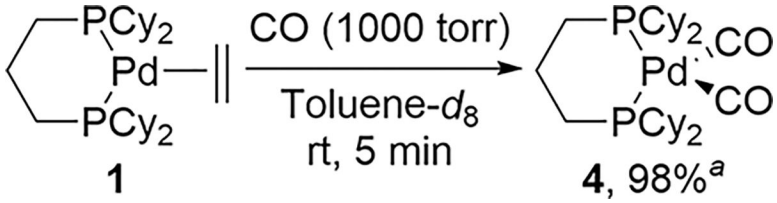


Figure 15.

Proposed mechanism for palladium-catalyzed aminocarbonylation of aryl chlorides with ammonia.

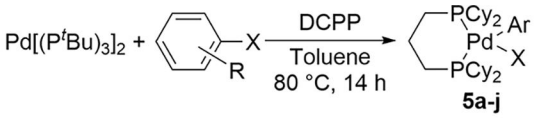


Scheme 1. Synthesis of (DCPP)Pd(C_2H_4) (1) from Pd[P(^{t}Bu)$_3$]$_2$



Scheme 2. Synthesis of (DCPP)Pd(CO)$_2$ (4) from Ethylene Complex 1

[a]Yield determined by ^{31}P NMR spectroscopy with PMes$_3$ as an internal standard.



5a-j

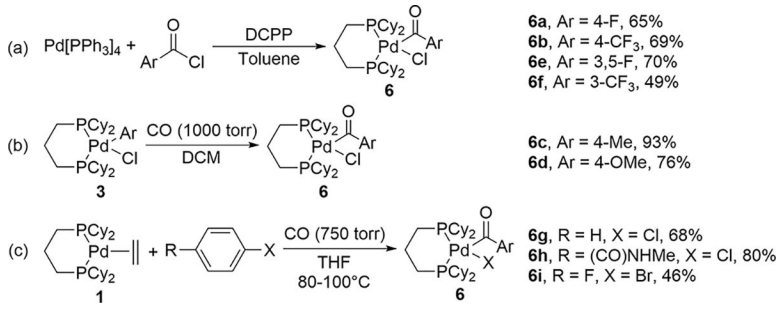
X = Cl

5a, Ar = 4-F, 45%
5b, Ar = 4-CF_3, 74%
5c, Ar = 4-Me, 61%
5d, Ar = 4-OMe, 65%
5e, Ar = 3,5-F, 31%
5f, Ar = 3-CF_3, 66%
5g, Ar = Ph, 58%
5h, Ar = 4-(CO)NHMe, 58%

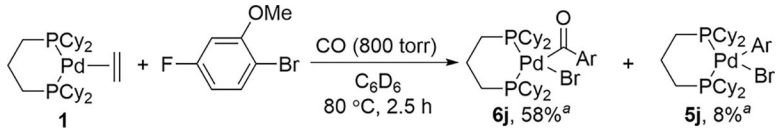
X = Br

5i, Ar = 4-F, 83%
5j, Ar = 2-OMe-4-F, 76%

Scheme 3. Synthesis of Pd(II) Aryl Halide Complexes

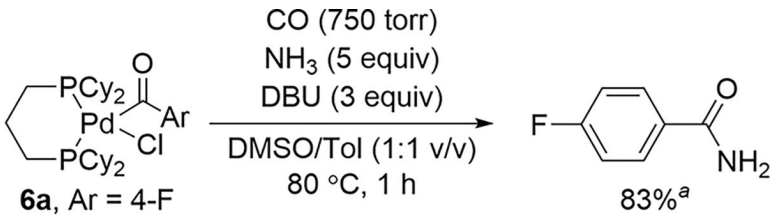


Scheme 4. Synthesis of Pd(II) Phenacyl Complexes by Oxidative Addition or Carbonylation



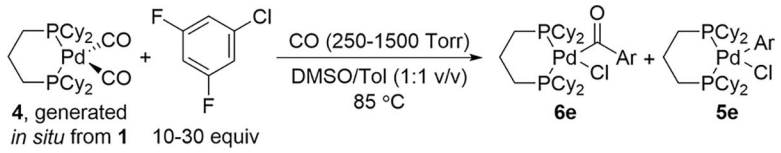
Scheme 5. Synthesis of Pd(II) Phenacyl Bromide Complex 6j via Oxidative Addition of the Corresponding Aryl Halide to *in Situ*-Generated (DCPP)Pd(CO)$_2$ in the Presence of CO

[a]Yield was determined by ^{1}H NMR spectroscopy with trimethoxybenzene as an internal standard.

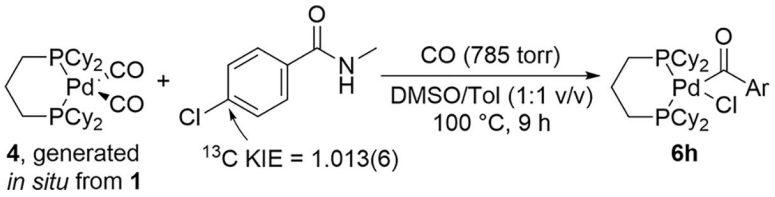


Scheme 6. Pd(II) Phenacyl Chloride Compound 6a Reductively Eliminates in the Presence of Ammonia To Form a Primary Benzamide

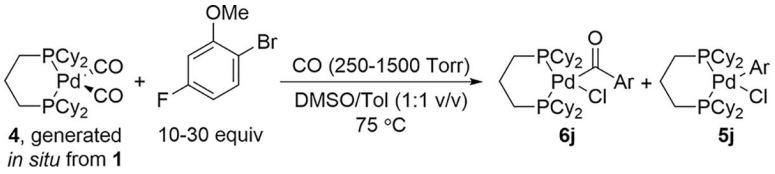
[a]Yield was determined by ^{1}H NMR spectroscopy with trimethoxybenzene as an internal standard.



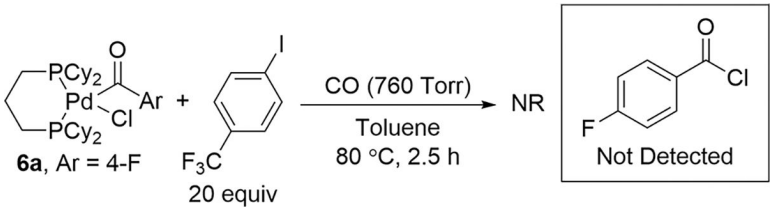
Scheme 7. Determination of Pseudo-First-Order Rate Constants k_{obs} from the Oxidative Addition of 3,5-Difluorochlorobenzene to (DCPP)Pd(CO)$_2$



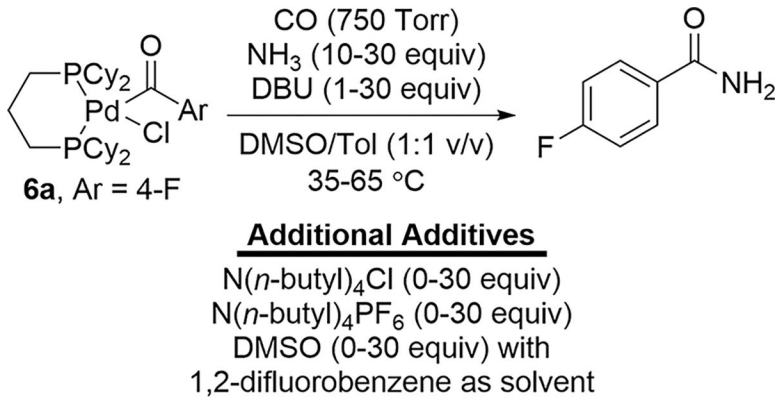
Scheme 8. Determination of ^{13}C KIE of the Oxidative Addition of 4-Chloro-*N*-methylbenzamide to 4



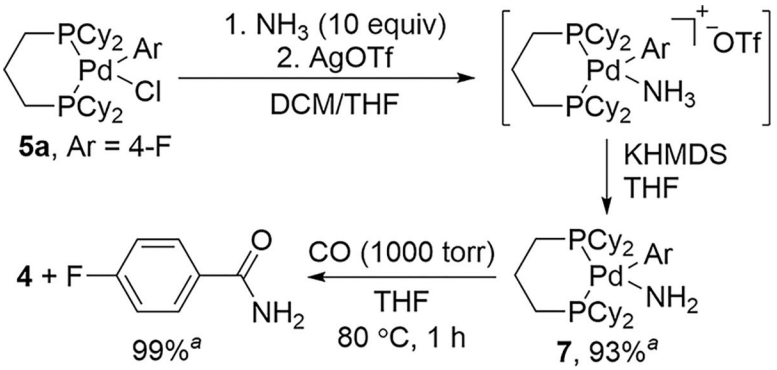
Scheme 9. Determination of Pseudo-First-Order Rate Constants k_{obs} from the Oxidative Addition of 2-Methoxy-4-fluoro-bromobenzene to (DCPP)Pd(CO)$_2$



Scheme 10. Reaction To Assess Whether Phenacylpalladium Complex 6a Reductively Eliminates 4-Fluorobenzoyl Chloride

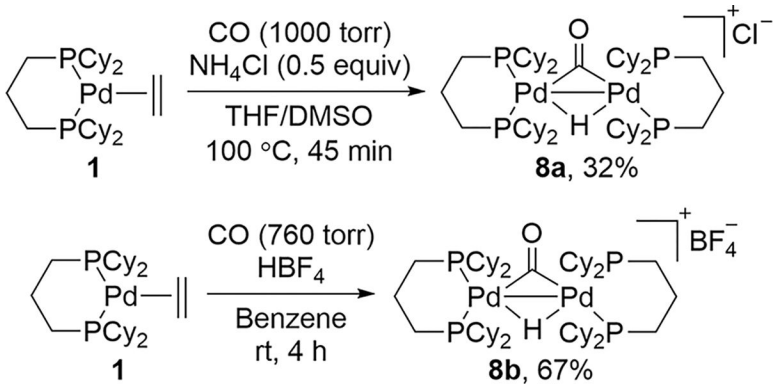


Scheme 11. Determination of Initial Rates and Pseudo-First-Order Rate Constants for the Formation of 4-Fluorobenzamide from Pd(II) Phenacyl Chloride Compound 6a

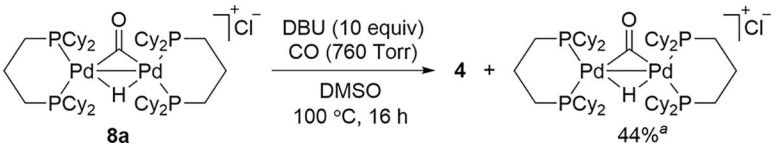


Scheme 12. Synthesis of Pd(II) Aryl Amido Complex 7 and Subsequent Reactivity with CO

[a]Yields were obtained by ^{19}F NMR spectroscopy with OTf^- as an internal standard.



Scheme 13. Synthesis of Pd(I) Dimers 8a and 8b

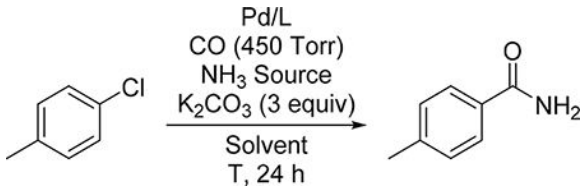


Scheme 14. Reduction of Pd(I) Dimer 8a to Pd Dicarbonyl Complex 4 in the Presence of CO and Base

[a]Yield was determined with $PMes_3$ as an internal standard.

Table 1.

Effect of Reaction Conditions on the Aminocarbonylation of *p*-Chlorotoluene[a]



entry	[Pd] (mol%)	L (mol%)	NH3 source (equiv)	solvent	*T* (°C)	yield (%)[c]
1[b]	(DCPP)Pd (OAc)$_2$ (2)	-	NH_4Cl (1.1)	NMP	120	0
2	Pd(OAc)$_2$, (2.5)	DCPP- 2HBF$_4$ (5)	NH_3 (4)	DMSO	120	50
3	Pd(OAc)$_2$, (2.5)	DCPP (5)	NH_3 (4)	DMSO	120	80
4	1 (2.5)	-	NH3 (4)	DMSO	110	91

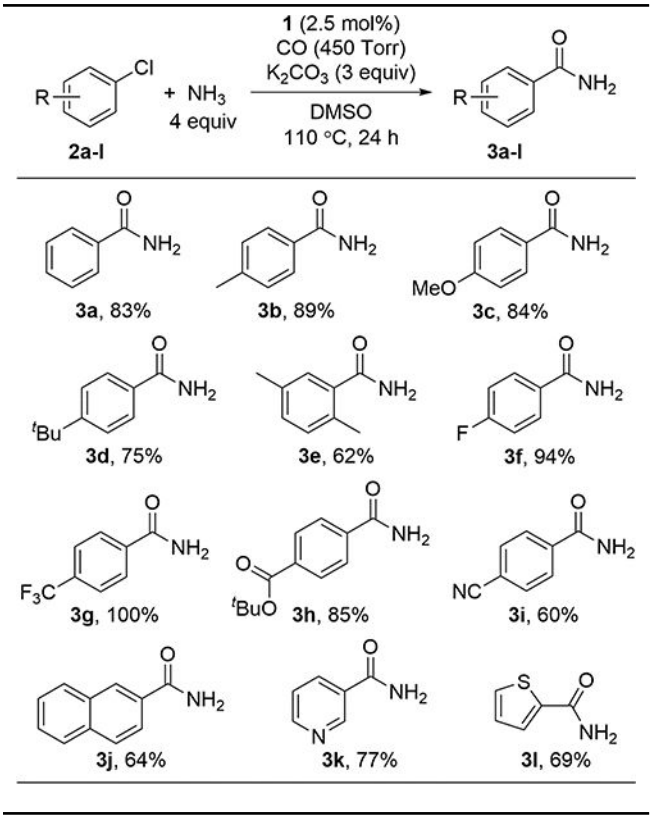
[a]Reaction conditions: *p*-chlorotoluene (0.4 mmol), CO (450 Torr), K_2CO_3 (3 equiv), 0.5 mL solvent, 24 h, 25 mL Schlenk bomb.

[b]760 Torr of CO.

[c]Determined by NMR spectroscopy.

Table 2.

Scope of Palladium-Catalyzed Aminocarbonylation of Aryl Chlorides with Ammonia[a]



[a]Reactions were performed in a 25 mL Schlenk vessel on a 0.4 mmol scale in 0.5 mL of solvent, and yields are reported as isolated yields.