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Oxidative Addition of Phenyl Bromide to Pd(BINAP) vs Pd(BINAP)(amine). Evidence for Addition to Pd(BINAP)

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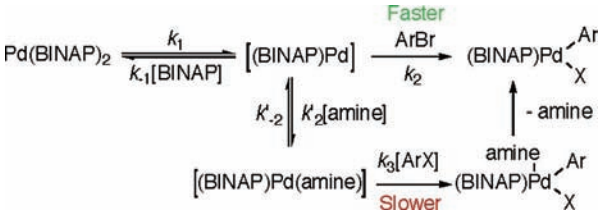
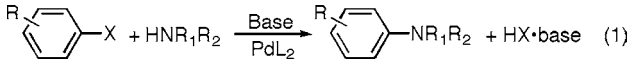
ABSTRACT



The rates of oxidative addition of phenyl bromide to [Pd(BINAP)$_2$] have been measured in the presence and absence of added amine to assess a previous hypothesis that addition to [Pd(BINAP)(amine)] is faster than addition to [Pd(BINAP)]. These data show that addition to the amine complex is not faster than addition to [Pd(BINAP)]. Instead, they are consistent with oxidative addition, even in the presence of amine, to [Pd(BINAP)] as the major pathway. These data underscore the value of studying the stoichiometric reactions of isolated complexes when assessing the mechanism of a catalytic process.

Palladium-catalyzed cross-coupling reactions have become one of the most common routes to substituted arenes. The first step in these cross-coupling processes, as well as in many other catalytic processes, is the oxidative addition of aryl halides.[1] The mechanism of the oxidative addition of aryl halides to palladium(0) complexes with several types of ligands has been studied, including complexes of monodentate[2] and bidentate[3,4] aromatic phosphines. Studies on complexes of aromatic phosphines have shown that oxidative addition typically occurs after ligand dissociation to form two-coordinate, 14-electron palladium complexes and that the products of these reactions are 16-electron palladium(II) complexes.

The conversion of a palladium(0) complex to an arylpalladium(II) halide complex is the turnover-limiting step of the coupling of amines with bromoarenes[5] catalyzed by complexes with aromatic bisphosphines,[6] such as BINAP and DPPF (eq 1). The presence of high concentrations of amine



in these systems and some recent kinetic data raised the

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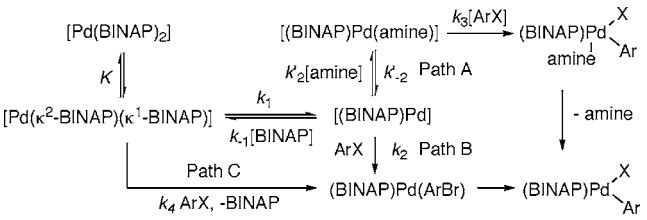
question of whether the amine could be a ligand on palladium(0) in the oxidative addition process.[7] Although amines are hard bases and palladium(0) is soft, the high concentration of the amine (often >1 M) could allow the generation of a palladium(0) complex of an amine.

Thus, three scenarios could occur during oxidative addition in the catalytic amination of bromoarenes: (1) the oxidative addition process could occur without participation of the amine because it is too hard a base to coordinate to the soft palladium(0) and because addition is typically faster to more unsaturated palladium(0) complexes; (2) the amine could inhibit the reaction by binding to the two-coordinate palladium(0) intermediate, or (3) the amine could accelerate oxidative addition after binding to palladium(0). Previous theoretical[8] and experimental[3,9] studies of the effect of coordination number on oxidative addition imply that binding of the amine is more likely to inhibit the oxidative addition than to accelerate it. However, recently published kinetic data on the rates of catalytic reactions led to the conclusion that oxidative addition occurred faster to [Pd(BINAP)(amine)] than to [Pd(BINAP)].[7] This conclusion inspired us to investigate more closely a potential effect of amine on the oxidative addition of bromoarenes to [Pd(BINAP)].

We have followed two approaches to gather more information on a potential role of the amine in the oxidative addition step. By one approach, we have conducted further kinetic studies of the catalytic system that gave rise to the apparent accelerating effect of the amine. By a second approach, we have assessed more directly the role of amine in the oxidative addition by studying the stoichiometric reaction of phenyl bromide with BINAP-ligated palladium(0) in the presence and absence of amine.[10]

We report here our results from studies following this second approach. The oxidative addition of bromoarenes to $[Pd(BINAP)]_2$ was studied under conditions that generate [Pd(BINAP)] in the presence and absence of a wide range of concentrations of amine. These were the first data we obtained to assess whether the amine was bound to Pd(0) during oxidative addition, and these data are inconsistent with addition to an amine complex, even in the presence of 1.0 M *N*-methylpiperazine. Although these studies address this particular mechanistic issue, they also have the broader pedagogical value of emphasizing that a simple experiment on a stoichiometric process can rule out a proposed mechanism for a multistep catalytic process.

Scheme 1



Scheme 1 shows three pathways for oxidative addition: reaction of the bromoarene with [Pd(BINAP)(amine)] after dissociation of BINAP and coordination of amine (path A), reaction with [Pd(BINAP)] after full dissociation of BINAP (path B), and reaction with [Pd(κ^2-BINAP)(κ^1-BINAP)] after partial dissociation of BINAP (path C). Faster reaction with [Pd(BINAP)(amine)] than with [Pd(BINAP)] would imply that the composite observed rate constant for path A would be faster than that for path B. The presence or absence of path C does not affect the general conclusions about whether path A or B is the major pathway for oxidative addition when these reactions are conducted in the presence of added amine, as long as path C is a minor reaction pathway in the absence of added amine (vide infra).[11]

k_{obs} for experiments in the absence of amine (paths B + C):

$$k_{obs} = \frac{Kk_1k_2[\mathrm{ArX}]}{k_{-1}[\mathrm{BINAP}]} + Kk_4[\mathrm{ArX}] \qquad (2)$$

k_{obs} for experiments in the presence of amine (paths A + B + C):

$$k_{obs} = \frac{Kk_1k'_2k_3[\mathrm{amine}][\mathrm{ArX}]}{k_{-1}k'_{-2}[\mathrm{BINAP}]} + \frac{Kk_1k_2[\mathrm{ArX}]}{k_{-1}[\mathrm{BINAP}]} + Kk_4[\mathrm{ArX}]$$

$$\text{or } k_{obs} = \frac{Kk_1(k_{obs(A)} + k_2)[\mathrm{ArX}]}{k_{-1}[\mathrm{BINAP}]} + Kk_4[\mathrm{ArX}]$$

$$\text{in which } k_{obs(A)} = k'_2k_3[\mathrm{amine}]/k'_{-2} \qquad (3)$$

The full rate equation for oxidative addition by the three pathways in Scheme 3 (see Supporting Information) was derived with the steady-state approximation and an assumption that partial dissociation of BINAP to generate [Pd(κ^2-BINAP)(κ^2-BINAP)] is fully reversible. The full rate equation can be simplified to that in eq 2 when Kk_{-1}[BINAP] ≫ k_2[ArX] (full dissociation of BINAP is reversible), and the reaction is conducted in the absence of amine. The full rate equation for a reaction in the presence of amine can be approximated by that in eq 3 when Kk_{-1}[BINAP] ≫ k_2[ArX] and Kk_{-1}[BINAP] ≫ k'_2[amine] (dissociation of BINAP and binding of amine are both reversible). The steady-state approximation is appropriate because no intermediates, such

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(10) Although previous studies on the oxidative addition of bromoarenes to $[Pd(BINAP)_2]$ showed that 0.58 mM of added octylamine did not affect the rate of oxidative addition,[3a] this experiment might be considered to have insufficiently addressed this issue because the concentration of amine in this experiment was much less than the concentration of amine in the catalytic system.

(11) The inverse dependence of k_{obs} on [L] at low [ArBr], the hyperbolic plot of $1/k_{obs}$ vs [PhBr], and the absence of accumulation of intermediates demonstrate that path C cannot be the major pathway because path C would be first order in [ArBr] at all concentrations (see Supporting Information for data).

as [Pd(BINAP)] or [Pd(BINAP)(amine)], are detected by NMR spectroscopy during the oxidative addition reactions (vide infra). Moreover, these studies were conducted under conditions in which Kk_{-1}[BINAP] is much greater than k_2[ArX]. Further, when reactions are run with added amine, any k'_2k_3/k'_{-2}[amine] term must be much greater than Kk_{-1}[BINAP] because the reactions are nearly first-order in ArBr and inverse first-order in ligand at the concentrations used (vide infra and Supporting Information).

Qualitatively, faster oxidative addition to an amine complex would predict that k_{obs} for this oxidative addition would depend strongly on the concentration of amine, as long as [Pd(BINAP)] is generated with either partial or full reversibility. An oxidative addition to [Pd(BINAP)$_2$] that occurs predominantly by the amine-first path A with reversible dissociation of BINAP would be approximately first order in added amine, and an oxidative addition process that occurs predominantly by the direct addition path B after reversible dissociation of BINAP would be closer to zero order in added amine.

The oxidative addition reactions in the presence and absence of 1 M amine were initially monitored by ^{31}P and ^{1}H NMR spectroscopy. The product of both reactions was the known [Pd(BINAP)(Ph)(Br)]. Careful monitoring of the reactions by ^{31}P NMR spectroscopy showed that the starting and final complexes were the only phosphine-ligated compounds present in amounts measurable by ^{31}P NMR spectroscopy. These data indicate that the added amine does not cause the accumulation of an amine complex in quantities that exceed a few percent of the total palladium.

Quantitative kinetic studies were conducted by UV−vis spectroscopy. These reactions were run with added BINAP to ensure that [BINAP] remains constant throughout the reaction. Plots of k_{obs} vs 1/[L] in the presence and absence of 0.5 M added *N*-methylpiperazine are shown in Figure 1.

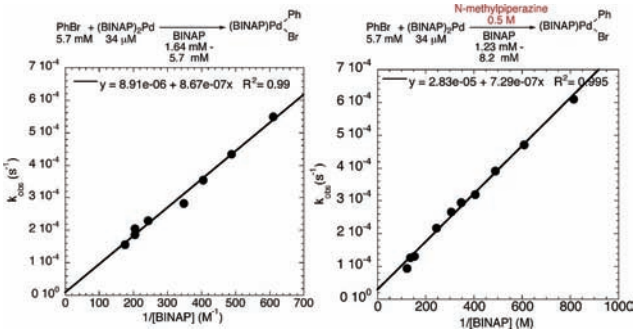

Figure 1. Plot of k_{obs} vs 1/[BINAP] for the reaction of Pd(BINAP)$_2$ (3.4×10^{-5} M) with PhBr (5.7×10^{-3} M) in the presence of BINAP and the absence (left) or presence (right) of *N*-methylpiperazine.

The left plot of Figure 1 shows a plot of k_{obs} vs 1/[BINAP] for reactions conducted at 70 °C with [Pd(BINAP)$_2$] of 34 μM, [PhBr] of 5.7×10^{-3} M, [BINAP] ranging from 1.6×10^{-3} to 5.7×10^{-3} M, and no added amine. The right plot of Figure 1 shows a plot of k_{obs} vs 1/[BINAP] for reactions conducted under identical conditions but with 0.50 M *N*-methylpiperazine. Clearly, the presence of 0.5 M *N*-methylpiperazine does not measurably affect the slope of this plot.

The slope of this plot for reactions in the absence of amine provides an approximate value for Kk_1k_2/k_{-1}. The y-intercept of this plot provides the value of the observed rate constant for reaction by path C involving displacement of the κ^1-BINAP by the bromoarene. The slope of the plot in the presence of amine provides an approximate value for $Kk_1(k_2 + k_{obs(A)})/k_{-1}$. The $k_{obs(A)}$ term refers to the overall observed rate constant for the steps of the amine path A after full dissociation of BINAP and contains the rate constants for binding and dissociation of amine, the rate constant for oxidative addition of bromoarene to the amine complex, and the concentration of amine. Thus, the ratio of the slopes of Figure 1 corresponds approximately to $(k_2 + k_{obs(A)})/k_2$. If the value of $k_{obs(A)}$ were small and the amine path A were a minor one, then the slope of the plots in Figure 1 would be similar, but if the value of $k_{obs(A)}$ were much larger than k_2 and the amine path A were the major one, then the slope of the plot obtained in the presence of added amine would be much larger. The similarity of the slopes of the plots in Figure 1 provides the first, and perhaps even sufficient, data to rule out a mechanism in which the majority of the oxidative addition in the presence of amine occurs by the previously proposed amine path A.

Figure 2 shows plots of k_{obs} vs [*N*-methylpiperazine] and

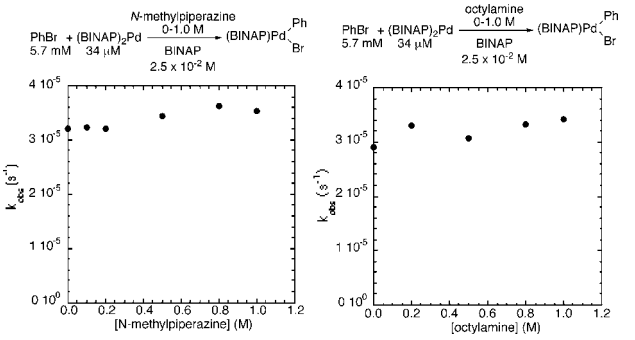

Figure 2. Plot of k_{obs} vs [*N*-methylpiperazine] (left) and k_{obs} vs [octylamine] (right) for the reaction of PhBr (5.7 mM) with [Pd(BINAP)$_2$] (3.4×10^{-5} M) in the presence of BINAP (2.5×10^{-2} M) and octylamine (0.0−1.0 M) at 70 °C.

k_{obs} vs [*n*-octylamine] with a 3.4×10^{-5} M concentration of [Pd(BINAP)$_2$], a 5.7×10^{-3} M concentration of PhBr, a 2.5×10^{-2} M concentration of added BINAP, and 0.0−1.0 M concentrations of amine. These data show that the observed rate constant depends little on the concentration of either amine when the ratio of aryl bromide to free ligand allows for almost fully reversible generation of [Pd(BINAP)] and, if present, [Pd(BINAP)(amine)]. This small dependence of k_{obs} on the concentration of amine is, again, inconsistent with

reaction of the bromoarene with [Pd(BINAP)(amine)] as the major pathway for oxidative addition in the presence of amine.

We also assessed the effect of amine on the oxidative addition when the concentration of bromoarene more closely resembles that of the catalytic system. To do so, we conducted the oxidative addition in the presence of varied concentrations of *N*-methylpiperazine when the concentration of bromoarene is 0.50 M, instead of 5.7 mM. These data are shown in Figure S1 of the Supporting Information. Even at this higher concentration of bromoarene, the reaction was closer to zero order in amine than to first order in amine. The slopes of these plots show that the difference between the rate constants for reactions of 5.7 mM phenyl bromide conducted with no added amine and with 1 M added amine is only 9% of the rate constant without added amine and only 19% of this value for reactions of 0.5 M phenyl bromide.[12]

The small, but measurable, slope of these plots might signal some role of the amine in a minor pathway for oxidative addition. However, no effect of the concentration or identity of amine on the rate of the catalytic coupling of amines with bromoarenes catalyzed by BINAP-ligated palladium has been measured when the catalytic process is initiated with pure precatalysts,[13] and the effect of amine on the oxidative addition at high concentrations of bromoarene remains much less than first order. Thus, we do not wish to speculate on the origin of this small effect of amine at this time.

Although we began this study to determine if the amine affected the rate of the carbon−halogen bond-cleavage step of the overall oxidative addition process, we also considered whether the amine could affect the rate of dissociation of ligands from [Pd(BINAP)$_2$]. To test for an effect of amine on the ligand dissociation, we conducted the reaction of tol-BINAP with [Pd(BINAP)$_2$] in the presence and absence of amine and measured the decay of [Pd(BINAP)$_2$]. We conducted these reactions with an excess of tol-BINAP to cause the equilibrium to lie nearly completely on the side of [Pd(tol-BINAP)$_2$] and [Pd(tol-BINAP)(BINAP)].

The decay of [Pd(BINAP)$_2$] in the presence and absence of amine is shown in Figure 3. The reaction of a 5.3 mM solution of [Pd(BINAP)$_2$] with 43 mM tol-BINAP without added amine was followed by ^{31}P NMR spectroscopy at 45 °C. Again, the effect of amine was far less than first order. The rate constant for the decay of Pd(BINAP)$_2$ in the absence of added amine was $1.1 \pm 0.1 \times 10^{-4}$ s^{-1}. The rate constant for ligand exchange in the presence of 0.5 M *N*-methylpiperazine was only slightly faster ($1.3 \pm 0.1 \times 10^{-4}$ s^{-1}) and most realistically within experimental error of the rate

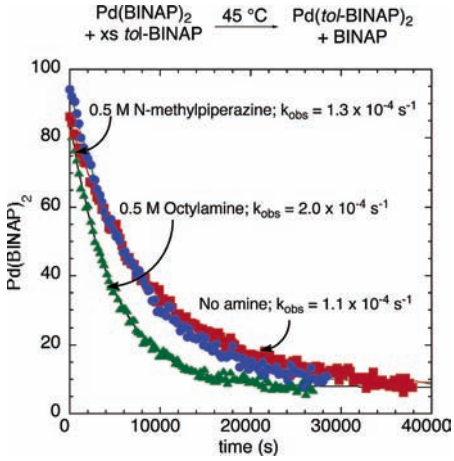

Figure 3. Plot of decay of Pd(BINAP)$_2$ vs time for the reaction of [Pd(BINAP)$_2$] (5.3 mM) with tol-BINAP (43 mM) at 45 °C. This plot illustrates the effect of added amine on the rate of the ligand substitution.

constant in the absence of added amine. The rate constant for ligand exchange in the presence of 0.5 M octylamine was measurably faster ($2.0 \pm 0.2 \times 10^{-4}$ s^{-1}). However, the increase in rate observed in the presence of the primary amine was still far less than a rate increase that would reflect a first-order dependence on the amine.

The results of these studies of a well-defined stoichiometric oxidative addition of phenyl bromide to [Pd(BINAP)$_2$] in the presence and absence of varying concentrations of amine demonstrate that oxidative addition of phenyl bromide to [Pd(BINAP)$_2$] under conditions in which [Pd(BINAP)] and, if present, [Pd(BINAP)(amine)] are generated reversibly depends little on the presence or absence of even a high 1 M concentration of amine. The faster addition to [Pd(BINAP)] than to [Pd(BINAP)(amine)] agrees better with the established reactivity of 2- and 3-coordinate Pd(0) species[9] than does a mechanism in which a Y-shaped 16-electron intermediate [Pd(BINAP)(amine)] undergoes oxidative addition, and the previous conclusion about the reactivity of [Pd(BINAP)(amine)] has recently been corrected (see ref 13). These studies demonstrate the value of assessing mechanisms of catalytic reactions from studies of pure isolated transition-metal complexes.

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Supporting Information Available: Reaction procedures, characterization of reaction products, and summary of the effect of varying reaction conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Essentially identical data to those obtained with bromoarene were obtained with 3-bromoanisole. These data were accumulated in addition to those data with bromobenzene because the data on the catalytic reactions were obtained with 3-bromoanisole as the bromoarene.[13] Data with this bromoarene are provided as Supporting Information.

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