Mechanism of Aryl Chloride Amination: Base-Induced Oxidative Addition

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Received June 25, 2001
Revised Manuscript Received August 31, 2001

Palladium-catalyzed cross-coupling reactions of aryl halides are now common synthetic procedures. However, aryl chloride substrates have become useful only since the discovery of unusually reactive catalysts bearing sterically hindered alkylmonophosphine and sterically hindered carbene ligands.[1−20] Aryl halide aminations were some of the first coupling reactions of aryl chlorides at low temperatures.[3,6,9] Much effort has since been devoted to ligand and reaction design, but little mechanistic information has been generated. One study, conducted nearly 10 years ago on the oxidative addition of aryl chlorides[21] to a modestly active Pd(0) catalyst for Heck coupling and carbonylation of aryl chlorides, remains the sole quantitative mechanistic study on aryl chloride coupling.

Oxidative addition of aryl chlorides to a mono- or bisphosphine Pd(0) complex is generally considered the turnover-limiting step of a catalytic cycle that involves oxidative addition, transmetalation, and reductive elimination. Yet, several results are inconsistent with this proposal. Heck, Suzuki, amination, and etherification reactions require different temperatures and reaction times for the same aryl halide and catalyst.[3,4,6,9,10,12−14,20] Most relevant to the work presented here, aryl halide aminations with weak and strong bases require dramatically different temperatures and catalyst loadings.[6,10] We provide evidence that the catalytic reaction of aryl chlorides with amine and alkoxide base occurs by two concurrent mechanisms. One of these mechanisms involves direct participation of the base in the oxidative addition step. This pathway dominates when a highly active catalyst containing a 1:1 ratio of P(*t*-Bu)$_3$ and palladium is used.

Identification of the major palladium−phosphine complex in solution is important for interpretation of the kinetic data. The reaction of *p*-Me-C$_6$H$_4$Cl with *N*-methylbenzylamine in the presence of NaO-*t*-Bu base, 10 mol % Pd[P(*t*-Bu)$_3$]$_2$ (**1**), and 1% added P(*t*-Bu)$_3$ showed only **1** and free ligand by ^{31}P{^{1}H} NMR spectroscopy. Treatment of **1** alone with excess amine led to no change in the ^{31}P{^{1}H} or ^{1}H NMR spectra of **1**. Treatment of **1** with NaO-*t*-Bu also led to no discernible change in the ^{31}P{^{1}H} NMR spectrum, but did lead to a small change in the ^{1}H NMR line shape of the *t*-Bu resonance for **1**. Thus, a small amount of adduct may be formed reversibly, but the negligible change in the ^{1}H NMR line shape implied that any adduct was only a minor component of the reaction solution and **1** is the major species.

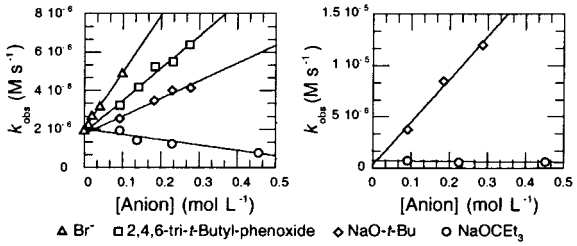

Figure 1. Dependence of k_{obs} on [base] and [Br$^-$] for the reaction of PhCl and *N*-methylbenzylamine catalyzed by **1** (left) or a 1:1 combination of **1** and Pd(DBA)$_2$ (right).

Three conventional classes of mechanisms for the amination of aryl chlorides with Pd(0) complex **1** as the catalyst resting state are turnover-limiting, oxidative addition of ArCl to bisphosphine complex **1**, turnover-limiting oxidative addition to a monophosphine complex **2** formed by ligand dissociation, and reversible oxidative addition of aryl halide to **2**, followed by irreversible reaction with either base or amine. We recently showed that P(*t*-Bu)$_3$-ligated arylpalladium halide complexes reductively eliminate aryl halide rapidly.[22] This result makes reversible oxidative addition possible. Each of these pathways can be distinguished by the dependence of k_{obs} on the concentration of added ligand, aryl halide, amine, and base.

Kinetic measurements were conducted on the reaction of *N*-methylbenzylamine with excess chlorobenzene and excess alkoxide base in the presence of 10% **1** (1.95 mM) and 1% P(*t*-Bu)$_3$ in toluene-d_8 solvent at 90 °C with [*N*-methylbenzylamine] = 19.5 mM, [NaOCEt$_3$] = 91.4 mM, and [ArCl] = 97.5 mM to 1.27 M. Linear plots of [amine] vs time and of k_{obs} vs [ArCl] showed the reaction to be zero order in amine and first order in ArCl.[23] A linear plot of $1/k_{obs}$ vs [P(*t*-Bu)$_3$] when varying [P(*t*-Bu)$_3$] from 0.098 mM to 6.8 mM showed the reaction to be inverse first order in [P(*t*-Bu)$_3$].[23]

These data rule out addition directly to **1**, which would be independent of added phosphine concentration. They also exclude reversible oxidative addition followed by irreversible reaction of the arylpalladium halide complex with amine. The remaining conventional mechanisms involve turnover-limiting oxidative addition (Path A) or reversible oxidative addition and irreversible reaction of base with the arylpalladium halide complex prior to reaction with amine (Path B).

The dependence of k_{obs} on the concentration of base was complex and ultimately inconsistent with either path A or B operating alone for reactions involving all bases. Figure 1 (left) shows a plot of k_{obs} vs varied concentrations of excess quantities of several bases and of bromide additive. The reaction is essentially zero order in [NaOCEt$_3$]. In contrast, the plot of k_{obs} vs the concentration of the more commonly used base NaO-*t*-Bu showed a positive linear relationship, along with a nonzero *y*-intercept. The dependence of k_{obs} on [2,4,6-tri-*t*-Bu-phenoxide]

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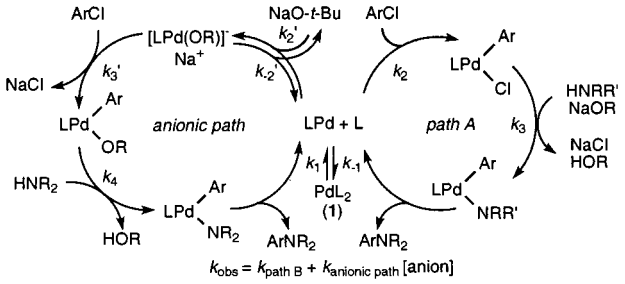
10.1021/ja016491k CCC: $20.00
Published on Web 11/29/2001

Scheme 1. Concurrent Mechanisms for Amination of ArCl by Pd/P(*t*-Bu)$_3$ Consistent with the Rate Data



was similar, but with an even larger slope. The same nonzero *y*-intercept was observed.

The zero order behavior in [NaOCEt$_3$] is consistent with the rate equation (eq 1)[24] for reaction exclusively by path A. However, the positive dependence of k_{obs} on [NaO-*t*-Bu] is inconsistent with eq 1. Moreover, these data are inconsistent with the rate expression for Path B in eq 2. This equation predicts a plot of k_{obs} vs [base] that intersect the *y*-axis at zero. One might imagine concurrent reaction by Path A and Path B for reactions containing NaO-*t*-Bu to account for the positive slope and nonzero *y*-intercept. However, it is not possible for paths A and B to occur simultaneously with the same base. These two paths follow the same individual steps and differ only in which step is irreversible.

$$\text{rate} = -k_{obs}; \quad k_{obs} = \frac{K_1 k_2 [PdL_2][ArCl]}{[L]} \qquad (1)$$

$$\text{rate} = -k_{obs}; \quad k_{obs} = \frac{K_1 k_2 k_3 [PdL_2][ArCl][NaOR]}{(k_{-2} + k_3[NaOR])[L]} \qquad (2)$$

An alternative explanation that is consistent with our data involves reaction by two concurrent pathways: one that follows path A and is zero order in base (eq 1) and one that follows a different path and is first order in base. The k_{obs} for path A, which is independent of [base], would correspond to the value of the *y*-intercept of Figure 1.

Amatore and Jutand have shown an accelerating effect of coordinated halide on the rates for oxidative addition of aryl iodides to Pd(PPh$_3$)$_4$.[25,26] Therefore, reversible displacement of phosphine in **1** by *tert*-butoxide or 2,4,6-tri-*tert*-butylphenoxide could initiate the second, base-dependent path. This ligand exchange would form an anionic Pd(0) monophosphine complex that could add aryl chloride (Scheme 1, left). The rate behavior for this anionic path is shown in eq 3, and the total rate by both

$$\text{rate} = -k_{obs}; \quad k_{obs} = \frac{K_1 k_2' k_3' [PdL_2][NaOR][ArCl]}{(k_{-2}' + k_3[ArCl])[L]} \qquad (3)$$

paths would be described by the sum of eqs 1 and 3. We do not fully understand the relative magnitude of the effect by the anions. However, $^-$O-*t*-Bu is less hindered than $^-$OCEt$_3$ and 2,4,6-tri-*tert*-butylphenoxide is softer than $^-$OCEt$_3$. These properties may lead to higher binding constants for reaction of *tert*-butoxide and 2,4,6-tri-*tert*-butylphenoxide with Pd(0) than for reaction of $^-$OCEt$_3$.

Measurements of k_{obs} for aryl chloride amination with added halide using NaOCEt$_3$ as base provided strong evidence for the proposed analogy between the effect of coordinated halide in previous studies and that of coordinated base uncovered here. Added [N(C$_8$H$_{17}$)$_4$]Cl had no measurable effect on k_{obs}, showing the absence of medium or ionic strength effects and weak binding by the hard Cl$^-$. However, added [N(C$_{18}$H$_{37}$)$_4$]Br led to the dependence of k_{obs} on the softer [Br$^-$] shown in Figure 1, which was even stronger than the effect of added alkoxide or phenoxide. Importantly, the *y*-intercept, which corresponds to the rate constant for the bromide independent pathway, was identical to that which we assigned to the rate constant for the base-independent pathway in reactions containing NaO-*t*-Bu or the phenoxide base and no halide.

The fastest rates for many reactions catalyzed by palladium complexes of P(*t*-Bu)$_3$ often occur with a 1:1 ratio of ligand to Pd(dba)$_2$.[4,6,12−14] We evaluated whether reactions containing 1 equiv of P(*t*-Bu)$_3$ per palladium generated by combining **1** and Pd(DBA)$_2$ in a 1:1 ratio would show the same dependence of k_{obs} on [base]. Reactions containing NaO-*t*-Bu as base catalyzed by **1** and Pd(DBA)$_2$ occurred at only 70 °C. The major pathway in this case is clearly first order in base (Figure 1, right). Yet reactions containing NaOCEt$_3$ as base were again essentially zero order in base. These data, again, imply the operation of two competing pathways. The relative contribution of the two paths depends on the identity of the anions present. Considering our results from the related catalyst **1**, we suggest that these two pathways are a conventional neutral path A and an anionic one. Further studies are required to fully understand the events prior to reaction with aryl chloride, but displacement of the weaker binding DBA instead of P(*t*-Bu)$_3$ could produce higher concentrations of anionic palladium and increase the fraction of catalysis by a Pd(0)−alkoxide complex.

Our previous studies on aryl halide aminations catalyzed by palladium complexes of BINAP and of DPPF showed rates that were cleanly zero order in base.[27,28] Consequently, the mechanism for aryl halide amination when using the sterically hindered monophosphine P(*t*-Bu)$_3$ is distinct from that for reactions catalyzed by complexes of bisphosphines.

During many methodological studies on cross-coupling, different bases generate different catalyst efficiencies, even when oxidative addition is proposed to be turnover-limiting. Many proposals have been used to explain anion effects on catalytic cross-couplings. Halide and acetate anions have been proposed to stabilize the palladium catalyst,[29] form stable Pd(II) intermediates from unstable arylpalladium triflato complexes,[30,31] accelerate transmetalation,[30,31] and accelerate oxidative addition.[26,32] Perhaps the effect of base uncovered here will be common for Suzuki, Heck, and aromatic carbon−heteroatom couplings, which are generally conducted with added base and catalysts bearing monophosphines. We are currently conducting studies to evaluate this proposal.

Acknowledgment. We are grateful to the NIH (R01-GM55382) for support of this work.

Supporting Information Available: Experimental procedures, derivation of rate equations, and kinetic plots (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016491K

(24) See Supporting Information for full steady-state treatment, derivation, and assumptions that generate the simplified rate equations.

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