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Reevaluation of the Mechanism of the Amination of Aryl Halides Catalyzed by BINAP-Ligated Palladium Complexes

Shashank Shekhar, Per Ryberg, and John F. Hartwig*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

Jinu S. Mathew and Donna G. Blackmond*

Department of Chemistry, Imperial College, London SW7 2AZ, United Kingdom

Eric R. Strieter and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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E-mail: John.Hartwig@yale.edu; D.Blackmond@imperial.ac.uk; sbuchwal@mit.edu

Abstract: Two previous mechanistic studies of the amination of aryl halides catalyzed by palladium complexes of 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphine) (BINAP) are reexamined by the authors of both studies. This current work includes a detailed study of the identity of the BINAP-ligated palladium complexes present in reactions of amines with aryl halides and rate measurements of these catalytic reactions initiated with pure precatalysts and precatalysts generated in situ from $[Pd_2(dba)_3]$ and BINAP. This work reveals errors in both previous studies, and we describe our current state of understanding of the mechanism of this synthetically important transformation. ^{31}P NMR spectroscopy shows that several palladium(0) species are present in the catalytic system when the catalyst is generated in situ from $[Pd_2(dba)_3]$ and BINAP, and that at least two of these complexes generate catalytic intermediates. Further, these spectroscopic studies and accompanying kinetic data demonstrate that an apparent positive order in the concentration of amine during reactions of secondary amines is best attributed to catalyst decomposition. Kinetic studies with isolated precatalysts show that the rates of the catalytic reactions are independent of the identity and the concentration of amine, and studies with catalysts generated in situ show that the rates of these reactions are independent of the concentration of amine. Further, reactions catalyzed by $[Pd(BINAP)_2]$ with added BINAP are found to be first-order in bromoarene and inverse first-order in ligand, in contrast to previous work indicating zero-order kinetics in both. These data, as well as a correlation between the decay of bromobenzene in the catalytic reaction and the predicted decay of bromobenzene from rate constants of studies on stoichiometric oxidative addition, are consistent with a catalytic process in which oxidative addition of the bromoarene occurs to [Pd(BINAP)] prior to coordination of amine and in which $[Pd(BINAP)_2]$, which generates [Pd(BINAP)] by dissociation of BINAP, lies off the cycle. By this mechanism, the amine and base react with [Pd(BINAP)(Ar)(Br)] to form an arylpalladium amido complex, and reductive elimination from this amido complex forms the arylamine.

Introduction

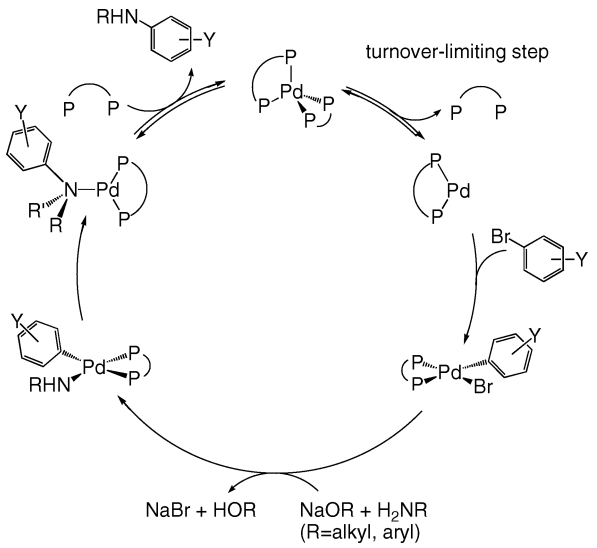
Palladium complexes of 1,1′-binaphthalene-2,2′-diylbis-(diphenylphosphine) (BINAP) and other bisphosphines are catalysts for the amination of aryl halides.[1,2] This reaction has become a widely used practical synthetic method for C−N bond formation and has been the subject of intensive mechanistic analysis. In 2000 and 2002, two papers were published in this journal describing kinetic and mechanistic studies on the (BINAP)Pd-catalyzed amination of bromobenzene. Each of these papers contained errors. In the current article we correct these errors in data and conclusions and describe our current state of understanding of the mechanism of this synthetically important transformation.

In 2000,[3] a series of synthetic, spectroscopic, and kinetic studies on the oxidative addition of aryl bromides to $[Pd(BINAP)_2]$ and $[Pd(DPPF)_2]$ and on the catalytic amination of bromoarenes catalyzed by these two compounds were reported. These data indicated that the catalytic process occurred by a pathway (Scheme 1) in which oxidative addition of the bromoarene occurred to [Pd(BINAP)], which was generated by dissociation of ligand from $[Pd(BINAP)_2]$. Subsequent work indicated that a minor pathway involving displacement of a

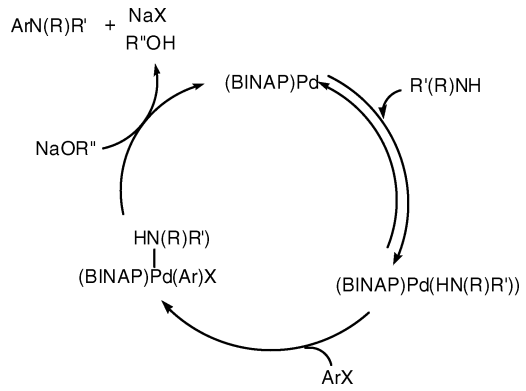
(1) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1051.
(2) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
(3) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618.

10.1021/ja045533c CCC: $33.50

Scheme 1



Scheme 2



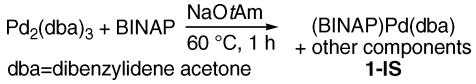
partially dissociated κ^1-BINAP in [Pd(κ^2-BINAP)(κ^1-BINAP)] by bromoarene prior to oxidative addition occurred in parallel.[4] In this mechanism, the complex [Pd(BINAP)$_2$] was proposed to lie on the catalytic cycle because the rate behavior had been measured to be zero order in ArBr and added ligand.

In 2002, Blackmond, Buchwald and co-workers[5] reported studies of in situ catalyst activation in amination reactions initiated with mixtures of $Pd_2(dba)_3$ and BINAP and with pure [Pd(BINAP)$_2$] as catalyst precursor. Kinetic modeling of reactions catalyzed by mixtures of $Pd_2(dba)_3$ and BINAP supported the proposal, shown in Scheme 2, that rate-limiting oxidative addition of ArX occurs to an amine-bound Pd complex and that oxidative addition to [Pd(BINAP)(amine)] is faster than oxidative addition to [Pd(BINAP)]. This work also proposed a role of the amine substrate in catalyst activation using BINAP and $Pd_2(dba)_3$ mixtures in which the amine displaced dba to form the palladium(0) amine complex [Pd(BINAP)(amine)]. In addition, these studies proposed an alternate interpretation of the results of ref 3, suggesting that the apparent zero-order kinetics in [ArBr] could be rationalized by a slow activation of a precatalyst complex. These studies implied that [Pd(BINAP)$_2$] lay off of the catalytic cycle and fed [Pd(BINAP)] into the cycle by ligand dissociation.

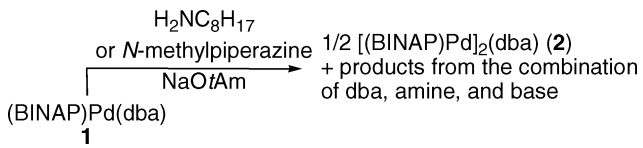
To address the differences between these mechanistic proposals, the authors of both previous papers report herein a series of studies that provide further insight into the mechanism of this important catalytic process. These studies have led to mechanistic conclusions that modify both reaction schemes.

(4) Alcazar-Roman, L. M.; Hartwig, J. F. *Organometallics* **2002**, *21*, 491.

Scheme 3



Scheme 4



Results and Discussion

1. Identification of the Major Catalyst Components and the Rates of Reactions with Pure Precatalysts. A. Identity of the Palladium Complexes in the Catalytic Solutions. To interpret rate data on a catalytic process and to draw mechanisms that correspond to these rate data, information should be gained on the identities of the species present in the catalytic process. In some cases, these observed species may be true intermediates, but in other cases they lead to intermediates by reversible or irreversible processes. The kinetic data reported in 2002 were collected on reactions with a catalyst generated in situ (**1**-IS) by combining BINAP and $Pd_2(dba)_3$ and incubating at 60 °C with alkoxide for 1 h (Scheme 3). In some other experiments, BINAP, $Pd_2(dba)_3$, base, and amine were incubated prior to addition of the bromoarene. No information on the palladium complexes in solution was provided. Thus, these and related reactions with various combinations of amine, base, and aryl halide were monitored by ^{31}P NMR spectroscopy to identify the major palladium complexes in solution.

The reactions of compounds generated from BINAP and $Pd_2(dba)_3$ with amine and base are summarized in Scheme 4. We first describe transformations starting with pure palladium phosphine complexes. The combination of BINAP and $Pd_2(dba)_3$ alone generates free dba and [Pd(BINAP)(dba)] (**1**),[6] which was the Pd(0)−dba complex included in the mechanisms of the 2002 report.[6] Purified complex **1** reacts with NaO*t*Am (Am = CMe_2-Et) and *N*-methylpiperazine or with NaO*t*Am and octylamine at 60 or 65 °C to form the new dinuclear complex [Pd(BINAP)]$_2$(dba) (**2**). This complex presumably forms because the amine adds to dba by a Michael addition under the basic conditions.[7] The dinuclear palladium complex was isolated in 85% yield and characterized by spectroscopy and X-ray diffraction (see Supporting Information).

When complex **1** was generated in situ from [$Pd_2(dba)_3$] and BINAP in the presence of amine and base, the Pd(0) species was different. The results of these reactions are shown in Scheme 5, and the ^{31}P NMR spectra of these mixtures are shown in Figure 1. When [$Pd_2(dba)_3$], BINAP, base, and *N*-methylpiperazine were mixed at once and stirred at 60 °C, a mixture of dimer **2** and [Pd(BINAP)$_2$] (**3**) was formed in a 0.7:1.0 ratio

(5) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104.
(6) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176.
(7) The reaction of free dba with NaOtBu and either the primary or secondary amine rapidly consumes dba at room temperature and generates several products.

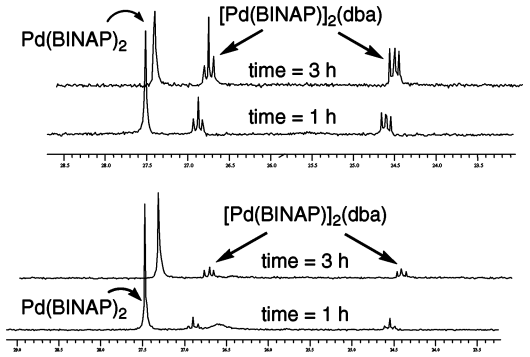
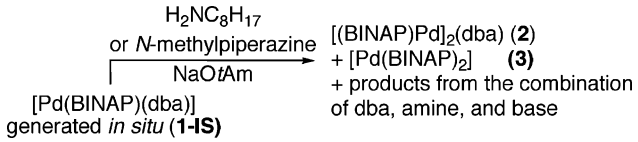
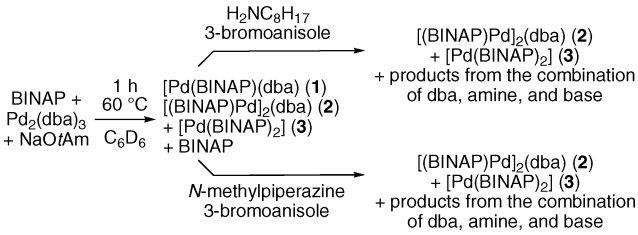


Figure 1. (Top) ^{31}P NMR spectra obtained during the reaction of 3-bromoanisole (0.13 M) with *N*-ethylpiperazine (0.93 M) catalyzed by $Pd_2(dba)_3$ (5.0 mM) and BINAP (10 mM) (**1**-IS) at 60 °C. (Bottom) ^{31}P NMR spectra during the same reaction with octylamine.

Scheme 5



Scheme 6



after 1 h, and in a 1:1 ratio after 3 h. When $[Pd_2(dba)_3]$, BINAP, base, and octylamine, instead of *N*-methylpiperazine, were mixed at once and stirred at 60 °C, a mixture of dimer **2** and monomer **3** was formed in a 0.2:1.0 ratio after 1 h, and in a 0.3:1.0 ratio after 3 h. Although the precise ratios of **2** to **3** varied from experiment to experiment, the amount of bis-BINAP **3** was always larger in reactions of primary amines than in reactions of secondary amines.

Most of the rate measurements by reaction calorimetry were conducted by incubating $[Pd_2(dba)_3]$, BINAP, and NaO*t*Am prior to the addition of amine and aryl halide. The compositions of the solutions generated from heating $[Pd_2(dba)_3]$, BINAP, and NaO*t*Am for 1 h were different from that just shown to form from heating of these three species with amine.[5] Scheme 6 shows a summary of the palladium complexes formed from combining $[Pd_2(dba)_3]$, BINAP, and NaO*t*Am. After 1 h of incubation of $[Pd_2(dba)_3]$, BINAP, and NaO*t*Am at 60 °C, the three complexes $[Pd(BINAP)_2]$, [Pd(BINAP)(dba)], and $[Pd(BINAP)]_2$(dba), as well as free BINAP, are all present.

The reactions catalyzed by the material formed from $[Pd_2(dba)_3]$, BINAP, and NaO*t*Am were also monitored by ^{31}P NMR spectroscopy. In the catalytic reactions of *N*-methylpiperazine with either PhBr (as reported in 2002) or 3-bromoanisole with complex **1** generated in situ, both dimer **2** and bis-BINAP **3** were present. ^{31}P NMR spectra were obtained of four sequential reactions. The first was initiated with a 7:1 ratio of amine to bromoarene, and the three subsequent reactions were run after addition of sequential portions of additional ArBr. This procedure of addition of multiple sequential portions of ArBr mimics a procedure in the 2002 report. These experiments showed that the ratio of **2** to **3** was relatively constant (2:3) after the first portion of bromoarene had reacted. However, the amount of free BINAP decreased initially, signals for **2** and **3** decreased in intensity, and broad or poorly resolved resonances in the region of coordinated BINAP grew in intensity.

These data lead to several conclusions about the palladium complexes in solution. The major palladium(0) species is $[Pd(BINAP)_2]$ (**3**); significant amounts of dinuclear complex $[Pd(BINAP)]_2$(dba) (**2**) are present; the ratios of **2** to **3** depend on the conditions by which the catalyst is generated; and complexes **2** and **3** are decomposing over the time of the catalytic reactions of secondary amines. The catalyst decomposition and dependence of the ratio of **2** to **3** on the type of amine are important for understanding the rate data. The identification of **2** and **3** as the major species allows one to propose a mechanism for the catalytic process that begins with a precatalyst defined by spectroscopic data.

B. Relative Rates of Reactions Initiated with Pure Forms of the Observed Palladium Complexes in the Catalytic Solutions. To determine the contributions of the different Pd(0) species to the rate of the catalytic process, the relative rates of the catalytic aminations initiated with isolated [Pd(BINAP)(dba)] (**1**), dinuclear **2**, and bis-BINAP complex **3** were studied. Because the reactions of PhBr and 3-bromoanisole contained the same three Pd(0) species, because the σ value of a 3-methoxy group is only 0.1, and because the concentration of 3-bromoanisole is easily followed by ^{1}H NMR spectroscopy, these comparisons were conducted with 3-bromoanisole instead of PhBr. However, reactions of PhBr catalyzed by **1**-IS were monitored by GC to ensure that the conclusions about induction periods and relative rates of reactions of primary and secondary amines would be the same for reactions of PhBr and 3-bromoanisole.

The reactions of some of these complexes occurred with induction periods, and reactions of both amines initiated with mononuclear dba complex **1** occurred with long induction periods. The rates of reaction of the different catalysts were measured after the induction period by the procedure in the 2002 report, in which sequential portions of aryl bromide were added to a mixture of the other reaction components. The decay of aryl bromide in each sequential reaction was monitored by ^{1}H NMR spectroscopy.

The rates of the reactions of *N*-methylpiperazine with 3-bromoanisole, conducted with isolated **1**, **2**, and **3** as precatalyst, obtained by ^{1}H NMR spectroscopy at 50 °C are illustrated

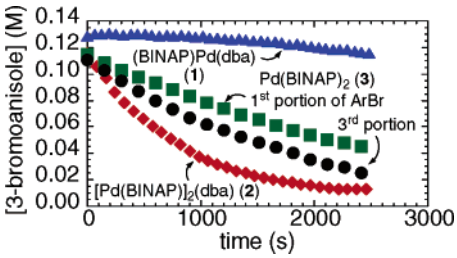


Figure 2. Comparison of the rates of reaction of *N*-methylpiperazine (0.93 M) with 3-bromoanisole catalyzed by [Pd(BINAP)(dba)] (**1**) (10 mM), $[Pd(BINAP)]_2$(dba)] (**2**) (10 mM), and $[Pd(BINAP)_2]$ (**3**) (10 mM) at 50 °C. The decay of the first portion of the bromoarene is shown for reactions initiated with catalysts **1** and **2**, and the decay of the first and third portions of bromoarene are shown for reactions initiated with catalyst **3**.

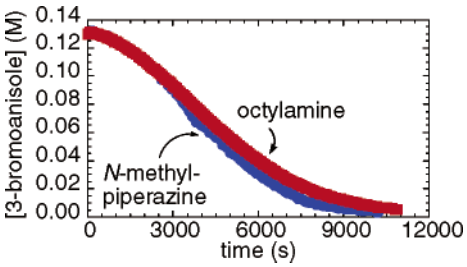


Figure 3. Comparison of the decay of 3-bromoanisole during the reactions of 3-bromoanisole (0.13 M) with *N*-methylpiperazine (0.93 M) and octylamine (0.93 M) catalyzed by 10 mM **1**-IS at 60 °C. This plot corresponds to the reaction of the first portion of aryl bromide in the experiments in which sequential portions of ArBr are added.

by the curves in Figure 2. Clearly, the relative reactivities of the precatalysts are **1** ≪ **3** < **2**. The reaction initiated with **1** occurs with a long induction period, and the initial rate with this catalyst was too slow to measure. The reaction initiated with **2** occurred without an induction period and with an initial rate that was $(1.1 \pm 0.1) \times 10^{-4}$ M s^{-1} at 50 °C. The reaction of these same reagents initiated with bis-BINAP complex **3** in the absence of added BINAP occurred with a small induction period (vide infra).[8] By NMR spectroscopy, the third and fourth portions of 3-bromoanisole reacted with the same decay profile. Whether the initial rate of reaction of the first portion of aryl bromide ($(3.5 \pm 0.2) \times 10^{-5}$ M s^{-1}) or the third portion of ArBr ($(5.2 \pm 0.2) \times 10^{-5}$ M s^{-1}) is used for comparison, the initial rate of reactions with [Pd(BINAP)$_2$] as precatalyst was smaller than that of reactions with **2** as precatalyst and larger than that of reactions with **1** as precatalyst. Thus, the long induction period during reactions catalyzed by **1**-IS results from the transformation of **1** to **2**, **1** to **3**, or **1** to a combination of **2** and **3**.

2. Evaluation of the Induction Periods of Reactions Initiated with 1-IS by ^{1}H NMR Spectroscopy. Because the data in section 1 showed that the distribution of Pd(0) complexes depended on subtle differences in the conditions of catalyst incubation, differences in the induction period were tested by monitoring the reactions of octylamine and *N*-methylpiperazine by ^{1}H NMR spectroscopy, in parallel with the same batch of catalyst. [Pd$_2$(dba)$_3$] was incubated with BINAP and NaO*t*Am for 1 h, and the resulting solution was split into two portions. To one portion was added octylamine, and to the other portion was added *N*-methylpiperazine. To both reactions were added four sequential portions of 3-bromoanisole, and the decay of each portion of 3-bromoanisole was monitored by ^{1}H and ^{31}P NMR spectroscopy in parallel in two instruments.

Instead of the reaction of the primary amine occurring with a much shorter induction period than the reaction of the secondary amine or with no induction period at all, as reported in 2002, the reactions of the two amines with the same batch of catalyst occurred with induction periods of nearly identical length. An overlap comparison of the decay of the reactions of octylamine and *N*-methylpiperazine is shown in Figure 3.

Further rate measurements by reaction calorimetry after incubation of a mixture of the catalyst components with both the amine and the base show that the activation behavior is extremely sensitive to the conditions of incubation. Figure 4

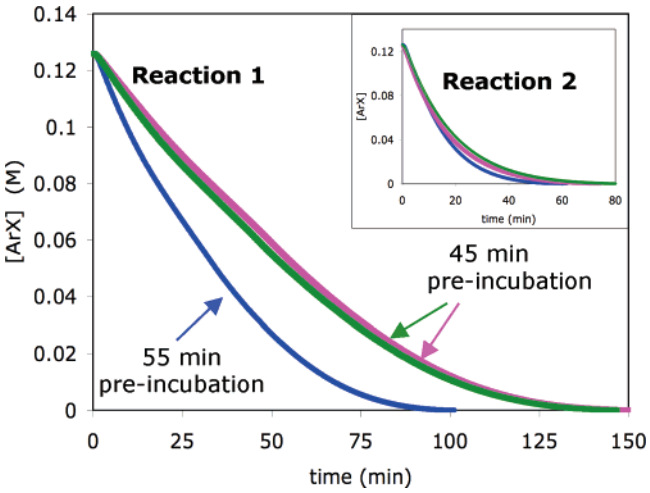


Figure 4. Comparison of the decay of ArX during sequential reactions of PhBr (0.13 M) with *N*-methylpiperazine (0.93 M) and octylamine (0.93 M) catalyzed by 10 mM **1**-IS at 60 °C. Influence of preincubation time on the rate of the first reaction in the sequence. (Inset) Comparison of second reactions in the same sequence.

shows that the first sequential reaction of *N*-methylpiperazine with PhBr using **1**-IS is significantly faster when the incubation time is increased by just 10 min. This large difference in catalyst activation presumably arises because the combination of amine and base serves as a better nucleophile for Michael addition to the dba than either base or amine alone. Figure 4 also shows that the length of the induction period does not affect the rate behavior of the catalyst once it attains steady state. If, however, the mixture of Pd$_2$(dba)$_3$ and BINAP is incubated with NaO*t*Am and the reaction is initiated by addition of amine and bromoarene, then less of the more reactive dinuclear **2** is generated than if the two catalyst components are incubated with alkoxide and amine together. Thus, the procedure for incubation affects the absolute measured rates of reaction.

3. Evaluation of Concentration Dependences for Amine and PhBr in Reactions Catalyzed by a Mixture of Pd$_2$dba$_3$ and BINAP. The 2002 study by Blackmond, Buchwald, and co-workers[5] reported concentration dependences of aryl halide and primary or secondary amine in amination reactions employing catalysts generated in situ by combining BINAP and Pd$_2$(dba)$_3$ with alkoxide base and amine prior to addition of the bromoarene. Consecutive reactions were monitored using reaction calorimetry by injecting equal aliquots of PhBr successively into the reaction mixture containing the catalyst and an excess of amine and base. After the initial induction period in the first reaction in the sequence, decreasing reaction rates for each consecutive reaction in the series were observed for secondary amines but not for primary amines.

In addition, the form of the rate profile reported in 2002 was different for reactions of secondary and primary amines, with primary amines exhibiting slightly less than overall first-order kinetics compared to apparent first-order kinetics for secondary amines. The data used in ref 5 for kinetic modeling of the mechanism in Scheme 2, comprising the second, third, and fourth reactions in the sequence for *n*-hexylamine and *N*-methylpiperazine, have recently been reproduced at both MIT and Imperial College.[9] This different kinetic behavior of the

(8) Rosner, T.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 4621.

(9) Data obtained in 2002 and in 2005 from MIT and Imperial College agree within 5%.

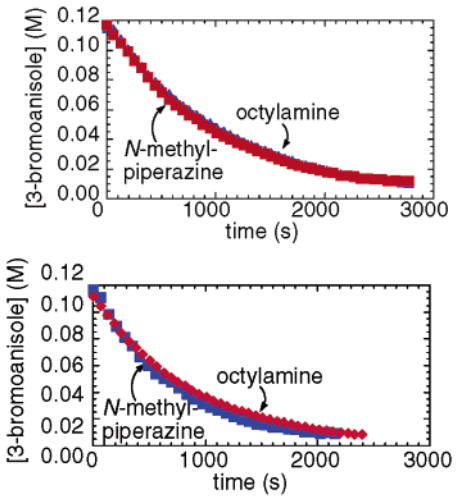


Figure 5. Comparison of the rates of reaction of 3-bromoanisole with octylamine (0.93 M) or *N*-methylpiperazine (0.93 M) catalyzed by 10 mM **2** at 50 °C (top) and by 10 mM **3** with 2 mM added BINAP at 70 °C (bottom). The reaction of octylamine is shown with red diamonds, and the reaction of *N*-methylpiperazine is shown with blue squares.

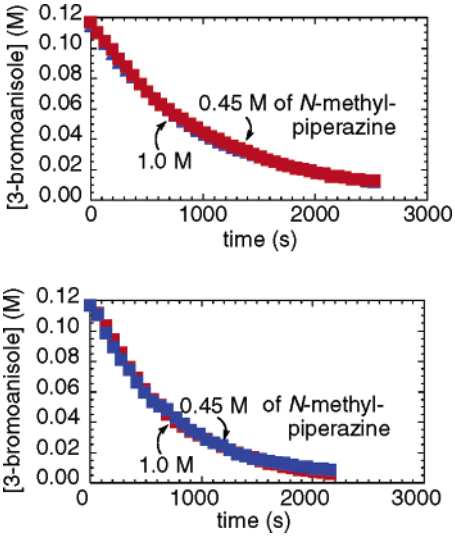


Figure 6. Comparison of the rates of reaction of 3-bromoanisole (0.13 M) catalyzed by 10 mM **2** at 50 °C (top) and by 10 mM **3** with 2 mM added BINAP at 70 °C (bottom) with different concentrations of amine. The reaction with 0.45 M amine is shown with blue squares, and the reaction with 1.0 M amine is shown with red squares.

aryl halide in the presence of the two different amines along with the apparent dependence of rate on the concentration of secondary amine led to the suggestion that the amine must be involved in the mechanism prior to the rate-limiting step.

This proposal was recently reevaluated by the Yale authors with a set of new experiments that probed the dependence of rate on the identity and concentration of the amine. Data were sought that would reveal whether this difference in rate was due to chemistry that occurred directly on the catalytic cycle or from chemistry that occurred off of the catalytic cycle. To study this, the rates of the reactions of primary and secondary amines initiated with pure **2** and **3** as precatalyst were measured, in this case by ^{1}H NMR spectroscopy. If the difference in rate were due to chemistry on the catalytic cycle, then the relative rates of reactions of the two amines with these pure complexes should mimic the relative rates of reactions of the two amines with the catalyst generated in situ.

The data on the reactions of 3-bromoanisole initiated with pure **2** and with pure **3** contrasted with the reactions of PhBr initiated with **1**-IS. The decay of 3-bromoanisole during reactions with octylamine was indistinguishable from that during reactions with *N*-methylpiperazine when catalyzed by pure **2**. These data are shown at the top of Figure 5. These reactions were conducted with 10 mM dimeric **2** as catalyst (2 mol % overall, 8 mol % based on each portion of bromoarene). Likewise, the decay of 3-bromoanisole during reactions with octylamine was indistinguishable from that during reactions with *N*-methylpiperazine when catalyzed by pure **3**. These data are shown at the bottom of Figure 5. These reactions were conducted with 10 mM **3** as catalyst (2 mol % overall, 8 mol % based on each portion of bromoarene) in the presence of 2 mM added BINAP (0.4 mol % overall, 1.6 mol % based on each portion of ArBr).

4. Evaluation of the Dependence of the Rate on the Concentration of Amine. If the dependence of the rate of the actual catalytic cycle depended on the concentration of amine, then a dependence of the rate on the concentration of amine should be observed during reactions initiated with the pure catalyst precursors **2** and **3**. To determine the order in amine of the reactions catalyzed by pure **2** and **3**, the decays of aryl bromide from reactions of 3-bromoanisole with 0.45 and 1.0 M concentrations of *N*-methylpiperazine in the presence of NaO*t*Am catalyzed by 10 mM **2** (Figure 6, top), or 10 mM **3** with 2 mM added BINAP (Figure 6, bottom), were measured at 50 °C. As shown clearly by the two plots in Figure 6, the reactions with the 2-fold different concentrations of amine were indistinguishable.

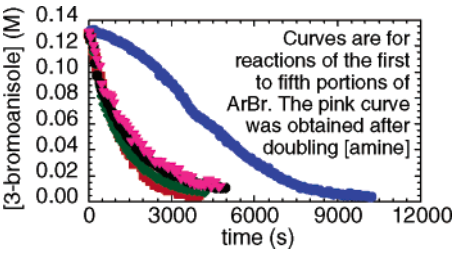


Figure 7. Decay of 3-bromoanisole during the sequential reactions of 3-bromoanisole with *N*-methylpiperazine catalyzed by 5.0 mM $Pd_2(dba)_3$ + 10 mM BINAP at 60 °C. The initial concentration of *N*-methylpiperazine was 0.93 M, and 0.13 M 3-bromoanisole was added five times. Legend: blue, decay of the first portion of 3-bromoanisole; red, decay of the second portion of 3-bromoanisole; green, decay of the third portion of 3-bromoanisole; black, decay of the fourth portion of 3-bromoanisole; pink, decay of the fifth portion of 3-bromoanisole after addition of amine to generate a concentration of *N*-methylpiperazine of 1.1 M.

To test whether the decrease in rate measured for reactions of secondary amines catalyzed by the mixture of [$Pd_2(dba)_3$] and BINAP was due to a dependence of the rate on the concentration of amine or other factors that retard catalytic reactions, such as catalyst decay, product inhibition, or change in medium, the rates of reactions of five portions of ArBr were measured, but an amount of *N*-methylpiperazine was added to the fifth portion of aryl bromide to *increase* the concentration of amine 2-fold. These reactions are shown in Figure 7. The decay of the first portion of bromoarene (shown in blue) is slow because of the induction period discussed in section 2. Most important for assessing the dependence of the rate on the concentration of amine, the decay of ArBr after the concentration of amine was increased 2-fold (shown in pink) is inconsistent

with a positive order in amine. This fifth portion of 3-bromoanisole did not decay with a faster rate than the fourth portion. The same lack of an increase in rate was observed if the additional *N*-methylpiperazine was added along with the third portion of aryl bromide. These experimental results have been confirmed by Blackmond, Buchwald, and co-workers.

These experiments show conclusively that the amination reaction does not exhibit positive order kinetics in secondary amine concentration. Instead, the apparent positive order in amine can be attributed to catalyst deactivation occurring during the reactions of secondary amines that were modeled. This catalyst deactivation is supported by the ^{31}P NMR spectroscopic evidence provided in section 2, showing that the decrease in concentration of **2** and **3** is more significant for secondary amines compared to primary amines in similar consecutive reaction sequences.

5. Evaluation of Concentration Dependences on PhBr and BINAP in Reactions Catalyzed by [Pd(BINAP)$_2$]. The data shown in Figure 3 for reactions conducted with pure Pd(BINAP)$_2$ in the absence of added ligand corroborate similar observations reported by Blackmond, Buchwald, and co-workers in ref 5. That report suggested that increasing rate could be attributed to an increase in the active catalyst concentration within the cycle over time. The slow step in the reaction sequence catalyzed by [Pd(BINAP)$_2$] in the absence of added BINAP was suggested to be the introduction of [Pd(BINAP)] from the off-cycle [Pd(BINAP)$_2$] complex, in analogy to an earlier example of false zero-order kinetics in Heck coupling.[8] The anomalous zero-order kinetics shown at early stages of the reaction of Figure 3 for the [Pd(BINAP)$_2$] system with no added ligand may thus be rationalized by an increase in the concentration of active catalyst at early stages of the reaction.

When the [Pd(BINAP)$_2$]-catalyzed reaction is carried out with 2 mol % added BINAP, however, the induction period is not observed, and the system obeys steady-state kinetics that are zero order in the concentration of amine and close to first-order in the concentration of ArX for both primary and secondary amines, as was shown in Figures 5 and 6. This confirms that the reactions show no dependence on the concentration or identity of the amine for the [Pd(BINAP)$_2$] catalyst system, just as was found above for the Pd$_2$dba$_3$/BINAP system. This observation of the absence of an induction period under these conditions contrasts with the induction period described in 2002 by Buchwald, Blackmond, and co-workers that has not been reproduced.

Reaction calorimetric studies of reactions catalyzed by a mixture of Pd$_2$dba$_3$ and BINAP, incubated with amine and base prior to addition of aryl bromide and of [Pd(BINAP)$_2$] under conditions similar to the reactions shown in Figures 5 and 6, illustrate a positive dependence on the concentration of ArBr and reveal (1) that the reaction of primary amines with the two catalysts gives a similar rate profile and (2) that the reaction catalyzed by [Pd(BINAP)$_2$] plus BINAP fortuitously occurs at about the same rate per Pd added to the system as the reaction catalyzed by the [Pd$_2$(dba)$_3$]/BINAP mixture (Figure 8a). Although the 1:1 stoichiometry of metal to ligand allows for only half the concentration of active catalyst to form, the spectroscopic studies reported in the first section of this paper show that a mixture of complexes **2** and **3** is formed from the mixture of [Pd$_2$(dba)$_3$] and BINAP. Thus, the presence of the more reactive **2** appears to compensate for the lower concentration of **3** generated with the 1:1 ratio of metal to ligand. This higher reactivity of **2** is illustrated by comparison of the rates of reactions catalyzed by the two complexes at 50 and 70 °C in Figure 6. The identical *form* of these rate curves is consistent with a reaction through a common intermediate, regardless of the provenance of the Pd precursor.

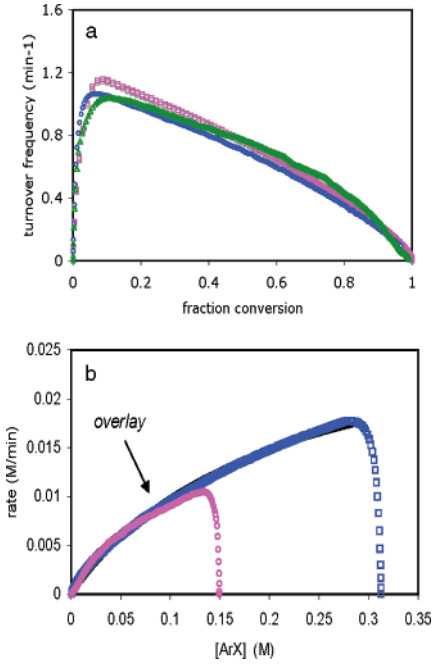


Figure 8. Reaction progress kinetic profiles for reactions of PhBr with *n*-hexylamine at 60 °C after the induction period. (a) Reactions using Pd$_2$dba$_3$/BINAP mixtures at 0.014 M Pd or Pd(BINAP)$_2$ at 0.01 M Pd with 0.002 M BINAP added: [PhBr]$_0$ ≈ 0.13−0.15 M; [amine]$_0$ ≈ 0.85 M; [NaO*t*Am]$_0$ = 0.85 M. Data are plotted as rate vs fraction conversion of PhBr. Magenta squares and blue circles, reactions using Pd$_2$dba$_3$/BINAP mixtures from MIT laboratories in 2002 and 2005, respectively; green triangles, reaction using Pd(BINAP)$_2$ from Imperial College laboratories in 2005. (b) Reactions carried out at same ["excess"] = 0.70 M. Blue circles, [PhBr]$_0$ = 0.31 M, [amine]$_0$ = 1.01 M, [NaO*t*Am]$_0$ = 1 M; magenta squares, [PhBr]$_0$ = 0.15 M, [amine]$_0$ = 0.85 M, [NaO*t*Am]$_0$ = 0.85 M. Data from Imperial College in 2005, plotted as reaction rate vs [PhBr]. Note that reaction progress is from right to left in panel (b).

Figure 8b reveals the important point that the catalytic cycle exhibits a steady state in catalyst concentration under the conditions of these reactions.[10] As described in a recent review of reaction progress kinetic analysis,[11] when "overlay" is demonstrated as in Figure 8b between kinetic plots of rate vs [ArX] from two experiments carried out at the same values of ["excess"] (["excess"] = [amine]$_0$ − [ArX]$_0$), the absence of an increase or decrease of [catalyst] within the cycle is established.

The dependence of the rate on the concentration of aryl halide revealed in Figures 6−8 contradicts the order in aryl halide from a mechanism in which [Pd(BINAP)$_2$] lies on the reaction pathway. Rate constants determined in the studies on the stoichiometric oxidative addition[12] may be used to predict the

(10) If a set of reactions similar to those in Figure 6 had been carried out with Pd$_2$dba$_3$/BINAP, a lack of overlay between the two curves could have confirmed that catalyst deactivation, rather than positive order kinetics in [secondary amine], accounted for the rate profiles observed in Figure 1b of ref 5.
(11) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302.
(12) These data were obtained as part of concurrent work on the oxidative addition of bromoarenes to [Pd(BINAP)$_2$] in the presence and in the absence of amine: Shekhar, S.; Ryberg, P.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 851.

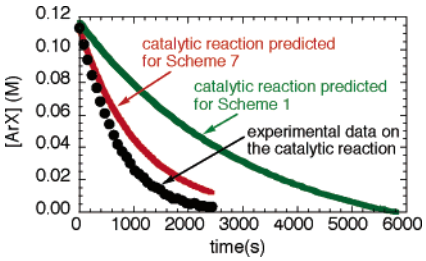


Figure 9. Decay of 3-bromoanisole during the catalytic reaction of 3-bromoanisole with *N*-methylpiperazine catalyzed by 10 mM [Pd(BINAP)$_2$] in the presence of 2 mM BINAP, predicted by the rate constants obtained from the study of stoichiometric oxidative addition of 3-bromoanisole to [Pd(BINAP)$_2$] at 70 °C.

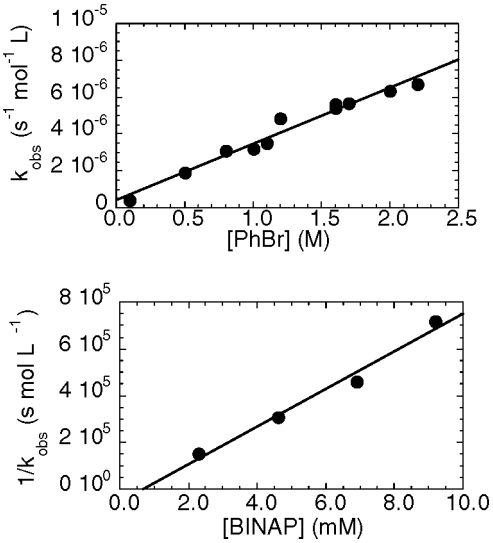


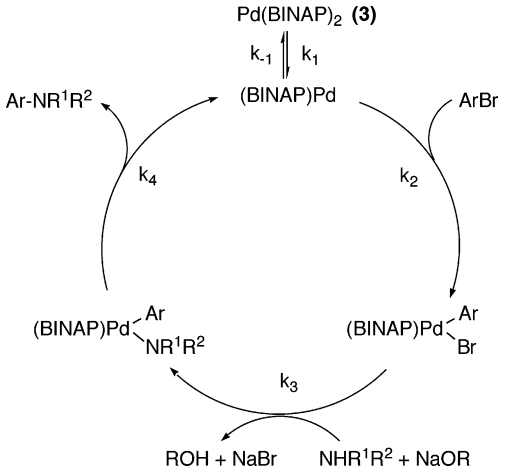
Figure 10. Dependence of the rate of the reaction of 0.10−2.7 M bromobenzene with 13 mM hexylamine catalyzed by 1.26 mM **3** with 2.3 mM BINAP at 50 °C on the concentration of PhBr (top) and of the rate of the reaction of 2.0 M bromobenzene with 13 mM hexylamine catalyzed by 1.26 mM **3** with 2.3−9.2 mM BINAP on the concentration of BINAP (bottom).

decay of bromoarene by a pathway with [Pd(BINAP)$_2$] on the reaction pathway under similar conditions. Figure 9 shows that the catalytic reaction is much faster than predicted for this mechanism from the rate constants of the study of oxidative addition and exhibits positive order kinetics at concentrations of [ArX] and [BINAP] where the mechanism with [L$_2$Pd] on the cycle should begin to be saturated in [ArX].

These inconsistencies led the Yale group to repeat the measurements of the order of the catalytic reaction in bromoarene and added ligand from ref 3. Inspection of the primary data and laboratory records makes clear that an error had been made when conducting the experiments that led to observation of the same reaction rate in experiments stated to have varied concentrations of ligand and bromobenzene. The set of experiments by the experimentalist in the current work (Figure 10) clearly shows that the reaction is first-order in bromoarene and inverse first-order in ligand. This is contrary to the previous report, where the kinetic data implied that the rate of the oxidative addition process and the rate of the catalytic cycle both depended only on the rate of dissociation of BINAP.

6. Mechanistic Conclusions. A pathway is shown in Scheme 7 in which the bromoarene reacts with [Pd(BINAP)], and [Pd(BINAP)] is generated by dissociation of the product amine, rather than the pathways in which a palladium(0) complex of

Scheme 7



the amine adds bromoarene to generate a five-coordinate Pd(II) product or the product amine is displaced associatively by BINAP from the 16-electron complex [Pd(BINAP)(product)] to regenerate [Pd(BINAP)$_2$]. The rate equation for the mechanism in Scheme 7 is provided in eq 1. This equation was derived

$$\frac{-\mathrm{d[ArX]}}{\mathrm{d}t} = \frac{k_1 k_2}{k_{-1}[\mathrm{L}]}[\mathrm{ArBr}][\mathrm{Pd}] \qquad (1)$$

using the steady-state approximation and simplifications based on experimental knowledge of the relative rate constants of different steps from studies of stoichiometric oxidative addition and reactivity of arylpalladium halide and arylpalladium amido complexes. The derivation of this equation and the approximations to simplify the full rate equation are provided in Supporting Information. The steady-state approximation is valid in this case because no intermediates accumulate, as determined by ^{31}P NMR spectroscopy. Further, numerical simulation of the palladium species in the catalytic system using known and estimated rate constants for the individual steps that lead to a close fit to the experimental decay of bromoarene shows that the palladium complexes within the cycle by this mechanism would not accumulate. These equations demonstrate that a reaction by the pathway in Scheme 7 will be zero-order in amine, first-order in bromoarene, and inverse first-order in added ligand. The equilibrium relationship between **3** and PdL manifested by the rate law for Scheme 7 holds for any case where a reversible "dead-end" step is linked to a steady-state catalytic cycle.[13] Equation 1 indicates that equilibrium may be established between a species off the cycle, such as **3**, and a species within the catalytic cycle, such as PdL, at concentrations that would provide a non-equilibrium steady-state concentration of PdL in an identical stoichiometric reaction sequence.

Several lines of data indicate that the major pathway for the catalytic process is the mechanism in Scheme 7. First, the zero-order dependence of the rate on the concentration of amine, first-order dependence of the observed rate constants on the concentration of bromoarene, and inverse dependence on the concentration of ligand measured most recently are consistent with the rate equation for reaction by the mechanism in Scheme 7, but are inconsistent with the rate equations for mechanisms

(13) Cornish-Bowden, A. In *Fundamentals of Enzyme Kinetics*; Portland Press: London, 1995; p 88.

in Schemes 1 and 2. Second, the observation of an induction period during reactions conducted with [Pd(BINAP)$_2$] as catalyst in the absence of any added ligand makes it unlikely that [Pd(BINAP)$_2$] lies directly on the reaction pathway. Third, the predicted decay of bromoarene by the mechanism in Scheme 7 from the rate constants measured independently by studying the stoichiometric oxidative addition[12] accounts for a majority of the rate constant of the observed catalytic process. These data provide strong evidence that a mechanism in which bromoarene reacts with [Pd(BINAP)], and [Pd(BINAP)] is generated by [Pd(BINAP)$_2$] lying off the cycle, is the major pathway. One could also consider that the difference between predicted and observed rates leaves open the potential that one or more additional minor pathways contribute to the total observed rate constant or that the rate constants measured in the medium of the oxidative addition process are slightly different from those for the same reactions in the medium of the catalytic system that contains base as well as alcohol and salt byproducts.

Summary

Studies of the identity of the palladium(0) species in the reactions of aryl halides with amines catalyzed by a complex generated in situ, and studies of the rates of reactions catalyzed by pure palladium components in this system, have shown that the palladium-catalyzed amination occurs by a mechanism in which the bromoarene undergoes oxidative addition prior to reaction with amine (Scheme 7), and not by a pathway in which amine coordinates to the palladium(0) prior to oxidative addition, as had been postulated in Scheme 2. At the same time, new data on the order of the reactions of [Pd(BINAP)$_2$] with added BINAP in the concentration of ArBr and BINAP show that [Pd(BINAP)$_2$] lies off the catalytic cycle, and not directly on the cycle, as had been postulated in Scheme 1.[3]

Most generally, these studies show the importance of combining rate data on a catalytic system with both spectroscopic measurements and kinetic data on stoichiometric reactions that provide information about the mechanism of the individual steps of the catalytic cycle. A comparison of the saturation in k_{obs} at high bromoarene concentration in the stoichiometric oxidative addition and the first-order dependence on bromoarene in the catalytic pathway demonstrates that the reaction orders of linear and cyclic reaction sequences can differ when they include a common reversible step that lies off the catalytic pathway. The deepest insight into the mechanism of a catalytic process is obtained by a series of techniques, including catalytic rate measurements, methods that identify the components present in the catalytic system, and quantitative and qualitative measurements of rates of stoichiometric reactions under wide ranges of concentrations.

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Note Added after ASAP Publication. After this paper was published ASAP on March 1, 2006, corrections were made to Scheme 7 and in the next-to-last sentence in the last paragraph of section 2 of the Results. The corrected version was published ASAP March 6, 2006.

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

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