Kinetics and Mechanism of the Formation of Palladium Bis(benzylamine) Complexes from Reaction of Benzylamine with Palladium Tri-*o*-tolylphosphine Mono(amine) Complexes

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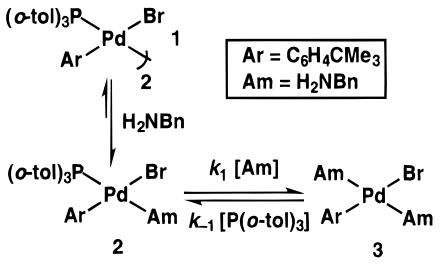
The kinetics of the conversion of the palladium mono(benzylamine) complex Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)[H_2-NBn]Br (**2**) to the bis(benzylamine) complex Pd(*p*-$C_6H_4CMe_3$)[H_2NBn]$_2$Br (**3**) established the second-order rate law: Rate $= k_1$[**2**][H_2NBn], where $\Delta H^{\ddagger} = 13.8 \pm 0.3$ kcal mol^{-1} and $\Delta S^{\ddagger} = -29.7 \pm 0.8$ eu. Kinetics were consistent with a mechanism initiated by direct attack of benzylamine on **2** via an associative or interchange mechanism. Benzylamine exchange with both **2** and **3** was $> 1.5 \times 10^3$ times faster than conversion of **2** to **3** under comparable conditions. Complex **2** underwent phosphine exchange in the presence of P(1-naphthyl)$_3$ to form Pd[P(1-naphthyl)$_3$](*p*-$C_6H_4CMe_3$)[H_2NBn]Br (**9**). Kinetics of the conversion of **9** to **2** were consistent with associative solvolysis of **9** to form Pd[P(1-naphthyl)$_3$](*p*-$C_6H_4CMe_3$)[solvent]Br (**V**) followed by attack of P(*o*-tolyl)$_3$ to form the mixed bis(phosphine) intermediate Pd[P(*o*-tol)$_3$][P(1-naphthyl)$_3$](*p*-$C_6H_4CMe_3$)Br (**VI**). Solvolytic displacement of P(*o*-tolyl)$_3$ from **VI** followed by reaction with amine would then form **2**.

Introduction

Palladium P(*o*-tol)$_3$ (*o*-tol = *o*-tolyl) complexes often exhibit reactivity which differs markedly from the corresponding PPh_3 complexes. For example, palladium P(*o*-tol)$_3$ complexes are effective catalysts for the cross-coupling of aryl bromides and aminostannanes[1−3] and for the cross-coupling of aryl halides and amines in the presence of sodium *tert*-butoxide.[4−7] In contrast, attempts to effect intermolecular C−N bond formation employing the corresponding palladium PPh_3 complexes led predominantly to reduction of the aryl halide. Palladium P(*o*-tol)$_3$ complexes have also been shown to produce higher reaction rates than palladium PPh_3 complexes in both the Heck arylation reaction[8] and Stille cross-coupling reaction.[9] The enhanced activity of palladium P(*o*-tol)$_3$ complexes relative to PPh_3 complexes has typically been attributed to the steric bulk of the P(*o*-tol)$_3$ ligand which promotes both phosphine lability and coordinative unsaturation of the metal.[9] In addition, P(*o*-tol)$_3$ is more resistant toward quaternization than PPh_3 which promotes catalyst stability.[10] Despite the high reactivity of palladium P(*o*-tol)$_3$ complexes and their relevance to synthetically significant C−C and C−N bond-forming protocols, ligand substitution of palladium P(*o*-tol)$_3$ and related complexes has been scarcely investigated.

We have previously investigated the reactions of palladium tri-*o*-tolylphosphine aryl halide dimers with amines in an effort to gain insight into the corresponding palladium-catalyzed amination of aryl halides.[11−13] For example, the palladium aryl bromide dimer {Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)(μ-Br)}$_2$ (**1**) reacted with 2 equiv of benzylamine (per dimer) to form the palladium mono(amine) complex Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)[H_2NBn]Br (**2**). Amine monomer **2** reacted with excess benzylamine in C_6D_6 at 25 °C to form a 1:1 mixture of free P(*o*-tol)$_3$ and the palladium bis(benzylamine) complex Pd(*p*-$C_6H_4CMe_3$)[H_2-NBn]$_2$Br (**3**) (Scheme 1).[13] Conversion of **2** to **3** was reversible; addition of P(*o*-tol)$_3$ to a solution of **3** regenerated **2** ($K_{eq} \approx 1$). While the high rate of bridge cleavage (**1** → **2**) precluded kinetic analysis, the conversion of **2** to **3** was conveniently monitored by NMR spectroscopy, facilitating kinetic analysis. Furthermore, the conversion of **2** to **3** is relevant as a potential turnover-limiting or chain-terminating step in the Pd−P(*o*-tol)$_3$-catalyzed arylation of primary amines.[4−7] As a result, we initiated a study of the kinetics and mechanism of the conversion of **2** to **3**.

Scheme 1



Results and Discussion

Kinetics of the Conversion of 2 to 3. In order to determine the dependence of the rate of conversion of **2** to **3** on benzylamine concentration, the pseudo-first-order rate constants were measured as a function of benzylamine concentration from 0.20 to 1.64 M in C_6D_6 at 55 ± 0.5 °C by ^{1}H NMR

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(1) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.
(2) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.
(3) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
(4) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348.
(5) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.
(6) Wolfe, J. N.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525.
(7) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
(8) (a) Mitsudo, T.; Fischetti, W.; Heck, R. F. *J. Org. Chem.* **1984**, *49*, 1640. (b) Fischetti, W.; Mak, K. T.; Stakem, F. G.; Kim, J. I.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.
(9) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(10) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.
(11) (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745. (b) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. Unpublished results.
(12) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.
(13) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics*, **1996**, *15*, 3534.

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Table 1. Temperature and Solvent Dependence of the Second-Order Rate Constants for the Conversion of **2** to **3** and **4** to **5**

reacn	solvent	temp, °C	$(10^4)k_1$, s^{-1} M^{-1}
2 → **3**	C_6D_6	25	1.42 ± 0.09
2 → **3**	C_6D_6	40	4.41 ± 0.24
2 → **3**	C_6D_6	55	12.5 ± 0.6
2 → **3**	C_6D_6	65	25.2 ± 1.3
2 → **3**	C_6D_6	77	56.0 ± 1.8
2 → **3**	toluene-d_8	25	1.46 ± 0.09
2 → **3**	THF-d_8	25	1.79 ± 0.10
2 → **3**	dioxane-d_8	25	0.71 ± 0.06
4 → **5**	C_6D_6	25	1.05 ± 0.24

spectroscopy.[14] Good pseudo-first-order plots for the disappearance of **2** were obtained by plotting ln $\{[\mathbf{2}]_t/[\mathbf{2}]_0\}$versus time (Figure S1, Table S1 (Supporting Information)), which established the first-order dependence of the rate on the concentration of **2**. A plot of the pseudo-first-order rate constants versus benzylamine concentration established the first-order dependence of the rate on benzylamine concentration (Figure S2).[15] Under these conditions, the reaction obeyed the second-order rate law shown in eq 1, where $k_1 = (1.25 \pm 0.06) \times 10^{-3}$ s^{-1} M^{-1} [$\Delta G^{\ddagger} = 22.7 \pm 0.2$ kcal mol^{-1}] (Table 1).

$$\text{rate} = -\frac{d[\mathbf{2}]}{dt} = k_1[\mathbf{2}][NH_2Bn] \qquad (1)$$

Pseudo-first-order rate constants for approach to equilibrium for the conversion of **2** to **3** were also measured as a function of P(*o*-tol)$_3$ concentration (0.048−0.21 M) in the presence of excess H_2NBn (∼0.33 M) in C_6D_6 at 55 °C.[16] Good pseudo-first-order plots for the approach to equilibrium were obtained by plotting ln$\{([\mathbf{2}]_t - [\mathbf{2}]_{eq})/([\mathbf{2}]_0 - [\mathbf{2}]_{eq})\}$ versus time (Figure S3, Table S1). A plot of $k_{obs}/[H_2NBn]$ versus [P(*o*-tol)$_3$]/[H_2NBn] was linear (Figure 1), in accord with the two-term rate law shown in eq 2, where $k_1 = (1.04 \pm 0.05) \times 10^{-3}$ s^{-1} M^{-1},

$$\frac{k_{obs}}{[NH_2Bn]} = k_1 + k_{-1}\frac{[P(o\text{-tol})_3]}{[NH_2Bn]} \qquad (2)$$

$k_{-1} = (2.7 \pm 0.1) \times 10^{-3}$ s^{-1} M^{-1}, and $K_{eq} = k_1/k_{-1} = 0.39 \pm 0.03$.[17] The value of k_1 was in good agreement with the value obtained under conditions of complete conversion, while the value of K_{eq} was in fair agreement with the value obtained independently (0.57),[13] considering the narrow P(*o*-tol)$_3$ concentration range employed in these kinetics.

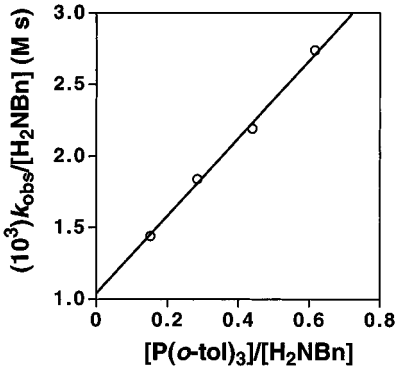
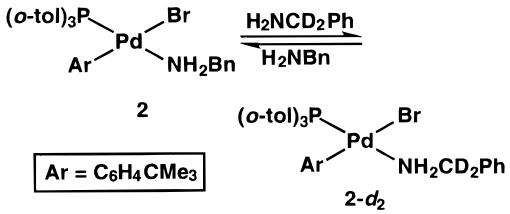


Figure 1. Plot of $k_{obs}/[H_2NBn]$ versus [P(*o*-tol)$_3$]/[H_2NBn] for the conversion of **2** to **3** in C_6D_6 at 55 °C.

Scheme 2



The second-order rate constant (k_1) for conversion of **2** to **3** was measured as a function of temperature from 25 to 77 °C (Table 1, Figure S2). An Eyring plot of the second-order rate constants provided the activation parameters: $\Delta H^{\ddagger} = 13.8 \pm 0.3$ kcal mol^{-1}, $\Delta S^{\ddagger} = -29.7 \pm 0.8$ eu (Figure S4). The second-order rate constant (k_1) for conversion of **2** to **3** was slightly solvent dependent and ranged from $(7.1 \pm 0.6) \times 10^{-5}$ s^{-1} M^{-1} in dioxane-d_8 to $(1.79 \pm 0.10) \times 10^{-4}$ s^{-1} M^{-1} in THF-d_8 at 25 °C (Table 1). The second-order rate constant for conversion of **2** to **3** at 25 °C was ∼25% greater than k_1 for conversion of the chloride mono(amine) complex Pd[P(*o*-tol)$_3$](*p*-C_6H_4-CMe_3)[H_2NBn]Cl (**4**) to Pd(*p*-$C_6H_4CMe_3$)[H_2NBn]$_2$Cl (**5**) (Table 1). In addition, although the second-order rate constant for the conversion of the iodide mono(amine) complex Pd[P(*o*-tol)$_3$]-(*p*-$C_6H_4CMe_3$)[H_2NBn]I (**6**) to Pd(*p*-$C_6H_4CMe_3$)[H_2NBn]$_2$I (**7**) was not determined, conversion of **6** to **7** at 25 °C in the presence of 0.87 M benzylamine was ∼10 times faster than conversion of **2** to **3** under comparable conditions ([H_2NBn] = 0.93 M).

Benzylamine Exchange with 2. Benzylamine exchange with mono(amine) complex **2** was considerably faster than conversion of **2** to **3**. For example, addition of α,α-benzylamine-d_2 (70 mM) to a solution of **2** (10 mM) in C_6D_6 at 25 °C led to complete amine exchange as evidenced by a 1:7 ratio of resonances corresponding to bound (δ 4.0, t, $J = 7.0$ Hz) and free benzylamine (δ 3.55, s) in the ^{1}H NMR spectrum (Scheme 2). Assuming that ≥15% unscrambled **2** would have been detected in this spectrum (δ 4.0:δ 3.55 ≥1:6), the observed 1:7 ratio of resonances indicates that amine exchange was ≥85% complete (∼3 half-lives) after 2 min. Therefore, a lower limit for the rate of amine exchange with **2** in the presence of 70 mM benzylamine of $\geq 1.7 \times 10^{-2}$ s^{-1} ($t_{1/2} \leq 40$ s) was estimated, which is $> 1.5 \times 10^3$ times faster than the conversion of **2** to **3** under similar conditions. Analogous results were

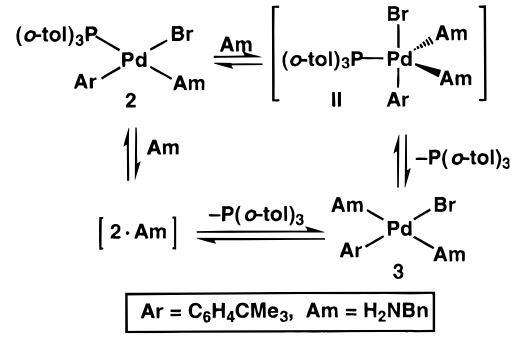
(14) Due to the slightly unfavorable equilibrium constant for the conversion of **2** to **3** ($K_{eq} = 0.57$ at 55 °C), a 35-fold excess of benzylamine relative to **2** was required to ensure ≥95% completion. As a result, the dependence of the rate on benzylamine concentration below <0.20 M could not determined under these conditions.

(15) Plots of the pseudo-first-order rate constants versus amine concentration also produced a small, positive intercept of the ordinate ($(7 \pm 6) \times 10^{-5}$ s^{-1} at 65 °C), approximately 5% of the magnitude of the second-order term. Although a nonzero intercept of the ordinate suggests the presence of a ligand-independent pathway, the large error associated with the intercept, particularly considering the lack of data at low amine concentrations, precludes this assignment. In addition, the temperature and solvent dependence of the intercept was inconsistent with the presence of an amine-independent pathway. Although an amine-independent pathway for conversion of **2** to **3** cannot be rigorously excluded, the mechanism of the conversion of **2** to **3** is clearly dominated by an associative pathway at all but very low benzylamine concentration.

(16) For related kinetics see: (a) Ohno, N.; Cusanovich, M. A. *Biophys. J.* **1981**, *36*, 589. (b) Pelizzetti, E.; Mentasti, E. *Inorg. Chem.* **1979**, *18*, 583. (c) Bosnich, B.; Dwyer, F. P.; Sargeson, A. M. *Aust. J. Chem.* **1966**, *19*, 2213. (d) Bosnich, B.; Dwyer, F. P. *Aust. J. Chem.* **1966**, *19*, 2051. (e) Butler, J.; Davies, D. M.; Sykes, A. G. *J. Inorg. Biochem.* **1981**, *15*, 41. (f) Below, J. F.; Connick, R. E.; Coppel, C. P. *J. Am. Chem. Soc.* **1958**, *80*, 2961.

(17) Howell, J. A. S.; Burkinshaw, P. M. *Chem. Rev.* **1983**, *83*, 557. (b) Darensbourg, D. J. *Adv. Organomet. Chem.* **1982**, *21*, 113. (c) Cross, R. J. *Chem. Soc. Rev.* **1985**, *14*, 197. (d) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 4.

Scheme 3



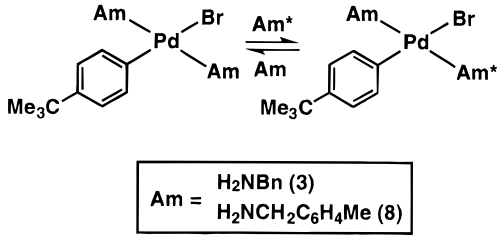
obtained from reaction of benzylamine (~70 mM) and Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)(H_2NCD_2Ph)Br (**2**-d_2) (~10 mM).

The mechanisms of ligand substitution at 16 electron square planar platinum(II) complexes have been extensively studied and are predominantly bimolecular in nature, initiated by attack of solvent or excess ligand at the metal center.[17−20] The first-order dependence of the rate of conversion of **2** to **3** on benzylamine concentration, the large negative entropy of activation, and the lack of P(*o*-tol)$_3$ rate inhibition were consistent with a mechanism initiated via direct attack of benzylamine on **2**. Furthermore, the absence of a significant intercept in the plot of pseudo-first-order rate constants versus benzylamine concentration (Figure S2) indicated that a solvolysis pathway via Pd(*p*-$C_6H_4CMe_3$)[H_2NBn](C_6D_6)Br (**I**) was not significant.[15] Similarly, because benzylamine exchange with **2** was much faster than solvolysis of **2** to form Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)(C_6D_6)Br (**III**) (see below), a bimolecular pathway for amine exchange was inferred.

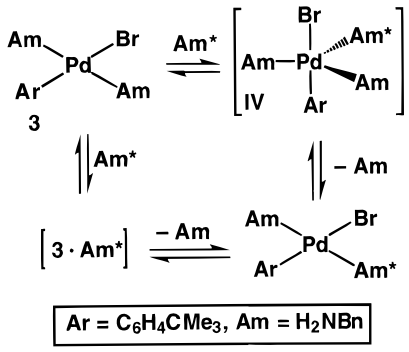
The bimolecular process which both exchanges benzylamine and converts **2** to **3** could occur by either an associative or interchange mechanism. In the associative mechanism, rapid and reversible attack of benzylamine on **2** would generate the trigonal bipyramidal five-coordinate bis(amine) mono(phosphine) intermediate Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)[H_2NBn]$_2$Br (**II**), which could undergo pseudorotation and loss of phosphine to form **3**. In the interchange mechanism, initial interaction of benzylamine with **2** could form the outer-sphere 1:1 amine adduct, **2**·H_2NBn. Concerted exchange of outer- and inner-sphere benzylamine ligands in **2**·H_2NBn would result in amine exchange while concerted exchange of the outer-sphere amine ligand with the phosphine ligand of **2**·H_2NBn would form **3** (Scheme 3).

Benzylamine Exchange with 3. The rate of benzylamine exchange with bis(amine) complex **3** was also considerably faster than the rate of conversion of **2** to **3**. For example, addition of α,α-benzylamine-d_2 (70 mM) to a solution of **3**·H_2-NBn (10 mM) in C_6D_6 at 25 °C led to complete exchange within 2 min as evidenced by the 1:2.3 ratio of peaks corresponding to bound (δ 3.8, br t, $J \approx 7$ Hz) and free (δ 3.55, s) benzylamine in the ^{1}H NMR spectrum (Scheme 4).[20] From this data, a lower limit for the rate of amine exchange with **3** in the presence of 70 mM benzylamine of $\geq 1.5 \times 10^{-3}$ s^{-1} ($t_{1/2} \leq 40$ s) was estimated. Analogous results were obtained from the reaction of benzylamine (~70 mM) with Pd(*p*-$C_6H_4CMe_3$)(H_2NCD_2-Ph)$_2$Br·H_2NCD_2Ph (**3**-d_4·H_2NCD_2Ph) (~10 mM).

Scheme 4



Scheme 5

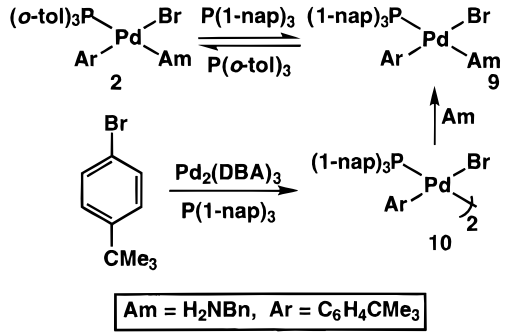


An upper limit for the rate of benzylamine exchange with **3** was estimated from the absence of detectable excess line broadening of the aryl methyl resonance of the closely related bis(amine) complex Pd(*p*-$C_6H_4CMe_3$)(H_2NCH_2-4-C_6H_4Me)$_2$Br (**8**) in the ^{1}H NMR spectrum in the presence of 0.40 M 4-methylbenzylamine at 25 °C.[20−23] Because the separation of the aryl methyl resonances for bound and free 4-methylbenzylamine ($\Delta\nu = 50$ Hz) was much larger than the excess broadening of the aryl methyl resonance of **8** ($\Delta\omega_{1/2} \leq 2$ Hz), the slow-exchange approximation ($\Delta\omega_{1/2} = k\pi^{-1}$)[24] was employed. Assuming that ≥2 Hz excess line broadening would have been detected, an upper limit for the rate of amine exchange with **8** in the presence of 0.40 M 4-methylbenzylamine of ≤6.2 s^{-1} was estimated.[25] Therefore, amine exchange with **3** or **8** was between 1.5×10^3 and 1×10^5 times faster than the conversion of **2** to **3** under comparable conditions.

A low-energy solvolysis pathway for amine exchange with **3** or **8** was confidently excluded as no low-energy pathway via **I** was detected in the conversion of **2** to **3**. Therefore, bimolecular amine exchange with **3** was inferred and could occur by either an associative mechanism via the five-coordinate tris(amine) intermediate Pd(*p*-$C_6H_4CMe_3$)[H_2NBn]$_3$Br (**IV**) or by an interchange mechanism via the 1:1 amine adduct Pd(*p*-C_6H_4-CMe_3)[H_2NBn]$_2$Br·H_2NBn (**3**·H_2NBn) (Scheme 5). The possibility of an interchange mechanism for amine exchange with **3** is suggested by the strong tendency of **3** and benzylamine to

(18) Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; Brooks/Cole: Monterey, CA, 1985; Chapter 4.
(19) Langford, C. H.; Gray, H. B. *Ligand Substitution Processes*; W. A. Benjamin: New York, 1965.
(20) Complexes **3**, **3**-d_4, and **8** were isolated as the corresponding hydrogen-bonded mono(amine)solvate complexes **3**·H_2NBn, **3**-d_4·H_2NCD_2Ph, and **8**·$H_2NCH_2C_6H_4Me$, respectively. As a result, solutions of these complexes contatined 1 equiv of free amine.
(21) Wilkins, R. G. *The Study of Kinetics and Mechanism of Reactions of Transition Metal Complexes*; Allyn and Bacon: Boston, MA, 1974.
(22) (a) Rabenstein, D. L.; Kula, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 2492. (b) Glass, G. E.; Schwabacher, W. B.; Tobias, R. S. *Inorg. Chem.* **1968**, *7*, 2471. (c) Taylor, P. W.; Feeney, J.; Burgen, A. S. V. *Biochemistry* **1971**, *10*, 3866. (d) Pignolet, L. H.; Horrocks, W. D. *J. Am. Chem. Soc.* **1968**, *90*, 922. (e) La Mar, G. N. *J. Am. Chem. Soc.* **1970**, *92*, 1806. (f) Rubini, P. R.; Poaty, Z.; Boubel, J. C.; Rodenhüser, L.; Delpuech, J. J. *Inorg. Chem.* **1983**, *22*, 1295.
(23) Merbach, A. E.; Moore, P.; Howarth, O. W.; McAteer, C. H. *Inorg. Chim. Acta* **1980**, *39*, 129.
(24) Bovey, F. A. *Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Academic Press: San Diego, CA, 1988.
(25) The rate of exchange of a single amine ligand is equivalent to the rate of complete exchange. (a) Mønsted. L.; Mønsted, O. *Acta Chem. Scand.* **1980**, *A34*, 259. (b) Helm, L.; Elding, L. I.; Merbach, A. E. *Inorg. Chem.* **1985**, *24*, 1719. (c) Swaddle, T. *Adv. Inorg. Biochem. Mech.* **1983**, 2, 95.

Scheme 6



form the 1:1 hydrogen-bonded adduct **3**·H_2NBn in both solution and in the solid state.[13]

Phosphine Exchange with 2. When a C_6D_6 solution of **2** (4 mM) was treated with excess P(1-nap)$_3$ (1-nap = 1-naphthyl) at 25 °C, the P(*o*-tol)$_3$ ligand was displaced with formation of the corresponding P(1-nap)$_3$ complex Pd[P(1-nap)$_3$](*p*-C_6H_4-CMe_3)(H_2NBn)Br (**9**) (Scheme 6). Phosphine exchange was reversible and addition of P(*o*-tol)$_3$ to a solution of **9** regenerated **2** {K_{eq} = [**9**][P(*o*-tol)$_3$]/[**2**][P(1-nap)$_3$] = 0.52 ± 0.03 at 25 °C}. In the presence of a ~7 fold excess of P(1-nap)$_3$ (55 mM), the disappearance of **2** {[**2**]$_0$ = 8 mM} obeyed first-order kinetics for approach to equilibrium over >3 half-lives with an observed rate constant of k_{obs} = (4.7 ± 0.3) × 10^{-4} s^{-1} at 25 °C, which corresponds to a half-life of ~25 min (Figure S5). Under these conditions, conversion of **2** to an 80:20 mixture of **9**/**2** was ~3 times faster than the complete conversion of **2** to **3** in the presence of ~1 M benzylamine (k_1 = (1.42 ± 0.09) × 10^{-4} s^{-1} M^{-1} at 25 °C).

In a preparative-scale reaction, treatment of {Pd[P(1-nap)$_3$]-(*p*-$C_6H_4CMe_3$)(*μ*-Br)}$_2$ (**10**) with 2 equiv of benzylamine (per dimer) led to the isolation of mono(amine) complex **9** in 83% yield as a cream-colored solid (Scheme 6). The requisite palladium aryl halide dimer **10** was isolated in 76% yield from reaction of a 1:4:10 molar mixture of $Pd_2(DBA)_3$, P(1-nap)$_3$, and 4-*tert*-butylbromobenzene in benzene at 40 °C for 1 h.

We initially considered two plausible mechanisms for the conversion of the P(*o*-tol)$_3$ complex **2** to the P(1-nap)$_3$ derivative **9**. In the first mechanism, solvolysis of **2** would form the mono-(amine) intermediate **I**, which could react with P(1-nap)$_3$ to generate **9**. In the second mechanism, direct attack of P(1-nap) on **2** via an associative or interchange mechanism could also form **9**. However, the rapid rate of conversion of **2** to **9** relative to conversion of **2** to **3** clearly precluded exchange via phosphine solvolysis, as no facile pathway via **I** was detected in the conversion of **2** to **3**. Likewise, it appeared unlikely that a bimolecular reaction involving **2** and sterically bulky P(1-nap)$_3$ would be faster than the bimolecular reaction involving **2** and benzylamine. We therefore considered a more complex mechanism for the conversion of **2** to **9** initiated by solvolytic displacement of the benzylamine ligand as outlined in Scheme 7.

The limited solubility of P(1-nap)$_3$ in C_6D_6 precluded direct kinetic analysis of the conversion of **2** to **9**. As a result, the kinetics of the conversion of **9** to **2** were investigated in an effort to probe the mechanism of phosphine exchange. In order to determine the rate dependence on P(*o*-tol)$_3$ concentration, the pseudo-first-order rate constants for the conversion of **9** to **2** were measured as a function of P(*o*-tol)$_3$ concentration from 0.064 to 0.29 M in C_6D_6 at 25 °C. Each reaction proceeded to ≥95% conversion and good pseudo-first-order plots for the disappearance of **9** were obtained (Table S2, Figure S6). In the absence of benzylamine, the rate was independent of P(*o*-tol)$_3$ concentration and the reaction obeyed the first-order rate law shown in eq 3, where k_{obs} = (3.3 ± 0.2) × 10^{-3} s^{-1} ($\Delta G^{\ddagger}$ = 20.8 kcal mol^{-1}). However, the rate was strongly inhibited by excess benzylamine. In order to probe the benzylamine concentration dependence of the rate of conversion of **9** to **2**, pseudo-first-order rate constants were measured as a function of benzylamine concentration from 0.88 to 5.3 mM[26] in the presence of ~55 mM P(*o*-tol)$_3$ at 45 °C in C_6D_6 (Table S2, Figure S7). A plot of the reciprocal of the observed rate constants versus the [H_2NBn]/[P(*o*-tol)$_3$] ratio established the inverse first-order dependence of the rate on the ratio of [benzylamine]/[P(*o*-tol)$_3$] for the conversion of **9** to **2** in the presence of benzylamine (Figure 2).

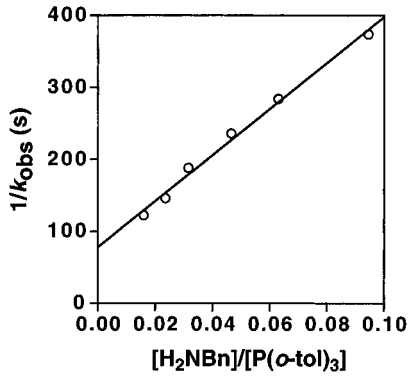
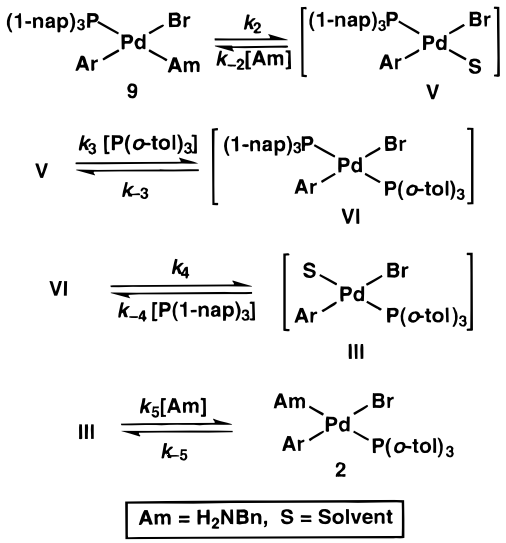


Figure 2. Benzylamine concentration dependence of the conversion of **9** to **2** in the presence of ~55 mM P(*o*-tol)$_3$ at 45 °C in C_6D_6.

Scheme 7



$$\text{rate} = -\frac{d[\mathbf{9}]}{dt} = k_{obs}[\mathbf{9}] \qquad (3)$$

Our kinetics for the conversion of **9** to **2** are consistent with the mechanism shown in Scheme 7. In this mechanism, solvolysis of **9** would form the mono(phosphine) intermediate Pd[P(1-nap)$_3$](*p*-$C_6H_4CMe_3$)Br(solvent) (**V**), which could react with P(*o*-tol)$_3$ to form the four-coordinate mixed bis(phosphine) intermediate Pd[P(1-nap)$_3$][P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)Br (**VI**). Solvolysis of **VI** would generate a second mono(phosphine) intermediate Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)Br(solvent) (**III**) which could react with benzylamine to form **2**. Because complete

(26) Kinetic analysis of the reaction at higher benzylamine concentration was precluded by the competitive formation of palladium bis(amine) complexes.

(>95%) conversion of **9** to **2** was achieved under experimental conditions, the reverse reaction (k_{-4}) was ignored in the kinetic analysis. Employing this assumption and assuming a steady-state concentration of intermediates **III**, **V**, and **VI** generates the rate law shown in eq 4a,b. This rate law is in accord with

$$\text{rate} = -\frac{d[\mathbf{9}]}{dt} = \frac{k_2k_3[P(o\text{-tol})_3][\mathbf{9}]}{k_3[P(o\text{-tol})_3] + \left(\frac{k_{-3}}{k_4} + 1\right)k_{-2}[NH_2Bn]} = k_{obs}[\mathbf{9}] \quad (4a)$$

$$\frac{1}{k_{obs}} = \frac{\left(\frac{k_{-3}}{k_4} + 1\right)k_{-2}}{k_2k_3}\frac{[NH_2Bn]}{[P(o\text{-tol})_3]} + \frac{1}{k_2} \quad (4b)$$

$$k_3[P(o\text{-tol})_3] \gg \left(\frac{k_{-3}}{k_4} + 1\right)k_{-2}[NH_2Bn] \qquad \text{rate} = k_2[\mathbf{9}] \quad (4c)$$

our experimental rate data obtained in the presence of H_2NBn, where $k_2 = (1.3 \pm 0.1) \times 10^{-2}$ s^{-1} and $(k_{-2}/k_3)(k_{-3}/k_4 + 1) = 41 \pm 5$ at 45 °C. In the absence of benzylamine, the second term of eq 4a approaches zero and eq 4a simplifies to eq 4c. This rate law is the same form as the experimental rate law obtained in the absence of benzylamine (eq 3), where $k_{obs} = k_2$.

Although dissociative ligand substitution at 16 electron square planar platinum complexes is rare,[27−30] solvated intermediates **V** and **III** could potentially be formed by an associative or dissociative mechanism (Scheme 7). In order to distinguish between these two possible pathways, the temperature and solvent dependence of the first-order rate constant k_2 for the conversion of **9** to **2** was determined.[31] An Eyring plot of k_2 obtained at 10, 25, and 45 °C provided the activation parameters: $\Delta H^{\ddagger} = 12.5 \pm 0.8$ kcal mol^{-1}, $\Delta S^{\ddagger} = -28 \pm 3$ eu (Figure S8); the sign and magnitude of the entropy of activation are clearly in accord with an associative pathway.

The first-order rate constant k_2 was solvent dependent and increased by a factor of ~5 in the order toluene-d_8 ($k_2 = 2.75 \times 10^{-3}$ s^{-1}) < C_6D_6 < THF-d_8 < DMF-d_7 ($k_2 = 12.7 \times 10^{-2}$ s^{-1}) at 25 °C. Although the rate of conversion of **9** to **2** in $CD_3OD/CDCl_3$ (5:1) at 25 °C was too fast to determine by NMR, a lower limit for k_2 of $\geq 4.6 \times 10^{-2}$ s^{-1} was estimated under these conditions.[32] The dependence on k_2 on solvent donicity is also in accord with an associative pathway, although the extent of rate acceleration is small considering the wide range of solvent donicity.[33] Although it is impossible to quantify the effect of solvent donicity on the rate due to the drastic changes in solvent polarity, the low sensitivity of the rate to solvent donicity could suggest the presence of a late, productlike transition state.[34]

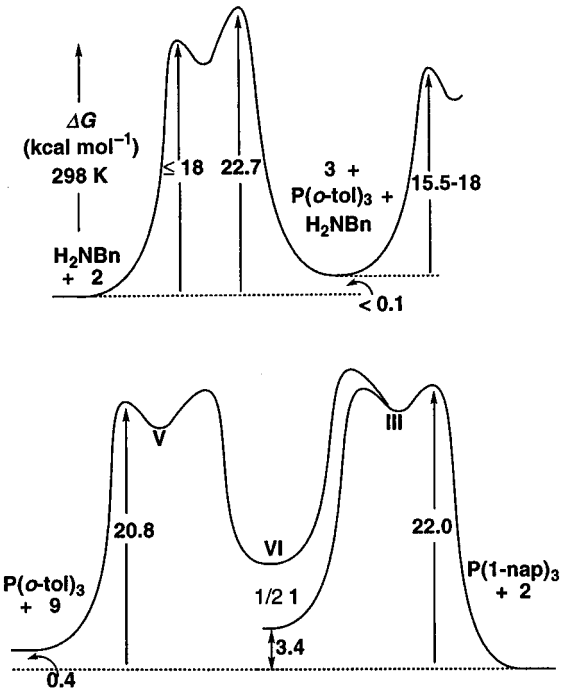


Figure 3. Free energy−reaction coordinate diagram for the conversion of **2** to **3** and for the conversion of **2** to **9**. The free energy of mono(amine) complex **2** is arbitrarily set equal to zero.

As noted above, saturation kinetics were observed for conversion of **9** to **2** in the absence of benzylamine at P(*o*-tol)$_3$ concentrations as low as 64 mM. It therefore appears likely that saturation kinetics were also achieved for the conversion of **2** to **9** in the presence of 55 mM P(1-nap)$_3$ at 25 °C. Therefore, from the observed rate constant for approach to equilibrium ($k_{obs\ 2\rightarrow 9} = (4.7 \pm 0.3) \times 10^{-4}$ s^{-1}), the first-order rate constant for solvolysis of **2** in C_6D_6 at 25 °C to form **III** was calculated to be $k_{-5} = (3.1 \pm 0.2) \times 10^{-4}$ s^{-1} ($\Delta G^{\ddagger} = 22.0 \pm 0.1$ kcal mol^{-1}).

From our kinetic and related thermodynamic studies,[12,13] a free energy diagram was constructed for the ligand exchange reactions involving **2**, **3**, and **9** (Figure 3). The overall conversion of **2** to **3** and the conversion of **2** to **9** is nearly ergoneutral ($\Delta G° < 0.5$ kcal mol^{-1}).[15] Benzylamine exchange with **2** is facile ($\Delta G^{\ddagger} \leq 18$ kcal mol^{-1}) with a barrier ~5 kcal mol^{-1} lower in energy than the barrier for conversion of **2** to **3** ($\Delta G^{\ddagger} = 22.7 \pm 0.1$ kcal mol^{-1}). Bimolecular benzylamine exchange with bis(amine) derivative **3** is also facile (15.5 kcal mol^{-1} < $\Delta G^{\ddagger}$ < 18 kcal mol^{-1}) and possesses a barrier ~5−7 kcal mol^{-1} lower in energy than the barrier for conversion of **2** to **3**. The barrier for solvolysis of **2** to form mono(phosphine) intermediate **III** was slightly lower than the barrier for conversion of **2** to **3** ($\Delta\Delta G^{\ddagger} \approx 0.7$ kcal mol^{-1}) and was ~1.2 kcal mol^{-1} higher in energy than the barrier for solvolysis of **9** to form **V**. Conversion of **2** to the palladium aryl halide dimer **1** via loss of benzylamine is facile but endoergic ($\Delta G° = $ ~3.4 kcal mol^{-1} Pd^{-1}).[12]

(27) Romeo, R.; Minniti, D.; Lanza, S. *Inorg. Chem.* **1979**, *18*, 2362.
(28) Lanza, S.; Minniti, D.; Romeo, R.; Moore, P.; Sachinidis, J.; Tobe, M. L. *J. Chem. Soc., Chem. Commun.* **1984**, 542.
(29) Romeo, R.; Arena, G.; Scolaro, L. M.; Plutino, M. R.; Bruno, G.; Nicolo, F. *Inorg. Chem.* **1994**, *33*, 4029.
(30) Romeo, R.; Grassi, A.; Scolaro, L. M. *Inorg. Chem.* **1992**, *31*, 4383. (e) Frey, U.; Helm, L.; Merbach, A. E.; Romeo, R. *J. Am. Chem. Soc.* **1989**, *111*, 8161.
(31) We thank several reviewers for suggesting these experiments.
(32) Conversion of **9** to **2** in $CD_3OD/CDCl_3$ (5:1) at 25 °C was complete within 1 min by ^{1}H NMR spectroscopy. Assuming ≥6% of **9** could have been detected in the initial ^{1}H NMR spectrum (~4 half-lives), a lower limit for the value of k_2 for the conversion of **9** to **2** $CD_3OD/CDCl_3$ (5:1) of $\geq 4.6 \times 10^{-2}$ s^{-1} was estimated.
(33) Cattalini, L. *Inorganic Reaction Mechanisms*; Edwards, J. O., Ed.; Wiley-Interscience: New York, 1970.
(34) (a) Belluco, A.; Oio, A.; Martelli, M. *Inorg. Chem.* **1966**, *5*, 1370. (b) Belluco, U.; Graziani, M.; Nicolini, M.; Rigo, P. *Inorg. Chem.* **1967**, *6*, 721. (c) Belluco, U. Martelli, Orio, A. *Inorg. Chem.* **1966**, *5*, 582. (d) Pearson, R. G.; Gray, H. B.; Basolo, F. *J. Am. Chem. Soc.* **1960**, *82*, 787.

Conclusions

Kinetics of the conversion of the mono(phosphine) mono(amine) complex **2** to the corresponding bis(amine) complex **3** were consistent with an associative or interchange mechanism. Benzylamine exchange with both **2** and **3** was considerably more facile than conversion of **2** to **3**. Kinetics of the conversion of the **2** to the tri(1-naphthylphosphine) derivative **9** were in accord with a mechanism initiated by associative solvolysis of the benzylamine ligand followed by reaction with P(1-nap)$_3$ to generate the mixed bis(phosphine) intermediate Pd[P(1-nap)$_3$][P(*o*-tol)$_3$](*p*-C$_6$H$_4$CMe$_3$)Br (**VI**). Presumably, the small steric size (cone angle = 106°)[35] and high nucleophilicity of benzylamine promotes direct attack of the amine at palladium. In contrast, the large steric bulk of P(1-nap)$_3$ and P(*o*-tol)$_3$ (cone angle = 195°)[36] precludes direct interaction of the phosphine and the palladium complex, leading to phosphine exchange via initial solvolysis of the benzylamine ligand of **2**.

Experimental Section

General Methods. Reactions were performed under an inert atmosphere of nitrogen or argon in a glovebox or by standard Schlenk techniques. Preparative-scale reactions were performed in flame- or oven-dried Schlenk tubes equipped with a stir bar, side arm joint, and a septum. ^{1}H and ^{31}P NMR spectra were obtained on a Varian XL-300 spectrometer. Elemental analyses were performed by E+R Microanalytical Laboratories (Corona, NY). Diethyl ether, hexane, pentane, benzene, C$_6$D$_6$, toluene-d_8, THF-d_8, and dioxane-d_8 were distilled from sodium/benzophenone ketyl under argon or nitrogen. Methylene chloride, methylene chloride-d_2, and DMF-d_7 were distilled from CaH$_2$; CDCl$_3$ was distilled from P$_2$O$_5$. Benzylamine (Aldrich, anhydrous) and CD$_3$OD (Cambridge Isotopes Laboratories) were used as received. Benzylamine-α,α-d_2[37] was synthesized from the LiAlD$_4$/AlCl$_3$ reduction of benzonitrile;[38] ^{1}H NMR and GCMS analysis indicated >95% chemical purity and ≥98% isotopic purity. Palladium aryl halide dimers **1**, **4**, and **6** and palladium−amine complexes **2**, **3**, and **8** were prepared by published procedures.[11a,13]

Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$CMe$_3$)[H$_2$NCD$_2$Ph]Br (2-d_2). Benzylamine-α,α-d_2 (1.2 μL, 1.1 × 10^{-2} mmol) was added via syringe to an NMR tube which contained a solution of {Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$CMe$_3$)(μ-Br)}$_2$ (**1**) (~7 mg, 5.5 × 10^{-3} mmol) in C$_6$D$_6$ (0.7 mL) to generate **2**-d_2 which was > 95% pure by ^{1}H NMR spectroscopy and was characterized by ^{1}H NMR spectroscopy without isolation. ^{1}H NMR (CDCl$_3$, 50 °C): δ 7.80 (br, 3 H), 7.22 (m, *J* = 6.4 Hz, 3 H), 7.07 (m, 4 H), 6.69 (s, 4 H), 3.01 (s, 2 H, *H*$_2$NCH$_2$Ph), 2.15 [br s, 9 H, P(*o*-tol)$_3$], 1.17 (s, 3 H, C$_6$H$_4$C*Me*$_3$).

Pd(*p*-C$_6$H$_4$CMe$_3$)[H$_2$NCD$_2$Ph]$_2$Br·H$_2$NCD$_2$Ph (3-d_4·H$_2$NCD$_2$Ph). A solution of **1** (50 mg, 0.08 mmol) and benzylamine-α,α-d_2 (150 μL, 147 mg, 1.3 mmol) in THF (2 mL) was stirred overnight at room temperature to give a colorless solution. Solvent was evaporated under vacuum, and the residue was dissolved in THF (5 mL) and diluted with pentane (5 mL). Cooling the resulting solution to −30 °C overnight produced a precipitate which was filtered out, washed with pentane, and dried under vacuum to give **3**·H$_2$NBn-d_6 (97 mg, 91%) as a white fibrous solid. ^{1}H NMR analysis indicated that **3**·H$_2$NBn-d_6 was >95% pure and was >98% deuterated at the benzylic positions. ^{1}H NMR (C$_6$D$_6$, 25 °C): in addition to resonances corresponding to free benzylamine-α,α-d_2 (δ 7.15 and 0.70), resonances were observed at δ 7.13−6.85 (m, 10 H), 2.43 (s, 4 H, *H*$_2$NCD$_2$Ph), and 1.27 (s, 9 H, C$_6$H$_4$C*Me*$_3$).

{Pd[P(1-naphthyl)$_3$](*p*-C$_6$H$_4$CMe$_3$)(μ-Br)}$_2$ (10). A purple solution of Pd$_2$(DBA)$_3$ (500 mg, 0.55 mmol), P(1-naphthyl)$_3$ (900 mg, 2.2 mmol) and *p*-*tert*-butylbromobenzene (780 mg, 3.7 mmol) in 30 mL of benzene was stirred at 40 °C for 1 h. The resulting brown solution was filtered through Celite, and benzene was evaporated under vacuum. The resulting oily residue was dissolved in Et$_2$O (50 mL) and allowed to stand at room temperature. The precipitate which formed over 3 h was filtered out, washed with Et$_2$O, and dried under vacuum to give **10** (599 mg, 76%) as a tan powder. ^{1}H NMR (CDCl$_3$, 55 °C): δ 8.30 (br), 7.79 (d, *J* = 7.0 Hz), 7.68 (d, *J* = 6.9 Hz), 7.10, 6.40, (br s, 2 H), 6.10 (d, *J* = 7.6 Hz), 0.86 (s, C$_6$H$_4$C*Me*$_3$). ^{31}P {^{1}H} NMR (CDCl$_3$, 25 °C): δ 28.8 (br). Anal. Calcd (found) for C$_{80}$H$_{62}$Br$_2$P$_2$Pd$_2$: C, 65.91 (65.67); H, 4.29 (4.38).

Pd[P(1-naphthyl)$_3$](*p*-C$_6$H$_4$CMe$_3$)[H$_2$NBn]Br (9). Benzylamine (20 mg, 0.19 mmol) was added to a brown solution of **10** (200 mg, 0.19 mmol) in CH$_2$Cl$_2$ (5 mL) and stirred at room temperature for 5 min. The resulting solution was concentrated to 2 mL under vacuum and diluted with 25 mL of hexane. Cooling the solution via concentration to 10 mL under vacuum formed a precipitate which was filtered out, washed with pentane, and dried under vacuum to give **9** (195 mg, 83%) as a cream-colored solid. ^{1}H NMR (300 MHz, CDCl$_3$, 55 °C): δ 7.85, 7.68, 7.30, 6.97, 6.34, 3.72 (br, 2 H, H$_2$NC*H*$_2$Ph), 2.88 (br, 2 H, *H*$_2$NCH$_2$Ph), 0.94 (s, C$_6$H$_4$C*Me*$_3$). ^{31}P {^{1}H} NMR (CDCl$_3$, 25 °C): δ 29.7. Anal. Calcd (found) for C$_{47}$H$_{40}$BrNPPd: C, 67.52 (67.27); H, 4.82 (5.10).

Kinetic Measurements. Samples for kinetic analysis were prepared from stock solutions of the appropriate palladium aryl halide dimer and/or benzylamine and were performed in oven-dried 5 mm thin-walled NMR tubes capped with rubber septa. Solvent volume in the NMR tubes was calculated from the solvent height measured at 25 °C according to the relationship *V* (mL) = *H* (mm) × 0.01384−0.006754 and from temperature dependence of the density of benzene.[39] Kinetic data was obtained by ^{1}H NMR spectroscopy in the heated probe of a Varian XL-300 spectrometer. Probe temperatures were measured with either an ethylene glycol or methanol thermometer and were maintained at ±0.5 °C throughout data acquisition. Syringes employed in measuring liquids for kinetic measurements were calibrated by mercury displacement and were accurate to >95%. Error limits for rate constants refer to the standard deviation of the slope and/or intercept of the corresponding least-squares-fit line.

Benzylamine Dependence of the Rate of Conversion of 2 to 3. Benzylamine (16 μL, 15.7 mg, 0.46 mmol, 0.20 M) was added via syringe to an NMR tube containing a solution of **1** (2.0 mg, 1.6 × 10^{-3} mmol, 2.2 mM) in C$_6$D$_6$ (total volume of 0.75 mL). Formation of the mono(amine) complex **2** from **1** and benzylamine is both rapid ($t_{1/2}$ ≤ 15 s at 25 °C) and exoergic (K_{eq} ≈ 1 × 10^5).[8] The tube was shaken and placed in the probe of an NMR spectrometer preheated to 55 °C. The concentrations of **2** and **3** were determined by integrating the *tert*-butyl resonances for **2** (δ 1.17) and **3** (δ 1.27) in the ^{1}H NMR spectrum and from the mass balance.[40] The concentration of free benzylamine was determined from the mass balance. The pseudo-first-order rate constant for the conversion of **2** to **3** was determined from a plot of ln([**2**]$_t$/[**2**]$_0$) versus time (Figure S1, Table S1). Pseudo-first-order rate constants were also obtained at benzylamine concentrations of 0.47, 1.06, and 1.64 M (Figure S1, Table S1). The second-order rate constant for the conversion of **2** to **3** was obtained from a plot of observed rate constants versus benzylamine concentration (Table 1, Figure S2).

The pseudo-first-order rate constants for the conversion of **2** to **3** in C$_6$D$_6$ at 25, 40, 65, and 77 °C (Figures S9−S12, Table S3), for the conversion of **2** to **3** in toluene-d_8, THF-d_8, and dioxane-d_8 at 25 °C

(35) Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc*. **1991**, *113*, 2520.
(36) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
(37) (a) Mukumoto, M.; Tsuzuki, H.; Tsukinoki, T.; Mataka, S.; Tashiro, M.; Nagano, Y. *J. Deuterium Sci.* **1995**, *4*, 85. (b) Mure, M.; Klinman, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 8707. (c) Tsukinoki, T.; Ishimoto, K.; Nakayama, K.; Kakinami, T.; Mataka, S.; Tashiro, M. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 839. (d) Kagabu, S.; Ando, C.; Ando, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 739. (e) Benincori, T.; Brenna, E.; Sannicolo, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 675. (f) Itoh, S.; Mure, M.; Ogino, M.; Ohshiro, Y. *J. Org. Chem.* **1991**, *56*, 6857. (g) Kim, J. M.; Cho, I. S.; Mariano, P. S. *J. Org. Chem.* **1991**, *56*, 4943. (h) Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Cuong, N. K.; Maumy, M. *Tetrahedron Lett.* **1990**, *31*, 3305.
(38) (a) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544. (b) Frejd, T.; Klingstedt, T. *Synthesis* **1987**, 40.
(39) *International Critical Tables of Numerical Data, Physics, Chemistry, and Technology*; Washburn, E. W., Ed.; McGraw-Hill: London, 1928; Vol. III, pp 29, 39, 221.
(40) The conversion of **2** to **3**, **4** to **5**, and **6** to **7** was quantitative in all cases.

(Figures S13−S15, Table S4), and for the conversion of **4** to **5** in C_6D_6 at 25 °C (Figure S16, Table S5) were determined by procedures analogous to that employed to determine k_{obs} for the conversion of **2** to **3** at 55 °C. Second-order rate constants (k_1) were determined from plots of k_{obs} versus [H_2NBn] (Table 1, Figures S2, S17).

P(*o*-tol)$_3$/H_2NBn Dependence of the Rate of Conversion of 2 to 3. Benzylamine (25 μL, 24.5 mg, 0.23 mmol, 0.34 M) was added via syringe to an NMR tube containing a solution of **1** (2.0 mg, 1.6×10^{-3} mmol, 2.4 mM) and P(*o*-tol)$_3$ (41.0 mg, 0.14 mmol, 0.21 M) in C_6D_6 (total volume of 0.65 mL). The tube was shaken and placed in the probe of an NMR spectrometer preheated at 55 °C. The concentrations of **2** and **3** and free benzylamine were determined as described above. The pseudo-first-order rate constant for approach to equilibrium was determined from a plot of $\ln\{([\mathbf{2}]_t - [\mathbf{2}]_{eq})/([\mathbf{2}]_0 - [\mathbf{2}]_{eq})\}$ versus time (Figure S3, Table S1). Pseudo-first-order rate constants for the approach to equilibrium were also obtained at P(*o*-tol)$_3$ concentrations of 0.048, 0.091, and 0.14 M in the presence of ∼0.32 M benzylamine (Figure S3, Table S1). The second-order rate constant k_1 for the conversion of **2** to **3** was obtained from the intercept of a plot of k_{obs}/[H_2NBn] versus [P(*o*-tol)$_3$]/[H_2NBn] (Figure 1); k_{-1} was obtained from the slope of this plot.

P(*o*-tol)$_3$ and Benzylamine Concentration Dependence of the Rate of Conversion of 9 to 2. A solution of **9** (2.3 mg, 2.7×10^{-3} mmol, 4.1 mM) and benzylamine (0.06 mg, 5.7×10^{-4} mmol, 0.88 mM) in C_6D_6 (0.65 mL) was added via syringe to an NMR tube containing P(*o*-tol)$_3$ (11.8 mg, 3.9×10^{-2} mmol, 0.055 M). The tube was shaken and placed in the probe of an NMR spectrometer preheated to 45 °C. The concentrations of **2** and **9** were determined by integrating the *tert*-butyl resonances for **2** (δ 1.17) and **9** (δ 1.03) in the ^{1}H NMR spectrum and from the mass balance. The pseudo-first-order rate constant for the conversion of **9** to **2** was determined from a plot of ln([**9**]) versus time (Figure S7, Table S2). Pseudo-first-order rate constants were also obtained at benzylamine concentrations of 1.3, 1.8, 2.6, 3.5, and 5.3 mM in the presence of ∼55 mM P(*o*-tol)$_3$ (Figure S7, Table S2). The first-order rate constant k_2 was obtained as the inverse of the intercept of a plot of the observed rate constants versus [H_2NBn]/[P(*o*-tol)$_3$] (Figure 2).

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Supporting Information Available: Tables and plots of kinetic data (12 pages). Ordering information is given on any current masthead page.

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