Halide and Amine Influence in the Equilibrium Formation of Palladium Tris(*o*-tolyl)phosphine Mono(amine) Complexes from Palladium Aryl Halide Dimers

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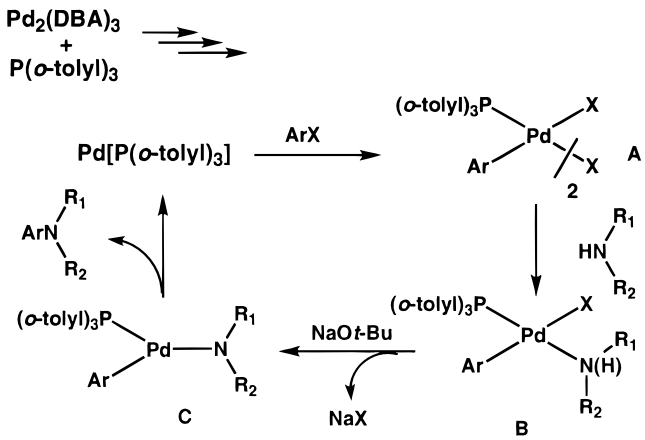
The relative binding constants (K_b) for the coordination of amines to the palladium fragment Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$Me)Cl were determined by ^{1}H NMR spectroscopy and decrease in the order hexylamine > benzylamine ≈ cyclohexylamine ≈ piperidine > dibutylamine ≈ diethylamine ≈ *N*-benzylmethylamine > morpholine > diisobutylamine > dibenzylamine ≈ *tert*-octylamine >> diisopropylamine > *N*-methylaniline. The palladium halide dimers {Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$Me)(*μ*-X)}$_2$ (X = Cl (**1**), Br (**2**), I (**3**)) react reversibly with dibenzylamine to generate the corresponding 1:1 palladium amine adducts Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$Me)(HNBn$_2$)X (X = Cl (**12**), $K = 6 \pm 1 \times 10^3$ M^{-1}; X = Br (**18**), $K = 3.5 \pm 0.5 \times 10^3$ M^{-1}; X = I (**22**), $K = 90 \pm 20$ M^{-1}), respectively. The related reaction of dibenzylamine with the iodide dimer {Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$OMe)(*μ*-I)}$_2$ (**21**) to form Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$OMe)(HNBn$_2$)I (**24**) provided the thermodynamic parameters $\Delta G_{298\ K} = -3.1 \pm 0.1$ kcal mol^{-1}, $\Delta H_{298\ K} = -11.9 \pm 0.1$ kcal mol^{-1}, and $\Delta S_{298\ K} = -30 \pm 4$ eu. Dimers **1**−**3** also react reversibly with diisopropylamine at 25 °C to form the amine adducts Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$Me)[HN(*i*-Pr$_2$)]X (X = Cl (**17**), $K = 14 \pm 3$ M^{-1}; X = Br (**19**), $K = 2.8 \pm 0.5$ M^{-1}; X = I (**26**), $K = 6 \pm 2 \times 10^{-3}$ M^{-1}), respectively.

Introduction

Palladium tris(*o*-tolyl)phosphine complexes catalyze the cross-coupling of aryl bromides with aminostannanes[1] and also catalyze the conversion of aryl bromides to anilines via reaction with free amine and sodium *tert*-butoxide.[2] The corresponding reaction of aryl iodides and amines required higher temperatures and produced somewhat lower yields of cross-coupled product than did aryl bromides.[3] Likewise, unbranched secondary amines such as *N*-benzylmethylamine were considerably more efficient as coupling partners than were either primary amines or bulky secondary amines. The tin-free reaction is believed to occur via initial oxidative addition of the aryl halide to a palladium mono(phosphine) species to form the palladium halide dimer **A**,[1c,4] which reacts with amine to form the corresponding palladium amine monomer **B** (Scheme 1).[5] Deprotonation of **B** and reductive elimination from the three-coordinate palladium amido complex **C**[1c] forms the corresponding aniline derivative and regenerates the catalytically active mono(phosphine) species Pd[P(*o*-tol)$_3$] (Scheme 1).[4]

We have been investigating the coordination chemistry of the 1:1 palladium amine adducts **B** in an effort to gain insight into the palladium-catalyzed amination reaction, particularly the observed sensitivity of the reaction to the nature of the halide and the amine. For example, we have recently shown that the palladium halide dimers {Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$Me)(*μ*-X)}$_2$ (*o*-tol = *o*-tolyl; X = Cl, (**1**) Br (**2**), I (**3**)) react with *N*-benzylmethylamine to generate the corresponding 1:1 amine adducts Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$Me)[HN(Me)Bn]X (X = Cl, (**4**) Br (**5**), I (**6**)) (Scheme 2).[6] The iodide mono(amine) adduct **6** was approximately 35% dissociated in $CDCl_3$ at room temperature, forming iodide dimer **3** and free amine, while the corresponding chloride derivative **4** and bromide derivative **5** revealed no evidence for amine dissociation.[6] Although formation of **6** was clearly less favorable than formation of **4** or **5**, the high binding affinity of *N*-benzylmethylamine precluded the quantitative thermodynamic comparison of the reaction of *N*-benzylmethylamine with dimers **1**−**3**. Here we report

Scheme 1



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(1) (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927. (b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (c) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

(2) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(3) Wolfe, J. N.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

(4) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.

(5) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

(6) Widenhoefer, R. A.; Zhong, A. H.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745.

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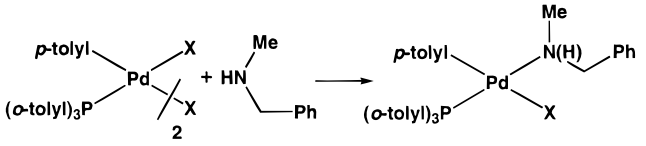
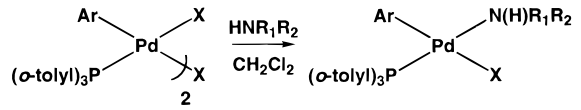
Scheme 2



X = Cl 1 4
Br 2 5
I 3 6

Scheme 3



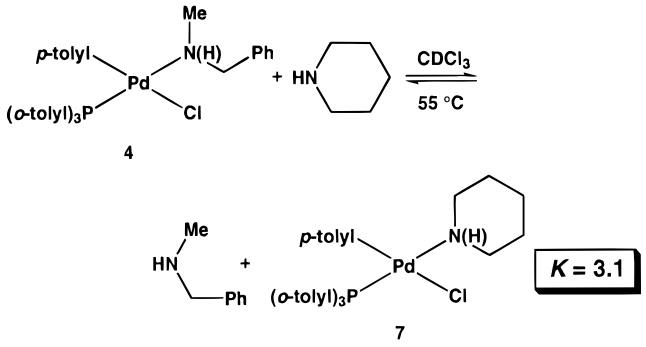
the binding constants (K_b) for the coordination of amines of varying pK_a and steric bulk to the palladium chloride fragment Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)Cl. We also report the quantitative comparison of the equilibrium constants (K) for the reaction of halide dimers **1**−**3** with weakly binding amines.

Results

Synthesis of Palladium Mono(amine) Complexes. Palladium amine adducts were synthesized by reaction of free amine and the desired palladium aryl halide dimers, as has been described previously (Scheme 3, Table 1).[6] For example, reaction of piperidine and chloride dimer **1** in CH_2Cl_2 gave a clear solution which was concentrated and diluted with hexane to give the 1:1 palladium−amine adduct Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(piperidine)Cl (**7**) in 81% yield (Table 1). Likewise, **1** reacted with dibutylamine, diethylamine, morpholine, diisobutylamine, dibenzylamine, hexylamine, benzylamine, cyclohexylamine, *tert*-octylamine, and diisopropylamine to form the corresponding amine adducts Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*n*-Bu)$_2$]Cl (**8**), Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNEt$_2$)Cl (**9**), Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(morpholine)Cl (**10**), Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Bu)$_2$]Cl (**11**), Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNBn$_2$)Cl (**12**), Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(H_2N-*n*-hex)Cl (**13**),[7] Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(H_2NBn)Cl (**14**),[6,7] Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(H_2NCy)Cl (**15**), Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(H_2NCMe$_2$CH$_2$CMe$_3$)Cl (**16**), and Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Pr)$_2$]Cl (**17**), respectively.

Amine adducts derived from cleavage of the halide bridge in palladium bromide and iodide dimers were isolated by a similar procedure (Scheme 3, Table 1). For example, bromide dimer **2** reacted with dibenzylamine and diisopropylamine to form Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNBn$_2$)Br (**18**) and Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Pr)$_2$]Br (**19**), respectively. Reaction of dibenzylamine with iodide dimers **3**, {Pd[P(*o*-tol)$_3$](*p*-C_6H_4CMe$_3$)(μ-I)}$_2$ (**20**),[6] and Pd[P(*o*-tol)$_3$](*p*-C_6H_4OMe)(μ-I)}$_2$ (**21**)[6] gave the corresponding amine adducts Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNBn$_2$)I (**22**), Pd[P(*o*-tol)$_3$](*p*-C_6H_4CMe$_3$)(HNBn$_2$)I (**23**), and Pd[P(*o*-tol)$_3$](*p*-C_6H_4OMe)(HNBn$_2$)I (**24**), respectively. Anisyl dimer **21** also reacted with *tert*-octylamine to form Pd[P(*o*-tol)$_3$](*p*-C_6H_4OMe)(H_2NCMe$_2$CH$_2$CMe$_3$)I (**25**). Addition of diisopropylamine to a CD_2Cl_2 solution of iodide dimer **3** formed the corresponding adduct Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Pr)$_2$]I (**26**), as determined by ^{1}H and ^{31}P NMR spectroscopy (see below), although the unfavorable equilibrium precluded isolation of **26**. For example, addition of hexane to a solution of dimer **3** in neat diisopropylamine followed by cooling to −20 °C led to the precipitation of dimer **3** only; the corresponding amine adduct **26** was not detected by ^{1}H NMR spectroscopy.

Scheme 4



Determination of Amine Binding Constants. Rapid displacement of the coordinated *N*-benzylmethylamine of **4** by free amine[6] allowed the determination of the relative binding constants (K_b) for the coordination of amines to the three-coordinate palladium fragment Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)Cl by ^{1}H NMR spectroscopy.[8] For example, addition of a 3.0:1.0 mixture of *N*-benzylmethylamine and piperidine (8×10^{-2} mmol total) to a solution of chloride dimer **1** (6×10^{-3} mmol) in $CDCl_3$ formed a ∼1:1 mixture of *p*-tolyl resonances corresponding to **4** (δ 2.03) and **7** (δ 2.08) in the ^{1}H NMR spectrum at 55 °C.[8] With K_b for *N*-benzylmethylamine arbitrarily set to unity, the binding constant for piperidine relative to *N*-benzylmethylamine was calculated to be K_b = [**7**][HN(Me)Bn]/[**4**][piperidine] = 3.1 ± 0.4 ($\Delta G_b = -0.8 \pm 0.1$ kcal mol^{-1}) (Scheme 4, Table 2). Likewise, the binding constants for dibutylamine (K_b = 1.1 ± 0.2), diethylamine (K_b = 1.1 ± 0.2), morpholine (K_b = 0.56 ± 0.09), diisobutylamine (K_b= 0.28 ± 0.04), hexylamine (K_b = 7 ± 1), benzylamine (K_b = 3.6 ± 0.6), cyclohexylamine (K_b = 3.3 ± 0.5), and *tert*-octylamine (K_b = 0.12 ± 0.02) were determined relative to *N*-benzylmethylamine by a procedure analogous to that used to determine K_b for piperidine (Table 2).

The *p*-tolyl resonances for *N*-benzylmethylamine adduct **4** and dibenzylamine adduct **12** were not well-separated in the ^{1}H NMR spectrum. Conversely, the

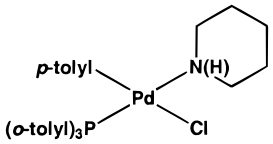
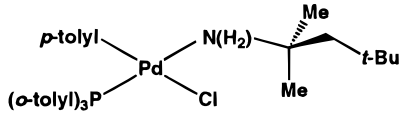
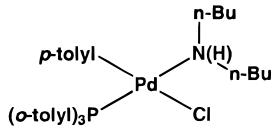
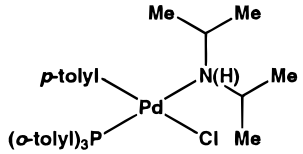
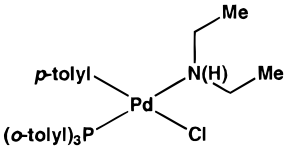
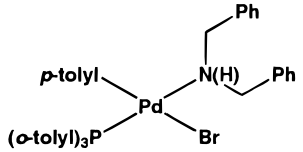
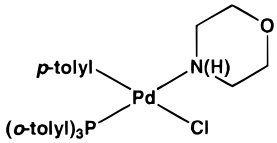
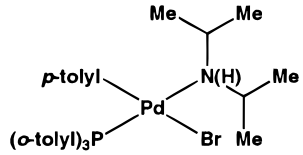
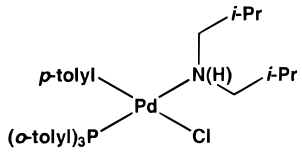
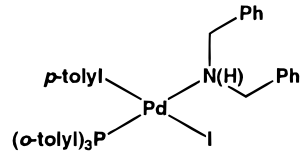
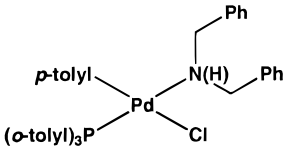
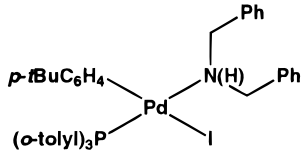
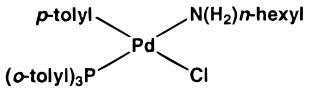
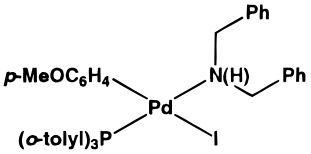
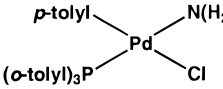
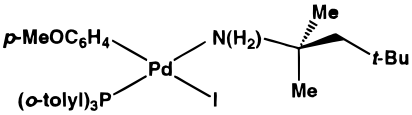
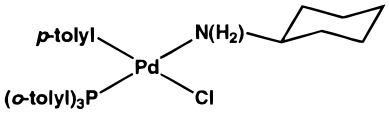
(7) The syntheses of the benzylamine derivative **11** and hexylamine derivative **13** were complicated by formation of the bis(amine) complexes Pd(*p*-C_6H_4Me)[H_2NBn]$_2$Cl and Pd(*p*-C_6H_4Me)[H_2N-*n*-hex]$_2$Cl, respectively. The rate and extent of formation of bis(amine) complexes is halide dependent. We are currently investigating the formation of palladium bis(amine) complexes in detail as a potential chain-limiting step in the catalytic cross-coupling of aryl bromides and primary amines.

(8) At 55 °C in $CDCl_3$, the *p*-tolyl methyl resonances of the amine adducts were sharp and well-resolved. At lower temperatures, the *p*-tolyl methyl resonances of the amine adducts were partially obscured by the broad P(*o*-tol)$_3$ methyl resonance. Likewise, the *p*-tolyl methyl resonances of the palladium amine adducts derived from palladium bromide dimer **2** or palladium iodide dimer **3** were considerably less sharp than were the corresponding chloride derivatives.

(9) (a) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 3rd ed.; Chapman and Hall: London, 1984. (b) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum Press: New York, 1989; Vol. 6, 2nd supplement. (c) Perrin, D. D. *Stability Constants of Metal-Ion Complexes: Part B- Organic Ligands*; IUPAC Pergamon Press: London, 1979.

(10) Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520.

Table 1. Palladium Amine Adducts Isolated from Reaction of Amine and Palladium Halide Dimers

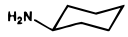
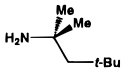
Cmpd	structure	isolated yield	Cmpd	structure	isolated yield
7		81	16		68
8		55	17		74
9		76	18		82
10		87	19		64
11		79	22		83
12		82	23		79
13		56	24		77
14		70[a]	25		90
15		68			

[a] Reference 6.

p-tolyl resonances for morpholine adduct **10** (δ 2.07) and dibenzylamine adduct **12** (δ 2.03) were well-resolved with an equilibrium constant of $K = [\mathbf{12}][\text{morpholine}]/[\mathbf{10}][\text{HNBn}_2] = 0.22 \pm 0.04$ (Scheme 5), which corresponds to a binding constant of $K_b = 0.13 \pm 0.04$ relative to HN(Me)Bn (Table 2). The ^{1}H NMR spectrum of *N*-benzylmethylamine adduct **4** (15 mM) in $CDCl_3$ which contained 0.15 M N-methylaniline showed no evidence for *N*-benzylmethylamine displacement. If we make the conservative assumption that ≥10% of the *N*-benzylmethylamine dissociation could be detected by ^{1}H NMR spectroscopy, a binding constant of ≤0.001 can be estimated for *N*-methylaniline. In addition, although the low affinity of diisopropylamine precluded direct comparison with *N*-benzylmethylamine, a binding constant of $K_b = \sim 1.6 \times 10^{-3}$ was estimated from the equilibrium constants (K) for the reactions of **1** with diisopropylamine and dibenzylamine to form **17** and **12**, respectively (see below).

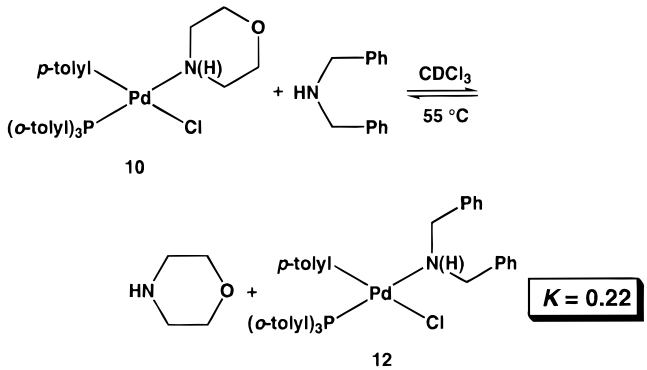
Equilibrium Formation of Palladium Amine Adducts from Reaction of Palladium Halide Dimers with Amines. In contrast to the corresponding *N*-benzylmethylamine adduct **4**,[6] palladium chloride complexes of weakly binding amines (Table 2, $K_b < 0.3$) dissociated in $CDCl_3$ to form an equilibrium mixture of chloride dimer, amine adduct, and free amine. For example, the ^{1}H NMR spectrum of dibenzylamine adduct **12** (16 mM) in $CDCl_3$ at 53 °C displayed a 21:79 ratio of *p*-tolyl resonances for **1** (δ 1.98) and **12** (δ 2.03) (**1**:**12** = 12:88), which corresponds to an equilibrium constant for formation of **12** of $K = [\mathbf{12}]^2/[\mathbf{1}][\text{NHBn}_2]^2 = 6 \pm 1 \times 10^3$ M^{-1} ($\Delta G_{326\ K} = -5.6 \pm 0.2$ kcal mol^{-1}) (Scheme 6, Table 3). The equilibrium constant for the formation of bromide adduct **18** from **2** and dibenzylamine was slightly less favorable ($K = (3.5 \pm 0.5) \times 10^3$ M^{-1}; $\Delta G_{326\ K} = -5.1 \pm 0.1$ kcal mol^{-1}) than the corresponding reaction of dibenzylamine and chloride dimer **1**. In addition, the equilibrium constant for the

Table 2. Comparison of Equilibrium Binding Constants (K_b) and Cone Angles for the Coordination of Amines with the Palladium Fragment Pd[P(*o*-tol)$_3$](*p*-C$_6$H$_4$Me)Cl, Determined at 55 °C in CDCl$_3$

entry	amine	K_b[a]	ΔG_b (kcal mol^{-1})[a]	pK_a[b]	cone angle (°)[c]
1	*n*-hexNH$_2$	7 ± 1	-1.3 ± 0.1	10.63	106
2	BnNH$_2$	3.6 ± 0.6	-0.8 ± 0.1	9.34	106
3		3.3 ± 0.5	-0.8 ± 0.1	10.62	115
4		3.1 ± 0.4	-0.8 ± 0.1	11.12	121
5		1.1 ± 0.2	0	10.95	127[d]
6		1.1 ± 0.2	0	10.95	125
7		1	0	—	—
8		0.56 ± 0.09	0.4 ± 0.1	8.50	121[e]
9		0.28 ± 0.04	0.8 ± 0.1	10.95[f]	138
10		0.13 ± 0.04[g]	1.3 ± 0.1	—	140
11		0.12 ± 0.02	1.4 ± 0.1	10.8[h]	127[i]
12		1.6 x 10^{-3} [j]	4.2	11.09	137
13		≤ 1 x 10^{-3}	>4.5	4.87	126

[a] Determined relative to HN(Me)Bn; each K_b value represents the average of two separate measurements. [b] pK_a values taken from ref 9. [c] Cone angles taken from ref 10. [d] Cone angle estimated to be equivalent to that of HN(*n*-Pr)$_2$. [e] Cone angle estimated to be equivalent to that of piperidine. [f] pK_a estimated to be equivalent to that of HNBu$_2$. [g] Determined relative to morpholine (see text). [h] pK_a estimated to be equivalent to that of H$_2$N-*t*-Bu. [i] Cone angle estimated to that of be equivalent to that of adamantylamine. [j] K_b estimated from reactions of HNBn$_2$ and HN(*i*-Pr)$_2$ with **1** (see text).

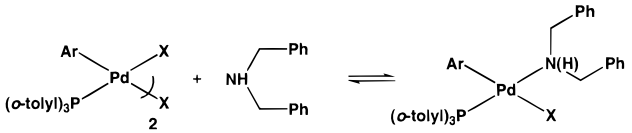
Scheme 5



formation of iodide adduct **22** from **3** and dibenzylamine (K = 90 ± 20 M^{-1}; $\Delta G_{326\ K}$ = −2.9 ± 0.1 kcal mol^{-1}) was considerably less favorable than for the reaction of dibenzylamine with **1** or **2** (Scheme 6, Table 3).

Determination of the solvent and temperature dependence of K for reactions of dibenzylamine with dimers **1**−**3** was precluded by the poor resolution of the respective *p*-tolyl resonances at temperatures lower than ∼55 °C and in solvents other than CDCl$_3$. However, the

Scheme 6



X	Ar	halide dimer	amine adduct
Cl	*p*-tolyl	**1**	**12**
Br	*p*-tolyl	**2**	**18**
I	*p*-tolyl	**3**	**22**
I	*p*-*t*-BuC$_6$H$_4$	**20**	**23**
I	*p*-anisole	**21**	**24**

solvent dependence of K was determined for the equilibrium formation of **23** from iodide dimer **20** and dibenzylamine and ranged from 75 ± 15 M^{-1} in CDCl$_3$ to 20 ± 4 M^{-1} in dioxane-d_8 (Scheme 6, Table 3). In addition, K was determined for the equilibrium formation of **24** from **21** and dibenzylamine over the temperature range 9−58 °C (Scheme 6, Table 3). A van't Hoff plot of the data allowed calculation of the thermodynamic parameters $\Delta G_{298\ K}$ = −3.1 ± 0.1 kcal mol^{-1}, $\Delta H_{298\ K}$ = −11.9 ± 0.1 kcal mol^{-1}, and $\Delta S_{298\ K}$ = −30 ± 4 eu (Figure 1). Similarly, K for the formation of **25** from reaction of *tert*-octylamine and **21** was determined over the temperature range 14−57 °C to provide the thermodynamic parameters $\Delta G_{298\ K}$ = −2.8 ± 0.1 kcal mol^{-1}, $\Delta H_{298\ K}$ = −12.0 ± 0.1 kcal mol^{-1}, and $\Delta S_{298\ K}$ = −31 ± 4 eu (Scheme 7, Table 4, Figure 1). The temperature dependence of the reactions of **21** with dibenzylamine and *tert*-octylamine reveal that ΔS is relatively insensitive to the amine.

The equilibrium constants were also determined for the reactions of palladium halide dimers **1**−**3** with diisopropylamine to form **17**, **19**, and **26**, respectively. These equilibria displayed similar halide dependence but were considerably less favorable than the corresponding reactions of **1**−**3** with dibenzylamine. For example, K for the reaction of **1** with diisopropylamine to form **17** was 14 ± 3 M^{-1} at 25 °C ($\Delta G_{298\ K}$ = −1.6 ± 0.2 kcal mol^{-1}) (Scheme 8). When the temperature dependence of K determined for reaction of **21** with dibenzylamine is employed, an equilibrium constant of ∼0.8 M^{-1} ($\Delta G_{328\ K} \approx$ 0.1 kcal mol^{-1}) can be estimated for the reaction of **1** with diisopropylamine to form **17** at 55 °C, which is ∼6 kcal mol^{-1} (∼3 kcal mol^{-1} per Pd−N bond formed) less favorable than reaction of **1** with dibenzylamine to form **12**. The equilibrium constant for the reaction of bromide dimer **2** with diisopropylamine to form **19** (K = 2.8 ± 0.5 M^{-1}; $\Delta G_{298\ K}$ = −0.6 ± 0.1 kcal mol^{-1}) was slightly less favorable than for the corresponding reaction of diisopropylamine with **1**. The equilibrium constant for the reaction of iodide dimer **3** with diisopropylamine to form **26** (K = (6 ± 2) × 10^{-3} M^{-1}; $\Delta G_{298\ K}$ = 3.0 ± 0.3 kcal mol^{-1}) was considerably less favorable than reaction of diisopropylamine with either **1** or **2** (Scheme 8). In addition, the free energy difference between the reaction of **1** and **3** with diisopropylamine ($\Delta\Delta G_{298\ K}$ = 4.6 ± 0.5 kcal mol^{-1}) was significantly larger than the free energy difference between the reactions of **1** and **3** with dibenzylamine ($\Delta\Delta G_{328\ K}$ = 2.7 kcal mol^{-1}).

Table 3. Equilibrium Constants for Reaction of $HNBn_2$ with Palladium Halide Dimers

entry no.	equilibrium	T (°C)	solvent	K (M^{-1})	ΔG (kcal/mol)
1	[**1**] + 2[$HNBn_2$] ⇌ 2[**12**]	53	$CDCl_3$	$(6 \pm 1) \times 10^3$	-5.6 ± 0.2
2	[**2**] + 2[$HNBn_2$] ⇌ 2[**18**]	53	$CDCl_3$	$(3.5 \pm 0.5) \times 10^3$	-5.1 ± 0.1
3	[**3**] + 2[$HNBn_2$] ⇌ 2[**22**]	53	$CDCl_3$	90 ± 20	-2.9 ± 0.1
4	[**20**] + 2[$HNBn_2$] ⇌ 2[**23**]	24	$CDCl_3$	75 ± 15	-2.5 ± 0.1
5	[**20**] + 2[$HNBn_2$] ⇌ 2[**23**]	24	C_6D_6	30 ± 5	-2.1 ± 0.1
6	[**20**] + 2[$HNBn_2$] ⇌ 2[**23**]	24	THF-d_8	26 ± 4	-2.0 ± 0.1
7	[**20**] + 2[$HNBn_2$] ⇌ 2[**23**]	24	dioxane-d_8	20 ± 4	-1.8 ± 0.1
8	[**21**] + 2[$HNBn_2$] ⇌ 2[**24**]	9	$CDCl_3$	$(3.7 \pm 0.7) \times 10^2$	-3.3 ± 0.1
9	[**21**] + 2[$HNBn_2$] ⇌ 2[**24**]	22	$CDCl_3$	$(2.1 \pm 0.4) \times 10^2$	-3.1 ± 0.1
10	[**21**] + 2[$HNBn_2$] ⇌ 2[**24**]	32	$CDCl_3$	$(1.0 \pm 0.1) \times 10^2$	-2.8 ± 0.1
11	[**21**] + 2[$HNBn_2$] ⇌ 2[**24**]	45	$CDCl_3$	43 ± 7	-2.4 ± 0.1
12	[**21**] + 2]$HNBn_2$] ⇌ 2[**24**]	58	$CDCl_3$	18 ± 3	-1.9 ± 0.1

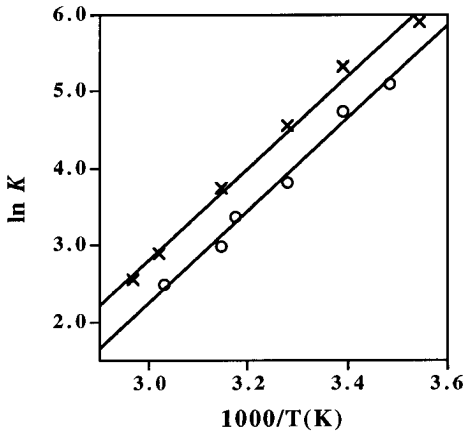


Figure 1. van't Hoff plots for the reaction of **21** with dibenzylamine to form **24** (denoted by ×) and reaction of *tert*-octylamine with **21** to form **25** (denoted by ○).

Scheme 7

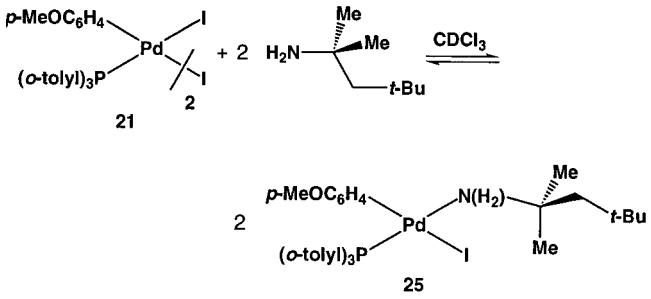


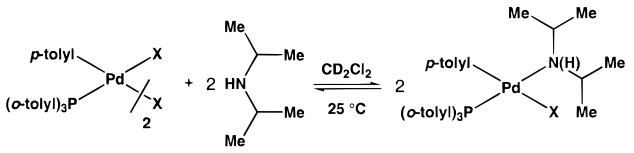
Table 4. Temperature Dependence of K for the Reaction of *tert*-Octylamine with 21 to form 25 in $CDCl_3$

T (°C)	K (M^{-1})	ΔG (kcal/mol)
14	$(1.6 \pm 0.3) \times 10^2$	-2.9 ± 0.1
22	$(1.1 \pm 0.1) \times 10^2$	-2.8 ± 0.1
32	47 ± 7	-2.3 ± 0.1
42	29 ± 5	-2.1 ± 0.1
45	20 ± 3	-1.9 ± 0.1
57	12 ± 2	-1.6 ± 0.1

Discussion

Binding Constants for Coordination of Amines to the Palladium Fragment Pd[P(*o*-tol)$_3$](*p*-C_6H_4-Me)Cl. The coordination or dissociation of an amine serves as a key step in a variety of catalytic processes such as the amination of aryl halides,[2] hydroamination of olefins,[11] hydrodenitrogenation,[12] asymmetric imine hydrogenation,[13] and nitrile reduction.[14] As a result, there has been an effort to correlate both amine basicity and steric bulk to the kinetic or thermodynamic binding affinity of amines to transition metals.[15] While pK_a has typically been employed as a measure of amine basicity, several measures of amine steric bulk have been developed.[16] For example, Trogler has determined amine cone angles (θ, in deg) from space-filling CPK models[10] by the method of Tolman.[17] Molecular mechanics were employed to determine a series of amine solid cone angles (θ') in an effort to more accurately assess the steric bulk of unsymmetric amines.[18] Likewise, molecular mechanics were employed to determine the ligand energy repulsive parameter (E_R, in kcal mol^{-1}) for a series of amines, which estimates the van der Waals repulsion between the lowest energy conformation of the amine and the carbonyl ligands in the hypothetical amine complexes $Cr(CO)_5$(amine).[19] The conformation of the amine determined from molecular mechanics minimization may differ significantly from the confor-

Scheme 8



X	halide dimer	amine adduct	K(M^{-1})	ΔG (kcal/mol)
Cl	1	17	14 ± 3	-1.6 ± 0.2
Br	2	19	2.8 ± 0.5	-0.6 ± 0.1
I	3	26	6 ± 2 x 10^{-3}	3.0 ± 0.3

(11) Gagne, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.

(12) (a) Baralt, E.; Smith, S. J.; Hurwitz, J.; Horvath, I. T.; Fish, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5187. (b) Gray, S. D.; Smith, D. P.; Bruck, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 5462. (c) Fish, R. H.; Baralt, E.; Smith, S. J. *Organometallics* **1991**, *10*, 54. (d) Satterfield, C. N. *Heterogeneous Catalysis in Practice*, 2nd ed.; McGraw-Hill: New York, 1991.

(13) Ball, G. E.; Cullen, W. R.; Fryzuk, M. D.; Henderson, W. J.; James, B. R.; MacFarlane, K. S. *Inorg. Chem.* **1994**, *33*, 1464.

(14) Volt, J.; Pasek, J. In *Catalytic Hydrogenation*: *Studies in Surface Science and Catalysis*; Cerverry, L., Ed.; Elsevier: Amsterdam, 1986; Vol. 27, Chapter 4.

(15) (a) Canovese, L.; Visentin, F.; Uguagliati, P.; Di Bianca, F.; Antonaroli, S.; Crociani, B. *J. Chem. Soc., Dalton Trans.* **1994**, 3113. (b) Dennenberg, R. J.; Darensbourg, D. J. *Inorg. Chem.* **1972**, *11*, 72. (c) Canovese, L.; Visentin, F.; Uguagliati, P.; Crociani, B.; Di Bianca, F. *Inorg. Chim. Acta* **1995**, *235*, 45. (d) Uruska, I.; Zielkiewicz, J.; Szpakowska, M. *J. Chem. Soc., Dalton Trans.* **1990**, 733. (e) Therien, M. J.; Trogler, W. C. *J. Am. Chem. Soc.* **1987**, *109*, 5127. (f) Burkey, T. J. *Polyhedron* **1989**, *8*, 2681. (g) Uruska, I.; Zielkiewicz, J.; Szpakowska, M. *J. Chem. Soc., Dalton Trans.* **1990**, 733. (h) Brown, H. C. *Boranes in Organic Chemistry*: Cornell University Press: Ithaca, NY, 1972. (i) Deeming, A. J.; Rothwell, I. P.; Hursthouse, M. B.; New, L. *J. Chem. Soc., Dalton Trans.* **1978**, 1490. (j) Odell, A. L.; Raethel, H. A. *J. Chem. Soc., Chem. Commun.* **1968**, 1323.

(16) Brown, T. L.; Lee, K. J. *Coord. Chem. Rev.* **1993**, *128*, 89.

(17) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(18) White, D.; Coville, N. J. *Adv. Organomet. Chem.* **1994**, *36*, 95.

(19) Choi, M. G.; Brown, T. L. *Inorg. Chem.* **1993**, *32*, 1548.

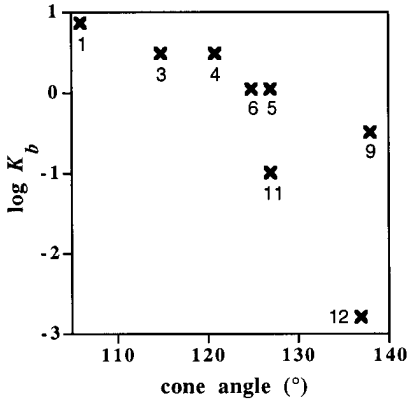


Figure 2. Plot of log K_b versus amine cone angle for hexylamine, cyclohexylamine, piperidine, diethylamine, dibutylamine, diisobutylamine, *tert*-octylamine, and diisopropylamine. Numerical labels correspond to entries in Table 2.[10]

mation of the free amine or the folded-back conformation assumed in the cone angle determination.[19]

The equilibrium binding constants (K_b) for coordination of amines to the palladium fragment Pd[P(*o*-tol)$_3$]-(*p*-C_6H_4Me)Cl were dependent on both the basicity and steric bulk of the amine (Table 2). For example, K_b for dibutylamine was >1100 times larger ($\Delta\Delta G_b \geq 4.5$ kcal mol^{-1}) than K_b for *N*-methylaniline, which possessed a nearly identical cone angle (±1°) but has a pK_a 6 units lower than that of dibutylamine. Likewise, K_b for hexylamine was ~4000 times larger ($\Delta\Delta G_b$ ~5.4 kcal mol^{-1}) than K_b for diisopropylamine, which has a comparable pK_a but possesses a cone angle 30° larger than that of hexylamine. In addition, a plot of log K_b versus cone angle for amines with comparable pK_a (10.9 ± 0.25) revealed a nonlinear dependence of log K_b on cone angle; log K_b decreased only slightly with increasing cone angle below ~120° but dropped rapidly with increasing cone angle above ~120° (Figure 2). The dependence of log K_b on the cone angle is consistent with the presence of a steric threshold which has been previously observed in the correlation of both amine[20] and phosphine[21] binding constants with the respective cone angles.

Although diisobutylamine and diisopropylamine possess nearly identical pK_a values and cone angles, the K_b value for diisobutylamine was ~170 times larger ($\Delta\Delta G_b \approx 3.5$ kcal mol^{-1}) than K_b for diisopropylamine. Likewise, dibenzylamine possesses a cone angle 2° larger than for diisopropylamine but has a K_b ~100 times greater ($\Delta\Delta G_b \approx 3$ kcal mol^{-1}). These discrepancies suggest that, despite the similarity in cone angles, bound diisopropylamine possesses greater steric bulk than either diisobutylamine or dibenzylamine. In accord with these observed binding constants, the ligand repulsive factor (E_R) for diisopropylamine (105 kcal mol^{-1}) is considerably larger than E_R for diisobutylamine (85 kcal mol^{-1}) (E_R for dibenzylamine has not been determined).[19] However, little overall correlation was observed between log K_b and E_R, which may point to different steric requirements for an amine bonded to the three-coordinate palladium fragment Pd[P(*o*-tol)$_3$]-(*p*-C_6H_4Me)Cl and an amine bound to the five-coordinate chromium fragment Cr(CO)$_5$.

Equilibrium Formation of Palladium−Amine Adducts from Aryl Halide Dimers. Reaction of dibenzylamine with palladium chloride dimer **1** to form the corresponding monomer **12** cleaves two dative Pd−(μ-Cl) bonds and forms two dative Pd−N bonds. The enthalpy for the reaction can therefore be expressed as $\Delta H = 2E[\text{Pd}(\mu\text{-Cl})] - 2E[\text{Pd}-\text{N}]$, where E designates the energy of the respective dative bond. Assuming that $\Delta S = -30$ eu (as determined for the reaction of dibenzylamine with **21**), the enthalpy for the reaction of dibenzylamine with **1** is estimated to be −14.5 kcal mol^{-1}. Because the dative Pd−N(piperidine) bond is 2.1 kcal mol^{-1} stronger than the Pd−N(dibenzylamine) dative bond (Table 2, assuming ΔS is amine independent), the enthalpy for the formation of **7** from **1** and piperidine is estimated to be −18.7 kcal mol^{-1}, which is slightly larger than the bridge-cleavage enthalpies of related reactions.[22] For example, the enthalpy for the cleavage of a dative dichloride bridge by piperidine ranges from −15.7 kcal mol^{-1}, for the reaction of piperidine with the rhodium dicarbonyl complex [Rh(CO)$_2$Cl]$_2$ to form Rh(CO)$_2$Cl(piperidine),[22a,23] to −9.4 kcal mol^{-1}, for the reaction of piperidine with the palladium π-allyl complex [Pd(η^3-$CH_2C(Me)CH_2$)Cl]$_2$ to form Pd(η^3-$CH_2C(Me)CH_2$)Cl(piperidine).[24]

The equilibrium constants (K) for the reaction of dibenzylamine and diisopropylamine with halide dimers **1**−**3** to form the corresponding amine adducts were halogen dependent and decreased in the order Cl > Br >> I. The resistance of a palladium iodide dimer to undergo bridge cleavage relative to the corresponding bromide and chloride derivatives has been previously observed. For example, reaction of PdI$_2$ and excess P(*o*-tol)$_3$ led to the exclusive formation of the mono(phosphine) iodide dimer {Pd[P(*o*-tol)$_3$](μ-I)I}$_2$.[6] Conversely, the corresponding reactions of P(*o*-tol)$_3$ with PdBr$_2$ or PdCl$_2$ formed only the respective bis(phosphine) monomers Pd[P(*o*-tol)$_3$]$_2$X$_2$ (X = Cl, Br).[6,25] Similarly, Chatt and co-workers observed that the palladium chloride bridged dimer {Pd[P(*n*-Pr)$_3$](μ-Cl)Cl}$_2$ reacted with *p*-toluidine to form the stable amine monomer Pd[P(*n*-Pr)$_3$]-(*p*-toluidine)Cl$_2$. Conversely, addition of *p*-toluidine to the palladium iodide bridged dimer {Pd[P(*n*-Pr)$_3$](μ-I)I}$_2$ (**27**) generated an equilibrium mixture of **27** and the corresponding amine monomer Pd[P(*n*-Pr)$_3$](*p*-toluidine)I$_2$ (**28**). Isolation of monomeric **28** required both the use of excess *p*-toluidine in the reaction with **27** and recrystallization of **28** from a *p*-toluidine solution of light petroleum ether.[26]

The enthalpy equation for cleavage of the halide bridge of a palladium halide dimer by amine to form

(20) Romeo, R.; Arena, G.; Scolaro, L. M.; Plutino, M. R.; Bruno, G.; Nicolo, F. *Inorg. Chem.* **1994**, *33*, 4029.

(21) (a) Liu, H. Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1990**, *9*, 1758. (b) Rahman, M. M.; Liu, H. Y.; Prock, A.; Giering, W. P. *Organometallics* **1987**, *6*, 650. (c) Romeo, R.; Arena, G.; Scolaro, L. M. *Inorg. Chem.* **1992**, *31*, 4879.

(22) (a) Pribula, A. J.; Drago, R. S. *J. Am. Chem. Soc.* **1976**, *98*, 2784. (b) Wang, K.; Rosini, G. P.; Nolan, S. P.; Goldman, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 5082. (c) Van Gaal, H. L. M.; Moers, F. G.; Steggerda, J. J. *J. Organomet. Chem.* **1974**, *65*, C43. (d) Van Gaal, H. L. M.; Van Den Bekerom, F. L. A. *J. Organomet. Chem.* **1977**, *134*, 237. (e) Partenheimer, W.; Durham, B. *Inorg. Nucl. Chem. Lett.* **1974**, *10*, 1143. (f) Gregory, N. W.; MacLaren, R. O. *J. Phys. Chem.* **1955**, *59*, 110.

(23) Drago, R. S.; Miller, J. G.; Hoselton, M. A.; Farris, R. D.; Desmond, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 444.

(24) Li, M. P.; Drago, R. S.; Pribula, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 6900.

(25) Bennett, M. A.; Longstaff, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 6266.

(26) Chatt, J.; Venanzi, L. M. *J. Chem. Soc.* **1957**, 2445.

the corresponding 1:1 palladium amine adduct ($\Delta H = 2E[\text{Pd}-(\mu\text{-halogen})] - 2E[\text{Pd}-\text{N}]$) indicates that K will decrease with increasing Pd−(μ-halogen) bond strength and with decreasing Pd−N bond strength (assuming ΔS is constant). The halide ligand can potentially affect both the Pd−(μ-halogen) and Pd−N bond strengths although the relative contributions of the two effects to the halide dependence of K cannot be determined. For example, the dative Pd−(μ-halogen) bond strength is expected to parallel the polarizability and hence donicity of the respective halide, which increases in the order Cl < Br < I. Similar donicity trends have been observed for the binding affinity of halocarbons to low-valent transition metals, which increases in the order RF << RCl < RBr < RI.[27]

Due to unfavorable steric interaction between the *cis* amine and halide ligands of the palladium amine adducts, the Pd−N bond strength should depend inversely on the van der Waals radii of the halide, which increases in the order Cl (1.75 Å) < Br (1.85 Å) < I (1.96 Å).[28,29] Unfavorable steric interaction between the *cis* amine and halide ligands of the palladium amine adducts is supported by the greater halide sensitivity of K in the case of diisopropylamine relative to the less bulky dibenzylamine. For example, the free energy difference for the reactions of **1** and **3** with diisopropylamine ($\Delta\Delta G_{298\ K} = 4.6$ kcal mol^{-1}) was considerably larger than the free energy difference for the reactions of **1** and **3** with dibenzylamine ($\Delta\Delta G_{328\ K} = 2.7$ kcal mol^{-1}). Likewise, steric interaction between the *cis* amine and halide ligands is supported by the observed halide effect on energy barriers for P−C and Pd−P bond rotation in palladium amine adducts, which increased in the order **4** < **5** < **6**.[6] Likewise, steric interaction of the *cis*-bromide ligand and the *o*-fluorine atoms of the C_6F_5 ring in the S,N-bonded palladium bromide complex ($Pd(C_6F_5)Br(SPPyPh_2)$) [Py = pyridin-2-yl] became so severe (2.02 Å) upon rotation of the C_6F_5 ring through the coordination plane that halide dissociation was required for complete aryl rotation.[30]

Conclusions

Although the efficiency and rate of the $Pd_2(DBA)_3$/P(*o*-tol)$_3$-catalyzed amination reaction are clearly affected by the binding constant (K_b) of the amine, no simple correlation between amine K_b value and catalytic proficiency was observed. For example, the reaction rate of 5-bromo-*m*-xylene with amines was inversely related to the amine binding constant, where k_{obs} decreased in the order HN(Me)Ph >> morpholine > *N*-benzylmethylamine ≈ dibutylamine > piperidine >> hexylamine.[31] Conversely, the reactions of aryl bromides with bulky amines which possess a low K_b value such as *tert*-butylamine, *tert*-octylamine, and diisopropylamine were also slow and produced lower yields of aniline.[32]

The equilibrium constant for bridge cleavage of the palladium iodide dimer **3** by amine to form the corresponding 1:1 palladium amine adduct is considerably less favorable than the corresponding reaction of palladium bromide dimer **2**. This halide effect on K may be responsible for the lower efficiency observed for aryl iodides relative to aryl bromides in the catalytic amination reaction. The correlation between K and catalytic proficiency is supported by the observation that both iodoamines and bromoamines undergo intramolecular cross-coupling with high efficiency, as chelation presumably renders amine coordination to palladium favorable for both halides.[3] For example, while acyclic iodide amine adducts such as **6** dissociate readily at room temperature, the corresponding chelated amine complexes such as Pd[P(*o*-tol)$_3$][2-$C_6H_4(CH_2)_2N(H)Bn$)]I show no evidence for amine dissociation even at 55 °C.[6]

Experimental Section

General Methods. All manipulations were performed under an atmosphere of nitrogen or argon in an inert-atmosphere glovebox or by standard Schlenk techniques. Preparative-scale reactions were performed in flame- or oven-dried Schlenk tubes equipped with a stirbar, side-arm joint, and septum. NMR spectra were obtained in $CDCl_3$ at 55 °C on a Varian XL-300 spectrometer unless otherwise noted. ^{1}H NMR spectra were referenced relative to the residual proton resonance of the solvent. Room-temperature ^{31}P NMR (96 MHz) spectra were referenced relative to external 85% H_3PO_4; low-temperature ^{31}P NMR spectra were referenced relative to external PPh_3 in $CDCl_3$ (δ −4.69). IR spectra were recorded on a Perkin-Elmer Model 6000 FTIR spectrometer. Elemental analyses were performed by E+R Analytical Laboratories (Corona, NY). Hexane, pentane, benzene, and benzene-d_6 were distilled from purple solutions of sodium and benzophenone. THF-d_8 and dioxane-d_8 were distilled from Na/K alloy, methylene chloride and methylene chloride-d_2 were distilled from CaH_2, and $CDCl_3$ was distilled from P_2O_5; all solvents were distilled under argon or nitrogen. All amines were purchased from Aldrich and were distilled from CaH_2 under N_2 prior to use. Compounds **1**−**6**, **20**, and **21** were prepared according to published procedures.[6]

The error limits for equilibrium constants (K and K_b) and the corresponding free energy values were estimated via extrapolation of ±10% error in the ratio of the respective palladium complexes determined by ^{1}H NMR spectroscopy. Duplicate determinations of equilibrium constants were consistently within the estimated error limits. The error limits for enthalpy values correspond to the standard deviation of the least-squares fit of the corresponding van't Hoff plot. The error limits for entropy values were estimated by extrapolation of the errors in the corresponding free energy and enthalpy values.

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[$HN(CH_2)_5$]Cl (7). Piperidine (200 mg, 2.3 mmol) was added to a yellow solution of **1** (210 mg, 0.18 mmol) in 5 mL of CH_2Cl_2 and stirred at room temperature for 10 min. The resulting colorless solution was concentrated to 1 mL under vacuum and diluted with 20 mL of hexane. Cooling the solution via concentration to 10 mL under vacuum formed a white precipitate, which was filtered, washed with hexane, and dried under vacuum to give **7** (194 mg, 81%) as a pale yellow microcrystalline solid which contained traces of hexane (<5% as determined by ^{1}H NMR analysis). ^{1}H NMR: δ 7.78 (br, 3 H), 7.33 (t, 3 H, J = 7 Hz), 7.15 (m, 6 H), 6.76 (br,

(27) Kulawiec, R. J.; Crabtree, R. H. *Coord. Chem. Rev.* **1990**, *99*, 89.

(28) Porterfield, W. W. *Inorganic Chemistry: A Unified Approach*; Addison-Wesley: Reading, MA, 1984; p 168.

(29) The Lewis acidity of the palladium center is expected to parallel the Pauling electronegativity of the bound halide ligand, which increases in the order I (2.66) < Br (2.96) < Cl (3.16) (Allred, A. *J. Inorg. Nucl. Chem.* **1961**, *17*, 215). However, the enhanced Lewis acidity of palladium should increase the strength of the dative Pd−N bond and the dative Pd−(μ-halogen) bond to a similar degree and therefore have no net effect on K.

(30) Cusares, J. A.; Coco, S.; Espinet, P.; Liu, Y. S. *Organometallics* **1995**, *14*, 3058.

(31) Widenhoefer, R. A.; Buchwald, S. L. Unpublished results.

(32) Wolfe, J. N.; Buchwald, S. L. Unpublished results.

2 H), 6.49 (d, J = 7.5 Hz, 3 H), 3.28 (br s, 1 H, HN), 3.22 (d, J = 13 Hz, 2 H, α-CH_2), 2.55 (d, J = 13 Hz, 2 H, α-CH_2), 2.26 [s, 9 H, P(*o*-tol)$_3$], 2.08 (s, 3 H, C_6H_4*Me*), 1.60 (m, 3 H), 1.36 (m, 3 H). $^{31}P\{^1H\}$ NMR: δ 25.6. IR (Nujol): 3200 cm^{-1}. Anal. Calcd (found) for $C_{33}H_{39}ClNPPd$: C, 63.67 (63.46); H, 6.31 (6.53); N, 2.25 (2.39).

The procedure employed in the synthesis of **7** was applied to the syntheses of complexes **8**−**16** and **18** by utilizing the appropriate palladium aryl halide dimer and amine. All complexes were isolated as cream or pale yellow powders; yields are given in Table 1.

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNBu$_2$)Cl (8). ^1H NMR: δ 7.75 (br s, 3 H), 7.28−7.11 (m, 9 H), 6.6 (br s, 2 H), 6.43 (d, J = 7.7 Hz, 2 H), 3.55 (br s, 1 H, NH), 2.25 [br s, 9 H, P(*o*-tol)$_3$], 2.06 (s, 3 H, C_6H_4*Me*), 1.80 (br s, 6 H), 1.30 (m, 6 H), 0.93 (t, J = 7.5 Hz, 6 H, -CH_2CH_3). $^{31}P\{^1H\}$ NMR: δ 27.4. IR (Nujol): 3215, 3200 cm^{-1}. Anal. Calcd (found) for $C_{36}H_{47}ClNPPd$: C, 64.87 (65.01); H, 7.11 (7.30); N, 2.10 (2.15).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNEt$_2$)Cl (9). ^1H NMR: δ 7.75 (br s, 3 H), 7.29 (t, J = 7.4 Hz, 3 H), 7.12 (t, J = 6.1 Hz, 6 H), 6.66 (br s, 2 H), 6.43 (d, J = 7.7 Hz, 2 H), 3.40 (br s, 1 H, NH), 2.61 (br s, 2 H, NCH_2CH$_3$), 2.42 (m, 2 H, NCH_2CH$_3$), 2.26 [br s, 9 H, P(*o*-tol)$_3$], 2.06 (s, 3 H, C_6H_4*Me*), 1.44 (t, J = 7.05, 6 H, NCH$_2$CH_3). $^{31}P\{^1H\}$ NMR: δ 27.3. Anal. Calcd (found) for $C_{32}H_{39}ClNPPd$: C, 62.96 (62.77); H, 6.44 (6.28); N, 2.29 (2.22).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(CH$_2$)$_2$O]Cl (10). ^1H NMR (20 °C): δ 7.30, 7.11, 6.45, 3.69 (br s, 1 H, HN), 3.64 (d, J = 11 Hz, 2 H, α-CH_2), 3.40 (dt, J = 2, 11 Hz, 2 H, α-CH_2), 2.93 (br, 2 H, β-CH_2), 2.65 (br, 2 H, β-CH_2), 2.21 [s, 9 H, P(*o*-tol)$_3$], 2.07 (s, 3 H, C_6H_4*Me*). $^{31}P\{^1H\}$ NMR: δ 25.9. IR (Nujol): 3174 cm^{-1}. Anal. Calcd (found) for $C_{32}H_{37}ClNOPPd$: C, 61.55 (61.38); H, 5.97 (5.95); N, 2.24 (2.33).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Bu)$_2$]Cl (11). ^1H NMR (**11**:**1** ≈ 12:1): δ 7.70 (br, 3 H), 7.29 (t, J = 6.7 Hz, 3 H), 7.12 (br t, J = 6.3 Hz, 6 H), 6.65 (br s, 2 H), 6.44 (d, J = 7.6 Hz, 2 H), 3.65 (br, 1 H, NH), 2.24 [br s, 9 H, P(*o*-tol)$_3$], 2.06 (s, 3 H, C_6H_4*Me*), 0.94 [d, J = 6.7 Hz, 6 H, NCH$_2$CH(CH_3)$_2$], 0.86 [d, J = 6.7 Hz, 6 H, NCH$_2$CH(CH_3)$_2$]. $^{31}P\{^1H\}$ NMR (25 °C): δ 27.9. Anal. Calcd (found) for $C_{36}H_{47}ClNPPd$: C, 64.87 (65.03); H, 7.11 (6.96); N, 2.10 (1.99).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNBn$_2$)Cl (12). ^1H NMR (20 °C; **12**:**1** > 20:1): δ 7.60 (br, 3 H), 7.32 (m, 13 H), 7.09 (m, 6 H), 6.31 (d, J = 7.2 Hz, 2 H), 6.03 (br, 2 H), 4.35 (dd, 2 H, J = 8.4, 13.8 Hz, HNCH_2Ph), 3.70 (br, 2 H, HNCH_2Ph), 3.20 (br, 1 H, HN), 2.23 [s, 9 H, P(*o*-tol)$_3$], 2.03 (s, 3 H, C_6H_4*Me*). $^{31}P\{^1H\}$ NMR: δ 27.2. IR (Nujol): 3221 cm^{-1}. Anal. Calcd (found) for $C_{42}H_{43}ClNPPd$: C, 68.67 (68.55); H, 5.90 (6.11); N, 1.91 (2.01).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[H$_2$N(CH$_2$)$_5$Me]Cl (13). ^1H NMR (20 °C): 7.76 (m, 3 H), 7.30 (t, J = 7 Hz, 3 H), 7.13 (m, 6 H), 6.63 (br s, 2 H), 6.47 (d, J = 7.5 Hz, 2 H), 2.60 (br s, 2 H, H_2N), 2.56 (br s, 2 H, H_2NCH_2−), 2.21 [s, 9 H, P(*o*-tol)$_3$], 2.07 (s, 3 H, C_6H_4*Me*), 1.40 (t, J = 6 Hz, 2 H), 1.20 (t, J = 7 Hz, 2 H), 1.11 (br s, 4 H), 0.80 [t, J = 7.5 Hz, 3 H, H_2N(CH$_2$)$_5$*Me*]. $^{31}P\{^1H\}$ NMR: δ 25.8. Anal. Calcd (found) for $C_{34}H_{43}ClNPPd$: C, 63.95 (64.11); H, 6.79 (6.75); N, 2.19 (2.21).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(H$_2$NCy)Cl (15). ^1H NMR: δ 7.76 (br, 3 H), 7.29 (t, 3 H, J = 7.13 Hz), 7.10 (m, 6 H), 6.62 (m, 2 H), 6.46 (d, 2 H, J = 7.46 Hz), 2.66, 2.47, 2.18 [br s, 9 H, P(*o*-tol)$_3$], 2.07 (s, 3 H, C_6H_4*Me*), 1.93 (d, J = 9.06 Hz), 1.60 (m), 1.46 (m), 1.05 (m). $^{31}P\{^1H\}$ NMR: δ 27.9. Anal. Calcd (found) for $C_{34}H_{41}ClNPPd$: C, 64.16 (63.97); H, 6.49 (6.50); N, 2.20 (2.18).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(H$_2$N-*t*-octyl)Cl (16). ^1H NMR (**16**:**1** ≈ 8:1): δ 7.70 (br, 3 H), 7.28 (t, 6 H, J = 6.04 Hz), 7.24 (m, 3 H), 6.65 (m, 2 H), 6.42 (d, 2 H, J = 6.49 Hz), 3.14 (br, 2 H, H_2N-*t*-octyl), 2.18 [br s, 9 H, P(*o*-tol)$_3$], 2.07 (s, 3 H, C_6H_4*Me*), 1.09 (m). $^{31}P\{^1H\}$ NMR: δ 30.0. Anal. Calcd (found) for $C_{36}H_{47}ClNPPd$: C, 64.87 (64.82); H, 7.11 (7.28); N, 2.10 (2.00).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNBn$_2$)Br (18). ^1H NMR (20 °C; **18**:**2** ≈ 20:1): δ 7.38−7.27 (13 H), 7.12−7.01 (6 H), 6.31 (d, J = 7.8 Hz, 2 H), 6.05 (br, 2 H), 4.38 (dd, 2 H, J = 7.7, 12.2 Hz, HNCH_2Ph), 3.76 (br, 2 H, HNCH_2Ph), 3.24 (br, 1 H, HN), 2.19 [s, 9 H, P(*o*-tol)$_3$], 2.04 (s, 3 H, C_6H_4*Me*). $^{31}P\{^1H\}$ NMR: δ 28.2. Anal. Calcd (found) for $C_{42}H_{43}BrNPPd$: C, 64.75 (64.74); H, 5.56 (5.55); N, 1.80 (1.80).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Pr)$_2$]Cl (17). A solution of **1** (120 mg, 0.22 mmol) and diisopropylamine (770 mg, 7.6 mmol) in CH_2Cl_2 (3 mL) was stirred for 5 min at room temperature. The yellow solution was concentrated to 1 mL under vacuum, diluted with 5 mL of hexane, and cooled to −20 °C overnight. The resulting precipitate was collected, washed with hexane, and dried under vacuum to give **17** (88 mg, 74%) as yellow blocks. ^1H NMR (CD_2Cl_2 [0.1 M HN(*i*-Pr)$_2$], 25 °C; **17**:**1** ≈ 2:1): δ 2.05 (C_6H_4*Me*); additional resonances corresponding to **17** were obscured by the resonances for **1** and free HN(*i*-Pr)$_2$. $^{31}P\{^1H\}$ NMR (CD_2Cl_2 [0.5 M HN(*i*-Pr)$_2$], 25 °C): δ 27.3. Anal. Calcd (found) for $C_{34}H_{43}ClNPPd$: C, 63.95 (64.05); H, 6.79 (6.63).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Pr)$_2$]Br (19). Reaction of diisopropylamine (1.4 g, 14 mmol) and **2** (100 mg, 0.17 mmol) employing a procedure analogous to that used to prepare **17** led to the isolation of **19** (76 mg, 64%) as yellow crystals. ^1H NMR (CD_2Cl_2 [0.1 M HN(*i*-Pr)$_2$], 25 °C; **19**:**2** ≈ 2:1): δ 2.05 (C_6H_4*Me*); additional resonances corresponding to **19** were obscured by the resonances for **2** and free HN(*i*-Pr)$_2$. $^{31}P\{^1H\}$ NMR (CD_2Cl_2 [0.5 M HN(*i*-Pr)$_2$], 25 °C): δ 26.6. Anal. Calcd (found) for $C_{34}H_{43}BrNPPd$: C, 59.79 (59.77); H, 6.35 (6.21).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)(HNBn$_2$)I (22). Dibenzylamine (205 mg, 1.04 mmol) was added to an orange solution of **3** (56 mg, 0.09 mmol) in CH_2Cl_2 (5 mL), and the resulting yellow solution was stirred for 5 min. Solvent was evaporated under vacuum to give an orange oil, which was diluted with 5 mL of hexane and cooled to −20 °C overnight. The resulting precipitate was collected, washed with hexane (10 mL), and dried under vacuum to give **22** (61 mg, 83%) as a yellow microcrystalline solid. ^1H NMR ($CDCl_3$ (0.09 M HNBn$_2$); **22**:**3** ≈ 4:1): δ 6.31 (d, J = 7.3 Hz), 6.10, 4.40 (br t, J = 7 Hz) and 2.06 (s, C_6H_4*Me*); additional resonances corresponding to **22** were obscured by the resonances for free HNBn$_2$ and **3**. $^{31}P\{^1H\}$ NMR ($CDCl_3$ (0.09 M HNBn$_2$), 25 °C; **22**:**3** ≥ 10:1): δ 28.0. Anal. Calcd (found) for $C_{42}H_{43}INPPd$: C, 61.07 (61.16); H, 5.25 (5.44).

The procedure employed in the synthesis of **22** was applied to the syntheses of complexes **23**−**25**, utilizing the appropriate halide and amine; yields are given in Table 1.

Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)(HNBn$_2$)I (23): orange needles. ^1H NMR [$CDCl_3$ (0.09 M HNBn$_2$); **23**:**20** ≈ 15:1]: δ 6.55, 6.20, 4.42 (br, HNCH_2Ph), 3.37, 1.14 ($C_6H_4CMe_3$); additional resonances corresponding to **23** were obscured by the resonances for free HNBn$_2$ and **20**. $^{31}P\{^1H\}$ NMR ($CDCl_3$ (0.09 M HNBn$_2$), 25 °C): δ 28.3. Anal. Calcd (found) for $C_{45}H_{49}INPPd$: C, 62.26 (62.19); H, 5.69 (5.65).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4OMe)(HNBn$_2$)I (24): yellow powder. ^1H NMR [$CDCl_3$ (0.09 M HNBn$_2$); **24**:**21** ≈ 15:1]: δ 6.24, 6.10, 4.43 (br, HNCH_2Ph), 3.60 (s, C_6H_4OMe); additional resonances corresponding to **24** were obscured by the resonances for free HNBn$_2$ and **21**. $^{31}P\{^1H\}$ NMR ($CDCl_3$ (0.09 M HNBn$_2$), 25 °C): δ 28.1. Anal. Calcd (found) for $C_{42}H_{43}INOPPd$: C, 59.91 (59.66); H, 5.15 (5.35).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4OMe)(H$_2$NCMe$_2$CH$_2$CMe$_3$)I (25): orange crystals. ^1H NMR ($CDCl_3$ (0.09 M *tert*-octylamine), **25**:**21** ≈ 15:1): δ 3.63 (s, C_6H_4OMe); additional resonances corresponding to **25** were obscured by the resonances for free *tert*-octylamine and **21**. $^{31}P\{^1H\}$ NMR ($CDCl_3$ (0.09 M *tert*-octylamine), 25 °C): δ 28.3. Anal. Calcd (found) for $C_{36}H_{47}INOPPd$: C, 55.86 (55.60); H, 6.12 (6.35).

Pd[P(*o*-tol)$_3$](*p*-C_6H_4Me)[HN(*i*-Pr)$_2$]I (26). Complex **26** was generated by addition of diisopropylamine to a solution of **3** in CD_2Cl_2 and was analyzed without isolation. ^1H NMR (300 MHz, CD_2Cl_2 [0.5 M HN(*i*-Pr)$_2$], 25 °C; **26**:**3** ≈ 1:2): δ 2.05 (C_6H_4*Me*); additional resonances corresponding to **26** were

obscured by the resonances for **3** and free HN(*i*-Pr)$_2$. ^{31}P{^{1}H} NMR (96 MHz, CD_2Cl_2 [3 M HN(*i*-Pr)$_2$], 25 °C; **26**:**3** ≈ 3:1): δ 26.2.

Determination of the Binding Constant (K_b) for Piperidine Relative to *N*-Benzylmethylamine. Piperidine (2.0 μL, 0.02 mmol) and *N*-benzylmethylamine (8.0 μL, 0.06 mmol) were added via syringe to an NMR tube containing a solution of **1** (5.9 mg, 5.5×10^{-3} mmol) in $CDCl_3$ (0.63 mL). The tube was shaken, and its contents were analyzed by ^{1}H NMR spectroscopy at 55 °C. The concentrations of **4** and **7** were determined from the area ($A = h\omega_{1/2}$) of the *p*-tolyl methyl resonances for **4** (2.03) and **7** (2.08) and from the mass balance. The concentrations of piperidine and *N*-benzylmethylamine were determined from the mass balance. The binding constant for piperidine relative to that of *N*-benzylmethylamine was determined from two separate experiments according to the formula $K_b = [\mathbf{7}][\text{HN(Me)Bn}]/[\mathbf{4}][\text{piperidine}]$. The binding constants for dibutylamine, morpholine, diisobutylamine, benzylamine, cyclohexylamine, and *tert*-octylamine were determined by an analogous procedure. Likewise, the binding constant of dibenzylamine relative to that of morpholine was determined by an analogous procedure.

Equilibrium Formation of 12 from 1 and $HNBn_2$. A solution of **12** (8.2 mg, 0.01 mmol) and $PhSiMe_3$ (1.8 mg, 0.01 mmol) in $CDCl_3$ was analyzed by ^{1}H NMR spectroscopy at 53 °C. The concentrations of **1**, **12**, and dibenzylamine were determined by integrating the *p*-tolyl resonances for **12** (δ 2.03) and **1** (δ 1.96) and the benzyl resonance of $HNBn_2$ (δ 3.82) relative to the trimethylsilyl resonance for $PhSiMe_3$ (δ 0.25). The equilibrium constant for the conversion of **1** + dibenzylamine to **12** was determined according to the formula $K = [\mathbf{12}]^2/[\mathbf{1}][HNBn_2]^2$.

Equilibrium Formation of 22 from 3 and $HNBn_2$. A solution of **3** (9.8 mg, 7.8×10^{-3} mmol) and $PhSiMe_3$ (0.74 mg, 5.0×10^{-3} mmol) in $CDCl_3$ (0.68 mL) was analyzed by ^{1}H NMR spectroscopy. The concentration of **3** was determined by integrating the P(*o*-tol)$_3$ + *p*-tolyl resonances of **3** relative to the trimethylsilyl resonance for $PhSiMe_3$. Dibenzylamine (1.5 μL, 0.012 mmol) was then added to the tube via syringe, the tube was shaken, and its contents were analyzed by ^{1}H NMR spectroscopy at 53 °C. The concentrations of **3** and **22** were determined from the area of the *p*-tolyl methyl resonances for **3** (δ 1.98) and **22** (δ 2.06) and from the mass balance. The concentration of $HNBn_2$ was determined from the mass balance. The equilibrium constant for the conversion of **3** + dibenzylamine to **22** was determined according to the formula $K = [\mathbf{22}]^2/[\mathbf{3}][HNBn_2]^2$. *K* for the formation of **18** from reaction of bromide dimer **2** and $HNBn_2$ was determined by an analogous procedure.

Equilibrium Formation of 23 from 20 and $HNBn_2$. Dibenzylamine (2.0 μL, 0.016 mmol) was added via syringe to an NMR tube containing a solution of **20** (9.8 mg, 6.4×10^{-3} mmol) and $PhSiMe_3$ (0.74 mg, 5.0×10^{-3} mmol) in $CDCl_3$ (0.68 mL). The tube was shaken, and its contents were analyzed by ^{1}H NMR spectroscopy at 24 °C. The concentrations of **20** and **23** were determined by integrating the *t*-Bu resonance for **20** (δ 1.08) and **23** (δ 1.14) relative to the trimethylsilyl resonance for $PhSiMe_3$ (δ 0.25). The concentration of dibenzylamine was determined from the mass balance. The equilibrium constant for the conversion of **20** + dibenzylamine to **23** was determined according to the formula $K = [\mathbf{23}]^2/[\mathbf{20}][HNBn_2]^2$. *K* values for formation of **23** from **20** + $HNBn_2$ in C_6D_6, dioxane-d_8, and THF-d_8 were determined by an analogous procedure. Likewise, the equilibrium formation of **24** from **21** and $HNBn_2$ was analyzed in an analogous manner by integrating the methoxy resonances for **21** (δ 3.53) and **24** (δ 3.60). The thermodynamic parameters for the conversion of **21** to **24** were determined from a van't Hoff plot of the data over the temperature range 9−58 °C (Figure 1).

Equilibrium between 17 and 1 + HN(*i*-Pr)$_2$. Diisopropylamine (5.0 μL, 3.9 mmol) was added via syringe to an NMR tube containing a solution of **1** (7.5 mg, 7.0×10^{-3} mmol) in CD_2Cl_2 (0.96 mL). The tube was shaken and analyzed by ^{1}H NMR spectroscopy at 25 °C. The concentrations of **1** and **17** were determined by cutting and weighing the *p*-tolyl methyl resonances for **1** (2.02) and **17** (2.05) and from the mass balance. The concentration of diisopropylamine was determined from the mass balance. The equilibrium constant for the conversion of **1** + diisopropylamine to **17** was determined as the average of three separate experiments according to the formula $K = [\mathbf{17}]^2/[\mathbf{1}][HN(i\text{-Pr})_2]^2$. *K* for the formation of **19** from **2** and diisopropylamine and *K* for the formation of **26** from **3** and diisopropylamine were determined analogously.

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