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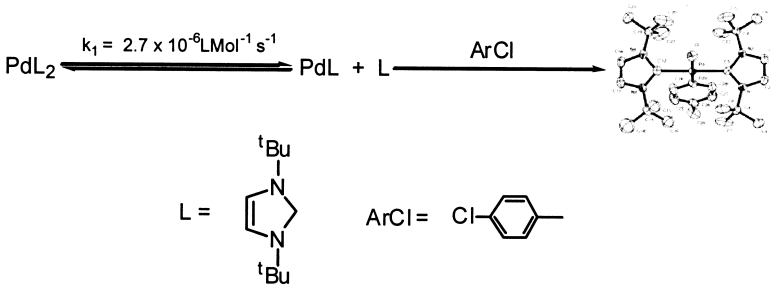

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Synthetic, Structural, and Mechanistic Studies on the Oxidative Addition of Aromatic Chlorides to a Palladium (*N*-Heterocyclic Carbene) Complex: Relevance to Catalytic Amination

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Abstract: The oxidative addition products *trans*-[Pd(NHC)$_2$(Ar)Cl] (NHC = *cyclo*-C{N^{t}BuCH}$_2$; Ar = Me-4-C$_6$H$_4$, MeO-4-C$_6$H$_4$, CO$_2$Me-4-C$_6$H$_4$) have been isolated in good yields from the reactions of ArCl with the amination precatalyst [Pd(NHC)$_2$] and structurally characterized. The former undergo reversible dissociation of one NHC ligand at elevated temperatures, and a value of 25.57 kcal mol^{-1} has been determined for the Pd−NHC dissociation enthalpy in the case where Ar = Me-4-C$_6$H$_4$. Detailed kinetic studies have established that the oxidative addition reactions proceed by a dissociative mechanism. Rate data for the oxidation addition of Me-4-C$_6$H$_4$Cl to [Pd(NHC)$_2$] compared to that obtained for the [Pd(NHC)$_2$]-catalyzed coupling of morpholine with 4-chlorotoluene are consistent with a rate-determining oxidative addition in the catalytic amination reaction. The relative rates of oxidative addition of the three aryl chlorides to [Pd(NHC)$_2$] (CO$_2$Me-4-C$_6$H$_4$Cl > Me-4-C$_6$H$_4$Cl > MeO-4-C$_6$H$_4$Cl) reflect the electronic nature of the substituents and also parallel observed trends in coupling efficiency for these aryl halides in aminations.

Introduction

In recent years the development of hindered phosphines as ligands for palladium complexes with excellent catalytic activity have provided new protocols, which significantly extend the scope of palladium-catalyzed coupling reactions.[1] Work by Amatore,[2] Hartwig,[3] Milstein,[4] Brown[5] Pfaltz,[6] Buchwald,[7] and Blackmond has contributed greatly to the understanding of various mechanistic aspects of palladium phosphine chemistry. Hartwig and Milstein have both demonstrated that oxidative addition to a palladium phosphine complex proceeds via dissociation of phosphine, although the resultant electron count of the palladium differs in the two systems studied: for [Pd(P(o-tolyl)$_3$)$_2$)$_2$] oxidative addition occurs via a 12-electron palladium center,[3] whereas in [Pd(dippp)$_2$] the active species is a 14-electron palladium center.[4] As is evident, the role of ligand has a significant effect upon the active intermediate. Brown has recently gathered further confirmation that the ligand can influence the mechanism of oxidative addition by comparing the reactivity of a series of palladium complexes containing ligands expressing a variety of steric properties ([Pd(PCy$_n$^{t}Bu$_{3-n}$)$_2$]; n = 0−3).[5] Complexes containing the less sterically hindered PCy$_3$ or PCy$_2$^{t}Bu underwent oxidative addition via an associative mechanism, whereas complexes containing P^{t}Bu$_3$ or PCy^{t}Bu$_2$ underwent oxidative addition via a dissociative mechanism.

In all cases previously mentioned, the active intermediate, prior to oxidative addition, has been identified as being either a neutral 12- or 14-electron palladium center. In stark contrast to this, Amatore has proposed that an anionic tricoordinated complex of the type Pd^{0}L$_2$Cl$^-$ or Pd^{0}L$_2$(OAc)$^-$ is the active intermediate as opposed to the traditionally postulated Pd^{0}L$_2$ complexes.[2] The possibility of an anionic intermediate as an active species is given more weight as a result of observations by us[8] and Beller[9] that additives such as tetrabutylammonium salts can significantly improve isolated yields of both inter- and intramolecular Heck reactions.

These detailed mechanistic studies have led to a greater understanding of palladium phosphine catalysis and, as such,

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(1) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371; Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163; Herrmann, W. A.; Reisinger, C. P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93; Herrmann, W. A Böhm, V. P. W.; Reisinger, C. P. *J. Organomet. Chem.* **1999**, *576*, 23; Wescamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348; McGuiness, D. S.; Green, M. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *565*, 165; McGuiness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596.
(2) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
(3) Stambuli, S. P.; Buhl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346.
(4) Portnoy, M.; Milstein, D. *Organometallics*. **1993**, *12*, 1665.
(5) Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1760.
(6) Rosner, T.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 4621.
(7) Singh, V. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104.
(8) Caddick, S.; Kofie, W. *Tetrahedron Lett.* **2002**, *43*, 9347.
(9) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031.

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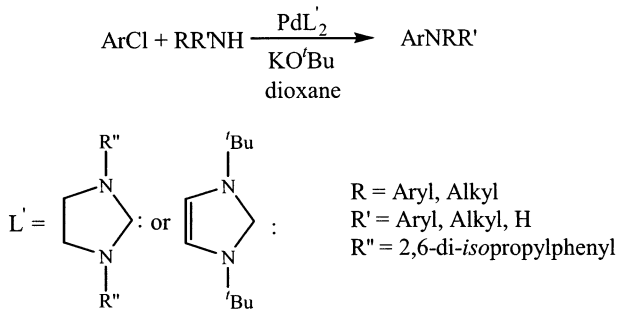


Figure 1. Typical amination reaction.

have resulted in improved synthetic procedures. However, despite the considerable advances made in this area, there are still several drawbacks to the use of phosphines as ligands, e.g., air sensitivity and P−C bond degradation. In this context, *N*-heterocyclic carbenes (NHCs) have been found to be excellent alternative ligands to phosphines and have been instrumental in extending the scope of palladium-catalyzed coupling reactions to involve aryl chlorides as substrates.[10] These improved catalytic systems have been attributed to the robust nature of the NHC−palladium bond and the improved donor capabilities of NHCs compared to those of phosphines.[11] Conventionally, synthetic organic chemists using NHC ligands for palladium-catalyzed protocols employ air-stable imidazolium or imidazolinium salts in the presence of base to generate a catalyst in situ.[8,12] In principle these procedures could generate neutral or cationic palladium species, and there is structural evidence for the formation of both types of complex.[13,14] A plethora of research has been devoted to optimizing synthetic applications of palladium−NHC systems, and although NHCs are often termed phosphine mimics there are, in fact significant electronic, steric, and physical differences between the two ligand classes; hence, it should not be assumed that NHCs would, necessarily, behave in the same manner as phosphines. The mechanisms of Pd−NHC catalyzed couplings remain unclear, and to date there have been no experimental mechanistic studies on these systems to aid in fundamental understanding and reaction optimization.[15]

We have previously described amination of aromatic chlorides catalyzed by the isolable, neutral, two-coordinate Pd(0) carbene complexes shown in Figure 1.[14]

A plausible mechanistic cycle for amination using isolated[16] or in situ generated $Pd(NHC)_2$ complexes is presented in Scheme 1. The active intermediate is proposed to be a neutral, 12-electron, monoligated palladium species as suggested by Hartwig for palladium phosphine systems.[3] Nolan's research into the use of imidazolium salts as precursors to NHCs in aminations has found that the optimum ratio of palladium to imidazolium salt is 1:1; addition of a second equivalent of imidazolium salt results

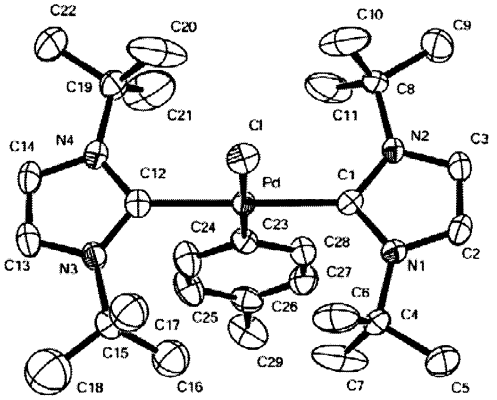
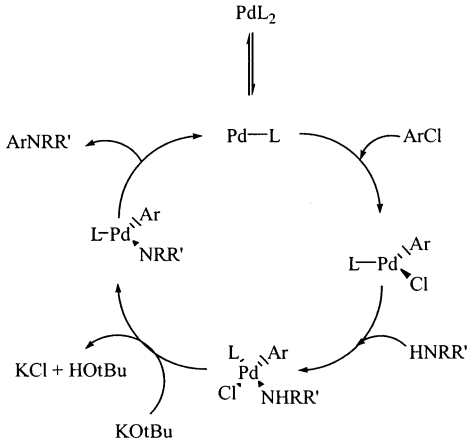


Figure 2. X-ray crystal structure of *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(4-Me-C_6H_4)Cl], **1**.

Scheme 1. Proposed Mechanism for Amination



in retardation of the rate of reaction.[12] These observations strongly indicate that a monoligated palladium species is an active intermediate.

We have previously shown that two-coordinate Pd(0) carbene complexes (PdL_2 in Scheme 1) can act as catalysts,[14] and on the basis of previous mechanistic studies on palladium phosphine systems,[3,4] we anticipated that oxidative addition might be the rate-determining step. Therefore, we have attempted to isolate and study this part of the reaction pathway. We have recently communicated the first structural evidence of oxidative addition of an aryl chloride to a palladium−NHC complex,[17] and this has now allowed us to carry out studies on the mechanism of oxidative addition with a view to developing a mechanistic picture for aryl chloride amination under catalytic conditions using palladium−NHC complexes.

Results and Discussion

Oxidative Addition Reactions of Aryl Chlorides to [Pd(*cyclo*-C{N^{t}BuCH}$_2$]. Isolation of the oxidative addition of aromatic halides to palladium carbene complexes are complicated by the fact that reductive elimination can occur at a competitive rate to generate the arylimidazolium species.[17,18] However, the complex [Pd(*cyclo*-C{N^{t}BuCH}$_2$] (PdL_2) undergoes smooth oxidative addition to generate exclusively *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(4-Me-C_6H_4)Cl] **1** (Figure 2), as we have recently communicated.[17]

(10) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1291; Littke, F. A.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
(11) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Beller, M.; Fischer, H. *J. Organomet. Chem.* **1995**, *491*, C1; Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
(12) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.
(13) Grundemann, S.; Albrecht, M.; Kovacevic, A.; Faller, J. W.; Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2002**, 2163.
(14) Caddick, S.; Cloke, F. G. N.; Clentsmith, G. K. B.; Hitchcock, P. B.; McKerrecher, D.; Titcomb, L. R.; Williams, M. R. V. *J. Organomet. Chem.* **2001**, *617*, 635.
(15) For a theoretical study see: Albert, K.; Gisdakis, P.; Rösch, N. *Organometallics* **1998**, *17*, 1608.
(16) Arnold, P. L.; Cloke, F. G. N.; Geldbach, T.; Hitchcock, P. B. *Organometallics* **1999**, *18*, 3228 and references therein.
(17) Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B.; Leonard, J.; Lewis, A. K. de. K.; Mckerrecher, D.; Titcomb, L. R. *Organometallics* **2002**, *21*, 4318 and references therein.

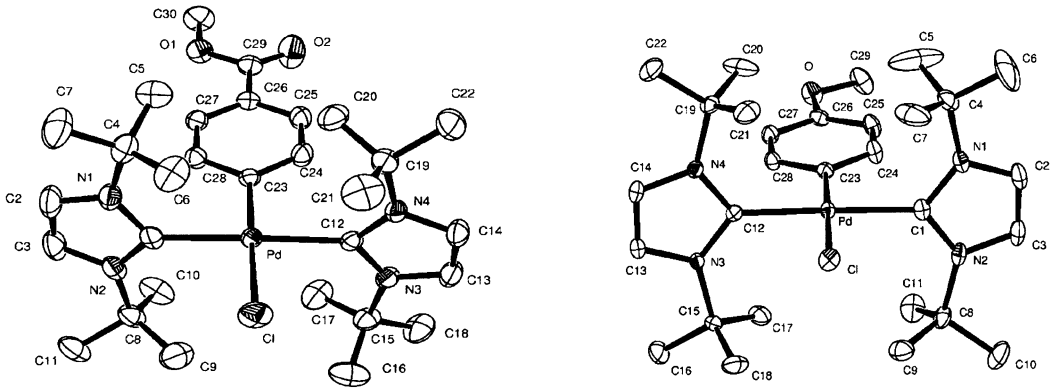


Figure 3. X-ray crystal structure of *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(CO$_2$Me-4-C$_6$H$_4$)Cl], **2**, and *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(OMe-4-C$_6$H$_4$)Cl], **3**.

Table 1. Selected Bond Lengths (Å) and Angles (deg) for **1**, **2**, and **3**

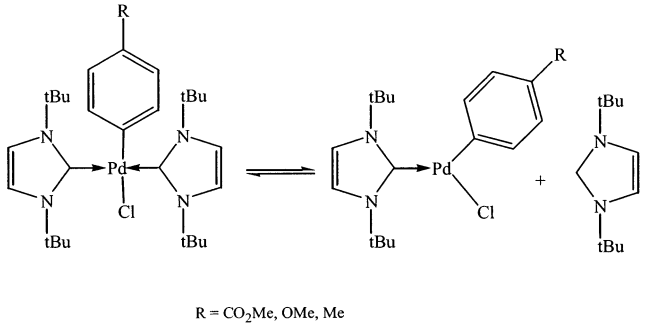
	1	2	3
Pd−C(1)	2.094(4)	2.091(2)	2.097(3)
Pd−C(12)	2.091(4)	2.106(2)	2.094(3)
Pd−C(23)	2.065(4)	2.060(2)	2.063(3)
Pd−Cl	2.445(1)	2.4284(6)	2.4456(7)
C(23)−Pd−C(12)	90.01(15)	92.91(8)	91.80(10)
C(12)−Pd−C(1)	178.35(14)	177.94(8)	178.01(10)
C(23)−Pd−C(1)	91.63(15)	89.12(8)	90.16(11)
C(23)−Pd−Cl	179.30(11)	179.27(6)	179.18(8)
C(12)−Pd−Cl	90.05(10)	86.45(6)	87.39(7)
C(1)−Pd−Cl	88.30(11)	91.52(6)	90.64(8)
N(3)−C(12)−Pd	128.1(3)	127.43(15)	127.81(18)

The successful isolation of **1** suggested that it would be possible to isolate other arylpalladiumchloride complexes via oxidative addition to PdL$_2$, and indeed addition of both methyl-4-chlorobenzoate and 4-chloroanisole to PdL$_2$ resulted in the sole formation of *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(CO$_2$MeO-4-C$_6$H$_4$)Cl], **2**, and *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(4-MeO−C$_6$H$_4$)-Cl], **3**, respectively. The X-ray structures of **2** and **3** are presented in Figure 3, with selected bond lengths and angles (together with those previously reported for **1**, for comparison) shown in Table 1; data collection parameters for **2** and **3** are detailed in Table 2.

1, **2**, and **3** exhibit the expected square-planar geometry, and both the Pd−C$_{carbene}$ and Pd−C$_{aryl}$ bond lengths are the same within all three complexes (within esds). However, the different substituents on the aryl groups of **2** and **3** have a noticeable effect on the trans Pd−Cl bond lengths: the presence of electron-withdrawing ester groups on the aryl ring in **2** results in a Pd−Cl bond length of 2.4248(6) Å, whereas the more electron-rich methoxy-substituted aryl ring in **3** leads to an increase in Pd−Cl bond length (to 2.4456(7) Å) as a result of the relative trans influences of the two aryl groups.

Reversible Dissociation of Carbene from 1, 2, and 3. Complex **1** was heated in C$_6$D$_6$ to 90 °C which led to the clean dissociation of carbene, as indicated by the appearance of free carbene in the ^{1}H NMR spectrum; cooling of the heated complex to 20 °C led to the regeneration of **1** (Scheme 2). Further studies at 10 °C intervals (20−90 °C) showed a gradual increase in free [1,3-^{t}butylimidazol-2-ylidene] (0% at 40 °C, 3% at 50 °C, 6% at 60 °C, 12% at 70 °C, 18% at 80 °C, 27% at 90 °C). Dissociation of a carbene ligand from a Pd(II) center has not been observed previously and is unexpected, given the powerful donor capabilities of NHCs; this result may have important implications for the mechanism of Pd−NHC-mediated coupling reactions. The equilibrium constant *K* for the dissociation at each temperature was determined from the NMR spectra, and from the temperature dependence of *K* (Van't Hoff Isochore), a value for the Pd−C$_{carbene}$ dissociation enthalpy of 25.57 Kcal mol^{-1} in **1** was determined. This value appears reasonable, although comparisons are difficult due to the lack of other, related data.

Scheme 2. Dissociation of 1,3-*tert*-Butylimidazol-2-ylidene from Arylpalladiumhalide Complexes

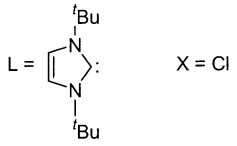


Analogous studies were carried out using **2** and **3**, which also led to the appearance of free carbene at elevated temperatures. Interestingly, **2** only began to dissociate carbene at temperatures >60 °C, whereas the onset for dissociation in **3** is 40 °C. These relative temperatures are presumably a reflection of the two electronically different aryl groups. Unfortunately, due to solubility issues, it was not possible to obtain accurate, quantitative data (and hence dissociation enthalpies) for **2** and **3**.

Theoretical Analysis of the Kinetics of Oxidative Addition. It is generally accepted that oxidative addition can proceed via two possible pathways, associative or dissociative, and therefore, two alternative kinetic models needed to be considered.

The stoichiometric equation for the reaction in question is

$$PdL_2 + ArX \rightarrow ArPdL_2X$$



(i) Associative Mechanism. An associative mechanism would imply a simple bimolecular reaction, following second-order

(18) McGuiness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596.

Table 2. Crystal Data and Structure Refinement for **2** and **3**

	2	**3**
diffractometer	Nonius Kappa CCD	
NN empirical formula	$C_{30}H_{47}ClN_4O_2Pd.(C_6D_6)$	$C_{29}H_{47}ClN_4OPd.2(C_6D_6)$
formula weight	679.62	777.8
temp, K	223(2)	223(2)
wavelength, Å	0.71073	0.71073
crystal system	monoclinic	triclinic
space group	$P2_1/n$	$P2_1/n$
unit cell dimensions		
a, Å	9.9479(2)	12.9986(1)
b, Å	13.4003(2)	13.6632(1)
c, Å	25.1111(3)	23.1150(2)
volume, Å^3	3347.19(9)	4049.89(6)
Z	4	4
density (calcd), Mg/m Å^3	1.35	1.28
$F(000)$	1420	1616
crystal size, mm	0.3 × 0.3 × 0.3	0.25 × 0.20 × 0.20
θ range for data collection, deg	3.75−25.67	3.75−25.35
goodness-of-fit on F^2	1.014	1.031
final R indices	R1 = 0.029	R1 = 0.037
[$I > 2\sigma(I)$]	wR2 = 0.068	wR2 = 0.089
R indices (all data)	R1 = 0.034	R1 = 0.045
	wR2 = 0.071	wR2 = 0.094

kinetics. If the initial concentrations of PdL_2 and ArX are set equal, then the concentration of PdL_2, which is measurable by ^{1}H NMR spectroscopy, should be given by:

$$\frac{1}{[PdL_2]} - \frac{1}{[PdL_2]_0} = kt \qquad (1)$$

(ii) Dissociative Mechanism. The dissociative mechanism, can be expressed in the form:

$$PdL_2 \xrightarrow{k_1} PdL + L$$

$$PdL + L \xrightarrow{k_{-1}} PdL_2$$

$$PdL + ArX \xrightarrow{k_2} \text{products}$$

In this case we have

$$\text{rate} = -\frac{d[PdL_2]}{dt} = -\frac{d[ArX]}{dt} = \frac{d[\text{products}]}{dt} = k_2[PdL][ArX] \qquad (2)$$

and applying steady-state kinetics to [PdL] gives:

$$\text{rate} = -\frac{d[PdL_2]}{dt} = \frac{k_1k_2[PdL_2][ArX]}{k_{-1}[L] + k_2[ArX]} \qquad (3)$$

This equation reduces to a simply analyzable form only if either one of the terms in the denominator is significantly larger than the other, a condition which, in principle, can be achieved by manipulation of either [L] or [ArX].

Effect of Ligand Concentration. A dissociative mechanism will be affected by the concentration of the free ligand in the reaction mixture. Specifically, if the ligand concentration is such that $k_{-1}[L] \gg k_2[ArX]$, then eq 3 becomes

$$\text{rate} = -\frac{d[PdL_2]}{dt} = \frac{k_2k_1[PdL_2][ArX]}{k_{-1}[L]}$$

This implies that association and dissociation of the ligand are much faster than addition of the monoligated species to the aryl halide and corresponds to a preequilibrium of the form:

$$PdL_2 \overset{K}{\rightleftharpoons} PdL + L$$

$$PdL + ArX \xrightarrow{k_2} \text{products}$$

where $K = k_1/k_{-1}$.

Provided that K is small, any ligand present from the dissociation of the complex is negligible, so that $[L] = [L]_{added}$. This gives:

$$K = \frac{[PdL][L]}{[PdL_2]}$$

and when $[PdL_2] = [ArX]$ eq 3 becomes:

$$\text{rate} = -\frac{d[PdL_2]}{dt} = \frac{Kk_2[PdL_2]^2}{[L]}$$

Thus, if the concentration of ligand is large enough, the loss of PdL_2 should follow second-order kinetics, with an apparent rate constant proportional to 1/[L].

A particular case arises if the preequilibrium condition is satisfied at the concentration of ligand arising solely from the dissociation equilibrium of the complex (i.e. no free ligand is added). If this is true, it can be assumed that K is small so that the dissociation has no significant effect on $[PdL_2]$.

We then have [PdL] = [L] and:

$$K = \frac{[PdL][L]}{[PdL_2]} = \frac{[PdL]^2}{[PdL_2]}$$

and

$$[PdL] = K^{1/2}[PdL_2]^{1/2}$$

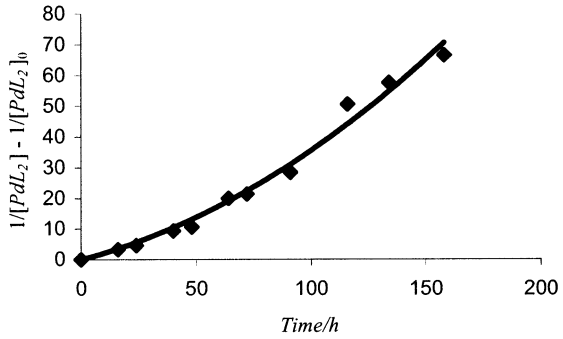


Figure 4. Rate of disappearance of PdL_2 plotted in second-order coordinates.

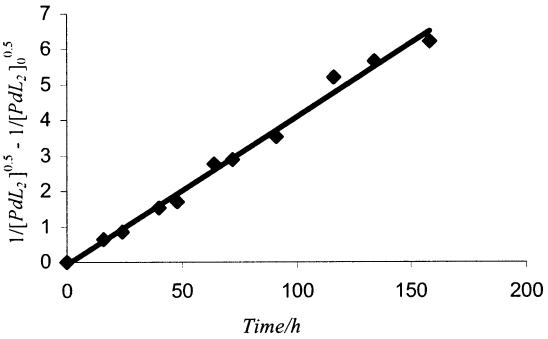


Figure 5. Rate of disappearance of PdL_2 plotted in 3/2-order coordinates.

the rate law can then be written as

$$-\frac{\mathrm{d}[\mathrm{PdL_2}]}{\mathrm{d}t} = k_2K^{1/2}[\mathrm{PdL_2}]^{1/2}[\mathrm{ArX}]$$

If $[PdL_2] = [ArX]$ then this becomes a 3/2-order reaction and we can write:

$$-\frac{\mathrm{d}[\mathrm{PdL_2}]}{\mathrm{d}t} = k_2K^{1/2}[\mathrm{PdL_2}]^{3/2}$$

which integrates to

$$\frac{1}{[\mathrm{PdL_2}]^{0.5}} - \frac{1}{[\mathrm{PdL_2}]_0^{0.5}} = \frac{k_{\mathrm{app}}}{2}t \qquad (4)$$

where the apparent rate constant k_{app} is given by $k_{app} = k_2K^{0.5}$

Effect of Substrate Concentration. The analysis applied thus far is based on the assumption that association and dissociation of the ligand are both sufficiently faster than addition of the monoligated species to the aryl halide, that $k_{-1}[L] \gg k_2[ArX]$. In principle, it is possible to increase the concentration of the aryl halide to the point where $k_{-1}[L] < < k_2[ArX]$. In this case eq 3 becomes:

$$\text{rate} = -\frac{\mathrm{d}[\mathrm{PdL_2}]}{\mathrm{d}t} = \frac{k_1k_2[\mathrm{PdL_2}][\mathrm{ArX}]}{k_2[\mathrm{ArX}]} = k_1[\mathrm{PdL_2}]$$

so that the reaction becomes zero-order in aryl halide and first-order in $[PdL_2]$. This corresponds to a consecutive reaction model in which the first step, dissociation of the ligand, is rate determining.

Experimental Kinetic Results

The reaction of equimolar (0.2 M) amounts of PdL_2 and 4-chlorotoluene in C_6D_6 solution was followed by ^1H NMR, monitoring the disappearance of PdL_2. The oxidative addition of 4-chlorotoluene to PdL_2 proceeds to completion in 1 h at 90 °C; however, to avoid complications from the reversible dissociation of carbene from **1** (vide supra), all studies were performed at 39 °C, where the latter process does not occur to any observable extent by NMR (indeed, the data obtained from initial studies at 90 °C were uninterpretable due to carbene dissociation). Figure 4 shows the ^1H NMR data in second-order coordinates. The reaction was followed to >90% conversion, and it is immediately clear that the data do not give a good fit to second-order kinetics, ruling out an associative mechanism.

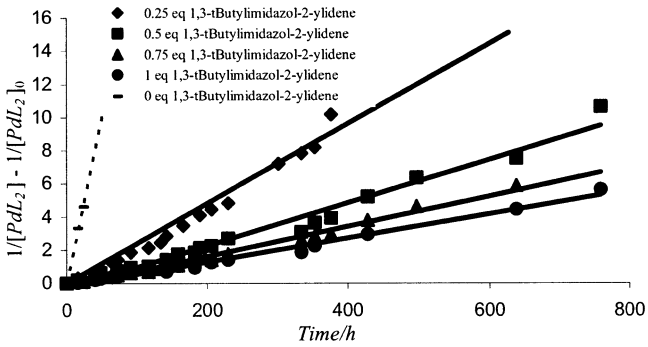


Figure 6. Effect of added L on the rate of disappearance of PdL_2 plotted in second-order coordinates (dotted line represents the reaction with no added L through one half-life).

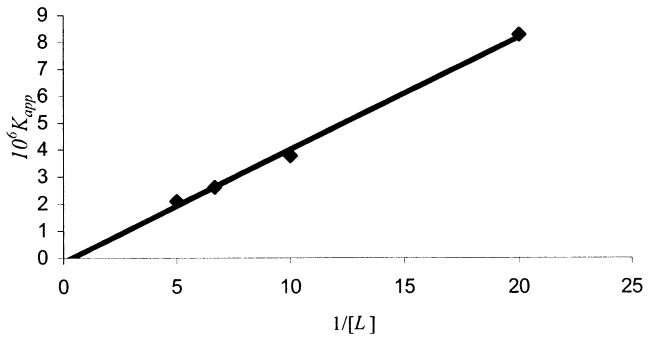


Figure 7. Gradients from Figure 6 plotted as function of 1/[L].

Figure 5 shows the experimental data from Figure 1, plotted according to eq 4. The fit to 3/2-order kinetics is excellent, and a linear regression gives $k_{app} = k_2K^{0.5} = 2.28 \times 10^{-5}$ mol$^{-1/2}$ L$^{1/2}$ s^{-1}. Plotting the same data in first-order coordinates also gives a significantly curved plot (not shown).

Effect of Addition of L. Confirmation of a dissociative mechanism was obtained by studying the effect of addition of the free ligand to the reaction mixture. Excess ligand (0.25, 0.5, 0.75, and 1 equiv) was added to the reaction of equimolar amounts of 4-chlorotoluene and PdL_2. The reaction was slowed significantly by the added ligand, and plotting the results in second-order coordinates (Figure 6) gives good straight lines.

A plot of k_{app} versus 1/[L] is linear with gradient $k_2K = 4.1 \times 10^{-7}$ L mol^{-1} s^{-1} (Figure 7).

Combining these data ($k_2K^{0.5} = 2.28 \times 10^{-5}$ mol$^{-1/2}$ L$^{1/2}$ s^{-1} and $k_2K = 4.1 \times 10^{-7}$ L mol^{-1} s^{-1}) gives values for k_2 (rate constant of oxidative addition) $= 1.26 \times 10^{-3}$ L mol^{-1} s^{-1} and

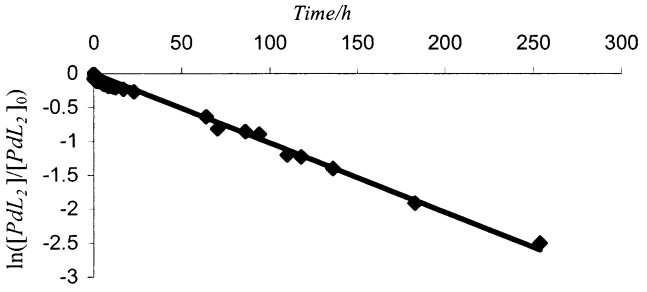


Figure 8. Effect of added ArX on the rate of disappearance of PdL_2 plotted in first-order coordinates.

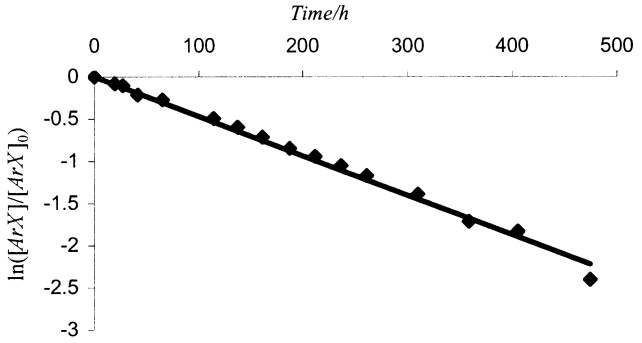


Figure 9. Catalytic amination: disappearance of ArX in first-order coordinates.

K (equilibrium constant for ligand dissociation) $= 3.2 \times 10^{-4}$ mol L^{-1}.

Effect of Substrate Concentration. Figure 8 shows the data for a reaction with 10 equiv of 4-chlorotoluene per mol of PdL_2, plotted in first-order coordinates.

The data fit a good straight line with a slope, $k_1 = 2.69 \times 10^{-6}$ s^{-1}. Plots of these data in 2- or 3/2-order coordinates (not shown) are markedly curved. In principle, these data now allow us to calculate all three rate constants. Since we have $k_1 = 2.69 \times 10^{-6}$ s^{-1} and $K = 3.2 \times 10^{-4}$, we obtain $k_{-1} = 8.32 \times 10^{-3}$ L mol^{-1} s^{-1}.

These data unequivocally confirm a dissociative mechanism. However, if the derived rate constants are used to calculate the equilibrium ligand concentration in experiments with equimolar reagents and no added ligand, it becomes apparent that the essential condition used in deriving eq 4 (i.e. that $k_{-1}[L] \gg k_2[ArX]$) is not true over a substantial part of the reaction. For most of the conversion range the two terms are comparable, but the preequilibrium condition is satisfied toward the end of the reaction when [ArX] falls to a sufficiently low value. The good fit to overall 3/2-order kinetics arises because the reaction is 3/2-order at high conversions and it is not possible to distinguish between orders at low conversions.

From the reaction in the presence of added ligand we know that $k_2K = 4.1 \times 10^{-7}$ L mol^{-1} s^{-1} and the reaction in the presence of excess ArX gives $k_1 = 2.69 \times 10^{-6}$ s^{-1}. It follows that $k_2/k_{-1} = 0.15$; for equal concentrations of free ligand and substrate the reaction of PdL with L to give PdL_2 is 7 times faster than its addition to ArX. However, since [L] is low, because K is small, the usual condition is [ArX] $\gg$ [L], and dissociation of the complex is rate determining over much of the concentration range. This is confirmed by the fact that the initial rate under conditions where [ArX] = 10[L] (5.4×10^{-7} mol L^{-1} s^{-1}) is only slightly faster than that where [ArX] = [L] (3.3×10^{-7} mol L^{-1} s^{-1}). The reaction with equimolar concentrations does not follow first-order kinetics because both terms in the denominator of eq 3 are contributing to different extents as a function of conversion. Some dissociation of the product at high conversion might also contribute but is not experimentally verifiable.

Relevance to Catalytic Amination. Thus far only the stoichiometric oxidative addition reaction has been considered; however, there is clearly value in attempting to relate these data to the overall *catalytic* amination. This can be achieved by measuring the rate of reaction of 4-chlorotoluene with an amine using PdL_2 as a catalyst at 39 °C. Under these conditions [PdL_2] is maintained constant by its regeneration, and the reaction should be first-order in aryl halide. If oxidative addition is the rate-determining step, the rate constant for amination can be calculated as:

$$\text{rate constant} = k_2K^{0.5}[PdL_2]^{0.5} \qquad (5)$$

The reaction of 4-chlorotoluene (0.2 M) with morpholine using PdL_2 (2 mol %) as catalyst at 39 °C was followed by ^1H NMR. Plotting the data in first-order coordinates with respect to 4-chlorotoluene (Figure 9) shows a good fit, which gives the rate constant for amination as 1.23×10^{-6} s^{-1}.

Since the concentration of PdL_2 was 0.004 M and $k_2K^{0.5}$ was found to be 2.28×10^{-5} $mol^{-1/2}$ $L^{1/2}$ s^{-1}, the rate constant for amination predicted by eq 5 is 1.44×10^{-6} s^{-1}, in agreement to that found experimentally.

The similarity of these values is consistent with a mechanism for catalytic amination involving rate-determining oxidative addition. If reductive elimination played a greater role in the rate, then the values obtained for the overall rate of amination would differ significantly from those calculated theoretically. However, we note the potential pit-falls in extending the data obtained from studying one part of a catalytic pathway under stoichiometric conditions. Our work for example does not take into consideration the potential change in mechanism that may occur when using a large excess of base or a variety of different amines.[7] Notwithstanding these limitations we believe that the analysis is of use in the design of new catalysts and protocols for amination using palladium−(NHC) complexes.

Substituent Effects. Having extensively studied the oxidative addition of 4-chlorotoluene to PdL_2, we now wanted to extend the scope of our investigation to include aryl chlorides with varying electronic properties. Experimental studies have found that aryl chlorides containing electron-withdrawing groups (EWG) result in higher yields of coupled product than those containing electron-donating groups (EDG);[10] this effect can be explained by the resonance structures shown in Scheme 3.

When EWGs are present, electron density is removed from the aryl chloride, thus making the Ar−Cl bond more susceptible to oxidative addition. With EDGs the reverse happens: the aryl chloride bond is more electron rich, thus decreasing the rate of oxidative addition. If oxidative addition were rate determining in aminations, aryl chlorides containing EWGs should have a much faster rate than 4-chlorotoluene, and likewise aryl chlorides containing strongly EDGs should have a markedly slower rate.

Oxidative Addition of Methyl-4-chlorobenzoate. The reaction was followed to greater than 90% conversion, and once again the data gave a good fit to 3/2-order kinetics (Figure 10),

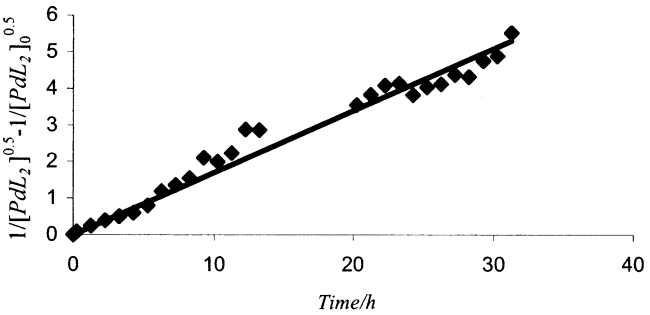
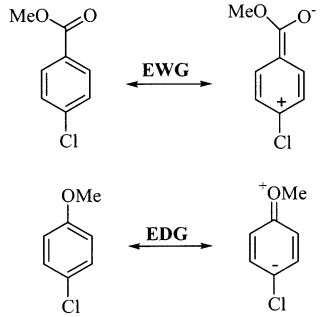


Figure 10. Rate of disappearance of PdL_2 plotted in 3/2-order coordinates.

Scheme 3. Electronic Effects on Para Substituents on Aryl Groups



with first- and second-order plots (not shown) being curved. These data conform to the original hypothesis of a reaction that approximates the preequilibrium model.

The gradient of Figure 6 gives $k_{app} = k_2K^{0.5} = 4.55 \times 10^{-5}$ $mol^{-1/2}$ $L^{1/2}$ s^{-1}. If it is assumed that K is unchanged by any solvent effect of the substrate then taking $K = 3.2 \times 10^{-4}$ gives, $k_2 = 2.54 \times 10^{-3}$ L mol^{-1} s^{-1}. The rate constant of oxidative addition for the electron-deficient aryl chloride is thus about twice that for 4-chlorotoluene. This demonstrates the effect on the rate of oxidative addition that occurs for the simple exchange of a methyl for a carboxylic ester. As with 4-chlorotoluene, the rate constant values must be viewed with some caution, but the data are entirely consistent with the dissociative mechanism.

Oxidative Addition of 4-Chloroanisole. The oxidative addition of 4-chloroanisole to PdL_2 was also followed to >90% at 39 °C. However, the onset of carbene dissociation in the resultant oxidative addition product **3** occurs at essentially the same temperature (vide infra), thus seriously complicating the present kinetic model; hence kinetic analysis of the results was not attempted. Nonetheless the reaction took 400 h to proceed to >90% completion (compared with 60 h for **2** and 150 h for **1**); thus, it is clear that the rate of oxidative addition is slowed by the addition of a strongly EDG at the para position.

Comparison of the rates shows that the functional group has a significant effect on the rate of oxidative addition and thus helps to explain the general observation that electron-rich aryl chlorides are often very poor coupling substrates, whereas electron-poor aryl chlorides are usually very competent coupling substrates.

Conclusions

We have shown that the catalytic amination of an aromatic chloride using a two-coordinate, Pd(0)−NHC complex proceeds by a rate-determining oxidative addition step. Detailed studies have established that oxidative addition occurs via a dissociative mechanism in which dissociation of the complex is rate determining under conditions typical of catalytic amination. Oxidative addition is significantly affected by the substituents on the aryl ring: this results in an increase in rate of oxidative addition for electron-poor aryl chlorides and a decrease in rate of oxidative addition for electron-rich aryl chlorides, in accord with experimentally observed C−X bond coupling trends.

We have also demonstrated the ability of the oxidative addition products **1**, **2**, and **3** to reversibly dissociate free carbene and thus determined a value for the Pd(II)−NHC dissociation enthalpy; the resultant three-coordinate arylpalladiumchloride complexes are likely important intermediates in aminations.

Experimental Section

General Methods. All manipulations were carried out in an inert atmosphere drybox under dinitrogen or on a standard Schlenk line under argon, unless otherwise stated. ^{1}H NMR spectra were recorded on a Brucker Avance 300DPX spectrometer operating at 300.13 MHz, and chemical shifts were referenced to residual solvent resonances. $(Me_3Si)_4Si$ was employed as an internal calibrant for integration. d_6-Benzene was dried by reflux over potassium and vacuum-transferred into an ampule equipped with a greaseless stopcock. 4-Chlorotoluene and morpholine were dried over activated molecular sieves, degassed, and vacuum-transferred into ampules equipped with greaseless stopcocks. [Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$],[14] [Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(4-Me-C_6H_4)Cl] **1**,[17] and 1,3-^{t}butylimidazol-2-ylidene[16] were prepared by literature procedures. [$NaOCEt_3$] was prepared by refluxing $HOCEt_3$ in toluene over sodium metal, filtering, and evaporating to dryness.

Synthesis of *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(CO_2Me-4-C_6H_4)Cl], 2. [Pd{*cyclo*-C(N^{t}BuCH)$_2$}$_2$] (500 mg, 1.07 mmol), methyl-4-chlorobenzoate (913 mg, 5.4 mmol) and benzene (10 mL) were added to a Schlenck (100 mL). The reaction was heated to 40 °C for 120 h, after which time a white crystalline solid had precipitated. The excess benzene was removed via cannula, and the solid was washed with pentane and then dried under vacuum. Yield 71%.

^{1}H NMR (d_6-benzene) 7.58 (2H, d, J = 8.6 Hz, ArH), 6.84 (2H, s, CH), 6.51 (2H, d, J = 8.6 Hz, ArH), 3.47 (3H, s, CH_3O), 1.93 (36H, s, ^{t}Bu). ^{13}C NMR (d_6-benzene): 177.6 (PdC(N^{t}BuCH)$_2$, 168.1 (CO_2-Me), 156.1 (Ar), 142.7 (Ar), 124.6 (Ar), 117.9 (PdC(N^{t}BuCH)$_2$, 59.8 (CCH_3), 51.1 (CO_2CH_3), 32.8 (CCH_3). MS (EI): m/z 601 (M^+ − Cl), 502 (M^+ − $ArCO_2Me$), 465 (M^+ − Cl and $ArCO_2Me$). Anal.: Calcd for $C_{30}H_{47}N_4O_2ClPd$: C: 56.51, H: 7.43, N: 8.76; Found C: 56.73, H: 7.28, N: 8.42.

Synthesis of *trans*-[Pd(*cyclo*-C{N^{t}BuCH}$_2$)$_2$(OMe-4-C_6H_4)Cl], 3. [Pd{*cyclo*-C(N^{t}BuCH)$_2$}$_2$] (500 mg, 1.07 mmol), 4-chloroanisole (1.31 mL, 10.7 mmol) and benzene (10 mL) were added to a Schlenck (100 mL). The reaction was heated to 40 °C for 120 h, after which time a white crystalline solid had precipitated. The excess benzene was removed via cannula, and the solid was washed with pentane and then dried under vacuum. Yield 66%.

^{1}H NMR (d_6-benzene) 6.79 (2H, s, CH), 6.45 (2H, d, J = 8.9 Hz, ArH), 6.31 (2H, d, J = 8.8 Hz, ArH), 3.30 (3H, s, CH_3O), 1.99 (36H, s, ^{t}Bu). ^{13}C NMR (d_6-benzene): 179.6 (PdC(N^{t}BuCH)$_2$, 156.0 (Ar), 143.3 (Ar), 126.8 (Ar), 117.5 (PdC(N^{t}BuCH)$_2$, 112.021 (Ar), 59.8 (CCH_3), 54.2 (CH_3O), 32.9 (CCH_3). MS (EI): m/z 607 (M^+), 502 (M^+ − ArOMe), 465 (M^+ − Cl and ArOMe). Anal. Calcd for $C_{29}H_{47}N_4OClPd$: C: 57.14, H: 7.77, N: 9.19; Found: C: 56.35, H: 7.56, N: 9.20.

General Procedure for the Oxidative Addition of Aryl Chlorides to [Pd(*cyclo*-C{N^{t}BuCH}$_2$]. [Pd(*cyclo*-C{N^{t}BuCH}$_2$] (0.12 mmol, 1 equiv), aryl chloride (0.12 mmol, 1 equiv), $(Me_3Si)_4Si$ (0.03 mmol, 0.25 equiv), and d_6-benzene (0.6 mL) were added to an NMR tube which was removed from the drybox and flame sealed. A ^{1}H NMR spectrum was acquired at room temperature, whereupon the reaction was placed in a thermostated heating block at 39 °C. ^{1}H NMR spectra

were acquired every 24 h at 39 °C until the reaction had gone through at least than two half-lives of [Pd(*cyclo*-C{N^{t}BuCH}$_2$].

General Procedure for the Reaction of 4-Chlorotoluene, [Pd(*cyclo*-C{N^{t}BuCH}$_2$] and 1,3-^{t}butylimidazol-2-ylidene (0.03 mmol, 0.06 mmol, 0.09 mmol, 0.12 mmol). [Pd(*cyclo*-C{N^{t}BuCH}$_2$] (50 mg, 0.12 mmol), 4-chlorotoluene (14 μL, 0.12 mmol), 1,3-^{t}butylimidazol-2-ylidene, (Me$_3$Si)$_4$Si (10 mg, 0.03 mmol) and d_6-benzene (0.6 mL) were added to an NMR tube which was removed from the drybox and flame sealed. A ^{1}H NMR spectrum was acquired at room temperature, whereupon the reaction was placed in a thermostated heating block at 39 °C. ^{1}H NMR spectra were acquired every 24 h at 39 °C until the reaction had gone through at least than two half-lives of [Pd(*cyclo*-C{N^{t}BuCH}$_2$].

Catalytic Amination of 4-Chlorotoluene and Morpholine. [Pd(*cyclo*-C{N^{t}BuCH}$_2$] (1 mg, 0.0024 mmol), 4-chlorotoluene (14 μL, 0.12 mmol), morpholine (12 μL, 0.14 mmol), [NaOCEt$_3$] (28 mg, 0.2 mmol), (Me$_3$Si)$_4$Si (10 mg, 0.03 mmol), and d_6-benzene (0.6 mL) were added to an NMR tube which was removed from the drybox and flame sealed. A ^{1}H NMR spectrum was acquired at room temperature, whereupon the reaction was placed in a thermostated heating block at 39 °C. ^{1}H NMR spectra were acquired every 24 h at 39 °C until the reaction had gone to completion (disappearance of 4-chlorotoluene).

Catalytic Amination of 4-Chlorotoluene and Morpholine Using 1. 1 (1.4 mg, 0.0024 mmol), 4-chlorotoluene (14 μL, 0.12 mmol), morpholine (12 μL, 0.14 mmol), [NaOCEt$_3$] (28 mg, 0.2 mmol), (Me$_3$Si)$_4$Si (10 mg, 0.03 mmol), and d_6-benzene (0.6 mL) were added to an NMR tube which was removed from the drybox and flame sealed. A ^{1}H NMR spectrum was acquired at room temperature, whereupon the reaction was placed in a thermostated heating block at 50 °C. ^{1}H NMR spectra were acquired every 24 h at 50 °C until the reaction had gone to completion (disappearance of 4-chlorotoluene).

Thermal Stability Studies on 1, 2, and 3. Arylpalladiumhalide complex (**1**, **2**, and **3**) (0.0085 mmol) was dissolved in d_6-benzene in an NMR tube, and the tube flame sealed. The ^{1}H NMR spectrum was monitored at 10 °C intervals over the range 20−90 °C, and then again at 20 °C.

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Supporting Information Available: Complete crystallographic details of the X-ray structures of **2** and **3** (CIF), Van't Hoff Plot and parameters, and variable temperature NMR spectra showing dissociation of carbene from **1** (PDF). This material is available free of charge via the Web at http://pubs.acs.org.

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