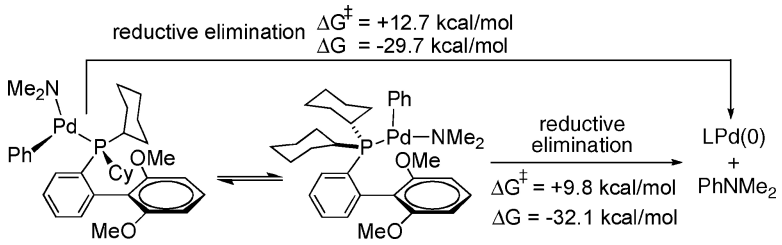
Article

Insights into Amine Binding to Biaryl Phosphine Palladium Oxidative Addition Complexes and Reductive Elimination from Biaryl Phosphine Arylpalladium Amido Complexes via Density Functional Theory

Timothy E. Barder, and Stephen L. Buchwald

J. Am. Chem. Soc., **2007**, 129 (39), 12003-12010• DOI: 10.1021/ja073747z • Publication Date (Web): 12 September 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 14 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 09/12/2007

Insights into Amine Binding to Biaryl Phosphine Palladium Oxidative Addition Complexes and Reductive Elimination from Biaryl Phosphine Arylpalladium Amido Complexes via Density Functional Theory

Timothy E. Barder* and Stephen L. Buchwald*

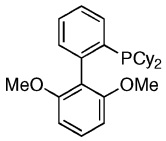
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139

Received June 13, 2007; E-mail: tbarder@mit.edu; sbuchwal@mit.edu

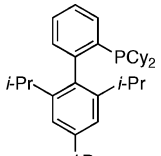
Abstract: We present results on the binding of a variety amines to monoligated oxidative addition complexes of the type $L_1Pd(Ar)Cl$, where L is 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, **1**) or 2-dicyclohexylphosphino-2′,4′,6′-tri-ispropylbiphenyl (XPhos, **2**). The binding of an amine to oxidative addition complexes composed of **1** and **2** is more complex than with smaller ligands as intermediate Pd(II) complexes with bulky biaryl phosphine ligands disfavor amine binding to favorable conformations of oxidative addition complexes. Additionally, thermodynamic and kinetic parameters for reductive elimination from complexes of the type $L_1Pd(amido)Ph$ (where amido = EtNH, Me_2N, PhNH) are discussed. From this data, we suggest a possible mechanism for (biaryl phosphine) Pd-catalyzed amination reactions that is more intricate than previously thought.

Introduction

The use of biaryl phosphines as supporting ligands in Pd-catalyzed cross-coupling reactions allows for the use of mild reaction conditions, low catalyst loadings, short reaction times, and in processes that display high functional group compability.[1] Catalysts based on this class of supporting ligand promote a variety of cross-coupling reactions, including C−N[2] and C−O[3] bond forming reactions, Suzuki−Miyaura[4] and Negishi[5] coupling processes, and the α-arylation of carbonyl-containing compounds.[6] Although these ligands are often-used in Pd catalysis, the structure and reactivity of specific intermediates that lie within catalytic cycles is still largely unknown, due to the difficulty in obtaining either solution or solid-state structural information.[7] This difficulty likely stems from the instability in the absence of substrates and the subsequent decomposition of complexes composed of bulky biaryl phosphines. Although we have been able to obtain limited data via NMR and X-ray crystallographic studies, much information remains elusive, e.g., the influence of the non-phosphine-containing aromatic ring of the ligand in regard to (1) the binding of an amine to complexes of the type $L_1Pd(Ar)X$ (where L_1 is **1** or **2**) and (2) reductive



1



2

elimination from $L_1Pd(Ar)(amido)$ (where L_1 is **1** or **2**). Since both of these processes are of obvious importance in Pd-catalyzed amination reactions and obtaining structural information on amine-bound intermediates may aid in the development of more effective catalysts, we undertook theoretical studies to help determine what aspect(s) of ligand structure are important for amine binding and for inducing reductive elimination. Some of the complexes used for analyzing amine binding are based upon our previous report regarding oxidative addition to **1**·Pd(0) and **2**·Pd(0).[8] Herein we present results on amine binding

(1) (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (b) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374. (c) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23−39.

(2) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174. (d) Huang, X. H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655.

(3) (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378. (b) Vorogushin, A. V.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146−8149. (c) Burgos, C. H.; Barder, T. E.; Huang, X. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321−4326.

(4) (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (b) Yin, J. J.; Rainka, M. P.; Zhang, X. X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (e) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484−3488.

(5) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028−13032.

(6) (a) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370. (b) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *123*, 7996−8002.

(7) We recently we able to synthesize and obtain an X-ray crystal structure of **1**·$Pd(PrNH_2)(Ph)Cl$, see: Biscoe, M. R.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.*. Early View Communication.

(8) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183−2192.

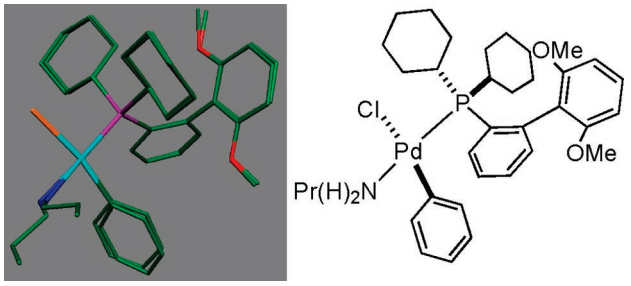


Figure 1. Overlay of the X-ray structure of **1**·Pd(PrNH$_2$)(Ph)Cl with the energetically favored calculated structure of **1**·Pd(PrNH$_2$)(Ph)Cl.

to oxidative addition complexes and reductive elimination of arylpalladium amido complexes composed of **1** and **2**.

Results

Computational Methods. All calculations were conducted on a home-built Linux cluster consisting of 12 dual Opteron processors. Ground state geometry optimizations, using all-atom DFT without any approximations, were conducted using Gaussian 03[9] with the B3LYP hybrid functional.[10] For complexes **3**−**21**, the 6-31G basis set was used for C, H, and O, the 6-31G(d) basis set was used for N, P, and Cl, and LANL2DZ+ECP[11] was employed for the Pd center. The smaller 6-31G basis set was used for C, H, and O since these atoms are not involved in the binding of an amine to the Pd(II) center and nearly identical geometries and energies were obtained for the 6-31G and 6-31G(d) basis sets for C, H, and O (see the Supporting Information for details). However, for complexes **22**−**33**, the 6-31G(d) basis set was used for C, H, O, N, P, and Cl and LANL2DZ+ECP[11] was employed for the Pd center to ensure more accurate kinetic parameters. All calculated structures were verified to be local minima (all positive eigenvalues) for ground state structures or first-order saddle points (one negative eigenvalue) for transition state structures by frequency calculations. The Gibbs free energies were calculated at 298.15 K and 1 atm, are unscaled, and based upon ideal gas-phase conditions.

Toward the end of this study, we were able to obtain an X-ray crystal structure of an amine-bound oxidative addition complex: **1**·Pd(PrNH$_2$)(Ph)Cl.[7] In **1**·Pd(PrNH$_2$)(Ph)Cl, the Pd center is positioned distal from the non-phosphine-containing ring of the ligand as predicted by the data in Table 1 (see below). In order to demonstrate the accuracy of the theoretical methods employed, we optimized **1**·Pd(PrNH$_2$)(Ph)Cl. Figure 1 contains an overlay of the X-ray structure with the calculated structure of **1**·Pd(PrNH$_2$)(Ph)Cl. Although the calculated structure is based in the gas phase, whereas the X-ray structure is based in the solid state, there exists good overlap between the two structures of **1**·Pd(PrNH$_2$)(Ph)Cl, which lends credence to the validity of the basis sets employed in this work regarding amine-bound complexes.

Amine Binding to Oxidative Addition Complexes. The binding of an amine to the Pd center must substantially decrease the pK_a of the bound amine such that deprotonation can readily occur with bases such as NaO*t*-Bu[2,12] or even K_3PO_4.[2c] Despite the importance of amine binding in C−N cross-coupling

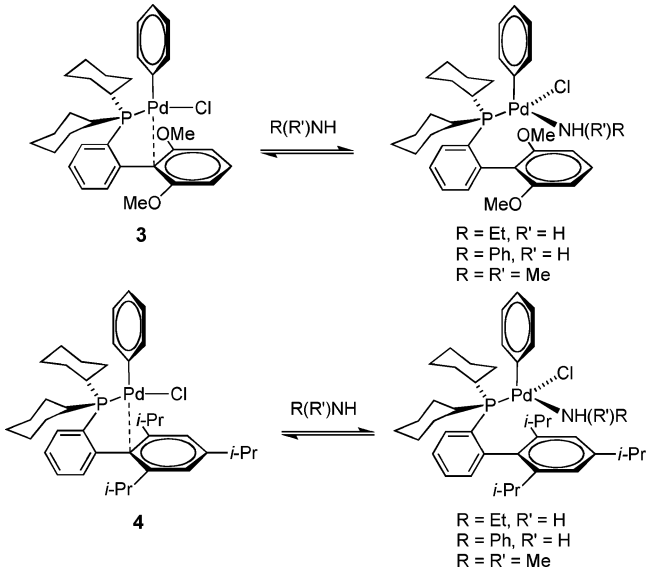


Figure 2. Proposed binding of various amines to **1**·Pd(Ph)Cl and **2**·Pd(Ph)Cl.

reactions, the only manuscript regarding biaryl phosphine−Pd(amine)(Ph)X complexes was recently reported from our group.[7] To the best of our knowledge, only three X-ray crystal structures of any phosphine-ligated amine-bound Pd(II) complex that possesses at least one N−H bond have been previously reported.[13,14] To gain a sense as to the nature of the interaction of an amine with a Pd(II) oxidative addition complex based upon **1** and **2**, several structures based upon a favored isomer of **1**·Pd(Ph)Cl and **2**·Pd(Ph)Cl[8] were optimized in which ethylamine, dimethylamine, and aniline were bound to the Pd center. We hypothesized that amine binding to the Pd(II) center may be difficult as a result of steric congestion around the non-phosphine-containing ring of the ligand and the Pd center (Figure 2, complexes **3** and **4**).

We first examined possible geometries of ethylamine bound to **1**·Pd(Ph)Cl. Initial ground state geometry optimizations on **5** and **5a** led to a dissociation of either the amine from the Pd center (>3.5 Å) or the chloride from the Pd center (>3.5 Å), respectively (Figure 3). On the basis of these results, it is clear that amine binding is not favored when the oxidative addition complex exists in this geometry. The inability of ethylamine to bind to **1**·Pd(Ph)Cl while in the geometry depicted in Figure 2 is not unanticipated, as the square plane around the Pd(II) center is already saturated with four ligands: the phosphorus center, phenyl group, chloride, and a Pd−arene interaction with the non-phosphine-containing ring of the ligand. As ethylamine is the smallest and the most nucleophilic amine in our study, it is expected that optimization of similar complexes to **5** and **5a**, but with different amines, would behave in a similar fashion.

In order for ethylamine to favorably bind to the Pd center in **1**·Pd(Ph)Cl, rotation of the square plane around the Pd center (Figure 4) to exclude the non-phosphine-containing ring of the ligand as a coordination site for the Pd center is required (complex **6**). Although this oxidative addition complex is

(9) Frisch, M. J.; et al. *Gaussian 03*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2004.
(10) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(11) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299−310.
(12) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860.
(13) Alcazar-Roman, L. M.; Hartwig, J. F. *Organometallics* **2002**, *21*, 491−502.
(14) (a) Albert, J.; Granell, J.; Luque, A.; Minguez, J.; Moragas, R.; Font-Bardia, M.; Solans, X. *J. Organomet. Chem.* **1996**, *522*, 87−95. (b) Albert, J.; Granell, J.; Zafrilla, J.; Font-Bardia, M.; Solans, X. *J. Organomet. Chem.* **2005**, *690*, 422−429.

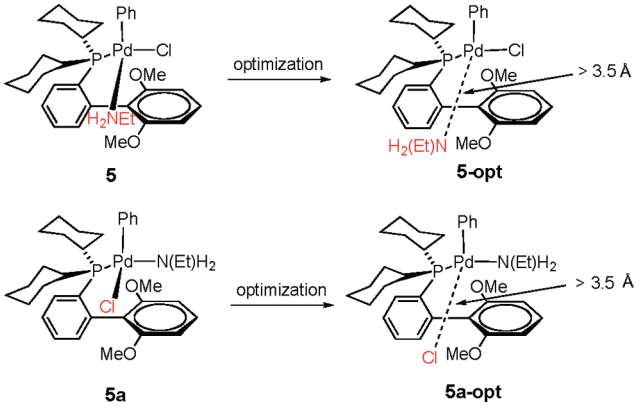


Figure 3. Ground state geometry optimizations on **1**·Pd(Ph)($EtNH_2$)Cl.

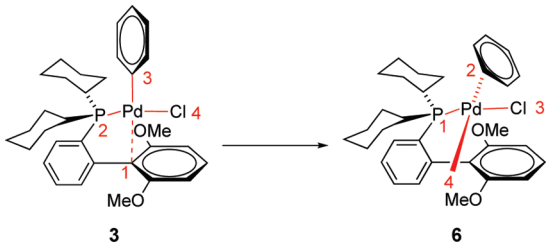


Figure 4. Rotation of the square plane around the Pd center to allow for amine binding.

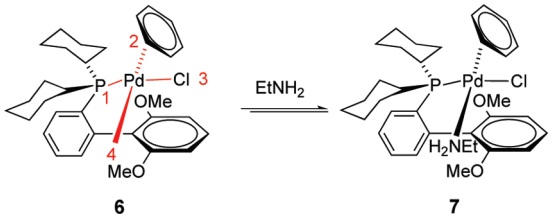


Figure 5. Binding of ethylamine to the open coordination site in **6**.

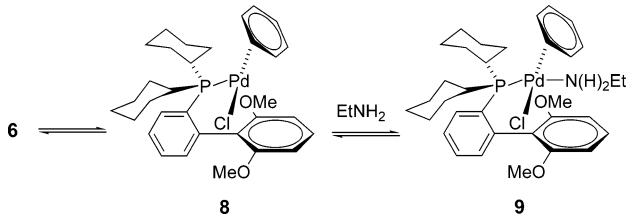


Figure 6. Isomerization of **1**·Pd(Ph)Cl followed by amine binding.

energetically less favored than **3**, ethylamine can readily bind to an open coordination site of the Pd center (site number 4 in complex **6**) which was made available by decoordination of the ipso carbon.

Upon binding of ethylamine to coordination site 4 in **6**, complex **7** is produced (Figure 5). Although **7** is a local minimum, it is not the favored isomer of **1**·Pd(Ph)($EtNH_2$)Cl. Previous experimental studies have shown that complexes of the type (PR_3)·Pd(amine)Cl exist with the amine trans to the phosphine.[15] This is due to the trans effect,[16] and it was determined that the species based upon **1**·Pd(Ph)($EtNH_2$)Cl with the amine trans to the phosphine (**9**) is favored by 11.4 kcal/mol (relative to **7**). Hence, it is likely that isomerization of the chloride in **6** to yield **8** (which is 5.2 kcal/mol higher in free energy than **3**), followed by amine binding allows for the formation of a more stable species, **9** (Figure 6). It is important to note that unlike oxidative addition complexes (**3** and **4**), a Pd−arene interaction does not exist in **9** as the shortest Pd−arene distance is 3.51 Å (Pd−C_{ipso}). Furthermore, the Pd center in **9** exists in a sterically congested environment due to the proximity of the non-phosphine-containing ring of the ligand. This congestion may preclude deprotonation by a bulky base such as the commonly employed NaO*t*-Bu. Additionally, for amines larger than ethylamine a complex of this geometry becomes less energetically favored as described below.

Chart 1. Potential Energy Surface (PES) Scan Varying the Torsion Angle C1−C2−P−Pd of **1**·Pd(Ph)Cl

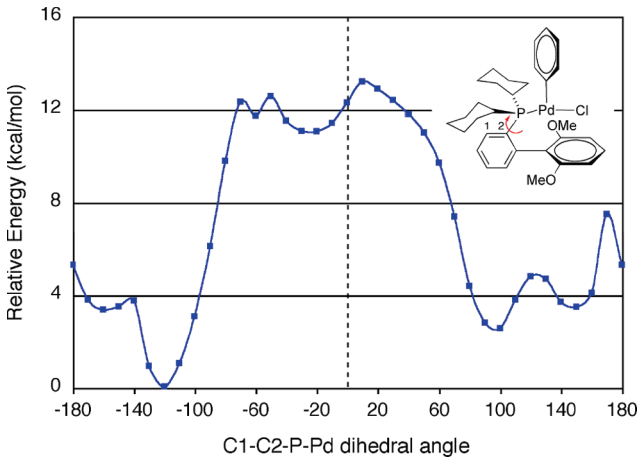
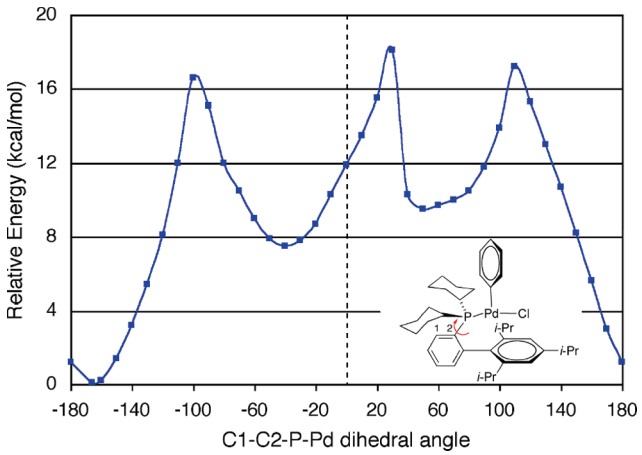


Chart 2. Potential Energy Surface (PES) Scan Varying the Torsion Angle C1−C2−P−Pd of **2**·Pd(Ph)Cl



Potential Energy Surface Scans of L_1Pd(Ph)Cl. We postulated that amine coordination and deprotonation of the bound amine would be more favored in a complex that positions the Pd center distal to the non-phosphine-containing ring of the ligand. To arrive at such a geometry, rotation around C2−P must occur (see Chart 1 for the numbering scheme). In order to determine if this rotation is viable in **1**·Pd(Ph)Cl, we conducted a potential energy surface (PES) scan varying the C1−C2−P−Pd dihedral angle in **1**·Pd(Ph)Cl. Chart 1 contains a PES scan of this rotation, where 36 structures were optimized with a constrained C1−C2−P−Pd dihedral angle ranging from 180° to −180°. It is clear from the PES scan that rotation from the

(15) (a) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 1745−2754. (b) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755−2763.

(16) (a) Quagliano, J. V.; Schubert, L. *Chem. Rev.* **1952**, *50*, 201−260. (b) Basolo, F. *Prog. Inorg. Chem.* **1962**, *4*, 381−453. (c) Coe, B. J.; Glenwright, S. J. *Coord. Chem. Rev.* **2000**, *203*, 5−80.

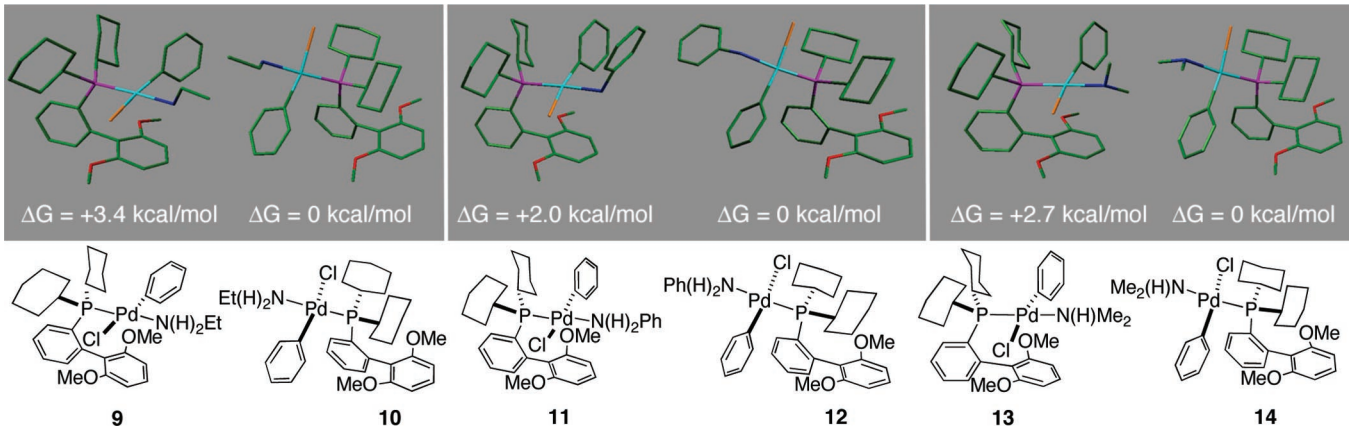


Figure 7. Optimized structures of two conformers of **1**·Pd(ethylamine)(Ph)Cl, two conformers of **1**·Pd(aniline)(Ph)Cl, and two conformers of **1**·Pd(dimethylamine)(Ph)Cl. Key: green = carbon, purple = phosphorus, turquoise = palladium, red = oxygen, orange = chlorine, blue = nitrogen.

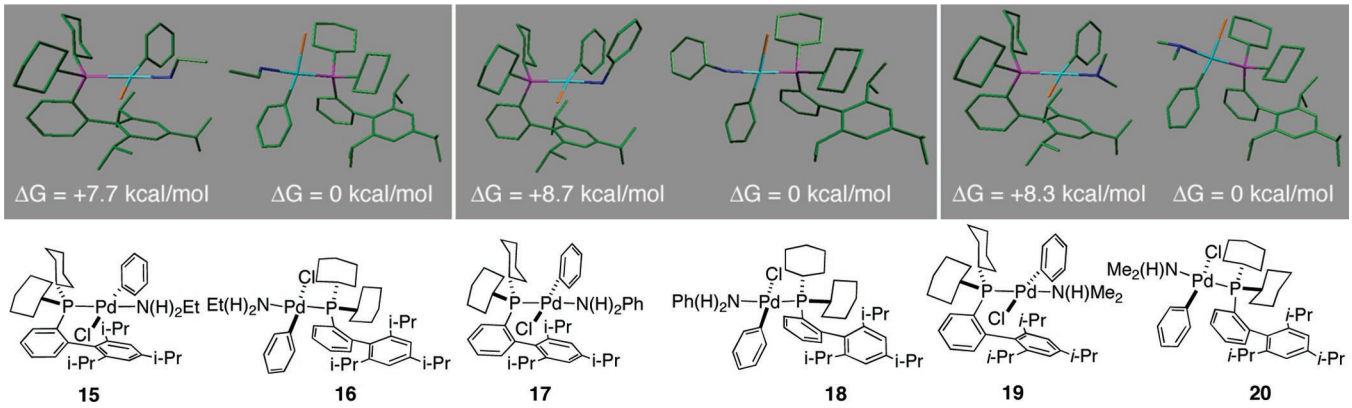


Figure 8. Optimized structures of two conformers of **2**·Pd(ethylamine)(Ph)Cl, two conformers of **2**·Pd(aniline)(Ph)Cl, and two conformers of **2**·Pd(dimethylamine)(Ph)Cl. Key: green = carbon, purple = phosphorus, turquoise = palladium, red = oxygen, orange = chlorine, blue = nitrogen.

global minimum in Chart 1 to a geometry where the Pd center is away from the non-phosphine-containing ring of the ligand should be possible at room temperature and facile at elevated temperatures through a structure where the dihedral angle for C1−C2−P−Pd is +20° ($\Delta G^{\ddagger} \approx 13.2$ kcal/mol). Rotation from the global minimum to a structure where the C1−C2−P−Pd torsion angle is −20° is slightly easier by avoiding a structure where the torsion angle is +20° and directly from −120° to −20° (in this case $\Delta G^{\ddagger} \approx 12.5$ kcal/mol). Although the PES scan in Chart 1 may not be the absolute lowest energy pathway for rotation around C2−P, it suggests that rotation of the Pd center away from the non-phosphine-containing ring of the ligand in **1**·Pd(Ph)Cl is likely facile under standard conditions for Pd-catalyzed amination reactions (25−100 °C).

A similar PES scan of rotation around C2−P in **2**·Pd(Ph)Cl was conducted (Chart 2). In this case, it appears that rotation around C2−P to arrive at a geometry such that the Pd center is pointing away from the non-phosphine-containing ring of the ligand is more difficult than in the case of **1**. We approximate $\Delta G^{\ddagger}$ to be 16.6 kcal/mol from the global minimum at C1−C2−P−Pd = −166° to the local minimum at C1−C2−P−Pd = −40°. However, on the basis of the calculated activation energy required for this rotation, it is likely facile under conditions for Pd-catalyzed amination reactions at elevated temperature (60−100 °C) and even possible at 25 °C.

Optimized Structures of Amine-Bound Complexes with 1 and 2. We next optimized amine-bound structures of the form L_1Pd(amine)(Ph)Cl (where amine = $EtNH_2$, Me_2NH, $PhNH_2$ and L_1 = **1** and **2**) with both the Pd center positioned distal from and proximal to the non-phosphine-containing ring of the ligand (Figures 7 and 8). For each pair of complexes, the more favored isomer is that with the Pd center distal to the non-phosphine-containing ring of the ligand. In **1**·Pd($EtNH_2$)(Ph)Cl (complex **9**), the Pd center is proximal to the non-phosphine-containing ring of the ligand although no Pd−arene interaction is present as the nearest distance between an atom of the non-phosphine-containing ring of the ligand (the ipso carbon) and the Pd center is 3.51 Å. The free energy difference between the two conformers of **1**·Pd($EtNH_2$)(Ph)Cl (**9** and **10**) is 3.4 kcal/mol, favoring the isomer with the Pd center distal to the non-phosphine-containing ring of the ligand, **10**. Additionally, there is substantially less steric congestion around the Pd center in complex **10**, relative to **9**, which likely allows for more rapid deprotonation of bound ethylamine to occur by a bulky base, e.g., NaO*t*-Bu. Similarly, the more favored conformers of complexes composed of **1**·Pd($PhNH_2$)(Ph)Cl and **1**·Pd(Me_2NH)(Ph)Cl are those with the Pd center distal to the non-phosphine-containing ring of the ligand, by 2.0 and 2.7 kcal/mol, respectively.

A similar analysis was conducted with complexes of the type **2**·Pd(amine)(Ph)Cl (Figure 8). It was determined that in each pair of complexes, the lower energy conformer was that with the Pd center distal to the non-phosphine-containing ring of the ligand. However, in each case, the energy difference between each pair of conformers was substantially greater than the respective complexes with **1**. Hence, the free energy difference

Table 1. Free Energies and Equilibrium Constants of Amine Binding to **1**·Pd(Ph)Cl (**9**−**14**) and **2**·Pd(Ph)Cl (**15**−**20**)

L-Pd(Ph)Cl + amine ⇌ L-Pd(amine)(Ph)Cl

complex	$\Delta G_{298.15}$ (kcal/mol)	$K_{298.15}$	complex	$\Delta G_{298.15}$ (kcal/mol)	$K_{298.15}$
9	−6.3	4.1×10^4	**15**	−0.4	2.0
10	−9.7	1.3×10^7	**16**	−8.0	7.3×10^5
11	−0.5	2.3	**17**	+6.7	1.2×10^{-5}
12	−2.7	95	**18**	−1.9	25
13	−3.4	3.1×10^2	**19**	+3.4	3.2×10^{-3}
14	−6.1	3.0×10^4	**20**	−4.9	3.9×10^3

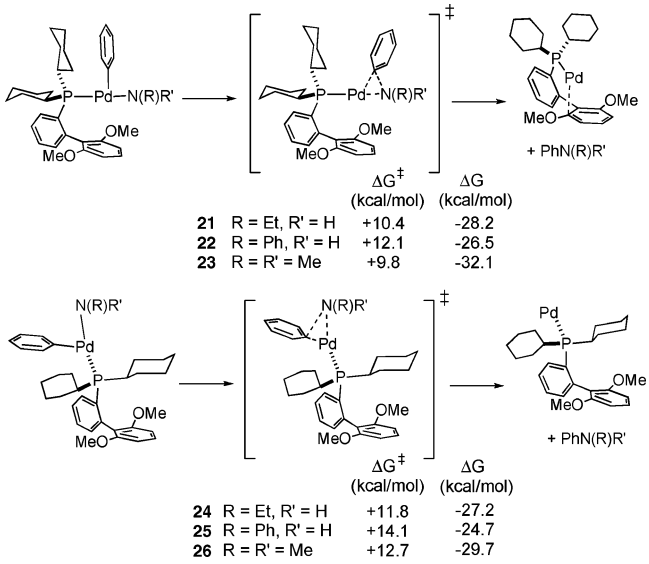


Figure 9. Thermodynamic and kinetic parameters for reductive elimination from **1**·Pd(amido)Ph (where amido = EtNH, PhNH, and Me_2N).

between the two conformers of **2**·Pd($EtNH_2$)(Ph)Cl was determined to be 7.7 kcal/mol, whereas the energy difference between **2**·Pd($PhNH_2$)(Ph)Cl and **2**·Pd(Me_2NH)(Ph)Cl was determined to be 8.7 and 8.3 kcal/mol, respectively. The difference in free energy between conformers based upon **2**·Pd(amine)(Ph)Cl relative to **1**·Pd(amine)(Ph)Cl is probably due to the destabilization of the conformers with the Pd center proximal to the non-phosphine-containing ring of the ligand in **2**. As this aromatic ring (2,4,6-tri-isopropylphenyl) is substantially larger than the aromatic ring in **1** (2,6-dimethoxyphenyl), the steric congestion that the Pd center (plus the ligands on the Pd center) resides in causes the conformers with the Pd center distal to the non-phosphine-containing ring of the ligand to be dramatically favored. Furthermore, in complexes **15**, **17**, and **19**, deprotonation of the bound amine is likely difficult as the 4-isopropyl group on the non-phosphine-containing ring of the ligand is in close proximity to the free N−H in each complexes. Formation of complexes **16**, **18**, and **20** relieves this congestion and allows much easier access for a base, such as NaO*t*-Bu, to deprotonate the bound amine.

From the optimized structures of L_1·Pd(amine)(Ph)Cl and our previous report on oxidative addition of PhCl to **1**·Pd and **2**·Pd,[8] binding constants for the amines used in this study were determined. Table 1 contains the free energy of binding values as well as the binding constants for each of the complexes in Figure 7 and 8. This data corresponds extremely well with experimental data from our group on the relative binding constants of various amines to complexes of the type **1**·Pd(Ph)Cl.[7] Specifically, the ratio of binding an equimolar amount of hexylamine and aniline to **1**·Pd(Ph)Cl was determined to be 3500:1 by ^{31}P NMR, whereas the predicted ratio was determined to be 7684:1 (obtained from optimizing the structure of **10** with hexylamine rather than ethylamine and obtaining the free energy of reaction of hexylamine with **1**·Pd(Ph)Cl, i.e., −8.0 kcal/mol). Furthermore, the trend that exists among the binding constants of $EtNH_2$, Me_2NH, and aniline to both **1**·Pd(Ph)Cl and **2**·Pd(Ph)Cl is consistent with experimental data.[7,15a] As can be expected from the structures in Figures 6 and 7, the binding of an amine is much more thermodynamically favored to complexes of **1**·Pd(Ph)Cl and **2**·Pd(Ph)Cl when the Pd center is distal to the non-phosphine-containing ring of the ligand. This is most dramatically demonstrated by the amine binding constants ($K_{298.15}$) of **17** and **19**: 1.2×10^{-5} and 3.2×10^{-3}, respectively. These values clearly demonstrate that amine binding is thermodynamically *unfavored* for complexes composed of **2**·Pd($PhNH_2$)(Ph)Cl and **2**·Pd(Me_2NH)(Ph)Cl when the Pd center is proximal to the non-phosphine-containing ring of the ligand. However, when rotation of the Pd center occurs away from the non-phosphine-containing ring of the ligand in **2**·Pd(Ph)Cl, amine binding becomes favored, albeit only slightly for complex **18** ($K_{298.15} = 25$). Taken together, the data in Table 1 suggests that although amine binding is thermodynamically favored when the Pd center is proximal to the non-phosphine-containing ring of the ligand (in certain cases), the binding is much more favored, for all complexes, when the Pd center is distal to this aromatic ring.

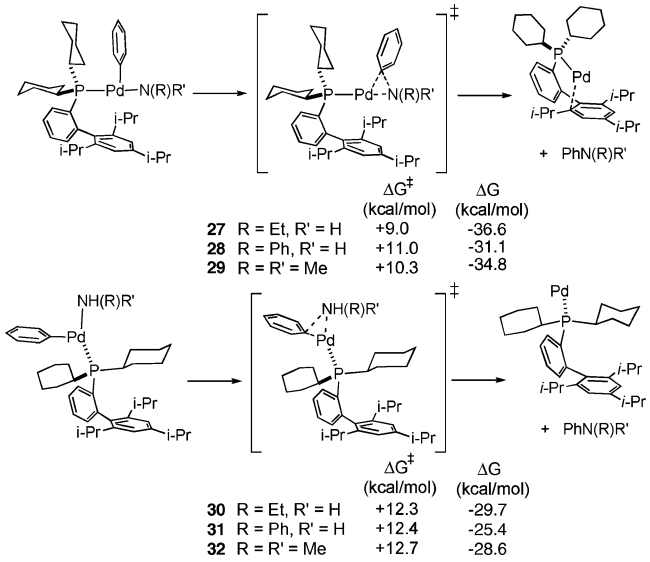


Figure 10. Thermodynamic and kinetic parameters for reductive elimination from **2**·Pd(amido)Ph (where amido = EtNH, PhNH, and Me_2N).

Reductive Elimination from L_1Pd(amido)(Ph). Following deprotonation of the L_1Pd(amine)(Ph)Cl species to afford compounds of the type L_1Pd(amido)(Ph), reductive elimination is required in order to form product. Although transition state structures of reductive elimination from phosphine-ligated Pd(II) complexes have been previously examined, the complexes investigated were those of the type L_n·Pd(Z)R where Z = $B(OR)_2$,[17] CR_3,[18] OR,[19] and F[20] and R is carbon-based. A trend exists among these complexes, such that as the Pd-bound atom

(17) Sumimoto, M.; Iwane, N.; Takahama, T.; Sakaki, S. *J. Am. Chem. Soc.* **2004**, *126*, 10457−10471.

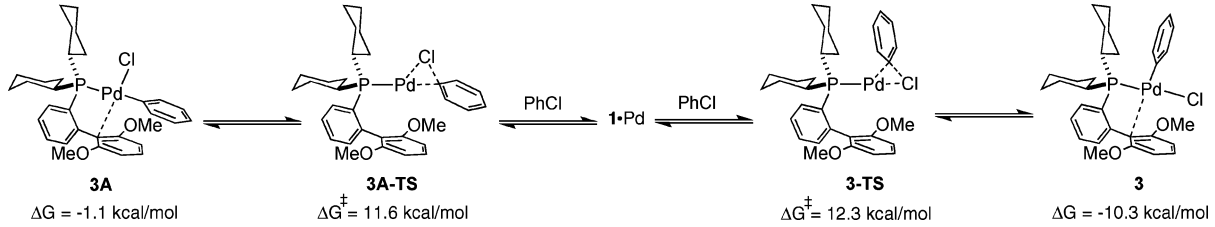


Figure 11. Oxidative addition of PhCl to **1**·Pd(0) to afford two isomers of **1**·Pd(Ph)Cl.

becomes more electronegative (B < C < O < F),[21] the rate of reductive elimination is retarded. On the basis of the Pauling electronegativity of N (3.04), reductive elimination from L_n·Pd(amido)Ar should be more facile than from L_n·Pd(aryloxide)-Ar, but more difficult than from L_n·Pd(Ar′)Ar.[22] In order to determine the activation energies for aryl−amido reductive elimination from phosphine-ligated Pd(II) complexes, we optimized several ground state and transition state structures composed of L·Pd(amido)(Ph) where L = **1** or **2** and amido = ethyl amide, dimethyl amide, and anilide. Since the energetically favored amine-bound complexes position the Pd center distal to the non-phosphine-containing ring of the ligand, we first analyzed the corresponding amide-bound structures in this orientation. However, we postulated that reductive elimination would be more facile when the Pd center is proximal to the non-phosphine-containing ring of the ligand due to increased steric pressure caused by this ring. The 12 complexes based upon **1** and **2** are depicted in Figures 9 and 10, respectively. A trend exists among these 12 complexes that is defined by a lower activation energy for reductive elimination from complexes with the Pd center proximal to the non-phosphine-containing ring of the ligand (e.g., $\Delta G^{\ddagger} = 9.8$ kcal/mol for **23**, whereas $\Delta G^{\ddagger} =$ 12.7 kcal/mol for **26**).

The activation energies for reductive elimination in the complexes depicted in Figures 9 and 10 are calculated from L·Pd(amido)(aryl) species where the aryl group is cis to the phosphine. In contrast, complexes of the type L·Pd(amido)(aryl) (where L is a phosphine) in which the aryl group is trans to the phosphine have been suggested to undergo reductive elimination faster than complexes with the aryl group cis to the phosphorus.[23] This is due to the destabilization in the ground state energy of the L·Pd(amido)aryl complex while the energy of the transition state structure remains nearly identical in each isomer. However, in order to form a complex of the type L·Pd(*trans*-aryl)amido, amine binding must occur to L·Pd(*trans*-Ph)X or isomerization of L·Pd(*cis*-aryl)amido to L·Pd(*trans*-aryl)amido must occur prior to reductive elimination. We have previously shown that although the activation energies for oxidative addition to **1**·Pd(0) to afford **1**·Pd(*cis*-Ph)Cl (**3**) and **1**·Pd(*trans*-Ph)Cl (**3A**) are similar (12.3 and 11.6 kcal/mol, respectively),[8] **3** is 9.2 kcal/mol lower in free energy than **3A** (Figure 11). Hence, reductive elimination of PhCl can readily occur from **3A** ($\Delta G^{\ddagger} = 12.7$ kcal/mol) to afford **1**·Pd(0) and PhCl, whereas

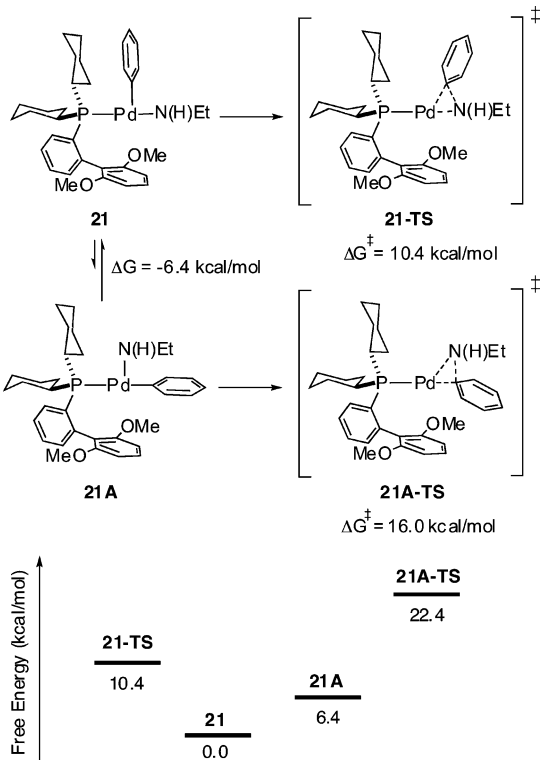


Figure 12. Reductive elimination from two isomers of **1**·Pd(Ph)EtNH and reaction coordinate diagram for the process.

the activation energy for reductive elimination from **3** is high enough ($\Delta G^{\ddagger} = 22.6$ kcal/mol) that other processes occur more rapidly (e.g., amine binding). Therefore it is unlikely that amine binding will occur directly to **3A**. Further evidence against the binding of an amine to **3A** is provided by ^{31}P NMR spectra of various species of the type **1**·Pd(amine)(Ph)Cl (where amine = 1°, 2°, and aniline derivatives).[7] These spectra contain only one signal, which corresponds to the structure with the amine trans to the phosphorus. This is consistent with the X-ray structure of **1**·Pd(Ph)(*n*PrNH$_2$)Cl (Figure 1). Finally, it is viable that the isomerization of L·Pd(*cis*-aryl)amido to L·Pd(*trans*-aryl)amido occurs prior to reductive elimination. However, ground state and transition state structures for an isomer of **21** were optimized with the phenyl group trans to the phosphorus (**21A**) (Figure 12). From structures **21A** and **21A-TS**, it was determined that the activation energy for reductive elimination is 16.0 kcal/mol. Thus, in this case, reductive elimination from the cis isomer (**21**) proceeds more readily than from the trans isomer (**21A**).

In order to determine to what extent the non-phosphine-containing ring aids in reductive elimination, the activation energies for each pair of complexes in Figures 9 and 10 cannot be merely subtracted from each other as the ground state energies are different for each set of complexes. Figure 13

(18) (a) Ananikov, V. P.; Musaev, D. G.; Morokuma, K. *Organometallics* **2005**, *24*, 715−723. (b) Braga, A. A. C.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2006**, *25*, 3647−3658.
(19) Zuidema, E.; van Leeuwen, P. W. N. M.; Bo, C. *Organometallics* **2005**, *24*, 3703−3710.
(20) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342−1358.
(21) Pauling electronegativity values for B, C, O, F are 2.04, 2.55, 3.44, 3.98, respectively.
(22) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936−1947 and references therein.
(23) Yamashita, M.; Cuevas Vicario, J. V.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 16347−16360.

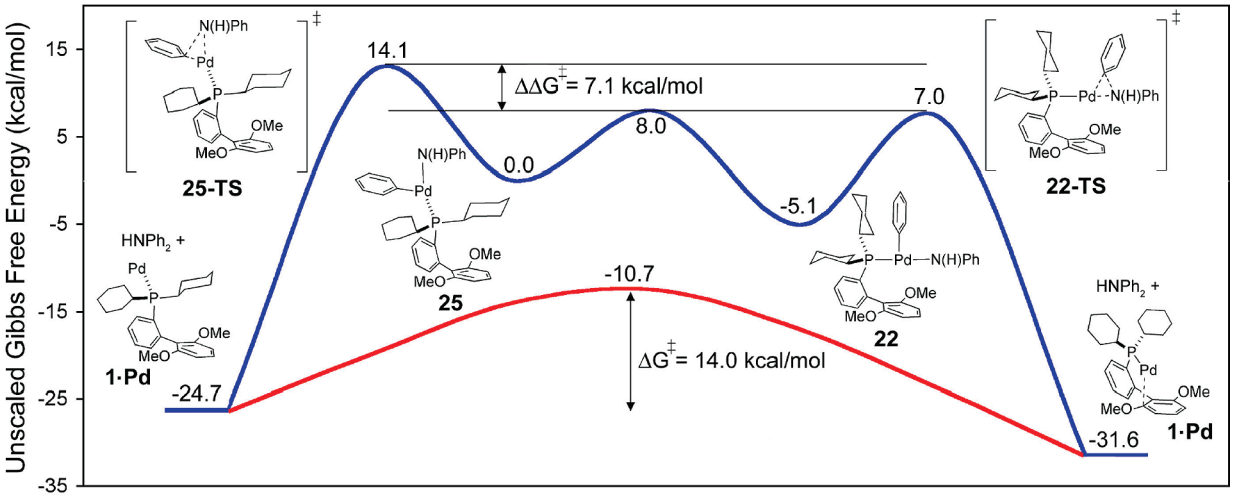


Figure 13. Reaction coordinate diagram of reductive elimination from **1**·Pd(anilido)Ph.

Table 2. Comparison of $\Delta\Delta G$ and $\Delta\Delta G^{\ddagger}$ for Each Set of Complexes in Figures 9 and 10

complexes	$\Delta\Delta G$ (kcal/mol)	$\Delta\Delta G^{\ddagger}$ (kcal/mol)	complexes	$\Delta\Delta G$ (kcal/mol)	$\Delta\Delta G^{\ddagger}$ (kcal/mol)
21/**24**	4.1	4.0	**27**/**30**	4.0	7.3
22/**25**	5.1	7.1	**28**/**31**	5.4	6.8
23/**26**	2.7	5.6	**29**/**32**	4.6	7.0

contains a reaction coordinate diagram for reductive elimination from **1**·Pd(PhNH)Ph that depicts the method used to obtain $\Delta\Delta G^{\ddagger}$ values (a discussion on the activation energy required for interconversion between the two isomeric reactants is presented below). The L_1Pd(amido)Ph complex with the Pd center distal to the non-phosphine-containing ring of the ligand (**25**) was arbitrarily set at 0.0 kcal/mol. From this complex, reductive elimination can directly occur ($\Delta G^{\ddagger} = 14.1$ kcal/mol). However, if rotation of the Pd center such that it is proximal to the non-phosphine-containing ring of the ligand occurs first, reductive elimination is more facile ($\Delta G^{\ddagger} = 12.1$ kcal/mol). Although these activation energies vary by 2.0 kcal/mol, the ground state structure of L_1Pd(amido)Ph was stabilized by 5.1 kcal/mol in complex **22** relative to **25**. Hence this value needs to be summed with the value of 2.0 kcal/mol to afford a difference in absolute activation energies of 7.1 kcal/mol. Table 2 contains $\Delta\Delta G^{\ddagger}$ values for each set of complexes of the type L_1Pd(amido)Ph. In all complexes, rotation of the Pd center such that it is proximal to the non-phosphine-containing ring of the ligand not only lowers the ground state energy of the L_1Pd(amido)Ph complex, it also lowers the activation energy of reductive elimination. Therefore, this rotation not only creates a more stable species, it creates a more reactive complex toward reductive elimination.

Additionally advantageous is the fact that directly following reductive elimination from complex **22**, the Pd−arene interaction can re-form in L_1Pd(0), thereby stabilizing the Pd center and ensuring entrance into the next catalytic cycle by reaction with an aryl chloride ($\Delta G^{\ddagger} = 12.3$ kcal/mol for PhCl). If however, reductive elimination occurs directly from complex **25**, the resulting Pd(0) complex likely rotates such that the Pd center is proximal to the non-phosphine-containing ring of the ligand ($\Delta G^{\ddagger} = 14.0$ kcal/mol)[8] prior to oxidative addition (red line in Figure 13).

Since the non-phosphine-containing ring of the ligand aids in inducing reductive elimination from complexes **21**−**23** and **27**−**29**, we wanted to determine if a solvent molecule (e.g., benzene or toluene) could explicitly bind the three-coordinate Pd center in an η^1 or η^2 fashion in complexes **24**−**26** and **30**−**32** thereby mimicking the non-phosphine-containing ring of the ligand. If binding indeed occurs, then reductive elimination from solvent-bound complexes **24**−**26** and **30**−**32** may be more facile than from the unbound complexes. However, upon conducting several geometry optimizations of **1**·Pd(Ph)(EtNH)(η^2-PhH), dissociation of PhH occurred such that the PhH molecule was ≥3.95 Å away from the Pd center. Hence, it does not appear that a local minimum exists in which PhH is bound to the Pd center in **24** and that reductive elimination directly occurs from **24**−**26** and **30**−**32**.

Finally, it is worth noting that the calculated activation energies in Figures 9 and 10 are consistent with rate constants for reductive elimination from complexes of the type (dppf)·Pd(Ar′)(RNAr), as described by Yamashita et al.[23]

Discussion

Proposed Mechanism for Pd-Catalyzed Amination Utilizing Biaryl Phosphines. A proposed mechanism utilizing data presented here and our previous paper[8] for the cross-coupling of chlorobenzene and an amine using **1**·Pd is given in Figure 14. As described in our previous report on oxidative addition of aryl chlorides to complexes of the type L_1Pd,[8] the most favored geometry of L·Pd(Ph)Cl is that with either a Pd−O interaction (in the case of **1**) or Pd−arene interaction (in the case of **2**). However, rotation of this complex as described above affords a complex to which an amine can readily and more favorably bind. Additionally, it is likely that deprotonation is much more facile in complex **14** as a base such as NaO*t*Bu can more readily access the amine proton due to the lack of bulk from the non-phosphine-containing ring of the ligand. After deprotonation occurs to afford **26**, reductive elimination may occur directly. However, as described above, rotation of the phosphorus center back to geometry where the Pd−arene interaction is re-created (**23**) allows for reductive elimination to occur more readily than from **26** for two possible reasons: (1) the re-creation of the Pd−arene interaction, which necessarily exists in a cis relationship, forces the aryl and amide ligands

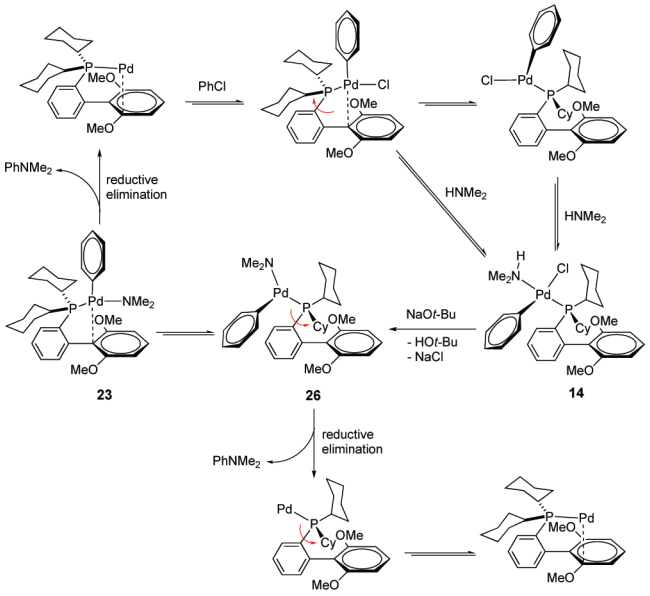


Figure 14. Proposed mechanism for the **1**·Pd-catalyzed reaction of chlorobenzene with dimethylamine. The arrows in red indicate rotation of the phosphorus center in and out of the plane of the paper.

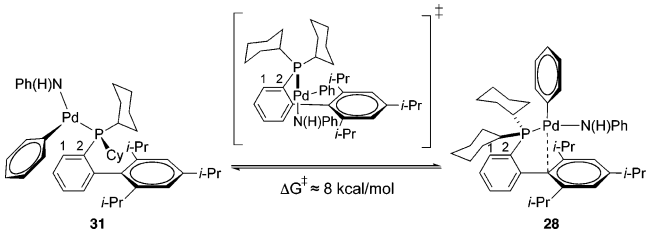


Figure 15. Approximation of the activation energy required for rotation around C2−P in **2**·Pd(HNPh)Ph.

on Pd to exist in a cis relationship and (2) the steric pressure from the non-phosphine-containing ring of the ligand pushes the arene and amido ligands in closer proximity to one other thereby causing this complex to more closely resemble the transition state for reductive elimination. We are currently conducting experimental work on this step of the catalytic cycle in order to further determine the effects of the non-phosphine-ring of the ligand during deprotonation.

In order to determine the feasibility of rotation of the Pd center such that it is proximal to the non-phosphine-containing ring of the ligand in complexes of the type L_1Pd(amido)(Ph), we undertook a potential energy scan of the rotation around C2−P in **2**·Pd(anilido)Ph (Figure 15). As this complex contains the largest ligand (**2**) and the largest Pd-bound amido species (PhNH), the rotation around C2−P will be the most difficult relative to combinations of **1**/**2** and EtNH, Me_2N, and PhNH. It was found that the approximate activation energy required for rotation around C2−P in complex **31** was 8 kcal/mol. Hence, not only is rotation around C2−P viable in **2**·Pd(anilido)Ph, it appears to be facile under the conditions used in Pd-catalyzed amination reactions (25−100 °C). More importantly, this activation energy is less than any activation energies for reductive elimination from the complexes in Figures 9 and 10 that position the Pd center distal from the non-phosphine-containing ring of the ligand (**24**−**26** and **30**−**32**). Importantly, the activation energy required for the conversion of **28** to **31** is 13.4 kcal/mol. Although this value is similar to the activation energy required for reductive elimination from **28** (11.0 kcal/mol), the fact that **28** is 5.4 kcal/mol more stable than **31** suggests that reductive elimination more often occurs from **28** due to $K_{298.15}$[**28**/**31**] ≈ 4000 (i.e., the pathway in Figure 13 in which the Pd center first rotates such that it is proximal to the non-phosphine-containing ring of the ligand prior to reductive elimination occurs more often than reductive elimination directly from **31**).

Conclusion

In conclusion, we have analyzed amine binding to two oxidative addition structures based upon **1** and **2**. From this data, we believe that rotation of the Pd center away from the bulk imparted by the non-phosphine-containing ring of the ligand may be important for amine binding to occur. This rotation would not likely be able to be determined via experimental studies, hence the value for all-atom computational studies. Furthermore, it was determined that reductive elimination from complexes of the type L_1·Pd(amido)Ph is more facile in complexes that position the Pd center proximal to the non-phosphine-containing ring of the ligand although the ground state structures of L_1·Pd(amido)Ph are energetically stabilized in this conformation relative to structures that position the Pd center distal from the non-phosphine-containing ring of the ligand. We believe the following features determined by this and our previous study[8] may aid in developing more effective phosphine ligands for Pd-catalyzed reactions: (1) ligands that can stabilize oxidative addition intermediates (e.g., via a Pd−arene or Pd−O interaction) within a catalytic cycle of Pd-catalyzed cross-coupling reaction may extend catalyst lifetime and therefore allow for the utilization of lower catalyst loadings, (2) although bulky ligands promote the formation of highly reactive L_1Pd(0) species (relative to L_2Pd(0)), ligand rigidity is not necessarily beneficial as the oxidative addition complex needs to be able to access a geometry such that nucleophile binding or transmetalation can readily occur, (3) following deprotonation or transmetalation, enforcement of a cis relationship between the two ligands to be reductively eliminated via a pseudobidentate interaction (the Pd−arene interaction is necessarily cis to phosphorus center) likely aids in reductive elimination. Any additional steric pressure imparted by the ligand architecture can dramatically lower reaction barriers for reductive elimination for complexes of the type L_1·Pd(amido)-Ph.

Acknowledgment. We thank the National Institutes of Health (NIH) for support (GM-46059 and GM-58160). We thank Merck, Amgen, and Boehringer Ingelheim for additional unrestricted support. T.E.B. was supported, in part, by an ACS Organic Division Award (sponsored by Novartis Pharmaceuticals), which he gratefully acknowledges. We thank Dr. Mark Biscoe for measuring the relative binding of hexylamine and aniline to **1**·Pd(Ph)Cl.

Supporting Information Available: Coordinates of all optimized structures, complete ref 9. This material is available free of charge via the Internet at http://pubs.acs.org.

JA073747Z