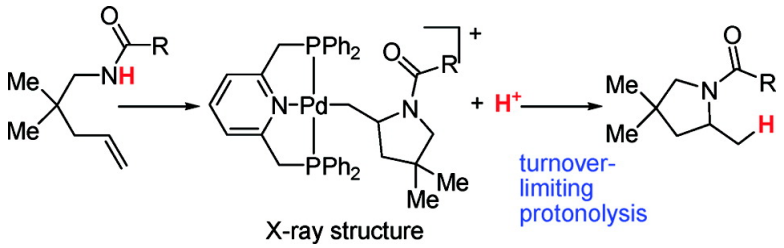
Article

Mechanistic Studies of a Palladium-Catalyzed Intramolecular Hydroamination of Unactivated Alkenes: Protonolysis of a Stable Palladium Alkyl Complex Is the Turnover-Limiting Step

Brian M. Cochran, and Forrest E. Michael

J. Am. Chem. Soc., **2008**, 130 (9), 2786-2792 • DOI: 10.1021/ja0734997



More About This Article

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

- Supporting Information
- Links to the 7 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 02/07/2008

Mechanistic Studies of a Palladium-Catalyzed Intramolecular Hydroamination of Unactivated Alkenes: Protonolysis of a Stable Palladium Alkyl Complex Is the Turnover-Limiting Step

Brian M. Cochran and Forrest E. Michael*

Department of Chemistry, University of Washington, Box 351700, Seattle, Washington 98195-1700

Received May 16, 2007; E-mail: michael@chem.washington.edu

Abstract: Mechanistic studies of the intramolecular hydroamination of unactivated aminoalkenes catalyzed by a dicationic [bis(diphenylphosphinomethyl)pyridine]palladium complex highlight the important role that protonolysis plays in this reaction. Coordination of the aminoalkene substrate to this complex activates the alkene toward intramolecular nucleophilic attack to form a dicationic palladium alkyl complex (**6**). A stable monocationic palladium alkyl complex (**7**) was isolated by in situ deprotonation of **6** with mild base, and its structure was confirmed by X-ray crystallography. Complex **7** reacted rapidly with a variety of strong acids to undergo protonolysis, resulting in formation of hydroamination product **3** and regenerating the active catalyst. Evidence that formation of the palladium alkyl complex is reversible under the catalytic conditions was obtained from observation of the protonolysis at low temperature. During the course of all catalytic reactions, the resting state of the catalyst was palladium alkyl complex **7**, indicating that protonolysis of the Pd−C bond was the turnover-limiting step. Kinetic studies reveal an unusual inverse dependence of the reaction rate on the concentration of the aminoalkene substrate. This effect can be accurately explained by a model in which the carbamate protecting group of the aminoalkene acts as a Brønsted base to remove free protons from the catalytic cycle and thereby inhibits the turnover-limiting protonolysis step. Formation of a 2:1 complex (**12**) between the carbamate and the proton is most consistent with the kinetic data.

Introduction

The direct addition of a nitrogen−hydrogen bond across an alkene (hydroamination)[1] is an economical way to form nitrogen−carbon bonds and an effective way to synthesize biologically active nitrogen-containing heterocycles.[2] In spite of the utility of this reaction, the hydroamination of unactivated alkenes containing synthetically useful functional groups remains a challenge. Strong acids[3] have been used to promote the hydroamination of unactivated alkenes; however, forcing conditions are usually required and acid sensitive functional groups are not tolerated. Lanthanides and Group IV metals[4] also efficiently catalyze the hydroamination of unactivated alkenes, but these catalysts are extremely air and water sensitive and are incompatible with many synthetically useful functional groups.[5] On the other hand, late transition metal catalysts[6] have been increasingly employed in hydroamination reactions because of their greater functional group tolerance. Unfortunately, these catalysts tend to be significantly less active, requiring activated alkenes, either via conjugation or substitution with electron-withdrawing groups, and elevated temperatures. Recently, we reported a new palladium-catalyzed intramolecular hydroamination of unactivated aminoalkenes.[7] This transformation takes place at room temperature and is tolerant of a variety of useful functional groups. Since this catalyst appears to be significantly more active than most late transition metal catalysts, understanding the mechanistic rationale for its enhanced activity is especially important.

(1) For recent reviews, see (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398. (c) Hartwig, J. F. *Pure Appl. Chem.* **2004**, *76*, 507−516.

(2) For examples of nitrogen containing heterocycles, see: (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (b) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773.

(3) (a) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179−4182. (b) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471−1474. (c) Li, Z. G.; Zhang, J. L.; Brouwer, C.; Yang, C. G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175−4178. (d) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *125*, 14542−14543.

(4) (a) Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731−4733. (b) Meyer, N.; Zulys, A.; Roesky, P. W. *Organometallics* **2006**, *25*, 4179−4182. (c) Thomson, R. K.; Bexrud, J. A.; Schafer, L. L. *Organometallics* **2006**, *25*, 4069−4071. (d) Kim, Y. K.; Livinghouse, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3645−3647. (e) Kim, Y. K.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 4391−4393. (f) Kim, Y. K.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737−1739. (g) Young, K. K.; Livinghouse, T.; Horino, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9560−9561. (h) Ryu, J. -S.; Marks, T. J.; McDonald, F. E. *Org. Lett.* **2001**, *3*, 2091−3094. (i) Meyer, N.; Löhnwitz, K.; Zulys, A.; Roesky, P. W.; Dochnahl, M.; Blechert, S. *Organometallics* **2006**, *25*, 3730−3734. (j) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983−8988. (k) Ryu, J. -S.; Marks, T. J.; McDonald, F. E. *J. Org. Chem.* **2004**, *69*, 1038−1052. (l) Ryu, J. -S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584−12605. (m) Sukwon, H.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768−14783.

(5) For example: alcohols, esters, ketones, carbamides, and carbamates.

(6) (a) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070−1071. (b) Brunet, J.-J.; Chu, N. C.; Diallo, O. *Organometallics* **2005**, *24*, 3104−3110. (c) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707−2710. (d) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747−1749. (e) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303−5305. (f) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828−1839. (g) Zhang, J. L.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798−1799. (h) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640−12646.

10.1021/ja0734997 CCC: $40.75

The mechanisms of several late transition metal-catalyzed hydroaminations of activated alkenes have been investigated.[8] Milstein has reported an iridium-catalyzed hydroamination of norbornene that proceeds by initial oxidative addition of the N−H bond of the amine, followed by alkene insertion into the Ir−N bond and reductive elimination.[9] Hartwig has studied ruthenium-,[10] palladium-,[11] and nickel[12]-catalyzed intermolecular hydroaminations of conjugated alkenes. The Ru-catalyzed hydroamination proceeds via initial η^6-arene coordination of the styrene substrate followed by nucleophilic attack by the amine, forming a Ru η^7-benzyl complex that is subsequently protonated to release the product. In contrast, the palladium- and nickel-catalyzed versions begin with alkene insertion into a metal hydride complex, generating an η^3-benzyl or allyl intermediate, respectively. Nucleophilic displacement with the amine completes the catalytic cycle. The formation of higher hapticity benzyl complexes in all three of Hartwig's reactions presumably prevents β-hydride elimination[13] but also inherently limits these additions to those of vinylarenes and dienes.

In addition to these systems, several hydroaminations of unactivated alkenes have been reported. Che,[6c] He,[6g] and Tilley[6h] have reported Au- and Pt-catalyzed intermolecular hydroaminations of simple alkenes using sulfonamide nucleophiles, and the latter two have characterized the active catalyst mixtures spectroscopically. He also demonstrated with a deuterium labeling experiment that the addition of N and H groups occurs with anti relative stereochemistry. However, HOTf is also a competent catalyst for these reactions under similar conditions,[3a−c] and recent reports have cast doubt on whether they actually proceed via metal catalysis.[3a] Widenhoefer has reported a Pt-catalyzed intramolecular hydroamination of secondary alkenylamines and has observed some of the intermediates stoichiometrically.[6a] Widenhoefer has also reported a Au-catalyzed intramolecular hydroamination of carbamates[6e] and ureas[6d] but to our knowledge has yet to report any mechanistic studies of this system.

In our palladium-catalyzed hydroamination reaction, a tridentate ligand is used to prevent β-hydride elimination. Because the inhibition of β-hydride elimination is controlled by the ligand, rather than by the substrate, unconjugated alkenes are effective substrates for this reaction. Reversible stoichiometric addition of amines to alkene complexes of this ligand had been previously observed.[14] However, the addition of carbamates and the protonolysis of the resultant alkyl complexes to complete the catalytic cycle had not. Herein we present a detailed mechanistic investigation of the palladium-catalyzed intramolecular hydroamination of unactivated alkenes.

Scheme 1. Proposed Catalytic Cycle

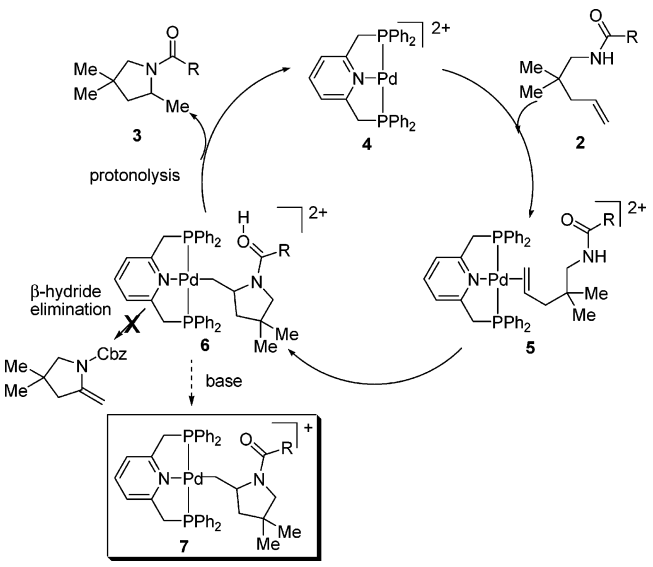
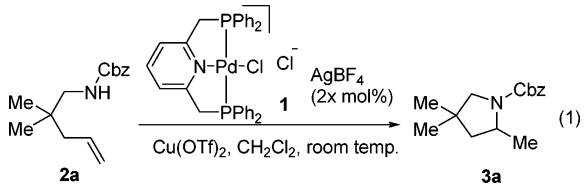


Table 1. Optimized Reaction Conditions without Copper(II) Triflate



[Pd] (*x* mol %)	$Cu(OTf)_2$ (mol %)	% yield (isolated)
5	10	82
0	10	0[a]
5	0	94

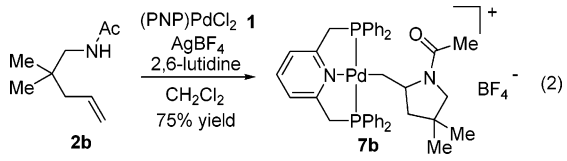
[a] Only starting material **2a** was isolated.

Results and Discussion

In the previous report,[7] dicationic palladium complex **4** was found to be an effective catalyst for the hydroamination of protected aminoalkenes. Based on literature precedent, the catalytic cycle depicted in Scheme 1 was proposed. Coordination of the alkene to the electron-deficient dicationic palladium center activates the substrate toward nucleophilic attack from the amide, forming protonated alkyl complex **6**. Since the tridentate ligand prevents β-hydride elimination, protonolysis of the Pd−C bond releases the hydroamination product **3** and regenerates the active catalyst.

The reaction conditions presented in our original report included a cocatalytic amount of copper(II) triflate additive (Table 1, entry 1). Recently, attention has been drawn to the potential of metal triflates to effect hydroamination reactions *via* acid catalysis.[3a] To rule out this possibility, substrate **2a** was treated with $Cu(OTf)_2$ in the absence of Pd. No conversion to product **3a** was observed. Additionally, $Cu(OTf)_2$ could be omitted from the reaction with no loss in yield. These experiments confirmed that the copper salt plays no significant role in the catalytic hydroamination.[15]

(7) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246−4247.
(8) For mechanistic studies of hydroaminations using lanthanides, see: (a) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584−12605. (b) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *Organometallics* **1999**, *18*, 1049−1960. (c) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770−3772.
(9) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738−6744. A later improvement to this reaction presumably proceeds via a similar mechanism: Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *117*, 10857−10858.
(10) Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756−5757.
(11) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166−1167.
(12) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669−3679.
(13) β-hydride elimination is normally quite facile for late transition metal alkyl complexes, see (a) Hegedus, L. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113−1116. (b) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166.
(14) (a) Hahn, C.; Morvillo, P.; Vitagliano, A. *Eur. J. Inorg. Chem.* **2001**, 419−429. (b) Cucciolito, M. E.; D'Amora, A.; Vitagliano, A. *Organometallics*, **2005**, *24*, 3359−3361. (c) Hahn, C.; Morvillo, P.; Herdtweck, E.; Vitagliano, A. *Organometallics* **2002**, *21*, 1807−1818.
(15) The initial beneficial effect of the addition of copper triflate to the reaction may have been to prevent reduction of the palladium catalyst, ensuring that the catalytic cycle went to completion.



Stoichiometric Studies. According to proposed catalytic cycle, protonolysis of the palladium−carbon bond of intermediate **6** is required to release the hydroamination product from the metal center (Scheme 1); therefore, addition of a base should inhibit this process and allow isolation of a palladium alkyl complex (**7**). Indeed, treatment of aminoalkene **2b** with (PNP)-$PdCl_2$ **1** (1 equiv), $AgBF_4$ (2 equiv), and 2,6-lutidine (1 equiv) in methylene chloride afforded the palladium alkyl complex **7b** as a bench-stable pale yellow solid (eq 2) in 75% yield. Complex **7b** was characterized by ^1H, ^{13}C, ^{31}P, and COSY NMR spectroscopy, as well as by X-ray crystallography (Figure 1). The structure of **7b** is similar to that of other palladium and platinum pincer ligand complexes.[16] Interestingly, the palladium metallacycle adopts a twisted conformation, causing the phenyl groups to be situated in pseudoequatorial and pseudoaxial positions.[17] The stability of **7b** is further confirmation of the ability of the tridentate ligand to inhibit β-hydride elimination.

After cyclization to form **7**, the next step in the catalytic cycle is the protonolysis of the palladium−carbon bond to form hydroamination product **3**. Treatment of alkyl complex **7b** with acid should result in protonolysis and completes the catalytic cycle (Scheme 2). Four different acids, TfOH, HBF_4·Et_2O, [Ph_2-NH_2][BF_4], and [Ph_2NH_2][OTf], were screened. With each acid, complete consumption of **7b** and clean formation of pyrrolidine **3b** was observed in less than 15 min at room-temperature. Additionally, a new palladium complex (**8**) was formed, as identified by a single new phosphorus resonance at 30.8 ppm. This chemical shift is typical of dicationic (PNP)Pd complexes with a neutral ligand in the fourth coordination site.[14] The exact identity of that ligand (L) has not been determined, but it is likely to be the carbonyl of product **3b**. When excess substrate **2b** was added to a solution of **8** and **3b** generated in this fashion,

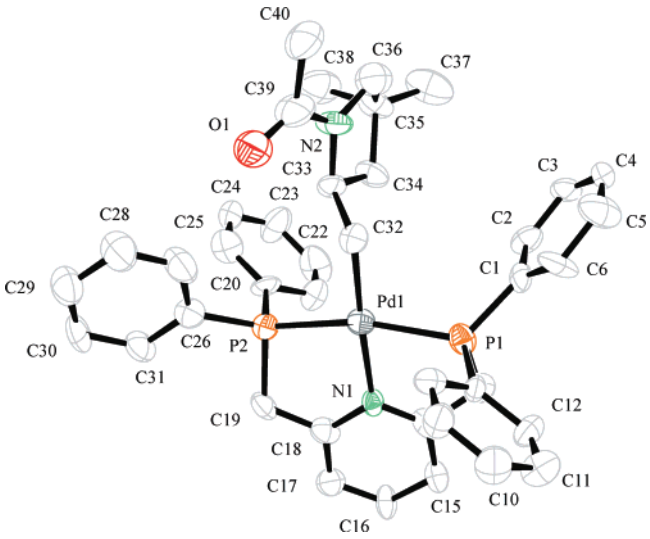
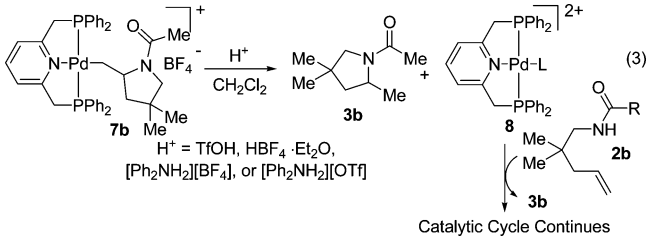
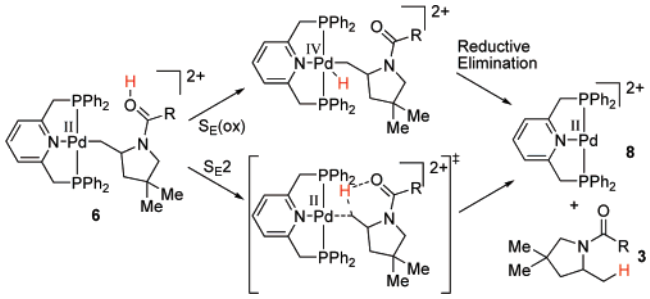


Figure 1. X-ray crystal structure of palladium alkyl intermediate **7b** (BF_4 counterion and a molecule of pentane are omitted for clarity). Selected bond distances (Å) and angles (deg): Pd1−P1 2.275; Pd1−P2 2.297; Pd1−N1 2.115; Pd1−C32 2.047; P2−Pd1−P1 165.50; C32−Pd1−N1 176.9; C32−Pd1−P1 94.6; C32−Pd1−P2 99.0; N1−Pd1−P1 82.7; N1−Pd−P2 82.8.

Scheme 2. Protonolysis of Palladium Complex **7b** and Continued Catalytic Activity



Scheme 3. Possible Protonolysis Mechanisms



complex **8** was completely converted to palladium alkyl complex **7b**, and conversion of **2b** to **3b** was observed over the next several hours. After 5 days, all of the aminoalkene was consumed, and complex **8** was the only palladium species remaining in solution. The fact that palladium alkyl complex **7b** was the only palladium complex in the reaction mixture under catalytic conditions is strong evidence that it is the resting state of the catalyst and that the turnover-limiting step of the catalytic cycle is the protonolysis of this complex.

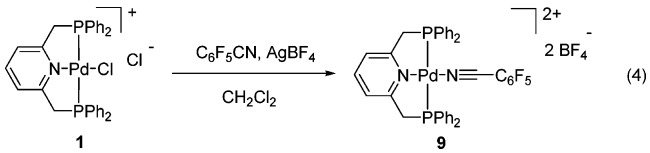
Two potential mechanisms for the protonolysis of metal−carbon bonds are commonly observed.[18] Protonation can occur at the metal center to form an intermediate palladium(IV) hydride complex, followed by reductive elimination (Scheme 3, S_E(ox) mechanism). Alternatively, direct electrophilic cleavage of the palladium−carbon bond with a proton can take place (S_E2 mechanism). The protonolysis of complex **7b** was monitored by ^1H NMR spectroscopy at low-temperature in an attempt to distinguish these two possibilities. TfOH was added to a solution of complex **7b** in CD_2Cl_2 at −78 °C, and the temperature of the reaction was increased in 5° increments at 5 min intervals. No change was observed until, surprisingly, at −18 °C substantial amounts of aminoalkene **2b** were observed. Aminoalkene **2b** was not observed in the room-temperature experiment described above. This observation suggests that the cyclization to form palladium alkyl complex **7b** from **2b** and **8** is reversible in the presence of added acid. Similar reversible addition of amines to alkenes under acidic conditions was observed by Vitagliano in their stoichiometric studies of this ligand system[14,19] and was invoked by Stahl in a related system. As the mixture was further warmed to room-temperature,

(16) (a) Gorla, F.; Venanzi, L. M.; Albinati, A. *Organometallics* **1994**, *13*, 43−54. (b) Steffey, B. D.; Miedaner, A.; Maciejewski-Farmer, M. L.; Bernatis, P. R.; Herring, A. M.; Allured, V. S.; Carperos, V.; DuBois, D. L. *Organometallics* **1994**, *13*, 4844−4855. (c) Hahn, C.; Vitagliano, A.; Giordano, F.; Taube, R. *Organometallics* **1998**, *17*, 2060−2066.
(17) Longmire, J. M.; Zhang, X.; Shang, M. *Organometallics* **1998**, *17*, 4374−4379.
(18) For a recent study of the rate of protonolysis of Pt−C bonds, see: Feducia, J. A.; Campbell, A. N.; Anthis, J. W.; Gagné, M. R. *Organometallics*, **2006**, *25*, 3114, for a review and discussion of the mechanistic possibilities, see: Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, *105*, 2471−2526.
(19) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888−17893.

aminoalkene **2b** and complex **7b** disappeared, and hydroamination product **3b** and complex **8** were formed. Throughout the course of the reaction, no signal was seen in the region of the spectra indicative of a late metal hydride (0 to −60 ppm).[18,20] Though the intermediacy of a palladium(IV) hydride in the protonolysis step cannot be ruled out, it is more likely that direct protonation of the Pd−C bond is occurring in this case (S_E2 mechanism). It is possible that the carbamate and amide-protected aminoalkenes are uniquely effective in the hydroamination reaction because of their ability to deliver a proton in an intramolecular fashion to the Pd−C bond, thus promoting the key protonolysis step.

Kinetic Studies. The stoichiometric studies described above indicated that the resting state of the catalyst was palladium alkyl complex **7**, and that protonolysis of this intermediate is the turnover-limiting step. In order to learn more about the rate of the key protonolysis step, kinetic studies were undertaken. However, the original (PNP)$PdCl_2$ precatalyst (**1**) was unsuitable for monitoring the kinetics of the hydroamination reaction by ^{1}H NMR spectroscopy, because of its poor solubility in methylene chloride and the need for activation with $AgBF_4$.

A stable palladium catalyst that does not need preactivation was required. Pentafluorobenzonitrile complex **9** ((PNP)Pd−NCC_6F_5) met the necessary requirements (eq 4). The reaction of (PNP)$PdCl_2$ **1**, $AgBF_4$, and C_6F_5CN in CH_2Cl_2 afforded complex **9** as a bench-stable light yellow powder. Complex **9** was, by itself, a competent catalyst for the hydroamination of aminoalkenes **2a** and **2b**. Furthermore, catalyst **9** displayed similar behavior to that observed in the protonolysis of complex **7** (Scheme 3); that is, as long as substrate **2a** remained in solution, the resting state of the catalyst was again found to be palladium−alkyl complex **7** by ^{31}P NMR spectroscopy. After the aminoalkene was completely consumed, the catalyst reverted back to the nitrile complex **9**.



(4)

With an appropriate catalyst in hand, the kinetics of the hydroamination reaction were monitored by ^{1}H NMR spectroscopy. A mixture of substrate **2a** (0.253 M), palladium complex **9** (0.001 M), and 1,4-dimethoxybenzene as an internal standard was prepared, and the rate of pyrrolidine **3a** formation was measured. Unfortunately, both zero-order and first-order kinetic plots displayed pronounced curvature, indicating that a more complex analysis of the reaction kinetics was required (Supporting Information).

The initial rate of product formation was measured at a number of different substrate concentrations to avoid the complications observed in monitoring the entire reaction (Figure 2). Surprisingly, a strong inverse dependence of the reaction rate on substrate concentration was observed. This same inverse dependence was also observed with the more basic acetamide **2b**. Furthermore, over a range of concentrations, the acetamide substrate reacts substantially slower than the carbamate (Table 2).

(20) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 3rd ed.; John Wiley & Sons, Inc.: New York, 2001; p 68.

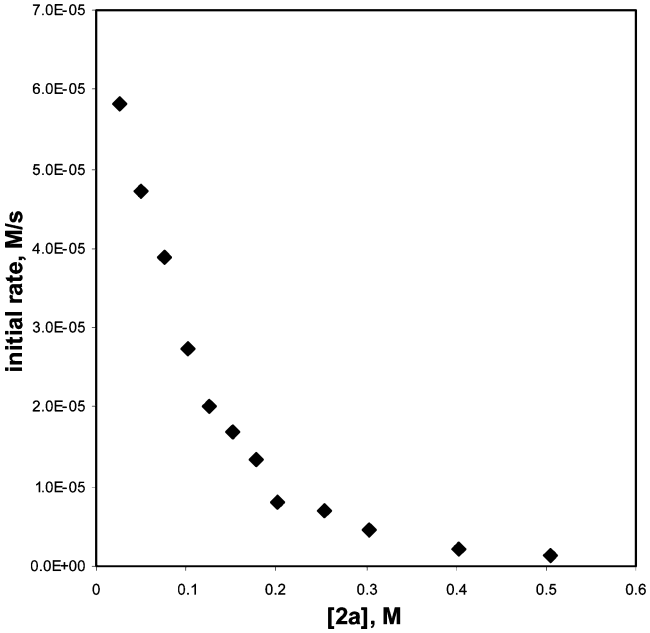
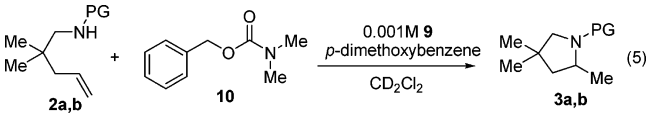


Figure 2. Initial reaction rates of product formation at different concentrations of aminoalkene **2a**. [**9**] = 0.001 M. The initial reaction rates were measured by comparing product concentration vs 1,4-dimethoxybenzene using ^{1}H NMR spectroscopy.

Table 2. Effect of Carbamate and Amide Protecting Groups on Reaction Rate



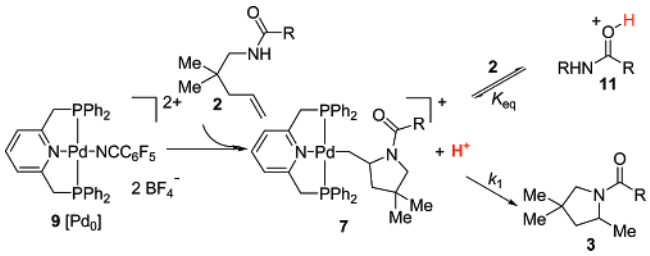
(5)

entry	PG	[**2**] M	[**10**] M	initial rate (s^{-1})
1	Cbz	**2a** 0.025	0	5.83×10^{-5}
2	Ac	**2b** 0.025	0	5.07×10^{-7}
3	Cbz	**2a** 0.051	0	4.73×10^{-5}
4	Ac	**2b** 0.051	0	9.29×10^{-8}
5	Cbz	**2a** 0.202	0	8.02×10^{-6}
6	Cbz	**2a** 0.202	0.202	1.46×10^{-6}

The reaction rate was measured in the presence of added carbamate **10** to determine if the observed rate decrease was due to the carbamate functional group. Carbamate **10** was also found to have a strong inhibitory effect on the rate of reaction (Table 2). It is notable that the rate of the reaction in entry 6 is comparable to the rate of the reaction measured when an initial **2a** concentration of 0.404 M was used. In other words, the effect on the initial rate of adding 0.202 M **10** was comparable to that of increasing the concentration of **2a** by 0.202 M. Despite this effect, the addition of **10** to the reaction mixture did not change the resting state of the catalyst, which was still palladium alkyl complex **7**.

The observation that palladium alkyl complex **7** is always the resting state of the catalyst indicates that the inhibitory effect of added substrate and/or **10** cannot be due to coordination of the carbamate to palladium, preventing alkene binding. If carbamate coordination were inhibiting catalytic turnover, significant amounts of a carbamate complex should be formed under the reaction conditions. No such carbamate complex was observed. Furthermore, if competitive carbamate coordination were occurring, increasing the substrate concentration should have no effect on the initial rate of the reaction because the concentration of the carbamate in the reaction mixture cannot

Scheme 4. Proposed Inhibition of Protonolysis by Aminoalkene **2**



be increased without also increasing the concentration of the alkene.[21] Overall, this should result in a zero-order dependence on substrate, not the observed inverse order. Therefore, carbamate coordination cannot be competing with alkene coordination, and the turnover-limiting step of pyrrolidine formation must be protonolysis of the palladium−carbon bond.

The stoichiometric experiments described above indicate that protonolysis of palladium alkyl complex **7** is the turnover-limiting step of the catalytic cycle, and therefore the added carbamate must be interfering with this process. It is unlikely that there is any appreciable interaction between the carbamate and the coordinatively saturated complex **7**.[22] However, in order to form complex **7**, a proton must be released into solution. In the turnover-limiting protonolysis step, complex **7** must react with this proton. This reveals a potential role of carbamate **2a** in slowing the overall reaction rate; namely, the carbamate of the aminoalkene could be acting as a Brønsted base, removing protons from the reaction. If the carbamate-bound protons are inactive in the protonolysis step, increasing the concentration of carbamate should inhibit protonolysis and thereby slow the overall reaction rate. This would also explain the much slower rates observed with acetamide substrate **2b**. Since amides are more basic than carbamates,[23] substrate **2b** should be better at sequestering protons and inhibiting protonolysis.

Based on the observations discussed above, a simplified model for the kinetic data can be constructed (Scheme 4). First, since palladium alkyl complex **7** appears to be the only catalyst-derived species in solution, we assume that *inter*molecular protonolysis of palladium alkyl complex **7** is the turnover-limiting step, and that the overall reaction rate can be described by a simple second-order rate equation for the reaction of **7** with a proton (eq 6). The proton also undergoes reversible binding with substrate **2** to generate **11**, which does not participate in protonolysis (eq 7). Note that since we are attempting to explain initial rates, we do not need to take into account the fact that the product **3** can also act as a base of comparable strength. Furthermore, the stoichiometry of the catalytic cycle requires that for every equivalent of **7** that is produced, an equivalent of H^+ is released (eq 8). Solving eq 7 for [**11**] and substituting for that quantity in eq 8 gives eq 9. Solving eq 9 for $[H^+]$ results in eq 10. Finally, substitution of eq 10 and eq 8 into the initial rate equation (eq 6) gives the reaction rate in terms of the concentrations of substrate (**2**) and catalyst ($[Pd]_0$).

$$\text{rate} = k_1[\mathbf{7}][H^+] \tag{6}$$

$$K_{eq} = \frac{[\mathbf{11}]}{[\mathbf{2}][H^+]} \tag{7}$$

$$\text{total proton concentration} = [H^+] + [\mathbf{11}] = [\mathbf{7}] \sim [Pd]_0 \tag{8}$$

$$[H^+] + K_{eq}[\mathbf{2}][H^+] = [Pd]_0 \tag{9}$$

$$[H^+] = \frac{[Pd]_0}{1 + K_{eq}[\mathbf{2}]} \tag{10}$$

$$\text{rate} = \frac{k_1[Pd]_0}{1 + K_{eq}[\mathbf{2}]} \tag{11}$$

Using eq 11, the unknown parameters k_1 and K_{eq} could be obtained by least-squares fitting to the experimental data (Figure 4). However, the fit obtained using this model was fairly poor, especially at high substrate concentrations (rms error $= 4.6 \times 10^{-6}$).

Examination of the fit obtained using Scheme 4 revealed that the simulated initial rates did not decrease with increasing substrate concentration as rapidly as the observed rates did. This raised the possibility that two aminoalkenes could bind to the proton, forming a proton-bridged dimer (**12**) (Figure 3). This 2:1 stoichiometry has been observed for a variety of protonated amides in nonpolar solutions.[24] Replacing compound **11** in the above rate expression with dimer **12** gives a new equilibrium constant (eq 12) and rate expression with an inverse second-order dependence on substrate concentration (eq 13).

$$K_{eq} = \frac{[\mathbf{12}]}{[\mathbf{2}]^2[H^+]} \tag{12}$$

$$\text{rate} = \frac{k_1[Pd]_0{}^2}{1 + K_{eq}[\mathbf{2}]^2} \tag{13}$$

A least-squares fit of the experimental rate data gave $k_1 = 62\ M^{-1}\ s^{-1}$ and $K_{eq} = 127\ M^{-2}$. The rates obtained from this simulation are a much better fit for the experimentally determined rates (rms error $= 1.1 \times 10^{-6}$, Figure 4). This strongly suggests that formation of proton-bridged dimer **12** is the cause for the retardation of the reaction rate at high concentrations of aminoalkene.

Inspection of eq 13 reveals that the reaction should be second order in catalyst concentration, despite the fact that none of the steps involves the interaction of two Pd complexes. This is a consequence of the fact that the turnover-limiting step requires the reaction of two species that are directly derived from the catalyst: the Pd alkyl complex **7**, and a proton which can only have been generated by the formation of **7.** A ln/ln plot (Figure 5) of the initial reaction rate versus initial concentrations of Pd catalyst **9** ranging from 0.001 to 0.005 M has a slope of approximately 2, indicating a second-order dependence, as predicted by the model.

(21) Since the rate of the reaction is being determined by initial rates, the carbamate of the product does not need to be considered.
(22) Pentacoordinate Pd(II) complexes are rare and usually bear tetradentate ligands. For an example, see Ghilardi, C. A.; Midollini, S.; Moneti, S.; Orlandini, A.; Ramirez, J. A. *J. Chem. Soc., Chem. Commun.* **1989**, 304−306.
(23) Carbamates are intermediate in basicity between amides and esters; see Armstrong, V. C.; Moodie, R. B. *J. Chem. Soc. B* **1968**, 275−277.
(24) For examples of 2:1 complexes of amides with Brønsted acids, see Wilhelm, M.; Koch, R.; Strasdeit, H. *New J. Chem.* **2002**, *26*, 560−566 and references therein.

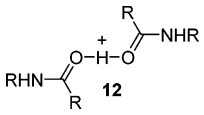


Figure 3. Proton-bridged dimer.

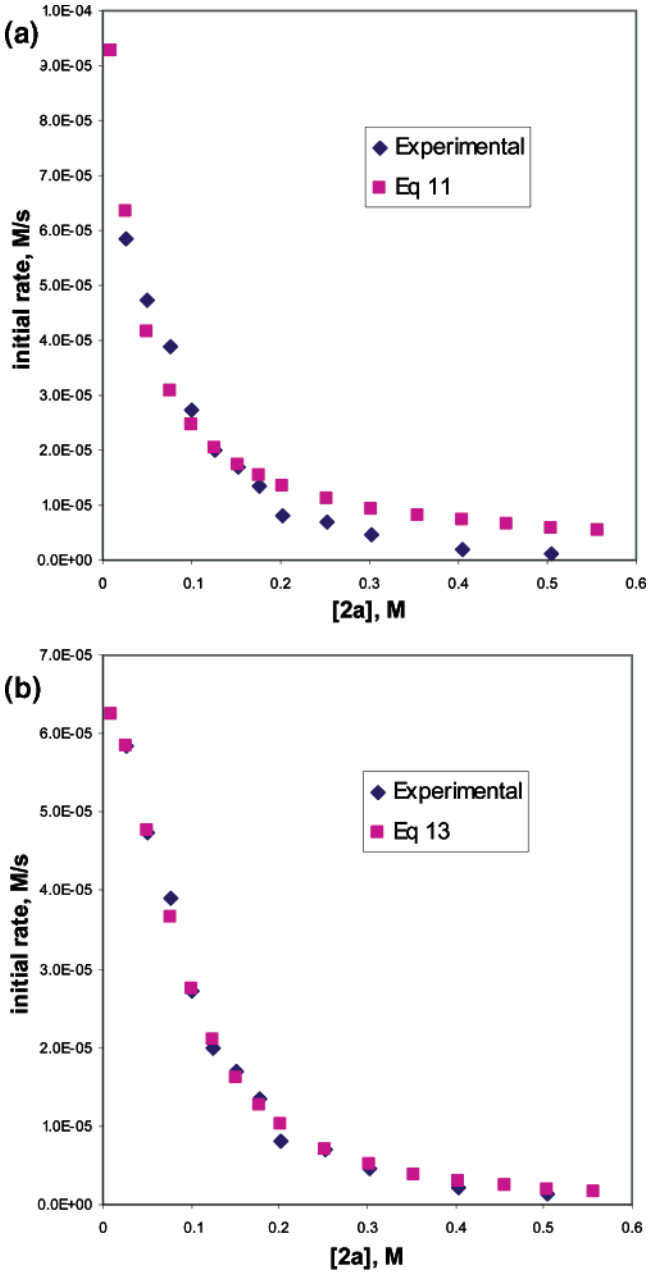


Figure 4. Simulated initial rates of product formation at different concentrations of aminoalkene **2a** vs experimental reaction rates (a) using 1:1 complex (eq 11); (b) using 2:1 complex (eq 13).

An alternate model involving rate-limiting *intra*molecular protonolysis of protonated palladium alkyl complex **6** and direct abstraction of the proton from **6** by two molecules of carbamate to form the same proton-bridged dimer **12** was also considered.[25] This model avoids invoking the presence of "free" protons in nonpolar media but leads to a much more complex rate equation (eq 14). Fitting the experimental data to this equation gave values of $k_1 = 0.08\ s^{-1}$ and $K_{eq} = 0.129\ M^{-1}$ and a slightly greater rms error of 2.29×10^{-6}. Given the small difference in error, it is difficult to definitively distinguish these conceptually similar mechanisms. In both models, the substrate acts as a base in a 2:1 stoichiometry to inhibit the key protonolysis step and thus inhibits the catalytic reaction.

(25) We are grateful to a reviewer who suggested this model. A more detailed discussion of this model is in the Supporting Information.

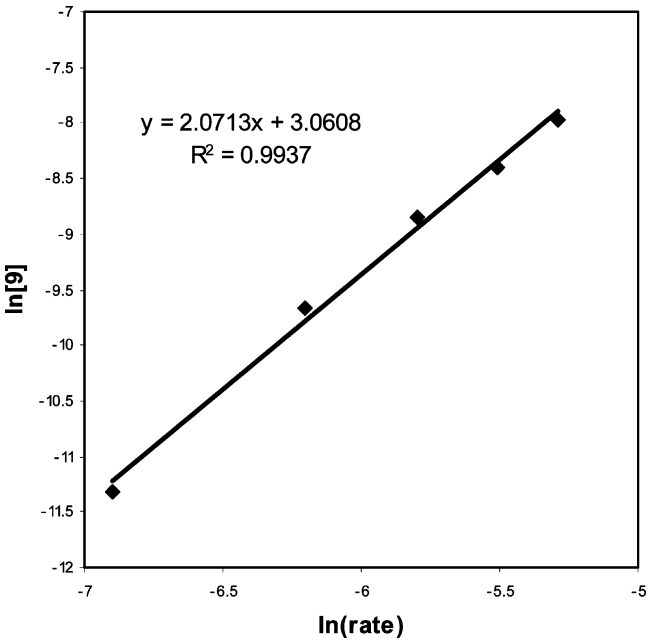
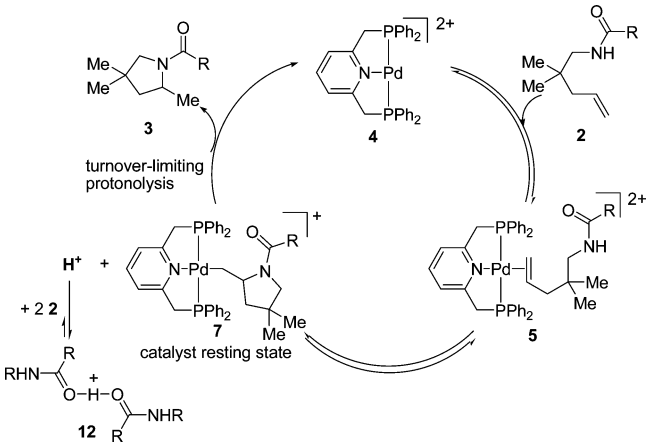


Figure 5. ln/ln plot for determination of the catalyst reaction order indicating second-order dependence.

Scheme 5. Complete Hydroamination Catalytic Cycle



$$\text{rate} = k_1\{2[\text{Pd}]_0 + K_{eq}[\mathbf{2}]^2 - (K_{eq}{}^2[\mathbf{2}]^4 + 4K_{eq}[\mathbf{2}]^2[\text{Pd}]_0)^{1/2}\}/2 \quad (14)$$

Conclusion

In conclusion, an unexpectedly complex mechanism for the palladium-catalyzed intramolecular hydroamination of unactivated alkenes has been elucidated (Scheme 5). Aminoalkene **2** coordinates to palladium complex **4** to form alkene complex **5**, which rapidly and reversibly cyclizes to give the protonated palladium alkyl complex **6**. Turnover-limiting protonolysis of the Pd−C bond of **6** results in formation of hydroamination product **3** and regenerates complex **4**. This simple catalytic cycle is complicated by deprotonation of **6** by mild bases to form

stable monocationic alkyl complex **7**, removing the catalyst from the catalytic cycle. The amide and carbamate protecting groups of the substrates are basic enough to deprotonate complex **6** and inhibit the key protonolysis step. This results in an inverse dependence of the reaction rate on substrate concentration. Formation of a 2:1 complex (**12**) between the carbamate and the proton is most consistent with the kinetic data. In all catalytic reactions, the resting state of the catalyst was palladium alkyl complex **7**, indicating that protonolysis of the Pd−C bond was the turnover-limiting step.

Stronger bases, such as tertiary amines and pyridines, form **7** irreversibly, allowing its isolation and characterization by X-ray crystallography. Isolated palladium alkyl complex **7** could be returned to the catalytic cycle by treatment with strong acid, resulting in formation of hydroamination product **3** and regenerating complex **4**, which readily catalyzes further conversion of aminoalkene **2** to product **3**. Although it cannot be conclusively ruled out, no evidence for a Pd(IV) hydride intermediate was observed, even at low-temperatures. Protonolysis of **7** appears to be significantly faster than that of the cationic (PPP)-PtMe complexes investigated by Gagné.[18] The ability of the carbonyl of the protecting group to deliver a proton intramolecularly may be responsible for this difference in reactivity.

These studies highlight the key role that in situ-generated Brønsted acid plays in determining the rate of the hydroamination reaction. Since protonolysis of the palladium alkyl complex is the turnover-limiting step of the catalytic cycle, the acidity of the reaction medium has a profound effect on the facility of the hydroamination reaction. The addition of basic moieties (e.g., protecting groups or solvents) to the mixture inhibits this reaction by sequestering protons from the catalytic cycle. On the other hand, the addition of cocatalytic Brønsted acids, such as TfOH or HBF_4, greatly accelerates the desired process. This concept can be used to further optimize the hydroamination of specific desired substrates.

Acknowledgment. Werner Kaminsky and Jason Benedict are acknowledged for X-ray crystallography and the University of Washington is acknowledged for financial support.

Supporting Information Available: Reaction conditions and experimental data for synthesis of all new compounds, details of the X-ray crystal structure of **7b**, and detailed kinetic data. This material is available is available free of charge on the Internet at http://pubs.acs.org.

JA0734997