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A New Pathway for Hydroamination. Mechanism of Palladium-Catalyzed Addition of Anilines to Vinylarenes

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Transition-metal-catalyzed hydroamination of olefins is an efficient route to alkyl- and benzylamines from readily available reagents.[1] Although the overall reaction is close to thermoneutral,[2] only a limited number of transition metal complexes show any catalytic activity for intermolecular addition of amines to olefins.[3] Several mechanistic schemes have been proposed or used in the design and selection of hydroamination catalysts. Over 20 years ago, activation of the C=C bond toward nucleophilic attack by coordination to a late metal had been studied.[4] A number of stoichiometric aminations and catalytic oxidative cyclizations resulted, but hydroaminations by this mechanism are rare. More recently, N−H activation, followed by alkene insertion, has been proposed as a viable mechanism for hydroamination. This mechanism operates in lanthanide-metal-catalyzed intra- and intermolecular hydroamination, developed by Marks and co-workers,[5] as well as Ir(I)-catalyzed additions of aniline to norbornene developed at DuPont.[6]

Recently, we described a new, palladium-catalyzed hydroamination of vinylarenes with arylamines.[7] The combination of Pd(PPh$_3$)$_4$ and trifluoromethanesulfonic acid, Pd(trifluoroacetate)$_2$, DPPF (1,1′-bis-(diphenylphosphino)ferrocene) and trifluoromethanesulfonic acid, or (DPPF)Pd(trifluoromethanesulfonate)$_2$ without added acid catalyzed the formation of Markovnikov addition products in high yields. Reactions catalyzed by [(*R*)-(BINAP)]Pd(OTf)$_2$ produced optically active *N*-1-(aryl)ethyl-*N*-phenylamines in up to 80% e.e.

We now report the isolation and reactivity of catalytic intermediates, the identification of the catalyst resting state, and the initiation of an understanding of the enantiocontrol. Our data support a new mechanism for olefin hydroamination catalyzed by these palladium complexes.

Monitoring by ^{31}P NMR spectroscopy of the reaction between vinylnaphthalene and aniline in the presence of [(*R*)-Tol-BINAP]Pd(OTf)$_2$ as catalyst precursor showed a pair of doublets as the predominant signals. Precipitation of this species and recrystallization gave the yellow compound {[(*R*)-Tol-BINAP][1-(2-naphthyl)-ethyl]Pd}(OTf) (**1a**). The connectivity of this complex was identified by multinuclear 2D NMR experiments.

Single crystals of **1a** were also obtained, and an ORTEP diagram is shown in Figure 1. The complex contains an η^3-naphthethyl ligand (Figure 1).[8] Although binding of the metal to the aryl carbon C4 is ∼0.2 Å more distant than that to the benzylic C1, stabilization from η^2-coordination of the aryl group favors the benzylic insertion product.[9] This insertion regiochemistry explains the Markovnikov selectivity for the catalytic hydroamination.

Naphthethyl **1a** most likely originated from migratory insertion of styrene into a palladium hydride. This hydride may form from the sequence of nucleophilic attack on a coordinated olefin and β-hydrogen elimination that occurs during Wacker-type oxidation processes.[10] Indeed, GC analysis of catalytic reaction mixtures

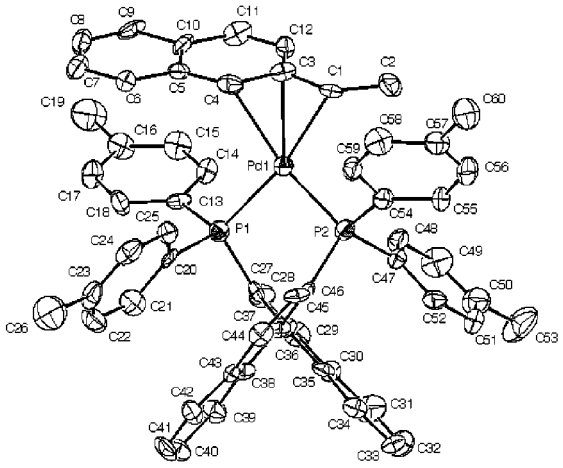
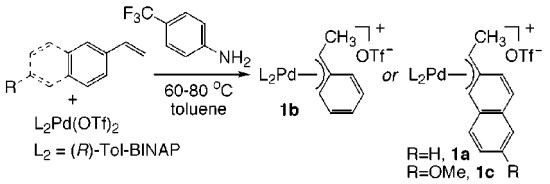


Figure 1. ORTEP plot of **1a** at 50% probability level (hydrogen atoms, triflate anion, and solvent molecules are omitted for clarity). Selected bond lengths: Pd−C1 = 2.157(9) Å; Pd−C4 = 2.323(10) Å; Pd−P1 = 2.329(3) Å; Pd−P2 = 2.285(2) Å.

showed the presence of the imine byproduct in a ratio of 0.77−0.98:1 versus the palladium catalyst.



The use of *p*-trifluoromethylaniline in analogous procedures with other vinylarenes enabled isolation in 76−90% yield of a series of η^3-arylethyl complexes **1a**−**c** that contained (*R*)-Tol-BINAP as ligand. Complexes **1a**−**c** were isolated as mixtures of diastereomers, with one isomer predominating. NMR measurements of purified complexes revealed a dependence of isomer distribution on solvent and temperature.[11]

To assess whether arylethyl complexes **1a**−**c** were kinetically and chemically competent to be intermediates, they were heated in toluene in the presence of excess aniline at 75 °C for 2 h. The corresponding *N*-(1-aryl)ethylanilines were formed in 61−83% isolated yield.

These results, however, do not demonstrate conclusively that **1a**−**c** are intermediates in the catalytic cycle. In particular, deinsertion of vinylarene would produce free styrene in the presence of aniline and a palladium complex that could catalyze the reaction by an alternative path or generate a different complex that is the true catalyst.

To obtain strong evidence for the intermediacy of **1a**−**c**, we allowed the methoxy-substituted complex **1c** to react with aniline

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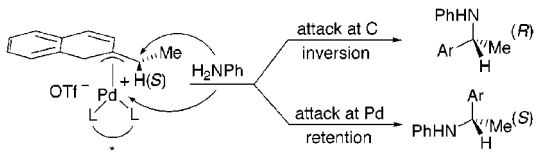
and free 2-vinylnaphthalene. If **1a**−**c** deinserted vinylarene to form the active catalyst, then the catalyst generated in this manner would react with the free vinylarene present in the highest concentration, which is the unsubstituted 2-vinylnaphthalene in this case. Control experiments catalyzed by [(*R*)-Tol-BINAP]Pd(OTf)$_2$ and employing 2-vinylnaphthalene and 6-methoxy-2-vinylnaphthalene as well as a 1:1 mixture as substrates showed that the two olefins were comparable in reactivity. Reactions of **1c** in the presence of 2 equiv of free 2-vinylnaphthalene were conducted with 100 equiv of aniline to ensure that reaction with aniline occurred faster than generation of other isomers or diastereomers of **1a**. ^{1}H NMR spectra obtained at the early stages of the reaction showed that *N*-1-(6-methoxy-2-naphthyl)ethylaniline formed prior to the unsubstituted naphthethylamine. These data strongly support the intermediacy of the isolated complexes in the catalytic process.

Additional support for formation of the amine product directly from the η^3-arylethylpalladium complexes was obtained from reactions of the analogous η^3-benzyl complex {[(*R*)-Tol-BINAP]-(benzyl)Pd}(OTf) (**2**), which cannot extrude olefin. Complex **2** was prepared as a single isomer by oxidative addition of benzyl bromide to [(*R*)-Tol-BINAP)]$_2$, followed by addition of silver triflate.[12] Reaction of **2** with aniline at 75 °C for 2 h formed *N*-benzylaniline in 87% yield.

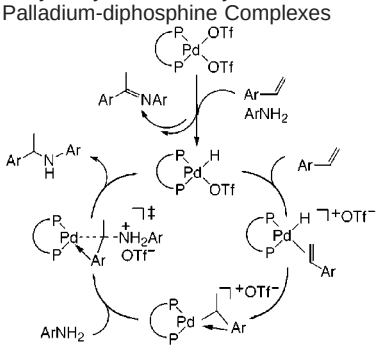
The C−N bond-forming process could occur by external attack on the η^3-benzyl complex in analogy to attack on an η^3-allyl, or it could occur by coordination of amine and C−N bond-forming reductive elimination with or without prior deprotonation of the N−H bond of the coordinated amine. The first path would lead to inversion of configuration and the second path to retention of configuration. With crystalline samples of enantio- and diastereomerically pure **1a**, we could distinguish between these mechanisms. Reaction of **1a** bearing the (*S*) configuration at C1 with excess aniline occurred by inversion of configuration and gave (*R*)-*N*-1-(2-naphthyl)ethylaniline in 84% yield and 71% e.e. Thus, external nucleophilic attack at carbon forms the C−N bond in the predominant benzylic amine product.

This stereochemistry for stoichiometric C−N bond formation was surprising because the reaction catalyzed by {[(*R*)-Tol-BINAP]Pd-(OTf)$_2$} produced predominantly the (*S*)-amine. We propose that the major isolated diastereomer produces the minor enantiomer in the catalytic system, as has been commonly observed in asymmetric hydrogenation.[13] ^{31}P NMR spectroscopy of the catalytic reaction (vide supra) showed that 17−20% of the total amount of palladium complexes were three isomers present in a ratio of 8:5:4. Due to the low concentrations of these isomers, complete structural assignment was not possible. However, ROESY and heteronuclear correlation experiments revealed a syn−anti arrangement of the phenethyl moiety for one of them.



Comparison of the rate constants for the stoichiometric reaction between **1c** and aniline with those for the reaction of aniline with 6-methoxy-2-vinylnaphthalene catalyzed by **1c** confirmed that the major diastereomer reacts more slowly than the ensemble of minor ones. The stoichiometric reaction at 40 °C occurred with a rate constant ($2.3(2) \times 10^{-5}$ M^{-1} s^{-1}) that was about 3.5 times slower than that for the overall catalytic reaction ($7.7(2) \times 10^{-5}$ M^{-1} s^{-1}). These ratios of rate constants are in rough agreement with the 60% e.e. observed in the reaction of aniline with 6-methoxy-2-vinylnaphthalene in the presence of either **1c** or [(*R*)-Tol-BINAP]Pd-(OTf)$_2$ as catalyst precursor.

Scheme 1. Catalytic Cycle for the Hydroamination of Vinylarenes Catalyzed by Palladium-diphosphine Complexes



In summary, we have uncovered the major pathway for hydroamination of vinylarenes using aniline substrates catalyzed by phosphine-ligated palladium triflates. This mechanism, summarized in Scheme 1, involves insertion of styrene into a palladium hydride and external, nucleophilic attack of amine on an η^3-benzyl complex. Further studies on the relationship between intermediate structure, reaction rates, and enantioselectivity for other substrate combinations are in progress.

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Supporting Information Available: Synthetic procedures, characterization data for compounds **1a**−**c**, **2**, **3**, and details of crystal structure analysis of **1a** and **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703.
(2) Benson, S. W. *Thermochemical Kinetics: Methods for the Estimation of Thermochemical Data and Rate Parameters*, 2nd ed.; John Wiley and Sons: New York, 1976.
(3) See for example: (a) Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744−751. (b) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366−4367. (c) Cheng, X.; Hii, K. K. M. *Tetrahedron* **2001**, *57*, 5445−5450. (d) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960−1964. (e) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E. *Eur. J. Inorg. Chem.* **1999**, 1121−1132.
(4) Åkermark, B.; Bäckvall, J. E.; Hegedus, L. S.; Zetterberg, K. *J. Organomet. Chem.* **1974**, *72*, 127−138.
(5) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275−294.
(6) (a) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738−6744. (b) Dorta, R.; Egli, P.; Zuercher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857−10858.
(7) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546−9547.
(8) The formation of related η^3-benzyl or 1-phenylethyl palladium complexes bearing diphosphine, phosphine−phosphite, or α-diimine donors has been observed in different catalytic reactions: (a) Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466−3478. (b) Nozaki, K.; Komaki, H.; Kawashima, Y.; Hiyama, T.; Matsubara, T. *J. Am. Chem. Soc.* **2001**, *123*, 534−544. (c) LaPointe, A. M.; Rix, F. C.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *1119*, 906−917. For structurally characterized examples of η^3-(1-aryl)alkyl palladium complexes see: (d) Gatti, G.; López, J. A.; Mealli, C.; Muso, A. *J. Organomet. Chem.* **1994**, *483*, 77−89. (e) Rix, F. C.; Brookhart, M.; White P. S. *J. Am. Chem. Soc.* **1996**, *118*, 2436−2448.
(9) Shortest nonbonding interactions between the phosphine and the naphthethyl ligand were C9−C19 (2.8166 Å), C8−C19 (3.0367 Å), and C11−C15 (3.3568 Å).
(10) Jira, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; pp 374−393.
(11) For example, crystals of **1a** that were dissolved in THF at room temperature showed two isomers in a ratio of 96:4. In CD_2Cl_2 the ratio was 84:16, decreasing to 80:20 at 50 °C.
(12) The intermediate [(*R*)-Tol-BINAP]Pd(benzyl)(bromide) complex **3** was also characterized by crystal structure analysis; see Supporting Information.
(13) Landis, C.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754.

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