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Isotope Effects and the Nature of Stereo- and Regioselectivity in Hydroaminations of Vinylarenes Catalyzed by Palladium(II)–Diphosphine Complexes

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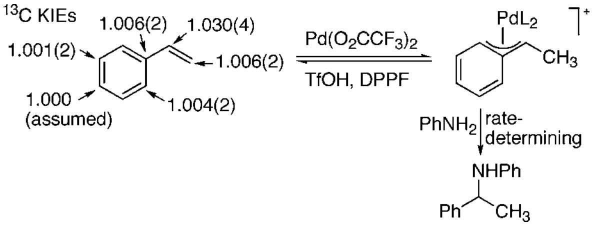
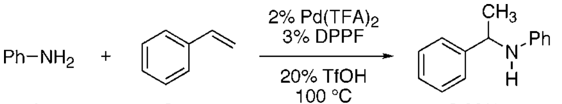
ABSTRACT



The hydroamination of styrene with aniline catalyzed by phosphine-ligated palladium triflates exhibits a substantial ^{13}C isotope effect at the benzylic carbon. This supports rate-determining nucleophilic attack of amine on a η^3-phenethyl palladium complex. Deuterium exchange observations and predicted isotope effects based on DFT calculations support this mechanism. Selectivity in these reactions is determined by the facility of palladium displacement after reversible hydropalladation of the alkene.

Due to the ubiquity of the amine functionality in natural products, there has been considerable interest in the development of transition metal-catalyzed hydroaminations of alkenes and alkynes.[1,2] One highly promising approach to the hydroamination of olefins, reported by Hartwig and coworkers, is the addition of anilines to vinylarenes catalyzed by a combination of Pd(OCOCF$_3$)$_2$, a chelating bis-phosphine such as DPPF, and a triflate ion source such as TfOH. This system exhibits high Markovnikov selectivity and high yields (eq 1). Enantioselective reactions can be achieved with BINAP as ligand.[3]



(1)

1 **2** **3** 99%

Future progress in broadening the range of effective substrates for this reaction and increasing control over selectivity may depend on a detailed understanding of the mechanism. A recent advance was Hartwig's isolation of η^3-benzyl palladium complexes under reaction conditions.[4] In stoichiometric reactions, these complexes are converted to hydroamination products prior to reaction of external arene. This

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(1) (a) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 8729. (b) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923. (c) Ackermann, L.; Bergman, R. G. *Org. Lett.* **2002**, *4*, 1475. (d) Heutling, A.; Doye, S. *J. Org. Chem.* **2002**, *67*, 1961. (e) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295. (f) Tian, S.; Arredondo, V. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 2568. (g) Douglass, M. R.; Ogasawara, M.; Hong, S.; Metz, M. V.; Marks, T. J. *Organometallics* **2002**, *21*, 283. (h) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Muller, T. L. *Eur. J. Inorg. Chem.* **1999**, *7*, 1121. (i) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608.

(2) (a) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Nobis, M.; Driessen-Holscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983.

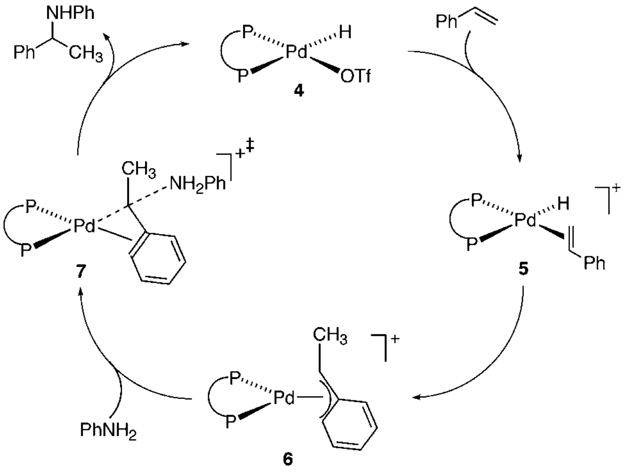
(3) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.

(4) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166.

10.1021/ol049137a CCC: $27.50

supports their catalytic intermediacy. From this and other observations, Hartwig proposed the mechanism of Scheme 1. In this mechanism, the Pd(II) hydride **4** effects hydropalladation of the vinyl arene via π-complex **5** to afford η^3-benzyl complex **6**. The product is then formed by external nucleophilic attack of amine on the η^3 complex.

Scheme 1



The observations above in stoichiometric reactions suggested that formation of the η^3 complex is irreversible, in which case the hydroamination's regio- and stereoselectivity would be determined by selectivity in the hydropalladation process. On the other hand, rate observations for the forward reaction of a η^3 complex versus the overall catalytic reaction were consistent with the observed reaction enantioselectivity,[4] suggesting that nucleophilic attack on the η^3 complex, not its formation, determines the selectivity. In addition, Hartwig made the interesting observation that an isolated η^3-benzylic complex, presumably the major stereoisomer formed, afforded the catalytic reaction's minor enantiomeric product. This seems unusual if the selectivity is determined at the stage of formation of the η^3 complex.

With the goal of deciphering the nature of the selectivity-determining step under synthetic conditions, we first determined ^{13}C kinetic isotope effects (KIEs) for the hydroamination of styrene with aniline. The complete set of ^{13}C KIEs were determined at natural abundance by NMR methodology.[5] Four hydroaminations of ≈5 M styrene in benzene with limiting aniline catalyzed by 2 mol % $Pd(OCOCF_3)_2$, 3 mol % DPPF, and 20 mol % TfOH at 90 °C were taken to 77−90% conversion. Under these conditions, the Markovnikov hydroamination product is formed in 92% isolated yield. The unreacted styrene was recovered by chromatography followed by fractional distillation and then analyzed by ^{13}C NMR. Changes in isotopic composition relative to the original styrene were determined using the aromatic para carbon as a standard, assuming that its isotopic composition does not change. From the changes in isotopic composition, the ^{13}C KIEs were calculated as previously described.[5] The isotope effects obtained from four independent reactions are summarized in Figure 1.

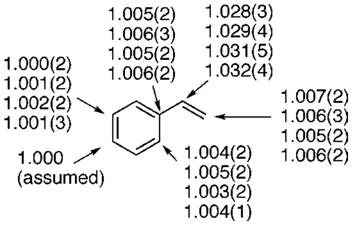


Figure 1. ^{13}C KIEs (k_{12_C}/k_{13_C}) for hydroamination of styrene with aniline catalyzed by $Pd(OCOCF_3)_2$, DPPF, and TfOH in benzene at 90 °C. Standard deviations ($n = 6$) in the last digit are shown in parentheses.

In a catalytic reaction, the observed KIEs need not reflect the rate-limiting or turnover-limiting step for the catalytic cycle, but the KIEs do reflect the first irreversible step between free substrate and product. Qualitatively, the large (≈1.030) ^{13}C KIE observed at the α-olefinic carbon indicates a major σ-bonding change at this carbon in this step. An S_N2 reaction, for example, might typically exhibit an isotope effect of this magnitude.[6] The formation of an alkene−metal π-complex such as the formation of **5** would be expected to exhibit much smaller, approximately equal ^{13}C KIEs at the olefinic carbons.[7] The β-olefinic ^{13}C KIE, at ≈1.006, is smaller than would be expected for an olefin insertion step, such as the conversion of **5** to **6**. For example, Landis observed a ^{13}C KIE of 1.017 at the analogous carbon in a Ziegler−Natta polymerization.[8] Within the confines of the Hartwig mechanism of Scheme 1, the ^{13}C KIEs strongly support nucleophilic attack on **6** as the selectivity-determining first irreversible conversion of styrene. Since **6** is the apparent resting-state of the catalyst, this step would also be the rate-determining step.

If this is the case, the η^3-benzyl ligand in **6** would have to be in rapid equilibrium with free styrene. To test this, a hydroamination reaction of styrene employing 65 mol % of partially deuterated aniline (78% deuterium content, prepared by equilibration of aniline with D_2O) was taken to 32% conversion (eq 2). Analysis of recovered unreacted styrene revealed approximately 25% deuterium in each of the olefinic positions (see **8**−**10**), but no detectable deuterium (<1%) was found in the aromatic ring. From the ^{2}H NMR, the ratio of **8**:**9**:**10** (ignoring multiply deuterated isomers) was 1.00:1.01:1.06. On the basis of calculated equilibrium isotope effects for styrene, the ratio of **8**:**9**:**10** at equilibrium would be 1.00:1.01:1.07.[9,10] From this, it appears that the exchange of deuterium into the olefinic positions of styrene had reached equilibrium.[11] This experiment cannot rule out H/D equilibration occurring via a side reaction that is unrelated to the catalytic cycle, but the formation of **8** and **9** supports the conclusion from KIEs that incorporation of styrene into the η^3 complex is reversible. In addition, the formation of **10**

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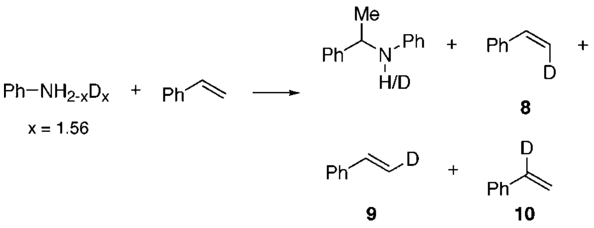
[5] Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.

[6] Lee, J. K.; Bain, A. D.; Berti, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 3769.

[7] Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288.

[8] Landis, C. R.; Rosaen, K. A.; Uddin, J. *J. Am. Chem. Soc.* **2002**, *124*, 12062.

suggests that the regioisomerically opposite hydropalladation of styrene also occurs reversibly.



(2)

Theoretical calculations were employed to provide a more detailed interpretation of the isotope effects and to explore the complete catalytic cycle. A problem in this system is the difficulty of accurately accounting for the charge−charge interaction of cationic complexes with the triflate counterion. This problem was made calculationally tractable by leaving out the triflate entirely but including a PCM solvent model. Comparison with experimental observations such as KIEs will be used to assess whether the resulting structures are reasonably representative of the solution chemistry.

The model catalytic cycle of Figure 2 was obtained in B3LYP calculations employing an SDD basis set and core potential on Pd, with a 6-31+G** basis set on other atoms. The π-complex **13** is predicted to be readily formed from **11** (the model for **4**), but it would also be accessible by simple proton transfer to the Pd(0)−styrene complex **12**. The energetics of **11** suggest that it is unlikely to be formed from protonation of a Pd(0)−bis-phosphine by an ammonium salt, but the catalytic cycle could readily shunt the high-energy **11** via **12**. There is virtually no barrier to formation of the η^3 complex **15** from **13**: after inclusion of zero-point energy, the transition structure for olefin insertion (**14**) is *lower* in energy than **13**. The highest predicted barrier in the cycle is the conversion of **15** to **17** via transition structure **16**. This is true also when estimates of entropy are taken into account: the predicted free energy barrier for the cycle versus standard-state reactants is 28.6 kcal/mol. This barrier is consistent with a reaction that takes several hours at 100 °C. Product **17**, after the nucleophilic substitution step, is actually higher in energy than the η^3 complex **15**, but it is downhill and presumably rapid for **17** to dissociate into the protonated product and the Pd(0)−bis-phosphine complex to continue the cycle. The free-energy barrier going backward from **15** is predicted to be 16.6 kcal/mol, much lower than the barrier going forward.[12] Overall, the calculations predict that the η^3 complex would be the resting point in the catalytic cycle with reversible incorporation of styrene to that point. This is in excellent qualitative agreement with the ^{13}C KIEs and deuterium incorporation observations.

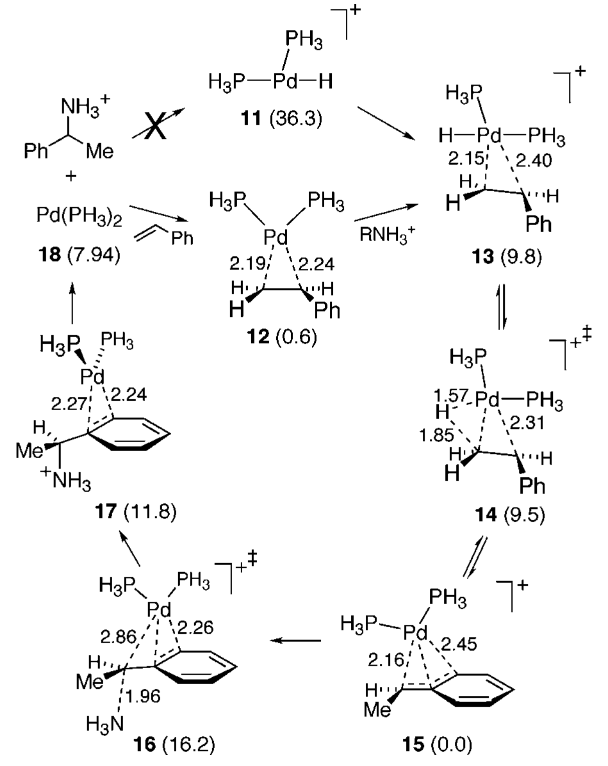


Figure 2. Calculated model catalytic cycle for the hydroamination of styrene in B3LYP calculations with an SDD basis set on Pd and 6-31+G** on all other atoms. The energies shown (in kcal/mol) include zpe and a PCM solvent model and are relative to **15** if going forward from **15** through the cycle. The overall cycle is downhill by 7.2 kcal/mol.

^{13}C KIEs for transition structures **14** and **16** (Figure 3) were predicted from the scaled vibrational frequencies[9] by the method of Bigeleisen and Mayer,[10] including a one-dimensional tunneling correction.[13] ^{13}C KIE predictions have proven to be highly accurate in reactions not involving hydrogen transfer, so long as the calculation accurately

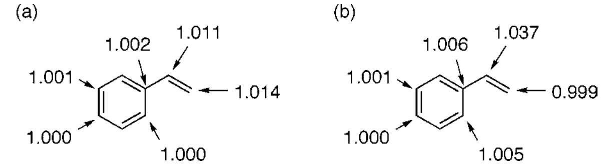


Figure 3. Predicted ^{13}C KIEs(k_{12_C}/k_{13_C}) at 90 °C. (a) KIEs if hydropalladation is irreversible, based on transition structure **14**. (b) KIEs if hydropalladation is reversible and nucleophilic attack of the η^3 complex is the first irreversible step for styrene, based on transition structure **16**.

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(9) The calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989). Becke3LYP frequencies were scaled by 0.9614.

(10) (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225. (c) Bigeleisen, J. *J. Chem. Phys.* **1949**, *17*, 675.

(11) The loss of integration in the ^{1}H NMR for the olefinic hydrogens was also consistent with complete equilibration, but the uncertainty in this measurement is relatively large.

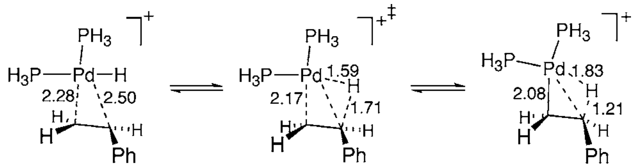
(12) A referee suggested that the observation of forward-going η^3 complex in stoichiometric reactions (ref 4) could be the result of use of 100 equiv of aniline. If so, then the barriers for forward and back reactions from **15** are much closer in energy than the calculations predict. Notably, however, the concentration of aniline in the KIE experiments here is roughly similar to that in stoichiometric reactions in ref 4.

(13) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: London, 1980; pp 60−63.

depicts the mechanism and transition-state geometry.[14] The hydrogen transfer associated with transition structure **14** makes the predicted KIEs for this step less quantitatively reliable, but the qualitative pattern of predicted isotope effects should be correct.

If hydropalladation of styrene is irreversible, medium-sized KIEs are predicted (Figure 3a) for both of the olefinic carbons of styrene, with very small KIEs for the aromatic carbons. This pattern does not fit with the experimental KIEs in Figure 1. In contrast, for nucleophilic attack on the η^3 complex, a large ^{13}C KIE is predicted at the α-olefinic carbon along with small but significant KIEs at the ortho and ipso aromatic carbons (Figure 3b). Considering the differences between the calculational model and the actual experimental system, the agreement between the predicted KIEs of Figure 3b and experiment is excellent.[15]

The regiochemically opposite hydropalladation of styrene suggested by the formation of **10** was also modeled theoretically. The π-complex **19** leading to the reverse hydropalladation is very similar in energy to **13** in the regular catalytic cycle. Although olefin insertion in **19** is less exothermic than the formation of η^3 complex **15**, there is little barrier predicted for the insertion process via **20** to afford **21**. This is consistent with the formation of **8** and **9** versus **10** at roughly similar rates. The electron-deficient Pd in **21** attempts to gain an extra ligand through an agostic interaction with an adjacent C−H bond. However, **21** is still much less stable than the alternative 16e^- **15**, and the reversed hydropalladation is predicted to be readily reversible.



19 (10.1) **20** (10.6) **21** (8.0)

The mechanistic picture that emerges from the combination of experimental observations and calculations provides insight into the selectivity in these reactions. The regiochemistry of the overall hydroamination is not derived from regioselectivity in the hydropalladation process but rather reflects the relative energy of transition states for nucleophilic displacement on a η^3 complex versus a primary alkyl Pd complex. Our model for the latter process was attack of NH_3 on **21**; a transition structure located for this displacement (see Supporting Information) was 11.8 kcal/mol higher than **16**. The high energy of this transition state accounts for the regiospecificity of the reaction.

The enantioselectivity observed in reactions employing BINAP-type ligands should reflect factors influencing the relative energy of diastereomeric transition states for nucleophilic attack on the η^3 complex. A qualitative model for this transition state was built by combining transition structure **16** and a molecular mechanics model of (*R*)-BINAP−Pd (with parameters chosen to approximate Hartwig's crystal structure[4] of a η^3 complex). At the stage of the η^3 complex, there was no obvious steric preference among the possible diastereomeric structures; this is in line with Hartwig's observation of multiple η^3 complexes present under the reaction conditions.[4] However, the η^3 complex must twist as it turns into a η^2-benzene complex in the process of nucleophilic displacement. In the complex leading to the major product (Figure 4a), this twist appears to relieve steric interactions. In the complex leading to the minor enantiomeric product, the necessary twist of the benzyl group seems to increase steric interactions. It should be emphasized that this is currently only a qualitative model, but it does account for the direction of the observed enantioselectivity.

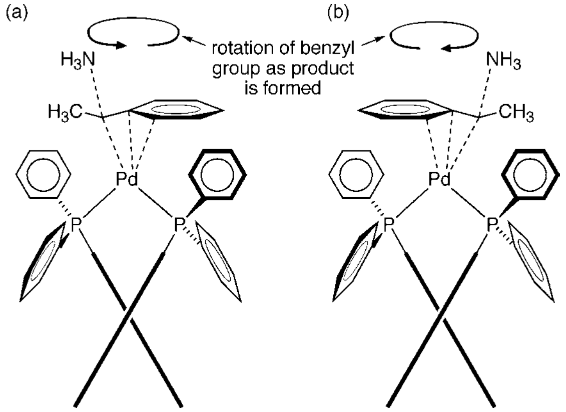


Figure 4. Model for understanding the enantioselectivity in hydroaminations mediated by BINAP-type ligands. (a) Transition state leading to the major enantiomer. (b) Transition state leading to the minor enantiomer.

In summary, a combination of kinetic isotope effects, deuterium exchange observations, and theoretical calculations supports a consistent mechanism in which the key selectivity-determining step is a nucleophilic displacement on a η^3 complex. This suggests ways to gain further control of selectivity in these reactions, and we plan to pursue such studies.

Acknowledgment. We thank the NIH (Grant GM-45617) and The Robert A. Welch Foundation for research support and the NSF (CHE-0077917) for NMR instrumentation.

Supporting Information Available: Experimental procedures, as well as energies and geometries of all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] (a) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984. (b) Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 10865. (c) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907. (d) Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385.

[15] The experimental KIE of ≈1.006 at the β-carbon of styrene is recognizably in the opposite direction of the predicted KIE of 0.999 at this carbon. This discrepancy may be the result of small amounts of polymerization during the reaction or the distillative reisolation of the unreacted styrene, as polystyrene was always observed in the pot residue. Polymerization of styrene would contribute to the observed β-carbon KIE but have little effect on the other carbons. For ^{13}C KIEs for free-radical polymerization, see: Singleton, D. A.; Nowlan, D. T., III.; Jahed, N.; Matyjaszewski, K. *Macromolecules* **2003**, *36*, 8609.