

Direct Measurement of the Thermodynamics of Vinylarene Hydroamination

Adam M. Johns, Norio Sakai, André Ridder, and John F. Hartwig*

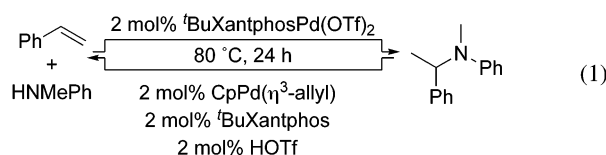
Department of Chemistry, Yale University, Post Office Box 208107, New Haven, Connecticut 06520-8107

Received April 20, 2006; E-mail: john.hartwig@yale.edu

The addition of amines to olefins catalyzed by transition metals has been a long-term target for catalysis,^{1,2} and efforts to develop catalysts for this reaction have intensified in recent years.^{3,4,5} Reviews have stated that the hydroamination of olefins is thermodynamically favored,² but experimental equilibrium constants, enthalpies, and entropies for olefin hydroamination in solution are lacking.

The enthalpy for additions of amines to olefins has generally been predicted from bond dissociation energies of only model substrates, such as ethylene and ammonia, and the entropy for this reaction in solution has been estimated from typical differences in translational entropy upon formation of a 1:1 adduct or ΔS values in the gas phase.⁶ Because the thermodynamics for hydroamination are close to thermoneutral, precise measurements of the thermodynamic parameters for the reactions between amines and olefins of varied structures are needed to establish benchmark values that can be used to predict which types of hydroaminations will be favorable and which will be unfavorable. To fill this void of basic information on olefin hydroamination, we report direct measurements of the equilibrium constants for addition of aromatic amines with varied steric and electronic properties to several types of vinylarenes. An appreciation of the thermodynamic constraints of this process has allowed us to observe the first intermolecular additions of amines to internal olefins that lack the high ring strain of norbornene.⁷

We began our assessment of the thermodynamics of hydroamination by studying the addition of *N*-methylaniline to styrene. Preliminary results showed that a series of catalysts formed the addition product in similar yields and that the major material in solution, other than the addition product, was the starting olefin and the aromatic amine. These observations suggested that this hydroamination might be controlled by thermodynamics rather than reaction rate and catalyst stability.



To determine the thermodynamics for this process, we conducted the addition of *N*-methylaniline to styrene, as well as the cleavage of the *N*-methyl-*N*-(1-phenylethyl)aniline, to form free styrene and *N*-methylaniline (eq 1). The use of the wide-bite angle bisphosphine Xantphos and a Pd⁰ precatalyst for the retrohydroamination⁴ allowed us to conduct the reaction in both directions with acceptable rates and minimal catalyst decomposition. The addition of *N*-methylaniline to styrene and the cleavage of *N*-methyl-*N*-(1-phenylethyl)aniline at the same starting concentrations formed equivalent amounts of reaction components. The equilibrium constant for the addition process was found to be $K = 1.5 \pm 0.1 \text{ M}^{-1}$ at 80 °C and $K = 0.52 \pm 0.05 \text{ M}^{-1}$ at 110 °C. This value is shown as entry 1 of Table 1.

Table 1. Thermodynamics of Hydroamination

entry	olefin	amine	catalyst ^a	$K \text{ (M}^{-1}\text{)}$	$\Delta G \text{ (kcal/mol)}$
1		HNMePh	A	1.5 ± 0.1	-0.28 ± 0.05
2			A	2.4 ± 0.1	-0.61 ± 0.03
3		HNMePh	A	1.30 ± 0.01	-0.18 ± 0.01
4		<i>m</i> -anisidine	A	155 ± 1	-3.54 ± 0.01
5		<i>m</i> -anisidine	B	0.69 ± 0.05	0.26 ± 0.05
6		<i>m</i> -anisidine	C	0.16 ± 0.04	1.31 ± 0.18

^a Catalyst composition: (A) Forward: 2 mol % *t*BuXantphosPd(OTf)₂. Backward: 2 mol % CpPd(η^3 -allyl)/*t*BuXantphos/HOTf. (B) Forward: 10 mol % Pd(TFA)₂/DPPF/HOTf. Backward: 10 mol % CpPd(η^3 -allyl)/DPPF/HOTf. (C) Forward: 5 mol % Pd(TFA)₂/DPPF/HOTf. Backward: 5 mol % CpPd(η^3 -allyl)/DPPF/HOTf.

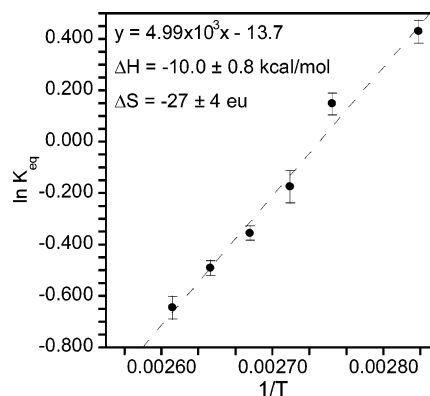


Figure 1. van't Hoff plot of eq 1.

To determine the enthalpic and entropic contribution to this equilibrium constant, we measured this equilibrium constant at different temperatures. A van't Hoff plot of these data showed that the enthalpy for addition was $-10.0 \pm 0.8 \text{ kcal/mol}$ and that the entropy was $-27 \pm 4 \text{ eu}$ (Figure 1). Thus, the hydroamination is favored enthalpically, but this favorable enthalpy is counterbalanced by a nearly equal $T\Delta S$ term.

Considering that several review articles² state that the unfavorable entropy of the intermolecular addition makes it necessary to conduct the reaction at low temperatures, a comment about the effect of temperature on equilibrium is warranted. The temperature dependence of an equilibrium constant and, therefore, the conversion results from ΔH . Le Châtelier's principle implies that the equilibrium constant for an exothermic reaction will be larger at lower temperatures than at higher temperatures.

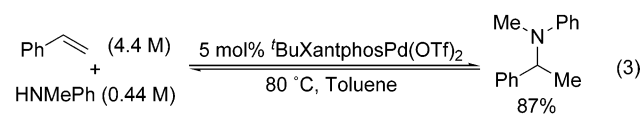
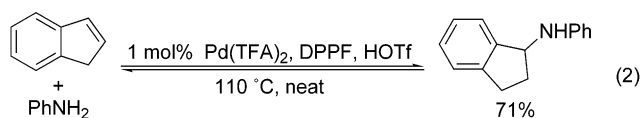
Additional equilibrium constants for additions of amines to vinylarenes are shown in Table 1. Because the palladium-catalyzed additions of electron-rich anilines occur in higher yields than additions of electron-poor anilines^{4,5} and additions to more electron-poor vinylarenes occur in higher yields than additions to more electron-rich vinylarenes,⁵ we sought to determine if the higher yields for these classes of substrates resulted from thermodynamic or purely kinetic factors. Thus, we measured the equilibrium constants for the addition of 4-methoxy-*N*-methylaniline to styrene (Table 1, entry 2) and for the addition of *N*-methylaniline to 2-vinylnaphthalene (entry 3). The equilibrium constants for these additions ($2.4 \pm 0.1 \text{ M}^{-1}$, and $1.30 \pm 0.01 \text{ M}^{-1}$) are similar to the equilibrium constant for the addition of *N*-methylaniline to styrene ($1.5 \pm 0.1 \text{ M}^{-1}$) in entry 1. Therefore, the electronic effect on this reaction is almost purely a result of kinetic, not thermodynamic, factors.

In contrast, steric properties of the amine significantly affected the equilibrium constant. The addition of aniline to styrene occurred at a higher conversion than the addition of *N*-methylaniline under equilibrium conditions. By conducting the forward and reverse of the addition of *m*-anisidine⁸ to styrene (Table 1, entry 4), the equilibrium constant for the addition process was found to be $155 \pm 1 \text{ M}^{-1}$. This value is substantially larger than the value for the addition of *N*-methylaniline.

Because disubstituted olefins are more stable than monosubstituted olefins,⁹ we also assessed the thermodynamics for the addition of *m*-anisidine to indene and 1,2-dihydronaphthalene. No metal-catalyzed additions of amines to these olefins have been reported.^{7f} In the presence of a combination of Pd(TFA)₂ (TFA = trifluoroacetate), 1,1'-bis-(diphenylphosphino)ferrocene, and triflic acid, the addition of aniline occurred to each of these olefins to generate equilibrium mixtures of reactants and products.

The addition of aniline to indene at a concentration of aniline of about 2 M with 4 equiv of indene formed the Markovnikov addition product in 50% yield, as determined by GC. The bulk of the remaining material was the starting indene and arylamine. Reaction of *N*-(3-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-amine with the same catalyst generated free indene and *m*-anisidine. From the ratio of indene, *m*-anisidine, and the addition product generated from both the forward and reverse reactions (Table 1, entry 5), an equilibrium constant of $0.69 \pm 0.05 \text{ M}^{-1}$ was calculated.

Likewise, the addition of aniline to 1,2-dihydronaphthalene occurred in yields that were limited by thermodynamics. The reaction of 1 M olefin with 1 M aniline generated the addition product in 8% yield. Again, cleavage of the addition product generated free olefin and free amine. From the ratio of 1,2-dihydronaphthalene, *m*-anisidine, and the addition product generated from reactions run in the forward and reverse directions, (Table 1, entry 6), an equilibrium constant of $0.16 \pm 0.04 \text{ M}^{-1}$ was calculated.



The realization that the additions of *N*-alkylanilines and additions to internal vinylarenes were constrained by thermodynamics led us to modify the reaction conditions by increasing the equivalents of olefin and increasing the overall concentration to obtain higher yields. The reaction of a 4:1 molar ratio of indene and aniline without solvent at 110 °C formed the addition product in 71% yield

(eq 2). As shown in eq 3, increasing the ratio of styrene to *N*-methylaniline to 10:1 (4.4 and 0.44 M, respectively) allowed the reaction to form the addition product in 87% yield. Unfortunately, the equilibrium for addition to 1,2-dihydronaphthalene was too unfavorable to obtain high yields.

In conclusion, we have shown the importance of considering the thermodynamics for additions of amines to olefins when targeting catalytic hydroamination processes. We have shown that the reactions are exothermic but nearly ergoneutral. Clearly an intramolecular reaction will not be constrained by as large a negative entropy, but an intramolecular reaction that generates a strained ring system is likely to experience similar and counterbalancing enthalpies from ring strain. At the same time, consideration that the reaction yield is controlled in large part by thermodynamics allows one to conduct reactions under conditions in which the addition processes do occur in high yields.

Acknowledgment. We thank the NIH (GM-55382) for support of this work. N.S. thanks Tokyo University of Science (TUS) for support of his stay.

Supporting Information Available: Spectroscopic and analytical data of new compounds and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (a) Haggin, J. *Chem. Eng. News* **1993**, 23. (b) Roesky, P. W.; Muller, T. E. *Angew. Chem., Int. Ed.* **2003**, 42, 2708. (c) Nobis, M.; Driessen-Holscher, B. *Angew. Chem., Int. Ed.* **2001**, 40, 3983. (d) Hultzsich, K. C. *Org. Biomol. Chem.* **2005**, 3, 1819. (e) Brunet, J. J. *Gazz. Chim. Ital.* **1997**, 127, 111. (f) Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, 39, 703. (g) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, 110, 6738. (h) Coulson, D. R. *Tetrahedron Lett.* **1971**, 429.
- (a) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579. (b) Hultzsich, K. C. *Adv. Synth. Catal.* **2005**, 347, 367. (c) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, 98, 675.
- (a) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Muller, T. E.; Thiel, O. R. *Chem.—Eur. J.* **1999**, 5, 1306. (b) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, 127, 1070. (c) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, 7, 1959. (d) Bieler, N.; Egli, P.; Dorta, R.; Togni, A.; Eyer, M.; Lonza, A. G., Switzerland. EP 909762, 1999. (e) Burgstein, M. R.; Berberich, H.; Roesky, P. W. *Organometallics* **1998**, 17, 1452. (f) Crimmin, M. R.; Casely, I. J.; Hill, M. S. *J. Am. Chem. Soc.* **2005**, 127, 2042. (g) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, 37, 673. (h) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, 20, 1960. (i) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, 7, 1737. (j) Kim, Y. K.; Livinghouse, T.; Horino, Y. *J. Am. Chem. Soc.* **2003**, 125, 9560. (k) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, 123, 4366. (l) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, 124, 1166. (m) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, 124, 3669. (n) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, 344, 795. (o) Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, 127, 5756. (p) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, 125, 14286. (q) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, 126, 2702. (r) Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, 23, 1649.
- Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, 128, 1828.
- Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, 122, 9546.
- (a) Steinborn, D.; Taube, R. *Z. Chem.* **1986**, 26, 349. (b) R. Taube In *Applied Homogeneous Catalysis*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Vol. 1, p 513.
- For examples of addition of anilines to norbornene, see: (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. *J. Org. Lett.* **2004**, 6, 2515. (b) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, 127, 14542. (c) Brunet, J. J.; Chu, N. C.; Diallo, O. *Organometallics* **2005**, 24, 3104. (d) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, 119, 10857. For examples of additions of carboxamides to internal olefins, see: (e) Aufdenblatten, R.; Diezi, S.; Togni, A. *Monatsh. Chem.* **2000**, 131, 1345. (f) Qian, H.; Widenhoefer, R. A. *Org. Lett.* **2005**, 7, 2635. For examples of additions of sulfonamides to internal olefins, see: (g) Karshtedt, D.; Bell, A. T.; Tilley, D. D. *J. Am. Chem. Soc.* **2005**, 127, 12640. (h) Zhang, J. L.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, 128, 1798.
- Because no significant electronic effect was observed for the addition of 4-methoxy-*N*-methylaniline to styrene, *m*-anisidine was substituted for aniline to facilitate characterization by ¹H NMR spectroscopy.
- March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992.

JA062773E