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Brønsted Base-Modulated Regioselectivity in the Aerobic Oxidative Amination of Styrene Catalyzed by Palladium

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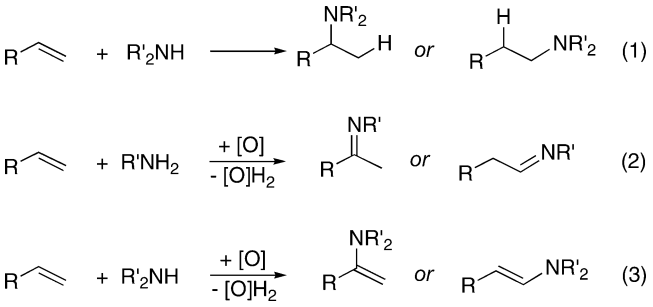
Abstract: Palladium(II)-catalyzed aerobic oxidative amination of styrene with oxazolidinone proceeds with catalyst-controlled regioselectivity: $(CH_3CN)_2PdCl_2$ (**1**) and $(Et_3N)_2PdCl_2$ (**2**) catalyze formation of the anti-Markovnikov and Markovnikov enecarbamate products, **3** and **4**, respectively. Kinetic studies and deuterium kinetic isotope effects demonstrate that these two reactions possess different rate-limiting steps, and the data indicate that the product regiochemistry arises from the presence or absence of an effective Brønsted base in the reaction. In the presence of a Brønsted base such as triethylamine or acetate, the kinetically preferred Markovnikov aminopalladation adduct of styrene is trapped via rapid deprotonation of a zwitterionic intermediate and leads to formation of **4**. In the absence of an effective Brønsted base, however, slow deprotonation of this adduct enables aminopalladation to be reversible, and product formation proceeds through the thermodynamically preferred anti-Markovnikov aminopalladation adduct to yield **3**.

Introduction

Aryl and alkyl olefins generally do not react with amines. In recent years, however, a number of catalysts have been identified that promote the intermolecular coupling of amines and alkenes.[1−10] The widespread interest in this chemistry arises from the prominence of nitrogen-containing functional groups in commercial organic molecules, ranging from commodity and fine chemicals to pharmaceuticals and agrochemicals. Metal-catalyzed addition of amines to terminal alkenes can yield several different products depending on the catalyst and reaction conditions, including alkylamines via hydroamination (eq 1) and imines or enamines via oxidative amination (eqs 2 and 3). These reactions may proceed with Markovnikov or anti-Markovnikov regioselectivity, and the desired isomer depends on the specific application. The ability to achieve catalyst control over regiochemistry represents an important target of ongoing research efforts.[11]



Oxidative amination reactions are synthetically attractive because they lead to a net increase in substrate functionality, and we recently reported methods for the oxidative amination

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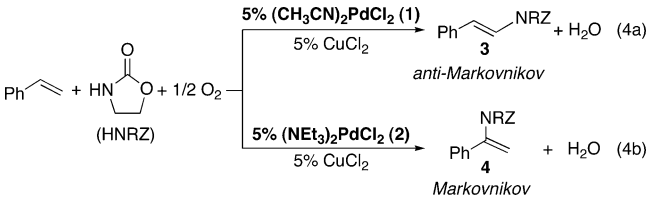
(11) White and co-workers recently reported an example of Pd-catalyzed allylic oxidation of terminal alkenes that preferentially forms the branched or linear allylic acetate, depending on the reaction conditions: Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346−1347.

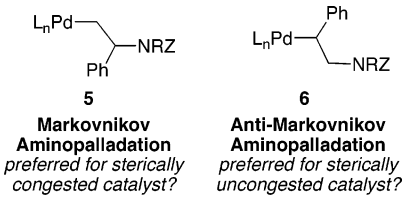
10.1021/ja0562806 CCC: $30.25

of both aryl and alkyl olefins that use molecular oxygen as the stoichiometric oxidant.[12,13] The reaction of styrene with oxazolidinone is noteworthy because an apparently subtle variation of the catalyst leads to a complete switch in product regiochemistry. Specifically, the use of $(CH_3CN)_2PdCl_2$ (**1**) and $(Et_3N)_2PdCl_2$ (**2**) as catalysts results in the formation of the anti-Markovnikov and Markovnikov oxidative amination products, respectively (eq 4). The synthetic implications of these observations prompted us to investigate the origin of this result, and mechanistic studies described below implicate a novel, Brønsted base-mediated mechanism for regiochemical modulation of metal-catalyzed alkene amination reactions.



Results and Discussion

Origin of Regiochemical Control: Evidence for a Brønsted Base Effect. Our initial hypothesis to explain the regiochemical outcome of the reactions in eq 4 focused on the coordination chemistry of triethylamine. Addition of NEt_3 to **1** results in amine coordination to the palladium center, and catalyst **2** was isolated from a 1:2 mixture of **1** and NEt_3 and characterized by X-ray crystallography (Figure 1). The trans stereochemistry, together with the large NEt_3 cone angle (158°),[14] suggested that ligand steric effects might alter the reaction regioselectivity. Namely, a sterically congested metal center might favor formation of aminopalladation intermediate, **5**, which possesses a primary alkyl ligand, over the other possible intermediate, **6**, which features a larger, secondary alkyl ligand. The steric effects may be amplified by the fact that the Pd−N bond lengths of 2.17 Å are considerably shorter than Pd−P bond lengths (∼2.33−2.35 Å) for structurally related *trans*-$(R_3P)_2PdCl_2$ complexes.[15]



This model is consistent with the regiochemical results; however, several additional observations forced us to consider an alternate explanation. Variation of the triethylamine concentration did not result in a systematic change in the **3**/**4** product ratio (Figure 2A). Addition of NEt_3 decreases the yield of **3**, but formation of **4** is not observed until a NEt_3:Pd ratio > 1 is present in solution. The yield of **4** maximizes at a NEt_3:Pd ratio of ∼3, but at elevated NEt_3 concentrations (NEt_3:Pd > 3), both the overall yield and initial rate of the catalytic reaction diminish substantially (Figure 2A,B).[16]

$(Et_3N)_2PdCl_2$ (**2**) =

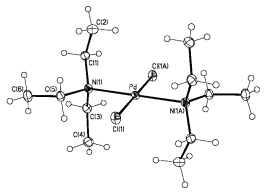


Figure 1. Molecular structure of **2** with 50%-probability thermal ellipsoids. Bond lengths: Pd−N(1) = Pd−N(1A) = 2.1716(15) Å; Pd−Cl(1) = Pd−Cl(1A) = 2.3179(6) Å.

Triethylamine is not unique in its ability to promote formation of the Markovnikov oxidative amination product. If anionic bases, such as acetate and bicarbonate, are used in combination with **1**, **4** is the only product obtained. For example, in the presence of 100 mol % sodium acetate[17] and 5 mol % **1** as the catalyst, **4** is obtained in nearly quantitative yield (>95%). Reactions conducted in the presence of NEt_3 or NaOAc proceed significantly faster (>5-fold) than those catalyzed by **1** in the absence of base. Furthermore, use of the lithium salt of deprotonated oxazolidinone in reactions catalyzed by **1** in the absence of NEt_3 also yields **4** as the exclusive amination product (62%). These observations are inconsistent with a ligand steric-effect model and suggest the change in reaction rate and regioselectivity arise from a Brønsted base effect.

Kinetic Studies. Kinetic studies reveal distinct differences between reactions catalyzed by **1** and **2**. The dependence of the initial reaction rate on styrene and oxazolidinone concentrations was evaluated in each case by monitoring the product by gas chromatography.[18] With **1** as the catalyst (eq 4a), the rate exhibits a linear dependence on [oxazolidinone] and a saturation dependence on [styrene] (Figure 3). In contrast, with **2** as the catalyst (eq 4b), the rate exhibits a saturation dependence on [oxazolidinone] (Figure 4A) but retains a linear dependence on [styrene] even to very high concentration (7.9 M, >90 vol %) (Figures 4B and S1 (Supporting Information)).

Deuterium kinetic isotope effects (KIEs) for both reactions were evaluated by comparing the reaction rates with oxazolidinone versus *N*-deuterooxazolidinone as the nucleophile. Formation of the anti-Markovnikov product, **3**, catalyzed by **1** exhibits a significant KIE, $k^H/k^D = 3.0(1)$ at 40 °C, whereas formation of the Markovnikov product, **4**, catalyzed by **2** exhibits essentially no isotope effect, $k^H/k^D = 1.1(1)$ at 40 °C. Furthermore, no isotope effect is observed in the formation of **4** catalyzed by a mixture of **1** (5 mol %) and NaOAc (100 mol %): $k^H/k^D = 0.98(5)$ at 40 °C. No statistically significant kinetic isotope effects are evident when styrene is replaced with styrene-d_8 in any of the reactions.

Thus far, attempts to characterize the catalyst resting state by in situ NMR spectroscopic studies have been unrewarding.

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(15) Based on analysis of *trans*-$(R_3P)_2PdCl_2$ complexes in the Cambridge Structural Database.

(16) Triethylamine can coordinate to the $CuCl_2$ cocatalyst; however, control experiments demonstrate that the [NEt_3] dependence correlates exclusively with [Pd] and not [Cu].

(17) The poor solubility of NaOAc requires elevated loading. NBu_4OAc, a soluble source of acetate, achieves identical results at 10 mol % loading.

(18) See Supporting Information for additional details. The estimated uncertainty for individual rate measurements is ±10%.

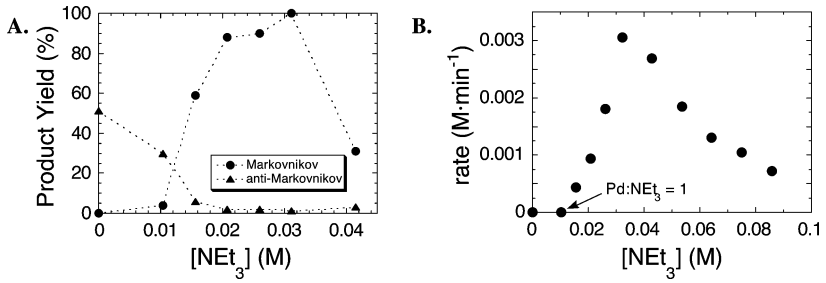


Figure 2. Effect of $[NEt_3]$ on the product distribution (A) and the initial rate of Markovnikov product formation (B). Reaction conditions: (A) [styrene] = 1.26 M, [HNRZ] = 0.21 M, $[(CH_3CN)_2PdCl_2] = [CuCl_2] = 0.011$ M, $[NEt_3] = 0-0.042$ M, $p(O_2) = 1$ atm, DME, 60 °C, 24 h; (B) [styrene] = 1.30 M, [HNRZ] = 0.25 M, $[(CH_3CN)_2PdCl_2] = [CuCl_2] = 0.013$ M, $[NEt_3] = 0-0.086$ M, $p(O_2) = 1$ atm, DME, 60 °C.

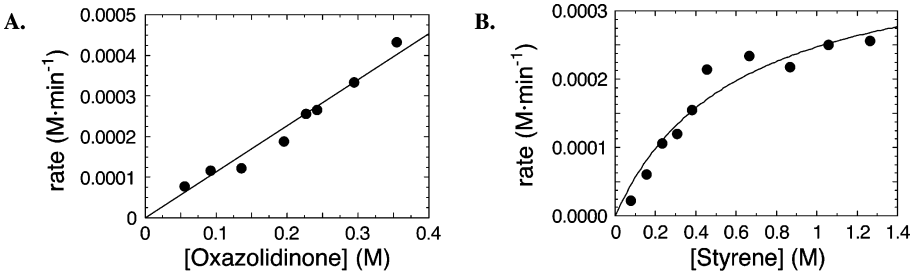


Figure 3. Kinetic data for the anti-Markovnikov oxidative amination of styrene with oxazolidinone (HNRZ) catalyzed by $(CH_3CN)_2PdCl_2$ (**1**). Reaction conditions: (A) [HNRZ] = 0.055−0.355 M, [styrene] = 1.26 M, [**1**] = $[CuCl_2]$ = 0.011 M, $p(O_2) = 1$ atm, DME, 60 °C; (B) [HNRZ] = 0.23 M, [styrene] = 0.079−1.27 M, [**1**] = $[CuCl_2]$ = 0.011 M, $p(O_2) = 1$ atm, DME, 60 °C. The line in plot A reflects a linear least-squares fit of the data. The saturation curve in plot B is obtained from a nonlinear least-squares fit to a generic hyperbolic function ($y = c_1[St]/(c_2[St] + c_3)$, the specific form of which is described in the Results and Discussion (eq 6).

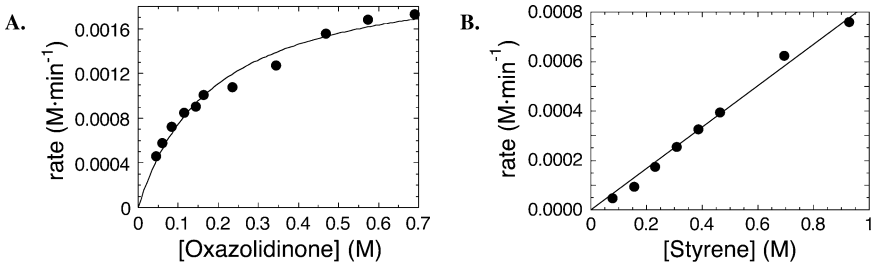


Figure 4. Kinetic data for the Markovnikov oxidative amination of styrene with oxazolidinone (HNRZ) catalyzed by $(Et_3N)_2PdCl_2$ (**2**). Reaction conditions: (A) [HNRZ] = 0.044−0.690 M, [styrene] = 2.62 M, [**1**] = $[CuCl_2]$ = 0.013 M, $[NEt_3] = 0.031$, $p(O_2) = 1$ atm, DME, 60 °C; (B) [HNRZ] = 0.23 M, [styrene] = 0.077−0.93 M, [**1**] = $[CuCl_2]$ = 0.011 M, $[NEt_3] = 0.031$ M, $p(O_2) = 1$ atm, DME, 60 °C. The line in plot B reflects a linear least-squares fit of the data. The saturation curve in plot A is obtained from a nonlinear least-squares fit to a generic hyperbolic function ($y = c_1[HNRZ]/(c_2[HNRZ] + c_3)$, the specific form of which is described in the Results and Discussion (eq 8).

These efforts have been complicated by the presence of a paramagnetic cocatalyst ($CuCl_2$) the need to have very high substrate:Pd ratios (≥ 50:1) to reach saturation substrate concentrations, and the relative instability of the palladium catalysts.

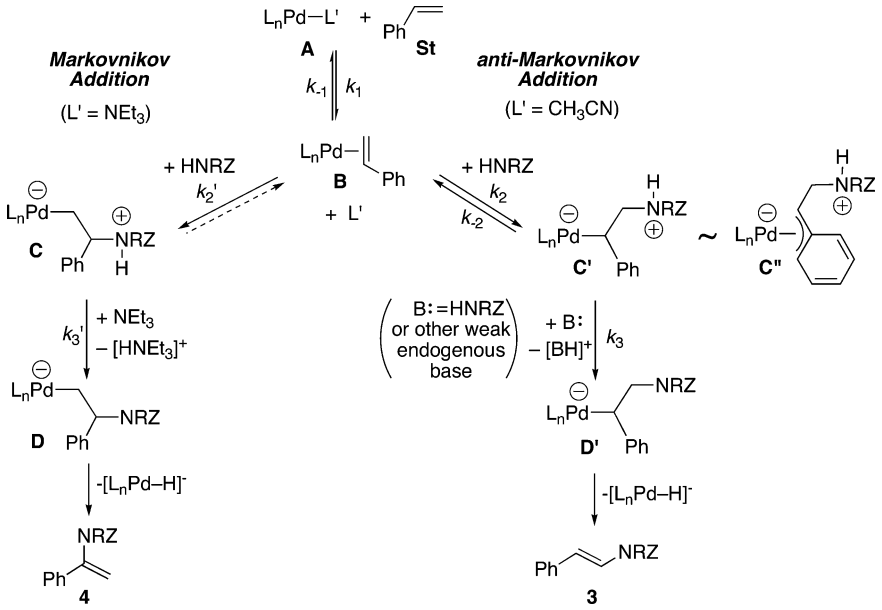
Proposed Mechanism and Analysis of Kinetic Data. The data outlined above provide valuable clues into the origin of regiochemical reversal in the oxidative amination of styrene. These experimental results, together with insights from several important studies of *stoichiometric* palladium-mediated alkene amination reactions (see below), underlie the following mechanistic proposal (Scheme 1).

Styrene enters the coordination sphere of Pd(II) via substitution of a neutral donor ligand, such as CH_3CN or Et_3N. Addition of oxazolidinone to styrene may proceed with Markovnikov or anti-Markovnikov regioselectivity, and we propose that formation of the Markovnikov aminopalladation intermediate **C** is kinetically favored. In the presence of triethylamine or another exogenous Brønsted base, such as acetate, this zwitterionic intermediate undergoes rapid, irreversible deprotonation to form **D**, and subsequent β-hydride elimination yields the Markovnikov oxidative amination product **4**. In the absence of triethylamine, deprotonation of **C** will proceed more slowly. Under these conditions, reversible aminopalladation of styrene enables formation of the thermodynamically preferred anti-Markovnikov intermediate, **C′**, which may be stabilized by formation of a π-benzylic structure (i.e., **C″**). Retention of this stabilizing effect in the subsequent transition state results in preferential formation of **D′** over **D** and, ultimately, yields the anti-Markovnikov product, **3**.[19,20]

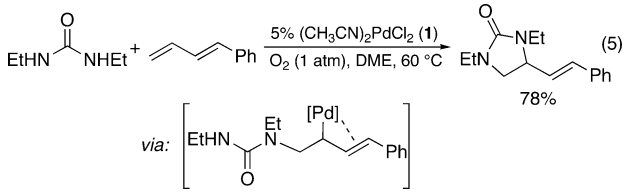
η^3-Benzylic structures of palladium(II) have substantial literature precedent,[6b,21] and their intermediacy in the formation of **3** will be favored by the presence of labile ligands in the Pd(II) coordination sphere (i.e., CH_3CN, DME). The recently reported 1,2-diamination of conjugated dienes (e.g., eq 5)[22] employs reaction conditions virtually identical with those in eq

(19) This mechanism is distinct from that of palladium-catalyzed *hydroamination* reactions that proceed via η^3-benzylic intermediates arising from insertion of vinyl arenes into a Pd−H bond. Subsequent nucleophilic attack by an external amine results in formation of *Markovnikov* hydroamination products (see ref 6b).

Scheme 1. Proposed Mechanism of Palladium-Catalyzed Oxidative Amination of Styrene that Rationalizes the Observed Regioselectivity



4a, and the reaction is believed to proceed through an η^3-allyl intermediate analogous to **C**″. Stereochemical evidence supports backside attack of urea on a coordinated diene in these reactions.



A qualitative energy diagram corresponding to the proposed catalytic mechanism illustrates the rate-limiting steps associated with formation of the regioisomeric products, **3** and **4** (Figure 5). In the absence of added base, the presence of a substantial kinetic isotope effect, $k^H/k^D = 3.0$, suggests that formation of **3** (blue pathway) proceeds via rate-limiting proton transfer from the aminopalladation adduct **C**′. The product regiochemistry reflects the difference in transition states energies associated with deprotonation of **C** and **C**′ ($\Delta\Delta G^{\ddagger}_{\text{no base}}$). In the formation of **4** (red pathway), no isotope effect is observed because the presence of a Brønsted base significantly reduces the barrier to proton-transfer (dashed curve), and under these conditions,

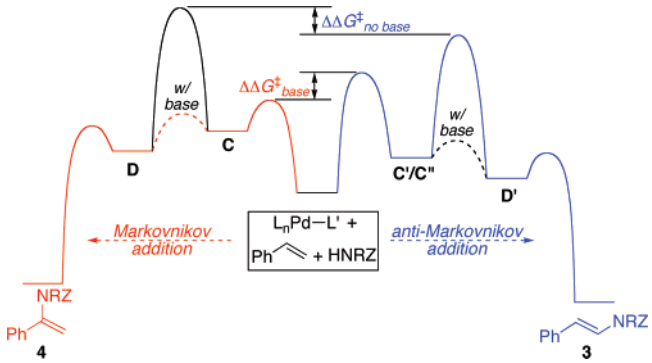


Figure 5. Qualitative energy diagram associated with the mechanism in Scheme 1. For clarity, the two-step aminopalladation of the styrene is presented as a single process. The dashed curves reflect the effect of a Brønsted base on the energy profile.

aminopalladation of styrene is rate-limiting. In this case, the product **4** arises from kinetically preferred formation of the Markovnikov aminopalladation adduct, **C** ($\Delta\Delta G^{\ddagger}_{\text{base}}$). Overall, this energetic profile explains both the reversal of product regiochemistry and the enhanced rates observed when the reaction is conducted in the presence of base.

According to this mechanism, a rate law for the production of **3** reflects a three-step mechanism consisting of (1) preequilibrium coordination of styrene, (2) steady-state addition of oxazolidinone to the activated alkene, and (3) rate-limiting deprotonation of the aminopalladation adduct **C**′ (eq 6).[23] At high [styrene], the preequilibrium will shift in favor of the Pd(II)−styrene adduct (**B**, Scheme 1), and further increases in the styrene concentration will have no effect on the rate (Figure 3B). Under these conditions, $K_1[\text{St}] \gg 1$, and the rate law simplifies to an expression that is first order in $[\text{Pd}]_t$ ($[\text{Pd}]_t = [\mathbf{A}] + [\mathbf{B}]$) and [HNRZ] (eq 7).

$$\frac{d[\mathbf{3}]}{dt} = \frac{K_1 k_2 k_3 [\text{Pd}]_t [\text{St}][\text{HNRZ}]}{(K_1[\text{St}] + 1)(k_{-2} + k_3)} \qquad (6)$$

$$\frac{d[\mathbf{3}]}{dt} = \frac{k_2 k_3 [\text{Pd}]_t [\text{HNRZ}]}{k_{-2} + k_3} \quad \text{(at high [St])} \qquad (7)$$

The rate law derived for $(Et_3N)_2PdCl_2$-catalyzed production of **4** (eq 8)[23] is based on a two-step sequence consisting of (1)

(20) This mechanistic discussion focuses on the steps associated with palladium(II)-promoted oxidative coupling of styrene and oxazolidinone. Because this portion of the catalytic cycle is turnover-limiting, we are unable to gain direct insights into the mechanism of Cu(II)-mediated regeneration of the oxidized catalyst with molecular oxygen. The proton equivalents from $[Et_3NH]^+$ (or $[BH]^+$) and the Pd(II)−hydride intermediate are utilized in the reduction of dioxygen to water.

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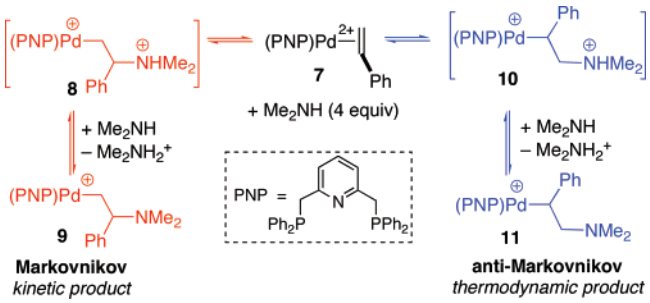
(23) Rate law derivations are provided in the Supporting Information.

Scheme 2. Reversible Aminopalladation Observed in the Stoichiometric Addition of Me_2NH to Pd(II)-Coordinated Styrene[25]



steady-state displacement of NEt_3 by styrene followed by (2) rate-limiting addition of oxazolidinone on the coordinated alkene. The rate saturates at high [oxazolidinone] (Figure 4A) because, under these conditions, $k_{2'}$[HNRZ] $\gg k_{-1}$[NEt_3] and displacement of NEt_3 by styrene is the rate-limiting step. The rate law simplifies to an expression that is first order in [**2**] and [St] (eq 9).[24]

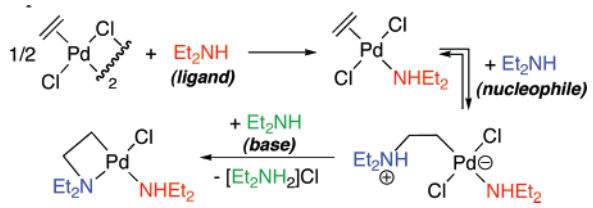
$$\frac{d[\mathbf{4}]}{dt} = \frac{k_1 k_{2'}[\mathbf{2}][\mathrm{St}][\mathrm{HNRZ}]}{k_{-1}[\mathrm{NEt_3}] + k_{2'}[\mathrm{HNRZ}]} \quad (8)$$

$$\frac{d[\mathbf{4}]}{dt} = k_1[\mathbf{2}][\mathrm{St}] \quad \text{(at high [HNRZ])} \quad (9)$$

This interpretation of the kinetic data finds support from studies of the stoichiometric addition of amines to dicationic Pd(II)−styrene complexes reported by Hahn and Vitagliano et al. (Scheme 2).[25] Addition of excess dimethylamine to the styrene adduct, **7**, in dichloromethane results in immediate formation of the Markovnikov addition product, **9**; however, isomerization to the anti-Markovnikov aminopalladation product, **11**, occurs within 1 h at room temperature.

Role of Triethylamine. Triethylamine plays a complex role in this chemistry, serving both as a ligand and as a Brønsted base.[26] The inverse relationship between the yield of the anti-Markovnikov product, **3**, and [NEt_3] (filled triangles, Figure 2A) appears to correlate with coordination of NEt_3 to palladium, which probably results in a less electrophilic metal center. Formation of the Markovnikov product, **4**, occurs only after >1 equiv of NEt_3 is added relative to palladium. This observation suggests that the first equivalent of NEt_3 coordinates to palladium and is unavailable to serve as a base. Between 1 and 2 equiv of NEt_3 relative to palladium, free amine base can be generated by displacement of the second NEt_3 ligand from Pd (step 1, Scheme 1), and the rate continues to rise to a maximum at NEt_3:Pd ∼ 3 (i.e., 15 mol % NEt_3, Figure 2B). The observed inhibition at higher [NEt_3] can be explained by the ability of triethylamine to hinder styrene coordination.

Scheme 3. Mechanism of Stoichiometric Palladium(II)-Mediated Amination of Ethylene Involving Three Independent Roles for Alkylamine



This interpretation of the effect of triethylamine (Figure 2) finds precedent in the *stoichiometric* amination of alkenes mediated by $(PhCN)_2PdCl_2$, which requires *3* equiv of the secondary alkylamine substrate.[27] Mechanistic studies of this reaction by Hegedus et al. revealed an independent role for each of the 3 equiv of amine (Scheme 3): the first amine coordinates to palladium as an ancillary ligand, the second equivalent undergoes nucleophilic attack on the coordinated olefin, and the third amine deprotonates the zwitterionic intermediate to yield a (β-aminoalkyl)palladium(II) product.[28,29] Furthermore, they observed that aminopalladation of the olefin, the second step in this mechanism, is reversible. The inability to achieve catalytic amination of olefins in this system reflects, in part, the strong coordinating ability of alkylamines, which inhibits alkene activation when a large excess of amine is present relative to palladium(II). In our *catalytic* system, the nitrogen nucleophile is only weakly coordinating, and triethylamine, which serves both as a ligand and as a base (cf. first and third steps of Scheme 3), is present in low, catalytic concentrations.

Conclusion and Implications

Efficient metal-catalyzed reactions for the intermolecular coupling of alkenes and nitrogen nucleophiles are still relatively rare, and the ability to achieve selective formation of either possible regioisomer is virtually unprecedented. On the basis of the studies described herein, we postulate a unique Brønsted base-modulated mechanism to achieve regiocontrol in the Pd(II)-catalyzed oxidative amination of styrene with oxazolidinone. Regiochemical reversal is possible because the kinetic and thermodynamic products of styrene aminopalladation exhibit opposite regiochemistry. The thermodynamic preference for anti-Markovnikov addition of oxazolidinone to styrene appears to reflect the stability of η^3-benzyl adducts, and therefore, application of these mechanistic principles may be limited to substrates that can achieve similar chelate-induced stabilization of the anti-Markovnikov adduct. Recently, however, Atwood and coworkers noted a similar regiochemical distinction between the kinetic and thermodynamic products of stoichiometric amine addition to Pt(II)-coordinated *alkyl olefins* (e.g., propene).[30] In this case, the *anti-Markovnikov* aminoplatination adduct is

(24) Our data cannot rigorously establish the aminopalladation mechanism. The presence of base may facilitate formation of a Pd(II)−amido complex that undergoes irreversible insertion of styrene with Markovnikov regioselectivity. Our kinetic data in Figure 4 are consistent with this pathway if the Pd(II)−amido complex is formed in a rapid preequilibrium (see rate law and analysis in the Supporting Information). ^{1}H NMR spectroscopic studies to detect formation of such an intermediate have been inconclusive. The specific pathway for aminopalladation, however, does not alter our principle conclusion concerning the presence of a base-induced switch in regioselectivity.

(25) (a) Hahn, C.; Vitagliano, A.; Giordano, F.; Taube, R. *Organometallics* **1998**, *17*, 2060−2066. (b) Hahn, C.; Morvillo, P.; Vitagliano, A. *Eur. J. Inorg. Chem.* **2001**, 419−429. (c) Hahn, C.; Morvillo, P.; Herdtweck, E.; Vitagliano, A. *Organometallics* **2002**, *21*, 1807−1818.

(26) For analysis of the complex kinetic influence of triethylamine on aerobic alcohol oxidation catalyzed by $Pd(OAc)_2$/NEt_3, see: Schultz, M. J.; Adler, R. S.; Zierkiewicz, W.; Privalov, T.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 8499−8507.

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(28) Hegedus, L. S.; Åkermark, B.; Zetterberg, K.; Olsson, L. F. *J. Am. Chem. Soc.* **1984**, *106*, 7122−7126.

(29) Recent mechanistic studies of platinum-catalyzed methods for the hydroamination of acrylonitrile and intramolecular hydroamination of alkenes indicate that exogenous amine serves as a Brønsted base to deprotonate the initially formed aminoplatination adduct: (a) Seul, J. M.; Park, S. *J. Chem. Soc., Dalton Trans.* **2002**, 1153−1158. (b) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070−1071.

favored kinetically, presumably for steric reasons,[31] and it isomerizes to the Markovnikov adduct at elevated temperatures. These results, together with the mechanistic principles outlined in our study, suggest that the development of catalytic methods for selective anti-Markovnikov addition of amines to alkylolefins may be feasible.

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Supporting Information Available: Kinetic plot (Figure S1), rate-law derivations, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0562806

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(31) The complexes studied by Atwood and co-workers, $PtCl_2(Ph_3P)$(alkene), possess a sterically encumbered triphenylphosphine ligand in the Pt(II) coordination sphere that may result in kinetically favored attack at the sterically less hindered alkene carbon.