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Reversible Alkene Insertion into the Pd−N Bond of Pd(II)-Sulfonamidates and Implications for Catalytic Amidation Reactions

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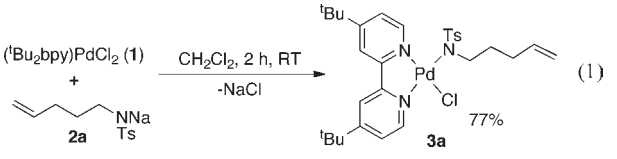
Supporting Information

ABSTRACT: Alkene insertion into Pd−N bonds is a key step in Pd-catalyzed oxidative amidation of alkenes. A series of well-defined Pd(II)-sulfonamidate complexes have been prepared and shown to react via insertion of a tethered alkene. The Pd−amidate and resulting Pd−alkyl species have been crystallographically characterized. The alkene insertion reaction is found to be reversible, but complete conversion to oxidative amination products is observed in the presence of O_2. Electronic-effect studies reveal that alkene insertion into the Pd−N bond is favored kinetically and thermodynamically with electron-rich amidates.

The discovery of Pd^{II}-catalyzed oxidative coupling of ethylene and water (the Wacker Process) >50 years ago inspired extensive efforts to develop methods for the oxidative amination of alkenes (aza-Wacker reactions).[1] Early studies showed that many alkyl- and arylamine nucleophiles coordinate strongly to Pd^{II} and inhibit catalytic turnover. Therefore, much of this work focused on stoichiometric reactions of nitrogen nucleophiles with preformed Pd^{II}−alkene complexes.[2] In 1982, Hegedus and McKearin demonstrated that *p*-toluenesulfonamides (tosylamides) could be used in catalytic intramolecular aza-Wacker reactions, with benzoquinone as the oxidant.[3] More recently, amide-type nucleophiles have been used in aerobic oxidative amination reactions,[4] including enantioselective[5] and intermolecular[6] applications. Mechanistic studies suggest that these aza-Wacker reactions often proceed via alkene insertion into the Pd−N bond of the amidate ligand, not attack of a nitrogen nucleophile onto a Pd^{II}-coordinated alkene.[7,8] The first fundamental studies of alkene insertion into Pd−N bonds were reported only recently by the groups of Wolfe and Hartwig with Pd^{II}−anilide complexes.[9−11] Analogous reactions with Pd-amidates are unknown. Here, we describe well-defined Pd^{II}−sulfonamidate complexes that undergo alkene insertion into the Pd−N bond, and the reactions are shown to be reversible. The presence of O_2 influences the fate of the resulting alkyl−Pd^{II} species. These observations, elaborated below, have important implications for catalytic reactions, including oxidative and non-oxidative transformations.

A well-defined Pd^{II}−sulfonamidate complex, suitable for fundamental investigation, was prepared by adding a solution of



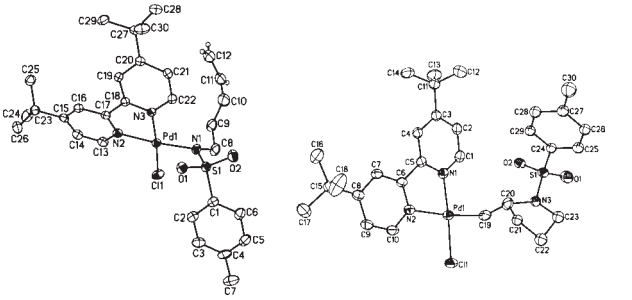
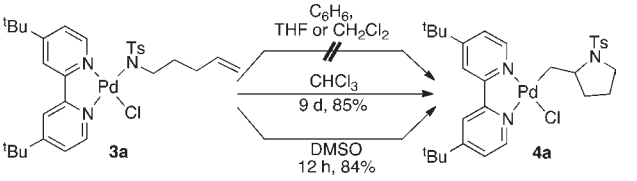


Figure 1. X-ray crystal structures of **3a** (left) and **4a** (right) with thermal ellipsoids shown at the 40% and 50% probability level, respectively. Most hydrogen atoms have been omitted for clarity.[12]

Scheme 1. Amidopalladation of an Alkene



(tBu$_2$bpy)PdCl$_2$ (**1**, tBu$_2$bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) to a suspension of sodium tosylamidate (**2a**) in CH_2Cl_2 at room temperature. The air-stable Pd−amidate complex **3a** was obtained in good yield (eq 1) and was characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray crystallography (Figure 1, left).[12] Initial attempts to observe alkene insertion into the Pd−N bond of **3a** were carried out in benzene, THF, and dichloromethane, but no reaction was observed (Scheme 1). In chloroform, however, **3a** reacted very slowly at room temperature, affording the alkyl−Pd^{II} amidopalladation (AP) product **4a** in good yield (Figure 1, right). At higher temperatures, **4a** underwent further reaction via β-hydride elimination and could not be obtained cleanly from the reaction mixture. The reaction proved to be much more efficient in dimethyl sulfoxide (DMSO) as the solvent, proceeding in 84% yield in 12 h.

The beneficial effect of a polar solvent (DMSO) suggested that the reaction proceeds via an ionic intermediate. At least two reasonable ionic mechanisms can be considered: (1) dissociation of the amidate, followed by alkene coordination and nucleophilic attack of the pendant amidate on the alkene (*trans*-AP), or (2) chloride dissociation, followed by alkene coordination and

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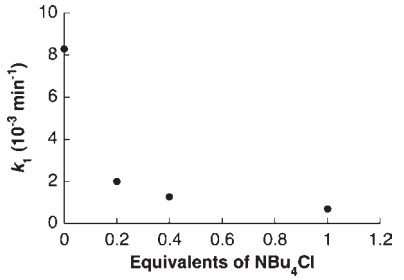
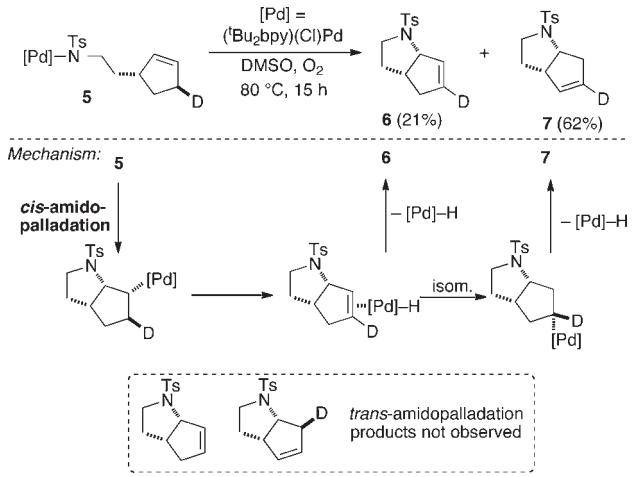


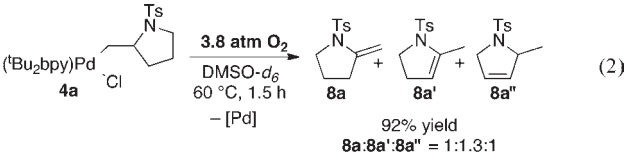
Figure 2. Chloride inhibition on amidopalladation for **3a**.

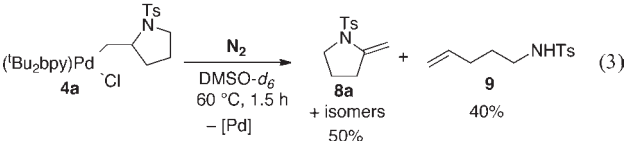
Scheme 2. Isotopic Labeling Study Demonstrating that C−N Bond Formation Proceeds via *cis*-Amidopalladation



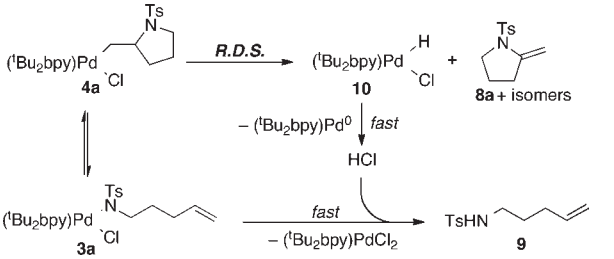
insertion into the Pd−N bond (*cis*-AP), and reassociation of the chloride ligand to the Pd^{II} center. Two experimental observations support the latter, *cis*-AP pathway. Addition of chloride to the reaction mixture strongly inhibits the reaction (Figure 2), consistent with a mechanism involving pre-equilibrium dissociation of chloride prior to the AP step. In addition, we prepared a Pd−sulfonamidate complex with a stereochemically defined, deuterium-labeled substrate probe (**5**, Scheme 2).[13] The reaction of this complex under an atmosphere of O_2 led to products **6** and **7**, which arise from *cis*-AP of the alkene, followed by β-hydride elimination. No products arising from competing *trans*-AP of the alkene were observed.

As expected from the reaction illustrated in Scheme 2, the alkyl−Pd^{II} complex **4a** is susceptible to β-hydride elimination. Heating a DMSO solution of **4a** to 60 °C under aerobic conditions led to a mixture of isomeric products **8a**, **8a′**, and **8a″** (eq 2).[14] A different outcome was observed, however, when the reaction was



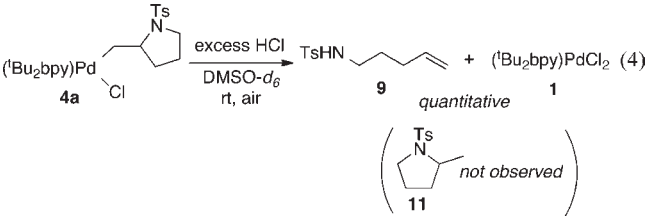


Scheme 3. Proposed Mechanism for the Parallel Formation of 8 and 9 under Anaerobic Conditions



performed under anaerobic conditions: the β-hydride elimination products **8a**−**8a″** were obtained in 50% yield, together with a 40% yield of 4-pentenyl tosylamide **9** (eq 3).

The formation of **9** in eq 3 was unexpected, but this result can be rationalized if alkene insertion into the Pd−N bond is reversible (i.e., **4a** ⇆ **3a**). According to the mechanism in Scheme 3, β-hydride elimination from **4a** forms the enamide products **8a**−**8a″** together with a Pd^{II}−hydride species **10**. In the absence of O_2,[15] HCl can form via reductive elimination from **10** and react with **3a** to afford the alkenyl tosylamide **9**. This proposal implies that HCl reacts much more rapidly with **3a** than with **4a**. In order to test this hypothesis, excess HCl (∼60 equiv) was added to a DMSO-d_6 solution of **4a** at room temperature. Rapid and quantitative formation of **9** was observed in this reaction, together with (tBu$_2$bpy)PdCl$_2$ (**1**, eq 4); pyrrolidine **11**, the product of protonolysis of the Pd−C bond of **4a**, was not observed.



Additional, more-direct evidence for reversible amidopalladation of the alkene was obtained in the investigation of a series of substituted Pd^{II}−sulfonamidate complexes (Figure 3). The reactions of four different *para*-substituted benzenesulfonamidate complexes [X = Me (**3a**), OMe (**3b**), Cl (**3c**), and NO_2 (**3d**)] were monitored by ^{1}H NMR spectroscopy at 30 °C in DMSO-d_6 under aerobic conditions (Figure 3a). Each of the Pd complexes underwent clean amidopalladation of the alkene to afford an equilibrium mixture of complexes **3a**−**d** and the corresponding alkyl−Pd^{II} species **4a**−**d** (Figure 3b), together with slower concomitant formation of heterocycles **8**−**8″a**−**d** via β-hydride elimination from **4a**−**d**. The data were fit to a simplified kinetic model, **3** ⇆ **4** → **8**−**8″**, that enabled quantitative comparison of kinetic and thermodynamic constants associated with the two observable steps (Figure 3c). Electronic effects on these parameters were probed via Hammett analysis (Figure 3d).[16]

Alkene insertion into the Pd−N bond (i.e., *cis*-AP, k_1) is favored for electron-rich amidates. This trend is similar to that observed previously for irreversible alkene insertion into Pd−anilides, and it is consistent with an alkene insertion mechanism that formally corresponds to intramolecular nucleophilic attack of the amidate ligand onto the coordinated alkene.[9]

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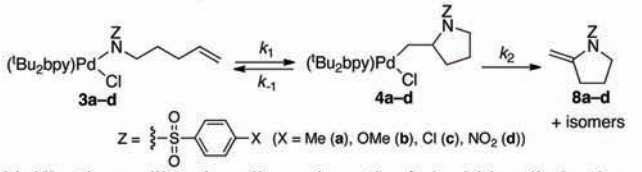
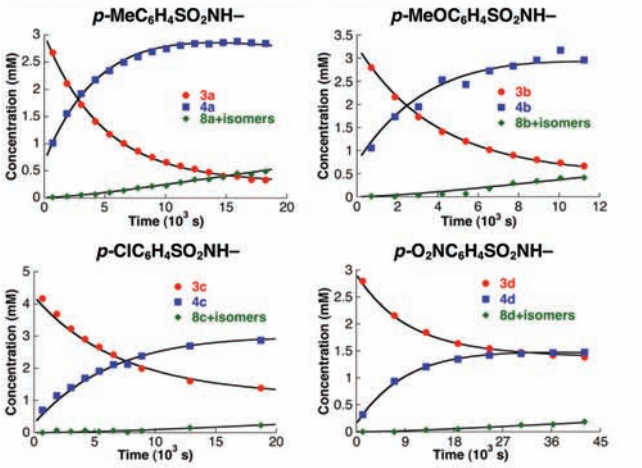
a) Alkene insertion/β-hydride elimination sequence



b) Kinetic profiles for alkene insertion/β-hydride elimination reactions with Pd-sulfonamidate complexes, 3a-d



c) Kinetic parameters derived from fits of the data

X	k_1 (10^{-5} s^{-1})	k_{-1} (10^{-5} s^{-1})	K_1	k_2 (est'd) (10^{-5} s^{-1})	$K_1 \cdot k_2$ (10^{-5} s^{-1})
CH_3 (**a**)	19.0	1.83	10.0	1.12	11.1
OMe (**b**)	22.6	3.64	6.21	1.53	9.50
Cl (**c**)	10.3	3.56	2.89	0.59	1.71
NO_2 (**d**)	5.64	5.16	1.09	0.33	0.36

d) Hammett analysis of the *cis*-amidopalladation (k_1), β-amidate elimination (k_{-1}) and β-hydride elimination (k_2) steps.

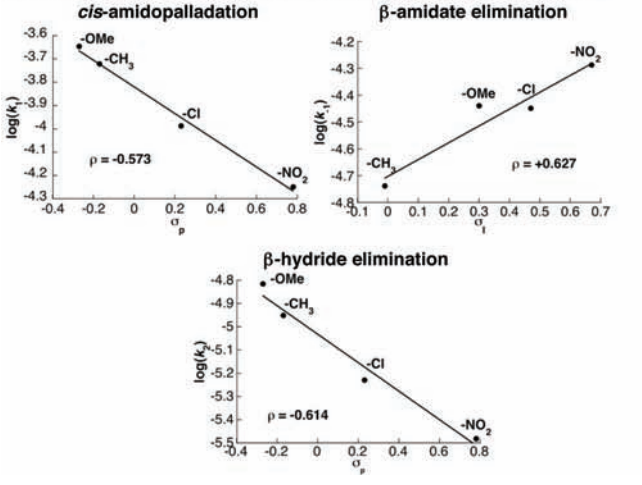
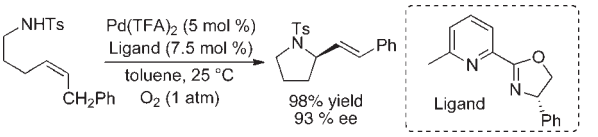


Figure 3. Kinetic studies of alkene insertion/β-hydride elimination reactions of four Pd^{II}–sulfonamidate complexes. Conditions: 3.68 mM **3**, 3.8 atm of O_2, DMSO, 30 °C, 7–12 h. Note: Every fifth data point is shown to enhance clarity.

The reverse reaction, β-amidate elimination, (k_{-1}) is favored for electron-deficient amidates (Figure 3c and 3d). Together, these trends cause the equilibrium constant to be largest for the *p*-Me derivatives **3**/**4a** ($K_1 \approx 10$) and smallest for the electron-deficient *p*-NO_2 derivative **3**/**4d** ($K_1 \approx 1$) (Figure 3c). That K_1 is largest for the *p*-Me, and not the *p*-OMe derivative, appears to reflect the lack of "resonance" electronic effects in the amidate elimination step k_{-1}; the Hammett correlation for k_{-1} is best fit with the "inductive" Hammett parameter σ_I, rather than σ_p, which incorporates both resonance and inductive effects. The k_2 values estimated from these fits show that β-hydride elimination is favored with more-electron-rich derivatives, consistent with a formal "hydride"-transfer mechanism in which electron-donating groups stabilize the buildup of positive charge on the adjacent carbon atom in the transition state. The combined electronic effects, $K_1 \cdot k_2$, reveal that the *p*-Me (tosylamidate) derivative **3a** is the most reactive complex toward formation of the oxidative amidation products **8**–**8″**.

Overall, these observations have important implications for catalysis. For example, the development of enantioselective Wacker-type oxidation reactions has been a long-standing challenge in the field of asymmetric catalysis.[17] Alkene insertion into the Pd–N bond of **3a** results in formation of a new stereogenic center (Scheme 1), and such steps provide the basis for enantioselective oxidative amination reactions (e.g., eq 5).[5c] Recent work has highlighted the importance of controlling the stereochemical course of the nucleopalladation step in enantioselective reactions (i.e., *cis*- vs *trans*-nucleopalladation).[1f] The results reported here reveal that nucleopalladation could be reversible, in which case β-hydride elimination or another termination step will be the stereochemistry-determining step of the reaction. To our knowledge, this possibility has not been considered previously in Wacker-type reactions.



(5)

Reversible C–N bond formation has been observed in reactions involving *trans*-AP of an alkene,[18] but reversible insertion of an alkene into a Pd–N bond has not been observed previously. The latter observation, combined with the significantly more-facile protonolysis of Pd–N bonds relative to Pd–C bonds (cf. eq 4), represents a key challenge for the development of Pd-catalyzed *hydroamination* reactions that proceed via *cis*-AP pathways.

In summary, this study has led to key insights into reactions of Pd^{II}-sulfonamidates with alkenes, perhaps most notably demonstrating that alkene insertion into the Pd–N bonds of such species is facile and reversible. This work provides an important foundation for more-thorough characterization of *cis*-amidopalladation reactions relevant to important catalytic transformations.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, kinetic data, and X-ray crystallographic data (CIF) for compounds **3a** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For the synthesis and previous application of this substrate probe, see ref 7d.

(14) This reaction was carried out in an NMR tube. Because gas−liquid mixing is slow in an NMR tube, an elevated pressure of O_2 was used to ensure at least 1 equiv of O_2 was dissolved in solution.

(15) The reaction of O_2 with (N−N)Pd(H)Cl complexes was the focus of a recent study: Decharin, N.; Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 13268–13271.

(16) Data acquisition focused on the alkene insertion/deinsertion steps (K_1). Thus, the reliability of the k_2 data is constrained by the limited data obtained for the β-hydride elimination step.

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