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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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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 O₂. 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, and 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 enantioselective⁵ and intermolecular⁶ 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 have been 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 reaction is shown to be reversible. The presence of O₂ 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.

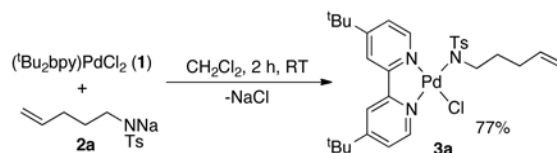
A well-defined Pd^{II}-sulfonamidate complex, suitable for fundamental investigation, was prepared by adding a solution of (*t*Bu₂bpy)PdCl₂ (**1**, *t*Bu₂bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) to a suspension of sodium tosylamidate (**2a**) in CH₂Cl₂ at room temperature. The air-stable Pd-amidate complex **3a** was obtained in good yield (eq 1) and was characterized

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ASSOCIATED CONTENT

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

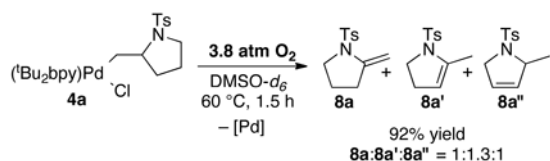
by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and X-ray crystallography (Figure 1, left).¹² Initial attempts to observe alkene insertion into the Pd–N bond of **3a** were carried out in benzene, THF and dichloromethane, but no reaction was observed (Scheme 1). In chloroform, however, **3a** reacted 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 dimethylsulfoxide (DMSO) as the solvent, proceeding in 84% yield in 12 h.



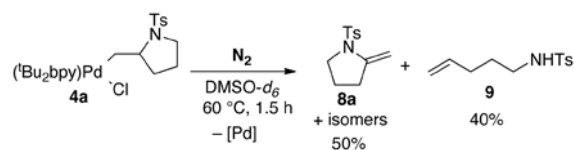
(1)

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 insertion into the Pd–N bond (*cis*-AP), and reassociation of the chloride ligand to the Pd^{II} center. Two experimental observations provide support for 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 O₂ 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 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).

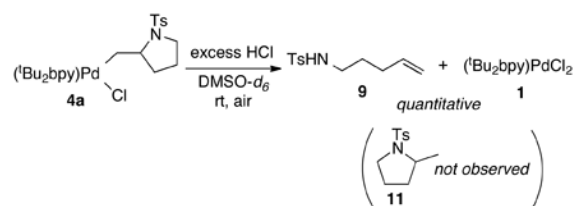


(2)



(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** \rightleftharpoons **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 O₂,¹⁵ 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 (*t*Bu₂bpy)PdCl₂ (**1**, eq 4); pyrrolidine **11**, the product of protonolysis of the Pd–C bond of **4a**, was not observed.



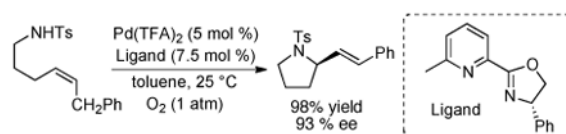
(4)

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 NO₂ (**3d**)] were monitored by ¹H 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** \rightleftharpoons **4** \rightarrow **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 The reverse reaction, β -amidate elimination, (k_{-1}) is favored for electron-deficient amidates (Figures 3c and 3d). Together, these trends cause the equilibrium constant to be largest for the *p*-Me derivatives **3/4a** ($K_1 \sim 10$) and smallest for the electron-deficient *p*-NO₂ derivative **3/4d** ($K_1 \sim 1$) (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 build-up 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. See Supporting Information for further details.
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 O₂ was used to ensure at least 1 equiv of O₂ was dissolved in solution.
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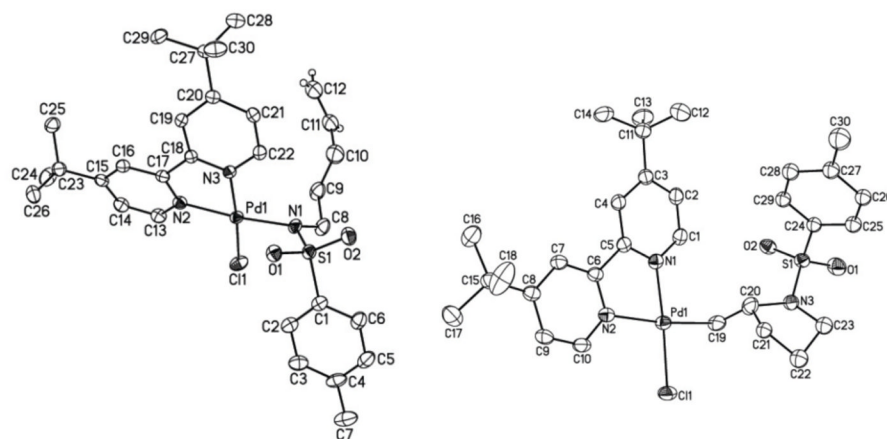


Figure 1. X-ray crystal structures of **3a** (left) and **4a** (right) with thermal ellipsoids shown at 40% and 50% probability level, respectively. Most hydrogen atoms have been omitted for clarity.¹²

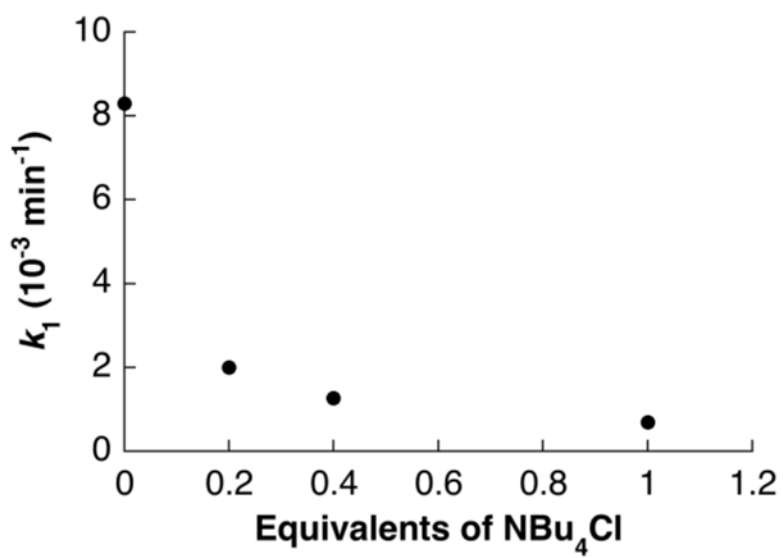
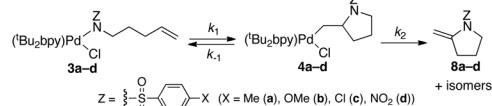
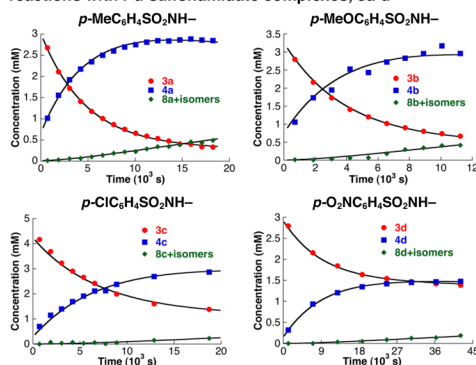
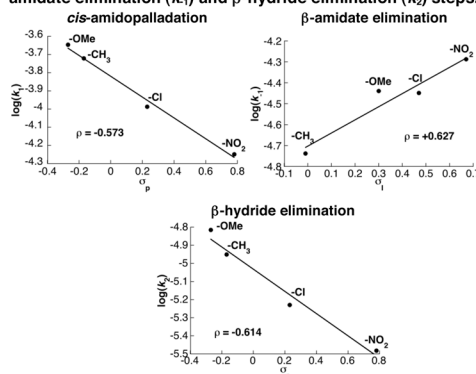


Figure 2.
Chloride inhibition on amidopalladation for **3a**

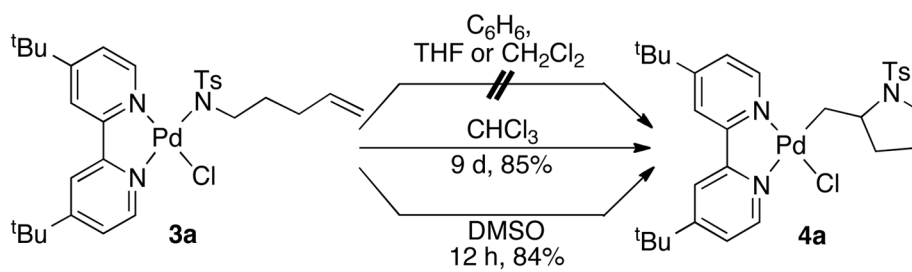
a) Alkene insertion/ β -hydride elimination sequenceb) Kinetic profiles for alkene insertion/ β -hydride elimination reactions with Pd-sulfonamidate complexes, **3a-d**

c) Kinetic parameters derived from fits of the data

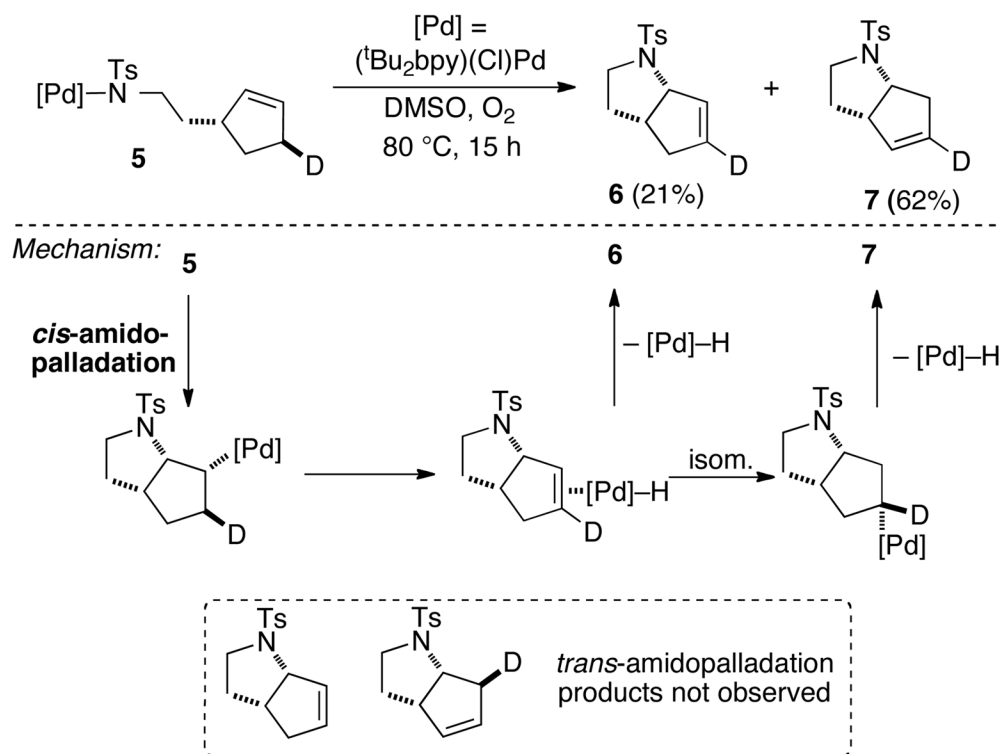
X	k_1 (10^{-5} s^{-1})	k_{-1} (10^{-5} s^{-1})	K_1	k_2 (est'd) (10^{-5} s^{-1})	$K_1 \cdot k_2$ (10^{-10} s^{-1})
CH ₃ (a)	19.0	1.83	10.0	1.12	11.1
OMe (b)	22.6	3.64	6.21	1.53	9.50
Cl (c)	10.3	3.56	2.89	0.59	1.71
NO ₂ (d)	5.64	5.16	1.09	0.33	0.36

d) Hammett analysis of the *cis*-amidopalladation (k_1), β -amidate elimination (k_{-1}) and β -hydride elimination (k_2) steps.**Figure 3.**

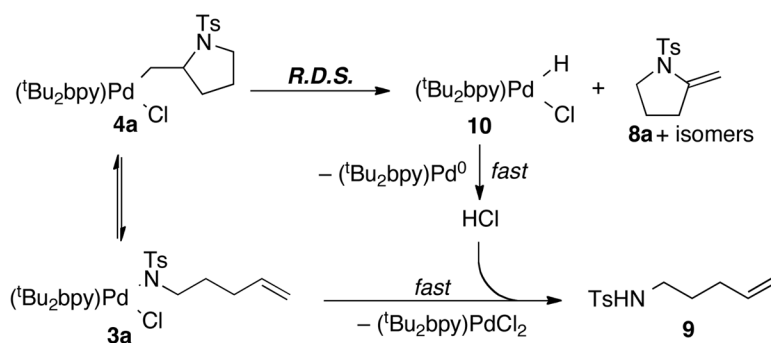
Kinetic studies of alkene insertion/ β -hydride elimination reactions of four Pd^{II}-sulfonamidate complexes. Conditions: 3.68 mM **3**, 3.8 atm O₂, DMSO, 30 °C, 7–12 h. Note: Every fifth data point is shown to enhance clarity.



Scheme 1.
Amidopalladation of an Alkene



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



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