J|A|C|S
ARTICLES
Published on Web 12/15/2007

Oxidative Diamination of Alkenes with Ureas as Nitrogen Sources: Mechanistic Pathways in the Presence of a High Oxidation State Palladium Catalyst

Kilian Muñiz,* Claas H. Hövelmann, and Jan Streuff

Contribution from the Institut de Chimie, UMR 7177, Université Louis Pasteur, 4 rue Blaise Pascal, F-67000 Strasbourg Cedex, France

Received July 24, 2007; E-mail: muniz@chimie.u-strasbg.fr

Abstract: A first palladium-catalyzed intramolecular diamination of unfunctionalized terminal alkenes has recently been reported. This study investigates the details of its mechanistic course based on NMR titration, kinetic measurements competition experiments, and deuterium labeling. It concludes a two-step procedure consisting of *syn*-aminopalladation with an unligated palladium(II) catalyst state followed by oxidation to palladium(IV) and subsequent C−N bond formation to give the final products as cyclic diamines. Related reactions employing sulfamides give rise to aminoalkoxy-functionalization of alkenes. This process was investigated employing deuterated alkenes and found to follow an identical mechanism where stereochemistry is concerned. It exemplifies the importance of cationic palladium(IV) intermediates prior to the final reductive elimination from palladium and proves that the nucelophile for this step stems from the immediate coordination sphere of the palladium(IV) precursor. These results have important implications for the general development of alkene 1,2-difunctionalization and for the individual processes of aminopalladation and palladium-catalyzed C_{alkyl}−N bond formation.

Introduction

The direct oxidative conversion of alkenes into vicinal diamines represents a challenging transformation. Over the past three decades, several protocols for transition metal mediated direct diamination of alkenes have been developed,[1] which rely on the use of thallium,[2] mercury,[3] palladium,[4] osmium,[5] selenium,[6] and copper,[7] and have even been extended to the development of stereoselective synthesis of chiral diamines[8] and chiral-at-osmium complexes.[9] This extensive investigation underlines the importance of oxidative alkene diamination as a direct approach to vicinal diamines. 1,2-Diamines constitute important functional groups that are present in a large variety of natural products, molecules of general pharmaceutical and biological interest, and functional metal complexes and catalysts.[10]

The development of a transition metal catalyzed alkene diamination is therefore of particular interest, but an efficient solution remained elusive. Problems in its realization departing from established stoichiometric metal reactivity originate from exceedingly high reoxidation potentials (thallium), the potential involvement of exceedingly toxic intermediates (mercury), and issues of catalyst regeneration due to diamine chelation (osmium, palladium).

In view of the broad versatility of palladium in homogeneous catalysis, this metal appears to be a particularly promising candidate. Development of a catalytic diamination process would emerge from the earlier seminal stoichiometric chemistry from Bäckvall.[4] In seminal studies on diamination and aminoalkoxylation of alkenes, a complex multistep scenario was elucidated.[11] As to its underlying key steps, the stoichiometric diamination reaction consists, hence, of alkene coordination to palladium (**A**) followed by amine coordination to palladium and clean *trans*-aminopalladation.[12] Intermediate **B** undergoes oxidation to palladium(IV) derivative **C**, which is attacked from an

(1) Muñiz, K. *New J. Chem*. **2005**, *29*, 1371.
(2) Gómez Aranda, V.; Barluenga J.; Aznar, F. *Synthesis* **1974**, 504.
(3) (a) Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* **1979**, 962. (b) Barluenga, J.; Aznar, F.; de Mattos, M. C. S.; Kover, W. B.; García-Granda, S.; Pérez-Carreño, E. *J. Org. Chem.* **1991**, *56*, 2930.
(4) (a) Bäckvall, J.-E. *Tetrahedron Lett.* **1978**, *19*, 163. (b) Earlier report on diamination as a side reaction in oxyamination: Bäckvall, J.-E. *Tetrahedron Lett.* **1975**, *16*, 2225.
(5) (a) Muñiz, K. *Chem. Soc. Rev.* **2004**, *33*, 166. (b) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. (c) Anhaus, J. T.; Kee, T. P.; Schofield, M. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 1642. (d) Schofield, M. H.; Kee, T. P.; Anhaus, J. T.; Schrock, R. R.; Johnson, K. H.; Davis, W. M. *Inorg. Chem.* **1991**, *30*, 3595. (e) Muñiz, K.; Iesato, A.; Nieger, M. *Chem.—Eur. J.* **2003**, *9*, 5581. (f) Deubel, D. V.; Muñiz, K. *Chem.—Eur. J.* **2004**, *10*, 2475. (g) Muñiz, K. *Eur. J. Org. Chem.* **2004**, 2243.
(6) (a) Sharpless, K. B.; Singer, S. P. *J. Org. Chem.* **1976**, *41*, 2504. (b) Bruncko, M.; Khuong, T.-A. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 454.
(7) (a) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (b) Zabawa, T. P.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 2035.
(8) (a) Muñiz, K.; Nieger, M. *Synlett* **2003**, 211. (b) Muñiz, K.; Nieger, M. *Chem. Commun.* **2005**, 2729.
(9) Muñiz, K.; Nieger, M.; Mansikkamäki, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5958.
(10) (a) For a general review on chiral diamines, see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) For a review on *trans*-1,2-diamino cyclohexane and chiral derivatives thereof, see: Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.
(11) (a) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335. (b) Åkermark, B.; Bäckvall, J.-E.; Zetterberg, K. *Acta Chem. Scand.* **1982**, *B36*, 577. (c) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415.
(12) (a) Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* **1984**, *106*, 5560. (b) Åkermark, B.; Bäckvall, J. E.; Siirala-Hansén, K.; Sjöberg, K.; Zetterberg, K. *Tetrahedron Lett.* **1974**, *15*, 1363. (c) Åkermark, B.; Bäckvall, J. E. *Tetrahedron Lett.* **1975**, *16*, 819.

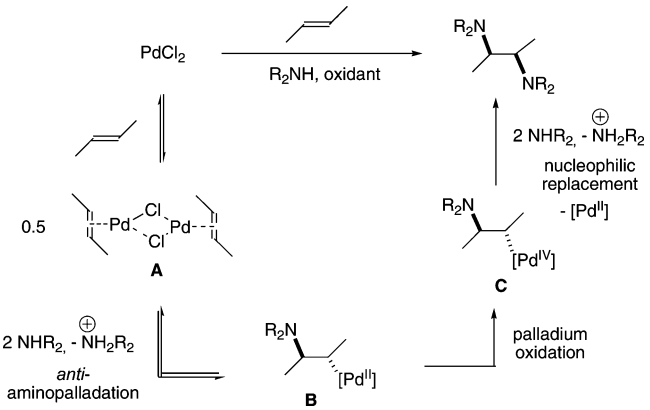
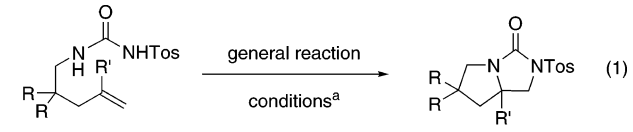
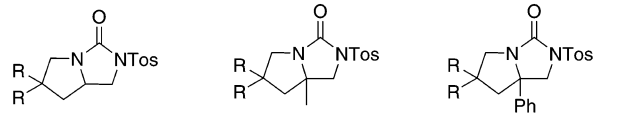


Figure 1. Key steps in the stoichiometric diamination of alkenes developed by Bäckvall. Oxidant = $Pb(OAc)_4$, Br_2, *m*CPBA.

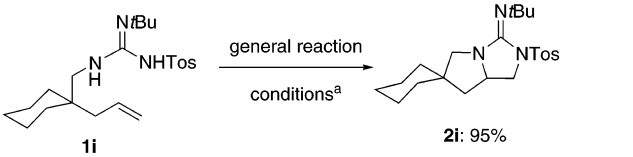
Scheme 1



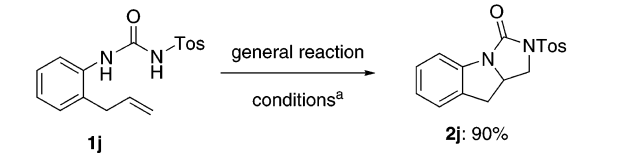
1a: R, R' = H
1b: R = Me, R' = H
1c: R = Ph, R' = H
1d: R_2 = -$(CH_2)_5$-, R' = H
1e: R, Me, R' = Me
1f: R = Ph, R' = Me
1g: R_2 = -$(CH_2)_5$-, R' = Me
1h: R = Ph, R' = Ph



2a: 92%
2b: 92%
2c: 95%
2d: 91%
2e: 94%
2f: 86%
2g: 68%
2h: 44%



1i
2i: 95%



1j
2j: 90%

[a] General reaction conditions: 5 mol % $Pd(OAc)_2$, $PhI(OAc)_2$ (2 equiv), NMe_4Cl/ NaOAc (1 equiv), CH_2Cl_2, RT, 12 h.

external amine to furnish the final diamine upon palladium reductive displacement (Figure 1). As a result of these steps, the reaction is highly stereospecific and generates *syn*-diamines from (*E*)-alkenes. Although the palladium is finally released in its original +II oxidation state, a catalytic transformation based on this chemistry was never reported.

Work from our laboratory recently described a first palladium-catalysis for alkene diamination, which relies on intramolecular reaction control (Scheme 1).[13] It employs iodosobenzene diacetate as stoichiometric oxidant and uses urea groups as sources for the two transferable nitrogen atoms to furnish cyclic urea products in order to prevent catalyst poisoning. These two changes allow for the use of catalytic amounts of palladium(II), which does not require ligand stabilization. At the same time, approaches toward oxidative palladium catalyzed diamination reactions of 1,3-butadienes furnishing vinylic cyclic ureas were reported.[14]

These examples of diamination add to the growing number of palladium-catalyzed oxidative alkene aminations and alkene 1,2-difunctionalizations, respectively. As a common feature, these reactions initiate by nitrogen transfer to the alkene.[15] Oxidative product diversification is then accomplished under specific reaction conditions. For example, recent research has seen the development of aminobromination[16] and aminochlorination, aminoalkoxylation,[17] aerobic aminocarbonylation,[18] aza-Wacker-type reactions,[19] and pyrrolidine formation.[20,21] Despite this growing number of impressive reactions, precise mechanistic knowledge on these transformations remains limited.

Herein, detailed investigation on the course of intramolecular diamination of alkenes with palladium catalysts is presented, which clarifies the role of the urea in the aminopalladation step and the stereochemical course of the second palladium-catalyzed C−N-bond formation via a Pd(II/IV) catalysis.

Results and Discussion

Reaction Conditions. Typical reaction conditions and examples for the palladium-catalyzed intramolecular diamination of terminal alkenes are given in Table 1 and Scheme 1. The reaction allows for a number of ureas ranging from alkylamine components to aniline derivatives and includes substrates with 2,2-disubstitution that give rise to quaternary stereogenic products **2a**−**2h**. This chemistry can also be extended to related guanidines such as **1i**. Tricyclic compounds of the type **2j** can be accessed through oxidative conversion of aniline **1j**.

The optimized reaction conditions call for 5 mol % palladium and do not require the stabilization by addition of conventional phosphine or carbene ligands, and common commercially

(13) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586.

(14) (a) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308. (b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (c) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (d) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688. (e) For a copper catalyzed variant: Yuan, W.; Du, H.; Zhao, B.; Shi, Y. *Org. Lett.* **2007**, *9*, 2689.

(15) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142.

(16) (a) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785−1788. (b) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618−5621. (c) Li, G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745.

(17) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc*. **2005**, *127*, 7690.

(18) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130.

(19) (a) Review: Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (b) Selected recent work: Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc*. **2003**, *125*, 12996. (c) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett*. **2006**, *8*, 2257.

(20) Scarborough, C. C.; Stahl, S. S. *Org. Lett*. **2006**, *8*, 3251.

(21) For additional recent oxidative alkene transformations under palladium catalysis that do not include an aminopalladation step, see: (a) For a review: Stahl, S. S. *Angew. Chem., Int. Ed* **2004**, *43*, 3400. For dialkoxylation, see: (b) Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460. (c) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 3076. For hydroalkoxylation, see: (d) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc*. **2006**, *128*, 2794. (e) Zhang, Y.; Sigman, M. S. *Org. Lett*. **2006**, *8*, 5557. (f) For acetal formation, see: Balija, A. M.; Stowers, K. J.; Schultz, M. J.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 1121. For dibromination, see: (g) El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett*. **2003**, *5*, 439. For Wacker-type cyclizations, see: (h) For a review, see: Cornell, C. N.; Sigman, M. S. *Inorg. Chem*. **2007**, *46*, 1903. (i) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc*. **2005**, *127*, 2796. (j) Cornell, C. N.; Sigman, M. S. *Org. Lett*. **2006**, *8*, 4117. (k) Muñiz, K. *Adv. Synth. Catal*. **2004**, *364*, 1425.

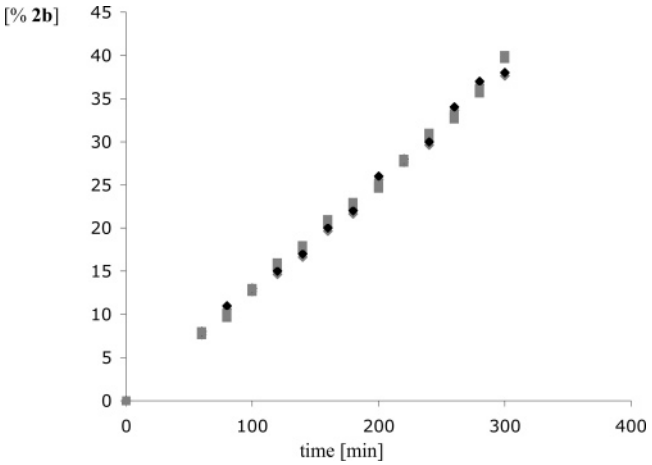
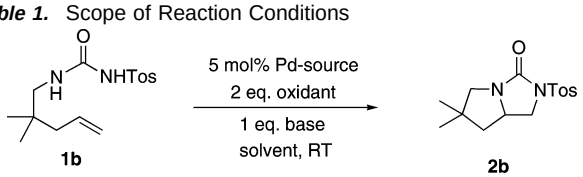


Figure 2. Initial reaction profiles for oxidative conversion of **1b** to **2b** under standard conditions in dichloromethane (gray ■) and acetonitrile (◆).

Table 1. Scope of Reaction Conditions



1b **2b**

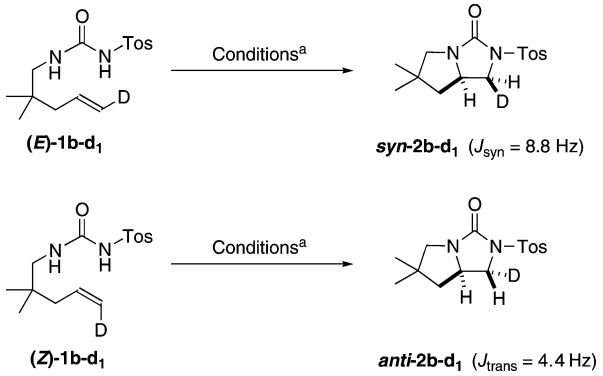
entry	palladium source	solvent	oxidant	base	yield [%]
1	$Pd(OAc)_2$	CH_2Cl_2	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	92
2	$Pd(OAc)_2$	CH_2Cl_2	$PhI(OAc)_2$	Me_4NOAc	91
3	$Pd(OAc)_2$	DMF	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	84
4	$Pd(OAc)_2$	CH_3CN	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	92
5	$Pd(OAc)_2$	*t*BuOH	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	70
6	$Pd(O_2CCF_3)_2$	CH_2Cl_2	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	90
7	$PdCl_2$	CH_2Cl_2	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	89
8	$Pd(NCCH_3)_2Cl_2$	CH_2Cl_2	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	90
9	$Pd_2(dba)_3$	CH_2Cl_2	$PhI(OAc)_2$	$Me_4NCl/NaOAc$	89
10	$Pd(OAc)_2$	CH_2Cl_2	$PhI(O_2CtBu)_2$	$Me_4NCl/NaOAc$	88
11	$Pd(OAc)_2$	CH_2Cl_2	PhI(OH)OTos	$Me_4NCl/NaOAc$	88

available palladium compounds such as $Pd(OAc)_2$, $PdCl_2$, $(MeCN)_2PdCl_2$, $Pd(O_2CCF_3)_2$, $Pd_2(dba)_3$ serve as catalyst source (Table 1, entries 1, 6−9). The presence of base is a major requirement and no diamination takes place in its absence. The oxidative diamination is a completely chemoselective process, proceeds under ambient air without the requirement of absolute conditions and uses hypervalent iodines as terminal oxidant. Commercial iodosobenzene diacetate is usually employed for convenience, while related iodosobenzene dipivalate and Koser's reagent work equally well (entries 10 and 11). The reaction is remarkably robust and does not show significant solvent dependences. For example, the diamination of **1b** proceeds well with over 90% isolated yield in CH_2Cl_2, DMF, CH_3CN and even reasonably well in *t*-BuOH (entries 2−5).

Monitoring of the reaction progress for reactions of **1b** in dichloromethane and acetonitrile over the initial period of 5 h revealed comparable reaction profiles (Figure 2). This is a surprising observation in view of the mostly required solvent optimization or even solvent dependence in palladium-catalyzed alkene functionalization and underlines the robustness of the present process.

Importantly, a stoichiometric reaction with palladium(II)-acetate did not promote any diamination of **1b** or **1e**. This indicates that the role of $PhI(OAc)_2$ consists not of a mere reoxidant to palladium, but must be involved during the course of the diamination. As a direct conclusion, a process based on Pd(II)/Pd(0) catalysis must appear improbable.

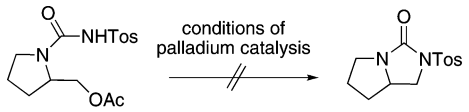
Scheme 2. Diamination of Selectively Deuterated Alkenes **1b**



[a] General reaction conditions same as from Scheme 1.

Overall Reaction. In initial experiments, a combination of tetramethylammonium chloride and sodium acetate was employed for a convenient in situ generation of tetramethylammonium acetate base. Although this formally adds a stoichiometric amount of chloride ions to the reaction mixture, these were found to have no effect on both reaction rate and product as reactions in the presence of $Me_4NCl/NaOAc$ and Me_4NOAc were found to proceed identically (Table 1, entries 1,2). Hence, a potential involvement of chlorinated intermediates can be excluded.

The overall reaction of urea transformation is carried out in the presence of acetate, which originates from the base and the oxidant. This acetate concentration is significantly enhanced during the course of the reaction with the formation of acetic acid. In order to exclude the involvement of intermediary species from acetate incorporation, and hence a diamine formation through nucleophilic substitution processes, compound **3** was synthesized independently from proline. When submitted to the conditions of the oxidation catalysis, no conversion to the respective diamination product **2a** was observed (eq 2):



3 **2a** (2)

As a result the intramolecular diamination of alkenes in the presence of palladium catalysts is understood to represent a two-step nitrogen transfer reaction, which consists of an aminometallation followed by an oxidative C−N-bond forming process. This sequence raises the question on the stereochemical course of each of these two steps. A deuterium-labeling showed that **(*E*)-1b-d$_1$** is cleanly transformed into ***syn*-2b-d$_1$** under the diamination conditions, whereas the corresponding **(*Z*)-1b-d$_1$** yields diastereomerically pure ***anti*-2b-d$_1$**.

It is to be noted within this context that the relative stereochemistry of **2b-d$_1$** was inadvertently misassigned in our earlier communication.[22] The corrected analysis is depicted in Scheme 2 and additional details on the NMR analyses are included in the Supporting Information.

(22) This incorrect assumption of a *trans*-aminopalladation was recently cited in related work on aminopalladation[24,25] and diamination.[7b,14b] The authors apologize for the resulting confusion.

In view of the stereochemical outcome of the two-step process, the overall sequence must contain one step with inversion of configuration, hence it must proceed either as a *syn*-aminopalladation/*anti*-C−N-bond forming process or, alternatively, as an *anti*-aminopalladation/*syn*-C−N-bond forming process.

First Step: Aminopalladation. The stereochemical course of intramolecular aminopalladation[23] and subsequent β-hydride elimination to form allylamines was recently the focus of elegant work from Stahl.[24] In this investigation, ω-alkenyl-tosylamides were employed and a *syn*-aminopalladation was revealed on the basis of detailed deuterium labeling experiments. Earlier work on intermolecular aminoalkoxylation had already suggested the involvement of *syn*-aminopalladation.[25,26]

The relative solvent independence of the overall diamination as observed from the initial kinetics suggests that solvent coordination to palladium does not play a decisive role and that the initial step is presumably a *syn*-aminopalladation with transfer of amine occurring from within the coordination sphere of a precomplexed palladium. Attempts to isolate defined palladium(II) complexes from these experiments remained unsuccessful.

In order to understand the initial reaction step, the coordination behavior of ureas to palladium is decisive. A first indication for metal−urea precomplexation prior to alkene functionalization arose from the observation that use of chiral bidentate ligands such as (−)-sparteine, BINAP, and TolBINAP only yielded racemic diamination products. ^{31}P NMR studies on the addition of equimolar amounts as well as 2-, 5-, and 20-fold excesses of **1e** and acetate base to BINAP-$Pd(OAc)_2$, DPPF-$Pd(OAc)_2$, or $(PPh_3)_2Pd(OAc)_2$ lead to rapid formation of complex mixtures that contained free phosphines as major components. For a mixture of $(PPh_3)_2Pd(OAc)_2$ and **1e**, free PPh_3 accounts for more than 80% of the ^{31}P signals after 30 min. These results suggest rapid and irreversible displacement of the phosphines from the Pd coordination sphere in favor of the urea and/or alkene favoring subsequent *syn*-aminopalladation events.

In order to further investigate the behavior of urea coordination to palladium, titration experiments were undertaken for the dimethyl derivative **1b**. It was again observed that a simple titration of a CD_2Cl_2 solution of **1b** with palladium acetate did not result in any change of the signals for urea **1b** and that the final 1:1-mixture of **1b** and $Pd(OAc)_2$ is that of two independent compounds. However, administering an equimolar amount of NMe_4OAc and treatment of a 1:1 mixture of **1b** and NMe_4-OAc gives conclusive information about the initial steps of the diamination reaction. First, complete and irreversible deprotonation of the tosylamide N−H group takes place, which is in accordance with an estimated pK_a of 4.0−5.0 for this group.[27] Addition of $Pd(OAc)_2$ to deprotonated **1b** gave rise to a final spectrum with two new sets of signals which correspond to the two new compounds **4** and **5**.

The decisive experiment consisted of an NMR tritration experiment of **1b** and $Pd(OAc)_2$ with the base NMe_4OAc.[28] This experiment led to the gradual formation of the same two new compounds already observed in the earlier experiment. The spectral progress is depicted in the Supporting Information, whereas Figure 3 reproduces the initial, the intermediate, and the final spectra.

The titration experiments suggest that the coordination of the urea to palladium is followed by the alkene entering the coordination sphere of the palladium in a second step. Upon addition of a second equivalent of base, the reaction proceeds to exclusive formation of **5** in a highly selective manner. Intermediate **5** shows clearly distinguished signals from the final product **2b**.

Formation of **5** from **4** is a temperature-dependent reaction. The reaction progress was monitored at different temperatures, and the aminopalladation was found to be irreversible.[29,30] For the overall transformation from **4** to **5**, different relative reaction rates in the range between $k_1 = 6.7 \times 10^{-5}$ s^{-1} and $k_1 = 9.0 \times 10^{-4}$ s^{-1} were determined in the temperature range from 273 to 308 K. The data for monitoring this reaction progress allow for an estimation of the activation energy, which was determined to $E_A = 52$ kJ/mol. Describing the process of activation by thermodynamic function leads to an activation enthalpy $\Delta H^{\ddagger} = 49.2$ kJ/mol, an activation entropy $\Delta S^{\ddagger} = -144$ J/mol and an overall reaction enthalpy of $\Delta G(298\ \mathrm{K})^{\ddagger} = 92.1$ kJ/mol. The negative value for $\Delta S^{\ddagger}$ reflects the enhancement in order for the transition state of aminopalladation including potential η^2-alkene coordination. It confirms that the process from **4** to **5** is indeed a slow reaction. The exact course from **4** to **5** might include additional events of ligand dissociation/association within the Pd coordination sphere. However, solvent coordination appears negligible on the basis of the observed rate similarity for coordinating and noncoordinating solvents (Figure 2).

All this data is consistent with the postulation of a *syn*-aminopalladation as the initial step. The spectrum of **5** represents a rare direct observation of an intermediate from alkene aminopalladation. In solution, **5** is stable for about 2 h before inconsistent decomposition and palladium black precipitation take place. With regard to the isolation of structural evidence in aminopalladation, we notice the report on the *N*-acetyl derivative **6** from **1k** by Hegedus.[31] However, this compound, which was found to be of low reactivity, has eluded attempts at complete characterization. We synthesized the corresponding urea derivative **1l**, which did not yield a stable aminopalladation product, but under our standard conditions, reacted with complete diastereoselectivity to the new tricyclic compound **2l**. This high diastereoselectivity should encourage application of the diamination in the synthesis of higher elaborate molecules.

(23) In a stricter sense, the nitrogen sources in this and related work are amides and, in a more correct manner, one should refer to these reactions as amidopalladation. See reference 15 for a general discussion. For convenience, we continue to use the term aminopalladation throughout this text.
(24) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.
(25) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.
(26) For related work that implies *syn*-aminopalladation, see: (a) Ney, J. E.; Wolfe, J. P *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (b) Ney, J. E.; Wolfe, J. P *J. Am. Chem. Soc.* **2005**, *127*, 8644. (c) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P *J. Am. Chem. Soc.* **2006**, *128*, 2893. (d) Isomura, K.; Okada, N.; Saruwatari, M.; Yamasaki, H.; Taniguchi, H. *Chem. Lett.* **1985**, 385.
(27) The pK_a value for **1b** was estimated to be in this range taking into account pK_a values of related compounds (in water): 5.16 for *N*-butyl, *N*′-tosyl urea [http://www.syrres.com/esc/physdemo.htm] and 3.70 for ethyl N-tosyl carbamate [Taylor, L. D.; Pluhar, M.; Rubin, L. E. *J. Polym. Sci., B: Polym. Phys.* **1967**, *5*, 77].
(28) For an NMR titration experiment on $(C_2H_4)PdCl_2$ with Et_2NH: Hegedus, L. S.; Åkermark, B.; Zetterberg, K.; Olsson, L. F. *J. Am. Chem. Soc.* **1984**, *106*, 7122.
(29) For an example of reversibility in intermolecular aminopalladation: Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888.
(30) For stoichiometric reactions in the presence of only equimolar or lower amounts of base, formation of **5** is slow.
(31) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.

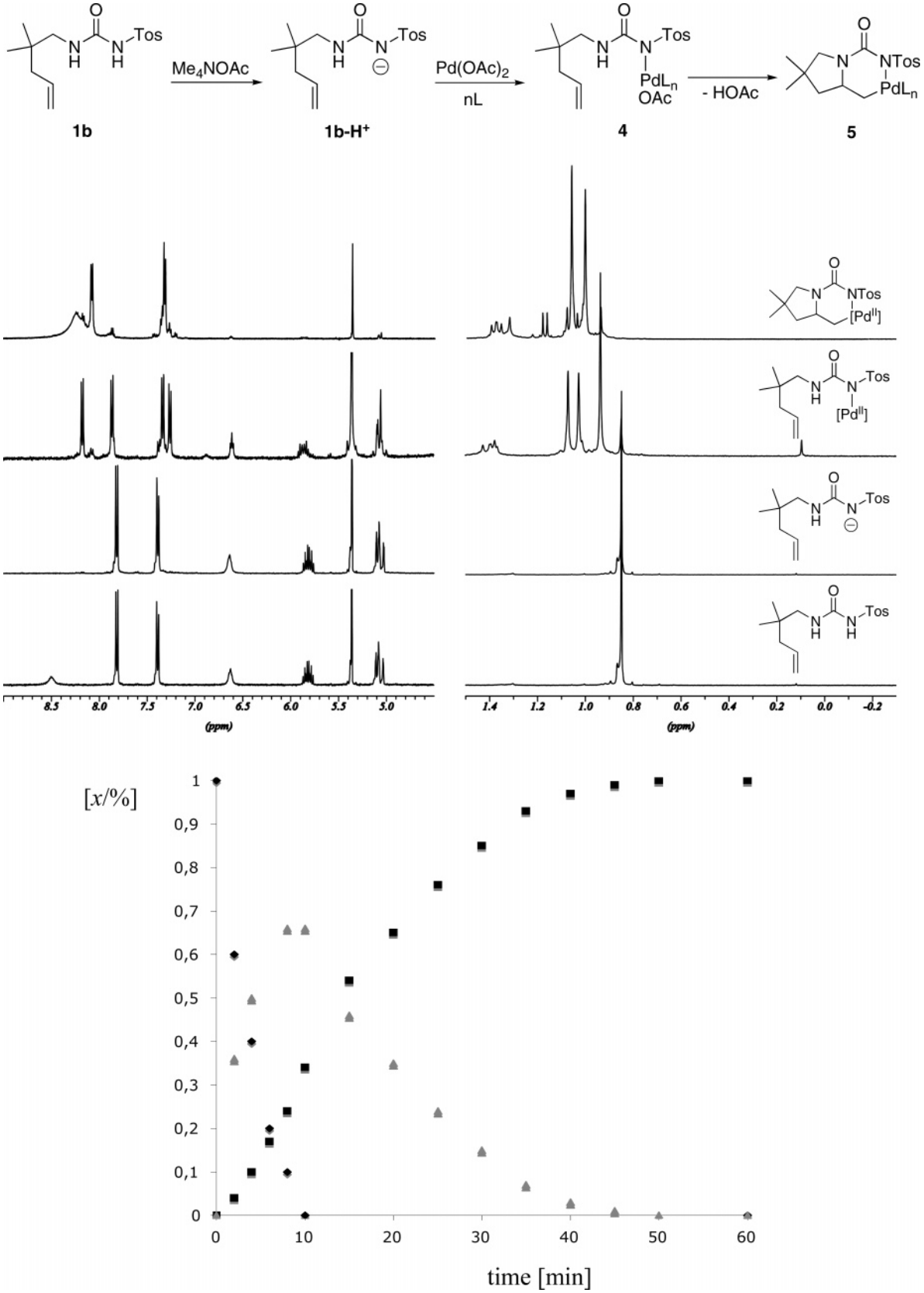
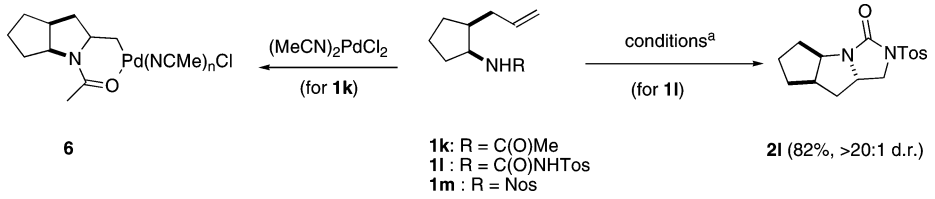


Figure 3. Aminopalladation scenario for compound **1b**: NMR spectroscopic monitoring (0.1M solution, CD_2Cl_2) and kinetic process regarding **1b**-H^+ (◆) **4** (△) and **5** (■) at 308 K.

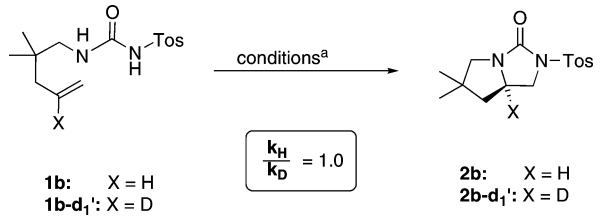
It furthermore exemplifies the reaction control that is exercized by the urea moiety on the initial course of aminopalladation as related aminoalkoxylation with **1m** under comparable conditions leads to mixtures of pyrrolidines and piperazines with different levels of diastereomeric induction.[17] The stereochemistry of the new stereogenic center in **2l** was deduced from 2D-NMR

Scheme 3. Diastereoselective Diamination with **1l**



[a] General reaction conditions same as from Scheme 1.

Scheme 4. Diamination of 2-Deuterated Compound **1b**



[a] General reaction conditions same as from Scheme 1.

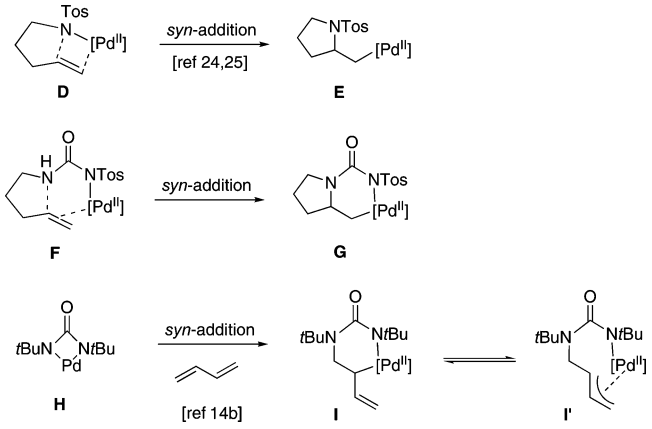


Figure 4. Different modes of *syn*-aminopalladation.

experiments. It matches a transition state of *syn*-aminopalladation preventing unfavorable pseudo-1,3-diaxial hydrogen interactions.

No secondary kinetic isotope effect was observed in the diamination of selectively 2-deuterated **1b** (Scheme 4). This result does not provide differentiation between *syn*- and *anti*-aminopalladation, but supports the former as it involves simultaneous transfer of nitrogen and palladium to the alkene.

In general, *syn*-aminopalladation reactions proceed through precoordination of the amine/amide to palladium prior to insertion of an alkene into the N−Pd bond.[15] For intramolecular reactions, such a process is equivalent to a step **D** to **E**, as recently discussed by Stahl[24] (Figure 4). A major feature of the NMR titration experiments reveals that for the present system, the *syn*-aminopalladation consists of a reaction of the remaining noncoordinated amine from the urea with the alkene. Therefore, the *syn*-addition results from geometric requirements of the urea tethering rather than from amine−palladium coordination. In general, symmetrical urea coordination to palladium has been known before.[32] A related syn-addition of urea-palladium(II) complexes is also involved in the catalytic diamination of butadienes and hexatrienes. The expected active catalyst state **H** is the direct consequence of oxidative homolytic cleavage of a N−N bond in a diaziridinone by palladium(0).[14b] After insertion of the butadiene, the reaction yields an allyl palladium complex **I**/**I′**, which represents the η^3-analogue[33] of intermediate **5**.

Aniline derivative **1j** was found to undergo slower diamination than related alkyl substrates **1a**−**1h** and **1i**. This behavior can be attributed to a less pronounced nucleophilic character of the aniline nitrogen in the aminopalladation step. A series of derivatives was employed for a Hammett correlation regarding the influence of aniline basicity on the reaction rate. A clear correlation was determined, and the negative slope of the Hammett plot ($\rho = -0.45$) suggests the importance of electron density at the aniline nitrogen as the decisive factor for rate enhancement in the aminopalladation step. The observation of such a correlation for the irreversible initial aminopalladation concludes that this first step must be rate-determining. This observation matches with the earlier outcome of the kinetic studies, where the negative value for $\Delta S^{\ddagger}$ characterized the aminopalladation as a slow reaction step.

Second Step: C_{sp3}−N-Bond Formation. This second step of the overall diamination is of particular importance because it represents the rare event of a catalyzed C_{sp3}−N-bond formation.

In particular, the ease of this step and the absence of any side-reaction are remarkable. Catalytic C_{sp3}−N-bond forming reactions are still not available by reductive elimination from the coordination sphere of a palladium(II) complex.[34,35] The only precedence of general C−N bond formation in palladium catalysis belongs to related C_{sp2}−N-bond formations as pioneered by Buchwald and Hartwig,[36] and allylations within the Tsuji−Trost reaction.[37,38]

(32) For isolated Pd-urea complexes: (a) Paul, F.; Fischer, J.; Ochsenbein, P.; Osborn, J. A. *C. R. Chimie* **2002**, *5*, 267. (b) Paul, F.; Moulin, S.; Piechaczyk, O.; Le Floch, P.; Osborn, J. A. *J. Am. Chem. Soc*. **2007**, *129*, 7294.

(33) (a) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887. (b) Zhou, H.-B.; Alper, H. *J. Org. Chem.* **2003**, *68*, 3439. (c) Inman, G. A.; Butler, D. C. D.; Alper, H. *Synlett* **2001**, 914. (d) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc*. **2003**, *125*, 11836.

(34) For recent attempts on reductive elimination of alkylamines from alkyl-amido-palladium complexes, see: (a) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc*. **2006**, *128*, 15415. (b) Esposito, O.; Lewis, A. K. de K.; Hitchcock, P. B.; Caddick, S.; Cloke, F. G. N. *Chem. Commun.* **2007**, 1157.

(35) For a C_{alkyl}−N bond formation from palladium under oxidative conditions, see: Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc*. **2005**, *127*, 2868.

(36) (a) Murci, A. R.; Buchwald, S. L. *Top. Curr. Chem*. **2002**, *219*, 131. (b) Hartwig, J. F. *Angew. Chem., Int. Ed*. **1998**, *37*, 2046. (c) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936. (d) Hartwig, J. F. *Acc. Chem. Res*. **1998**, *31*, 852. (e) Schlummer, B.; Scholz, U. *Adv. Synth. Catal*. **2004**, *346*, 1599. (f) Hartwig, J. F. *Synlett* **2006**, 1283. (g) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal*. **2006**, *348*, 23. (h) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805. (i) For a mechanistic investigation, see: Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc*. **2006**, *128*, 3584.

(37) (a) Amatore, C.; Genin, E.; Jutand, A.; Mensah, L. *Organometallics* **2007**, *26*, 1875 and cited lit. (b) Mora, G.; Deschamps, B.; van Zutphen, S.; Le Goff, X. F.; Ricard, L.; Le Floch, P. *Organometallics* **2007**, *26*, 1846. (c) For a different approach, see: Devine, S. K. J.; Van Vranken, D. L. *Org. Lett*. **2007**, *9*, 2047.

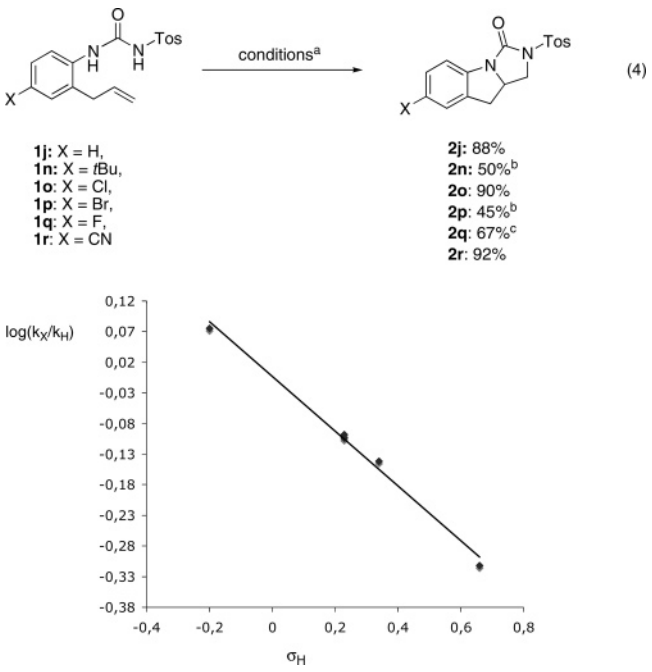
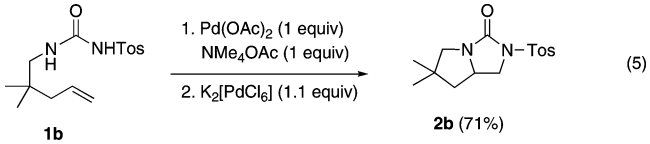


Figure 5. Hammett correlation for competitive diamination of aniline derivatives ($R^2 = 0.9925$). Yields from eq 4 refer to those from independent diamination reactions. [a]General reaction conditions same as from Scheme 1. [b]Nonoptimized yield. [c]Together with 30% recovered starting material.

It is important to note that the present C-sp^3−N bond formation proceeds readily at room temperature while related C-sp^2−N bond forming reactions with urea do require high temperatures and show pronounced ligand dependence.[39] For the present reaction, this significant difference in reactivity is best understood by the involvement of a palladium(IV) intermediate[40] in the C−N reductive elimination. Such an oxidation state had been postulated by Bäckvall for stoichiometric oxidation of alkyl palladium compounds[4a,11] with bromine, lead tetraacetate, or mCPBA and was recently confirmed by Sanford in a study on stoichiometric benzyl-N and aryl-N-bond formation from Pd(IV).[41,42]

For the present diamination, the isolated intermediate **5** does not give rise to diamine formation under the NMR conditions and no product formation is observed in the absence of the hypervalent iodine under the catalytic conditions. The involvement of a palladium(IV) by oxidation of the alkyl-palladium-(II) intermediate after aminopalladation is the consequence of a suitable difference in oxidation potential between simple palladium(II) chloride and acetate salts and alkyl palladium complexes.[40] The latter undergo rapid irreversible oxidation in the presence of hypervalent iodine reagents.[43] This difference in oxidation potential could be illustrated by a diamination reaction of **1b** with stoichiometric amounts of palladium acetate. Stirring equimolar amounts of **1b**, $Pd(OAc)_2$ and base for 45 min at room-temperature prior to addition of hexachloropalladate gave rise to the expected formation of diamine **2b** which was isolated in 71% yield:



This oxidation of alkylpalladium(II) to alkylpalladium(IV) under conditions that do not oxidize palladium(II) salts is key for the overall transformation. In this context, the nature of the metal and its oxidation potential are decisive to the course of the catalytic reaction. In contrast to palladium, platinum(II) catalysis does not promote the reaction efficiently since oxidation of **1b** in the presence of 2 equiv of $PhI(OAc)_2$ and 10 mol % $PtCl_2$ gave only less than 5% product even after prolonged reaction time of 72 h. No other product was formed and unreacted **1b** was reisolated. In contrast, when **1b** was treated with a stoichiometric amount of $PtCl_2$ for several hours prior to oxidation with $PhI(OAc)_2$ a yield of 49% of **2b** was isolated.[44] This difference is due to the presence of $PhI(OAc)_2$ already at the outset of the catalysis. Due to the lower oxidation potential for Pt(II)/Pt(IV),[45] all platinum(II) is readily oxidized and removed from a potential catalytic cycle.[46]

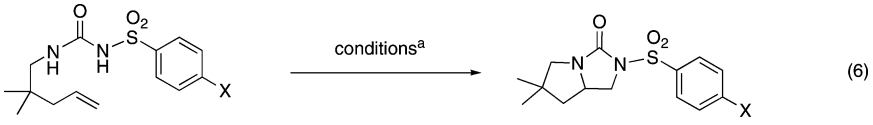
The observation of rapid oxidation of the alkyl-palladium intermediate confirms the rate-limiting nature of the aminopalladation step. As a consequence, the second C−N bond will be formed rapidly via reductive elimination of palladium(II). This fast process must hence prevent any detectable observation on a potential electronic influence regarding the nitrogen source. Indeed, use of electronically different arylsulfonyl substituents for the second nitrogen atom did not lead to a measurable difference in relative rate (Scheme 5).

This second step of diamination is strongly dependent on the electronic nature of the second nitrogen. Substituents other than sulfonyl such as phenyl, benzyl, or trichloromethylcarbonyl do not react or do not undergo diamination. This underlines that partial sp^3 character at nitrogen due to the sulfonyl substituent is important as it induces the required nucleophilicity for the second amination.

The stereochemical course of this second step of amination must proceed with inversion of configuration in order to be in agreement with the observed overall stereochemistry from the

(38) For a recent palladium-catalyzed allylic C-H to C-N conversion, see: Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.
(39) (a) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381. (b) Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. P. *Tetrahedron Lett.* **2003**, *44*, 4719. (c) Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2003**, *39*, 1741. (d) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Russ. J. Org. Chem*. **2003**, *38*, 538. (e) Popkin, M. E.; Bellingham, R. K.; Hayes, J. F. *Synlett* **2006**, 2716.
(40) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83.
(41) Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2007**, *26*, 1365.
(42) For selected examples of Caryl-O and C-X bond forming processes from Pd(IV), see: (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (b) Canty, A. J.; Denney, M. C.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 1122. (c) Canty, A. J.; Denney, M. C.; van Koten, G.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 5432. (d) Canty, A. J.; Jin, H.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1998**, *37*, 3975. (e) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2005**, *24*, 482. (f) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.
(43) A redox potential of −1.53 eV was recently reported for the $PhI(OAc)_2 + 2e^-/PhI^+2OAc^-$ system: Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083.
(44) Amino-platination as the initial step in this sequence is a well-established process, for leading references, see: (a) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070. (b) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640. (c) Qian, H.; Widenhoefer, R. A. *Org. Lett*. **2005**, *7*, 2635. (d) Krogstad, D. A.; Cho, J.; DeBoer, A. J.; Klitzke, J. A.; Sanow, W. R.; Williams, H. A.; Halfen, J. A. *Inorg. Chim. Acta* **2006**, *359*, 136.
(45) The oxidation potential for $PdCl_6^{2-} + 2e^-/ PdCl_4^{2-} + 2Cl^-$ is 1.29 V and 0.74V for $PtCl_6^{2-} + 2e^-/PtCl_4^{2-} + 2Cl^-$. Values from Weast, R. C. *Handbook of Chemistry and Physics*, 50th ed.; The Chemical Rubber Co.: Cleveland, 1969; D-110.
(46) Stahl, S.S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180 and refs therein.

Scheme 5. Investigation on Potential Acidity Influence in Second Step C−N Bond Formation



1s: X = H,
1b: X = Me,
1t: X = Cl,
1u: X = F

2s: 93%
2b: 92%
2t: 92%
2u: 86%

competition experiments:

$\frac{k_H}{k_{Me}} = 1.04$ $\frac{k_H}{k_{Cl}} = 0.95$ $\frac{k_H}{k_F} = 1.06$

[a] General reaction conditions same as from Scheme 1. Yields from eq 6 refer to those from independent diamination reactions.

deuteration experiments (Scheme 2). This stereochemical process had previously been confirmed for related C−O bond forming processes in platinum(IV) chemistry.[46,47] The stereochemical course of C−N bond formation in reactions of palladium(IV) was first investigated by Bäckvall,[4,11a,b] who concluded clean inversion for his intermolecular palladium-mediated amination reactions. Here, this step is understood to proceed through a state **J** (Figure 6), for which stereoelectronic reasons require weakening the bonding extent for the palladium-alkyl bond upon formation of the new alkyl-N bond.

For the present diamination, the prerequisite of backsite attack in the second C−N bond formation requires displacement of the tosylamide from the palladium coordination sphere prior to this final step.[48] This generates a cationic octahedral palladium-(IV) state within an ion pair, enhances the electrophilicity of the palladated methylene group, and thereby induces the propensity for Pd reductive elimination.[49−51] Prior to this, the reaction requires rotation of the Pd−C bond with respect to the amide. An alternative pathway of reductive elimination from a state **K** as encountered in related reductive elimination reactions from Pd(II) centers in aryl[36] and vinyl[52] aminations would not agree with the observed overall stereochemistry of the deuteration experiments (Scheme 2). In addition, such reductive eliminations are particularly rare for electron-demanding amides and usually require high temperatures.[53,54]

Sulfamides. Additional conclusive evidence for the involvement of *syn*-aminopalladation and release of the nucleophile for the final alkyl-X-bond formation from the palladium(IV) coordination sphere was obtained from an investigation with sulfamides. Related to ureas, sulfamides represent a potential coordination group for palladium and a potential nitrogen source for alkene diamination. These precursors are conveniently accessed by treatment of primary amine precursors with Burgess reagents.[55,56] Attempts to employ these compounds as substrates in palladium-catalyzed diamination met with little success.[57] Instead, standard reaction conditions of the urea-based diamination reaction gave a mixture of aminochlorination and diamination products **8** and **9**. In this case, however, the diamine product **9** is not formed directly, as a control experiment revealed that it is generated under the basic reaction conditions from the aminochlorination product **8** over time.

When the reaction was shifted to tetramethylammonium acetate or simply sodium acetate as base, i.e., processing at a lower base concentration, competing aminoacetoxylation instead of diamination dominated. Importantly, selectively deuterated precursor **10-d$_1$** gave a diastereomerically enriched product **11-d$_1$**. The major isomer was selectively transformed into the free cyclic sulfamide **12** via a sequence of acetate cleavage and Mitsunobu cyclization. Comparison of the NMR coupling constants allowed for the unambiguous deduction of a relative *anti*-position of the two hydrogen atoms of the former alkene and hence for a formal *syn*-/*anti*-sequence to **11-d$_1$**. This outcome is reminiscent of the overall process of our diamination with ureas and the corresponding aminoacetoxylations from Sorensen[17] and Stahl.[25] In particular, Stahl recently presented an investigation on related intermolecular aminoacetoxylation reactions[25] and concluded a sequence of *syn*-aminopalladation-followed by S_N2-type acetoxylation at the palladated carbon.[58] When changing the oxidant further, we were able to observe selective amino-X-functionalization processes for use of PhI-

(47) (a) Williams, B. S.; Holland, A. W.; Goldberg, K. I. *J. Am. Chem. Soc.* **1999**, *121*, 252. (b) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576.

(48) Through oxidation of the intermediate **5**, formation of a palladium(IV) intermediate of octahedral geometry is assumed. Figure 6 describes this compound as a *syn*-diacetate, based on a recent X-ray structure of a related palladium(IV) compound.[42b] The remaining coordination sites should be filled by additional donor groups L, which are unknown to date and might include solvent molecules, additional urea groups, acetic acid, acetate or halides (where present). The latter two would result in formation of formally anionic intermediates, which cannot be discarded completely at present.

(49) The importance of cationic metal states in related Pt(IV) chemistry was established both for alkyl-X and aryl-X bond formation. See ref 44 and (a) Goldberg, K. I.; Yan, J. Y.; Winter, E. L. *J. Am. Chem. Soc.* **1994**, *116*, 1573. (b) Goldberg, K. I.; Yan, J. Y.; Breitung, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 6889. (c) Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2006**, *128*, 8710. (d) Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560.

(50) For methanol elimination from neutral Pt(IV) complexes under basic conditions, see: (a) Vedernikov, A. N.; Binfield, S. A.; Zavalij, P. Y.; Khusnutdinova, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 82. (b) Khusnutdinova, J. R.; Zavalij, P. Y.; Vedernikov, A. N. *Organometallics* **2007**, *26*, 3466.

(51) While this manuscript was in the refereeing process, Goldberg described an identical mechanistic scenario for formation of achiral C−N bonds via reductive elimination from a methyl, tosylamido-Pt(IV) complex: Pawlikowski, A. V.; Getty, A. D.; Goldberg, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 10382.

(52) Barluenga, J.; Valdés, C. *Chem. Commun.* **2005**, 4891.

(53) (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (b) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (c) Sergeev, A. G.; Artamkina, G. A.; Khrustalev, V. N.; Antipin, M. Y.; Beletskaya, I. P. *Mendeleev Commun.* **2007**, *17*, 142. (d) Fujita, K.-i.;Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044. (e) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734.

(54) For an exception, see: Muñiz, K.; Iglesias, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6350.

(55) Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. *Org. Lett.* **2001**, *3*, 2241.

(56) Nicolaou introduced Burgess reagents for stoichiometric transformation of vicinal amino alcohols into cyclic sulfamides: (a) Nicolaou, K. C.; Longbottom, D. A.; Snyder, S. A.; Nalbanadian, A. Z.; Huang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3866. (b) Nicolaou, K. C.; Snyder, S. A.; Longbottom, D. A.; Nalbanadian, A. Z.; Huang, X. *Chem.—Eur. J.* **2004**, *10*, 5581.

(57) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125.

Scheme 6. Aminoacetoxylation Reactions of Sulfamides. DIAD = Diisopropyl Azodicarboxylate

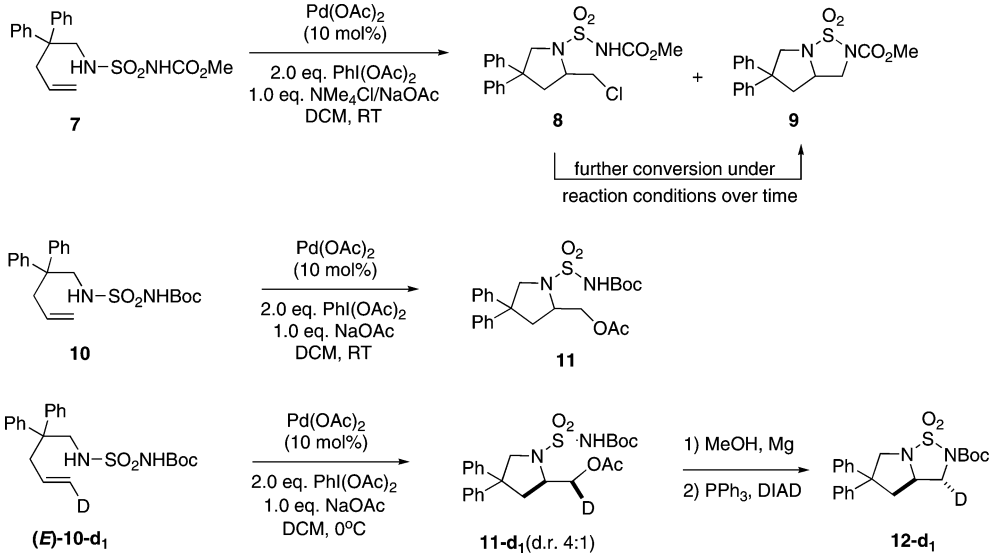
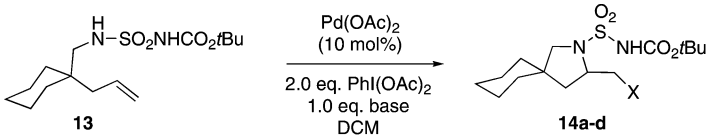
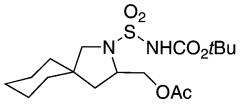
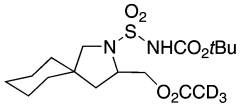
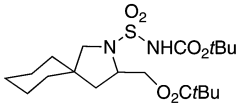
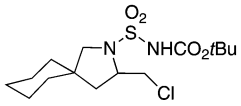


Table 2. Pd-Catalyzed Vicinal Amino-X-Functionalization



(7)

Entry	Oxidant	Base	Additive	Product	Yield [%][a]
1	$PhI(OAc)_2$	NaOAc			84
2	$PhI(OAc)_2$	NaO_2CtBu			74
3	$PhI(O_2CCD_3)_2$	NaOAc			86
4	$PhI(O_2CtBu)_2$	NaOAc			62
5	$PhI(O_2CtBu)_2$	NaO_2CtBu			72
6	$PhI(O_2CtBu)_2$	NaOAc	Me_4NCl		60
7	$PhI(OAc)_2$	NaOAc	Me_4NCl		65

[a] Isolated yield after column chromatography.

$(O_2CtBu)_2$, $PhI(O_2CCD_3)_2$, and under conditions of Me_4NCl addition. Control experiments confirmed that these reactions are indeed metal-catalyzed and that there is no uncatalyzed background reaction involved.[59]

Interestingly, all of these vicinal functionalization reactions occur with complete selectivity regarding the transfer of the second nucleophile. For all of these reactions, the nucleophile originates from the oxidant, and in no case from the anionic base. This selectivity depends on the crucial absence of acids because protons are known to promote exchange of the anions in hypervalent iodine reagents of type $ArIX_2$.[60] Indeed, formation of chlorinated products must stem from partial or complete exchange of acetate for chloride where tetramethylammonium is involved.

This observation was further corroborated from experiments with deuterated material and acetate/pivalate bases (Table 2, entries 2−4). Again, in all of these cases, only the anion that is transferred to palladium within the oxidation step finally finds

(58) For a recent cascade reaction with open relative stereochemistry in C−OAc bond formation from Pd(IV), see: Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836.

(59) For a direct aminoalkoxylation with $PhI(O_2CCF_3)_2$, see: Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316.

(60) Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272.

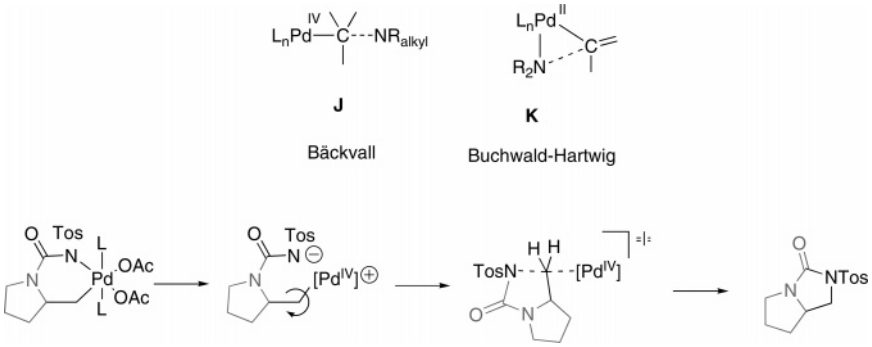


Figure 6. Mechanistic pathway for C−N bond formation from Pd(IV).

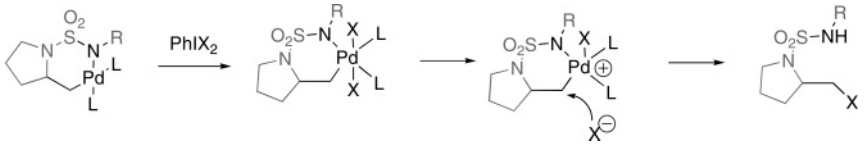


Figure 7. Overall sequence for amino-X functionalization of alkenes employing sulfamides.

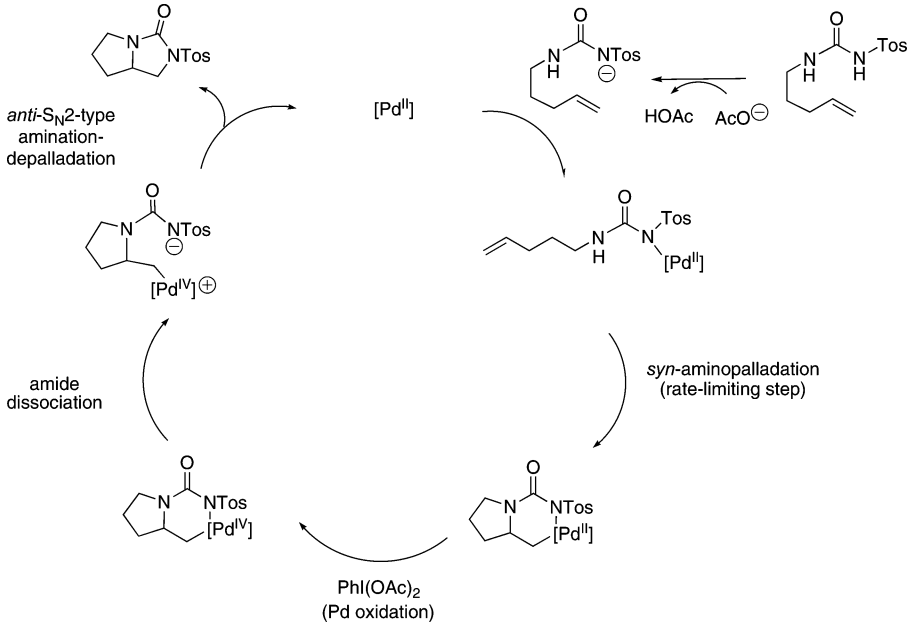


Figure 8. Overall catalytic cycle for palladium-catalyzed intramolecular diamination.

incorporation into the product. This observation is equivalent to the conclusion that the anion X in eq 7 proceeds from the immediate coordination sphere of the palladium(IV) oxidation state where it is introduced within the oxidation step of Pd(II) to Pd(IV) and hence plays a role reminiscent of the dissociating tosylamide in the diamination (Figure 6). Such a course has precedence for oxygenation reactions in platinum(IV) chemistry,[47,49] but to the best of our knowledge, has never been proven in conclusive detail for palladium(IV) chemistry.[51]

The importance of the transfer of the anion from palladium to carbon within a sequence of dissociation and S_N2-type nucleophilic substitution is of particular importance to the related course of the diamination reactions. It exemplifies that the NMR observation of a coordination of the tosylamide group to tetrahedral palladium(II) is obviously reversed after oxidation to octahedral palladium(IV), enabling a subsequent nucelophilic substitution/reductive depalladation with clean inversion of configuration. Palladium catalysis for oxidative alkene 1,2-difunctionalization with sulfamides yields different products depending on the reaction conditions, but proceeds throughout identical stereochemical pathways (Figure 7). The difference in product formation is contributed to the different leaving group character of the involved groups. Although the amide in tosyl ureas represents a leaving group character comparable to acetate, the related sulfamide cannot compete with the latter with respect to dissociation from the palladium center. Since the mechanistic pathway for final C−X bond formation proceeds via nucleophilic attack and not through direct reductive elimination, intramolecular diamination does not represent a feasible pathway for sulfamides.[57]

Conclusion

On the basis of the presented data, it is reasonable to conclude a two-step mechanism for the palladium-catalyzed oxidative diamination of alkenes employing urea groups as nitrogen sources. The resulting catalytic cycle is given in Figure 8. The reaction is initiated upon base-mediated coordination of palladium to the urea moiety. Coordination of the alkene to

palladium gives rise to aminopalladation. This occurs with the urea and the alkene being subsequently placed within the coordination sphere of palladium and hence constitutes a process with *syn*-stereochemistry. The step from **4** to **5** is slow and for the first time could be studied as a stoichiometric process under NMR conditions. The product from aminopalladation is a square-planar alkyl-palladium(II) complex that was detected by NMR spectroscopy. It undergoes rapid oxidation to octahedral palladium(IV). Its high oxidation state is a prerequisite for the formation of the diamination product since at oxidation state +IV, palladium enhances the electrophilicty of the neighboring carbon of its alkyl ligand. This electrophilic character is pronounced further upon dissociation of the urea ligand from the coordination sphere of palladium. Diamine formation is accomplished via nucleophilic nitrogen-carbon bond formation under clean S_N2-type conditions with clean *anti*-stereochemistry. This latter step leads to concomitant depalladation and regenerates the palladium catalyst in its original oxidation state.

All of these steps are in excellent agreement with the investigation on individual reaction steps including deuterium labeling, kinetics, solvent influence, electronic substitution effects, in situ NMR investigation and comparison with related aminoalkoxylation processes of sulfamides. It is interesting to compare the two stereochemistry-defining steps to the earlier stoichiometric protocol from Bäckvall.[4] Here, the nature of simple aliphatic amines precludes clean *anti*-aminopalladation of precoordinated alkenes and hence marks the stereochemical difference with respect to the catalytic intramolecular transformation employing ureas. The second C−N bond formation requires previous dissociation of the amide from the palladium coordination sphere. Hence, both the catalytic and the stoichiometric variant proceed with clean inversion of stereochemistry at this stage.

Our work has thus detailed the mechanistic basis of the first catalytic diamination of alkenes with a palladium-catalyst. It has further led to the discussion of the first general palladium-catalyzed C_{sp3}-N bond forming processes, the importance of nitrogen-tethered groups on a stereospecific reaction course in related amino-X-functionalizations. In addition, the reaction is catalyzed by simple ligand-free palladium salts and does not require ligand fine-tuning. All of these points should set the basis for additional development in the area of palladium-catalyzed alkene oxidation reactions.

Acknowledgment. We thank Dr. A. Núñez for experimental contributions, and Prof. Dr. José González and Esther Campos-Gómez for a generous gift of compound **1i**. K.M. acknowledges the German Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, the German-Israeli Science Foundation, the Otto-Röhm-Gedächtsnisstiftung, and the French Agence Nationale de la Recherche for financial support over the course of this project. We thank Prof. Dr. J. M. Lehn and Prof. Dr. N. Winssinger at ISIS, Prof. Dr. K. H. Dötz for his support at Bonn University during the early stages of this project, and U. Weynandt (Bonn) and J.-L. Schmitt (Strasbourg) for assistance with several NMR experiments.

Supporting Information Available: Experimental details, full characterization of new compounds, spectral reproduction for NMR experiments, and additional graphical material. This material is available free of charge via the Internet at http://pubs.acs.org.

JA075041A