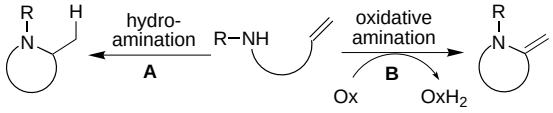
Efficient Intramolecular Oxidative Amination of Olefins through Direct Dioxygen-Coupled Palladium Catalysis**

Shannon R. Fix, Jodie L. Brice, and Shannon S. Stahl*

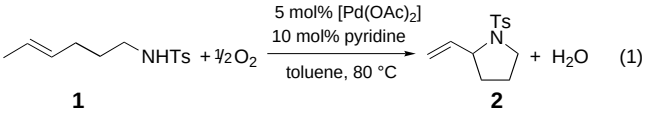
The prominence of five-membered nitrogen-containing heterocycles in natural products and biologically active molecules[1] has prompted considerable efforts toward their synthesis. Intramolecular hydroamination[2, 3] and oxidative amination[4, 5] of olefins represent powerful synthetic strategies for heterocycle formation (Scheme 1).[6] The latter is



Scheme 1. Strategies for the heterocyclization of olefinic amines or amides.

particularly attractive in the context of target-[7] and diversity-oriented[8] synthesis, because the product retains the olefin functionality. Nevertheless, oxidative methods exhibit added complexity associated with redox catalysis, specifically the need for a stoichiometric oxidant, which is typically an organic or a transition metal reagent such as benzoquinone or $CuCl_2$.[9] Furthermore, catalytic rates ($<1\ h^{-1}$) and turnover numbers ($\leq 10-20$) are significantly lower than those of hydroamination reactions, for which turnover numbers of ≥ 300 and frequencies of $50\ h^{-1}$ are not uncommon.[2] We describe herein the application of a very simple and efficient catalyst system, $[Pd(OAc)_2]$/pyridine (1:2), for the intramolecular oxidative amination of olefins to produce pyrrolidine and pyrroline heterocycles in high yields. These reactions utilize molecular oxygen as the stoichiometric oxidant, require no co-catalyst to facilitate the dioxygen-coupled catalytic turnover, and achieve unprecedented catalytic activity for such reactions.

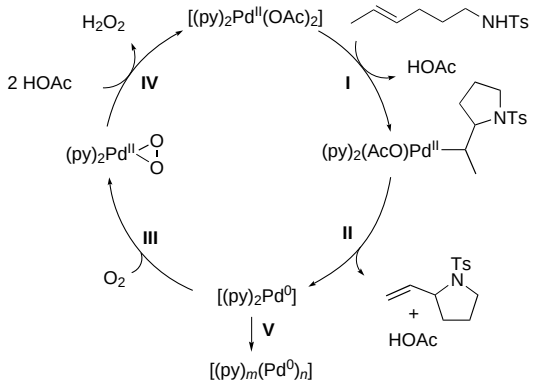
Our recent mechanistic studies of the $[Pd(OAc)_2]/O_2$/DMSO catalytic oxidation system[9] revealed that oxidation of reduced palladium by molecular oxygen is the turnover-limiting step of the catalytic cycle.[10] By analogy to recent aerobic oxidation reactions of alcohols,[11–13] we reasoned that pyridine or other imine donor ligands might promote palladium oxidation and thereby increase catalytic efficiency in oxidative amination reactions. Indeed, the oxidative cyclization of (*E*)-4-hexenyltosylamide (**1**) worked remarkably well with a catalyst composed of $[Pd(OAc)_2]$ (5 mol%) and pyridine (10 mol%) under one atmosphere of molecular oxygen [Eq. (1)]. The pyrrolidine product **2** was obtained in high yield (87%) within two hours.



Unlike previous aerobic oxidative amination reactions, this catalyst system operates successfully in a diverse array of solvents ($\geq 80\%$ yield), ranging from nonpolar (toluene, xylenes, heptane, and diphenyl ether) to polar (dimethoxyethane, acetonitrile, dimethylsulfoxide, and dimethylformamide). The precise role of pyridine in more polar, potentially coordinating solvents remains to be determined.

Nonpolar solvents proved to be distinctly superior at lower catalyst loading. The use of $[Pd(OAc)_2]$ (0.2 mol%)/pyridine (0.4 mol%) in *p*-xylene resulted in turnover rates of $70\ h^{-1}$ during the first two hours of the reaction and overall turnover numbers up to 250–300.[14] These catalyst activities far surpass those of previous oxidative amination reactions, and match or exceed the activities of most lanthanide-catalyzed hydroamination reactions. Particularly noteworthy is the lack of necessity for a co-catalyst to achieve efficient dioxygen-coupled turnover.

A possible catalytic cycle based upon experimental findings is shown in Scheme 2, although numerous details remain to be elucidated. The product arises from aminopalladation of the olefin (step I) followed by β-hydride elimination from the



Scheme 2. Hypothetical catalytic cycle.

alkyl palladium(II) intermediate (step II). The allylic disposition of the tosylamide in **2** arises from β-hydride elimination toward the methyl group, which is favored sterically and statistically over elimination that leads to the enamide product.[15] Oxygenation of palladium(0) (step III) followed by protonolysis of the peroxopalladium(II) species (step IV), as was recently demonstrated for a diimine-coordinated palladium(0) complex,[16] regenerates the active palladium(II) species.[17] Consistent with a mechanism in which palladium

[*] Prof. S. S. Stahl, S. R. Fix, J. L. Brice
Department of Chemistry, University of Wisconsin-Madison
1101 University Avenue, Madison, WI 53706 (USA)
Fax: (+1) 608-262-6143
E-mail: stahl@chem.wisc.edu

[**] We gratefully acknowledge funding from the University of Wisconsin-Madison, the Camille and Henry Dreyfus Foundation (New Faculty Award), Merck Research Laboratories, Research Corporation (Innovation Award), the Petroleum Research Fund, and a generous donation of laboratory equipment by Abbott Laboratories. We thank J. Coleman for experimental assistance. SRF was supported by a Chemistry Biology Interface NIH training grant. The National Science Foundation provided financial support for NMR spectroscopic instrumentation.

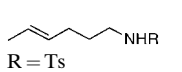
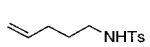
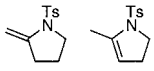
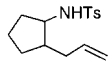
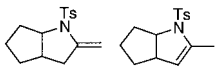
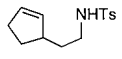
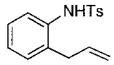
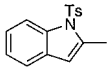
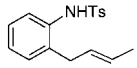
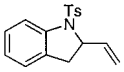
  1433-7851/02/4101-0164 $ 17.50+.50/0

alternates between the 0 and +2 oxidation states, a good yield of **2** (75%) is also obtained if the reaction is initiated with $[Pd_2(dba)_3]$ (2.5 mol%),[18] a palladium(0) catalyst source.

The qualitative observation of higher activities at lower catalyst loading, together with eventual catalyst inactivation, implicates a competition between catalytic turnover (e.g., step III) and irreversible inactivation of the catalyst (step V).[19] Pyridine may promote catalytic turnover by enhancing this branching in favor of step III. The pyridine/$[Pd(OAc)_2]$ stoichiometry of 2:1 in Scheme 2 reflects the optimal ratio determined experimentally; however, up to six equivalents could be added with only a small decrease in yield ($\leq$5%).[20]

This catalyst system proved to be effective for a series of related substrates (Table 1). Although most of the examples utilize *p*-toluenesulfonamide-substituted starting materials, the reactions of synthetically more attractive *o*-nitrobenzenesulfonamide (Ns) and benzyl carbamate (Cbz) derivatives of 1-amino-4-hexene also proceed in good yield, albeit with longer reaction times (Table 1, entry 1).

Table 1. Intramolecular Oxidative Amination of Olefinic Substrates.[a]

Entry	Substrate	*t* [h]	Product[b]	Yield[c]
1				
	R = Ts	2		87
	R = Ns	8		87
	R = Cbz	48		76
2		1.5		81 (7:3)
3		2		94 (1:1)
4		2		91
5		16		60
6		1.5		91

[a] Reaction Conditions: substrate (0.1 mmol), $[Pd(OAc)_2]$ (5 μmol), pyridine (10 μmol), O_2 (1 atm), xylenes (1 mL), 80 °C. [b] All products were isolated and identified by comparison with published ^{1}H NMR spectral data.[4d, 9c] [c] GC yields (internal standard: anthracene). Entries 1 (R = Ts), 4, and 6 were scaled up (0.8–3 mmol) and the isolated products were obtained in somewhat lower yields: 81, 84, and 87%, respectively.

The products of these reactions diverge between tosyl enamides and allylic tosylamides, although both arise from initial 5-exo cyclization (step I, Scheme 2). Whenever possible, β-hydride elimination (step II) occurs remotely from the tosylamide group to yield an allylic amide product (Table 1, entries 1, 4, and 6). If this path is not available (Table 1, entries 2, 3, and 5), the enamide is formed. In the latter cases, kinetically formed exo methylene products slowly isomerize under the reaction conditions to the more stable internal olefin products.

The present studies demonstrate the versatility and remarkable activity of the $[Pd(OAc)_2]$/pyridine catalyst system in aerobic oxidation catalysis, specifically for the intramolecular oxidative amination of olefins. The selective formation of allylic amides by means of oxidative cyclization provides an attractive, atom-economical alternative to allylic substitution reactions.[21] Furthermore, the intermediacy of alkyl palladium(II) species in these reactions raises the possibility of tandem reactions to create more complex heterocyclic structures.[22] The distinct simplicity of this catalyst system renders it amenable to high-throughput screening studies to evaluate alternative ligands and other reaction parameters. Specifically, the use of chiral ligands might permit asymmetric C–N bond formation.[13]

Experimental Section

General procedure (cyclization of **1**): (*E*)-4-hexenyltosylamide (25.3 mg, 0.1 mmol), pyridine (0.8 μL, 0.01 mmol; 16.7 mM stock solution in xylene), anthracene (1.78 mg, 0.01 mmol; 16.7 mM stock solution in xylene), xylene (150 μL, Aldrich), and a teflon coated stirrer bar were added to a 13 × 100-mm disposable culture tube. The tube was placed in one of the ports of a Radleys 12-place carousel reaction station with reflux head. After purging the headspace with molecular oxygen, $[Pd(OAc)_2]$ (1.1 mg, 0.005 mmol; 2.08 mM stock solution in xylene) was added just prior to heating to 80 °C. The total reaction volume was 1 mL. Reaction progress was monitored by gas chromatography (Shimadzu GC-17A gas chromatograph).

Received: September 24, 2001 [Z17958]

[1] See for example, D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446.

[2] a) M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1989**, *111*, 4108–4109; b) M. R. Gagné, S. P. Nolan, T. J. Marks, *Organometallics* **1990**, *9*, 1716–1718; c) M. R. Gagné, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 275–294; d) M. R. Gagné, L. Brard, V. P. Conticello, M. A. Giardello, C. L. Stern, T. J. Marks, *Organometallics* **1992**, *11*, 2003–2005; e) M. A. Giardello, V. P. Conticello, L. Brard, M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1994**, *116*, 10241–10254; f) Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1998**, *120*, 1757–1771; g) S. Tian, V. M. Arredondo, C. L. Stern, T. J. Marks, *Organometallics* **1999**, *18*, 2568–2570; h) J.-S. Ryu, T. J. Marks, F. E. McDonald, *Org. Lett.* **2001**, *3*, 3091–3094. See references in these publications for related hydroamination reactions of alkynes and allenes.

[3] a) G. A. Molander, E. D. Dowdy, *J. Org. Chem.* **1998**, *63*, 8983–8988; b) G. A. Molander, E. D. Dowdy, *J. Org. Chem.* **1999**, *64*, 6515–6517; c) Y. K. Kim, T. Livinghouse, J. E. Bercaw, *Tetrahedron Lett.* **2001**, *42*, 2933–2935.

[4] a) L. S. Hegedus, G. F. Allen, E. L. Waterman, *J. Am. Chem. Soc.* **1976**, *98*, 2674–2676; b) L. S. Hegedus, G. F. Allen, J. J. Bozell, E. L. Waterman, *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807; c) L. S. Hegedus, G. F. Allen, D. J. Olsen, *J. Am. Chem. Soc.* **1980**, *102*, 3583–3587; d) L. S. Hegedus, J. M. McKearin, *J. Am. Chem. Soc.* **1982**, *104*, 2444–2451; e) L. S. Hegedus, B. Akermark, K. Zetterberg, L. F. Olsson, *J. Am. Chem. Soc.* **1984**, *106*, 7122–7126; f) P. J. Harrington, L. S. Hegedus, K. F. McDaniel, *J. Am. Chem. Soc.* **1987**, *109*, 4335–4338.

[5] a) B. Pugin, L. M. Venanzi, *J. Am. Chem. Soc.* **1983**, *105*, 6877–6881; b) Y. Tamaru, M. Hojo, H. Higashimura, Z. Yoshida, *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002; c) Y. Tamaru, H. Tanigawa, S. Itoh, M. Kimura, S. Tanaka, K. Fugami, T. Sekiyama, Z. Yoshida, *Tetrahedron Letters* **1992**, *33*, 631–634.

[6] For recent important advances in intermolecular hydro- and oxidative amination of olefins, see: a) M. Beller, M. Eichberger, H. Trauthwein, *Angew. Chem.* **1997**, *109*, 2306–2308; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2225–2227; ; b) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller, O. R. Thiel, *Chem. Eur. J.* **1999**, *5*, 1306–1319; c) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 9546–9547; d) M. Kawatsura, J. F. Hartwig, *Organometallics* **2001**, *20*, 1960–1964; e) O. Löber, M. Kawatsura, J. F. Hartwig, *J. Am.*

  1433-7851/02/4101-0165 $ 17.50+.50/0

Chem. Soc. **2001**, *123*, 4366 – 4367; f) M. J. Gaunt, J. B. Spencer, *Org. Lett.* **2001**, *3*, 25 – 28. See also references cited in these publications.
[7] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, New York, **1996**.
[8] S. L. Schreiber, *Science* **2000**, *287*, 1964 – 1969.
[9] More recently, aerobic intramolecular oxidative amination has been achieved with a $[Pd(OAc)_2]/O_2$/DMSO catalyst system that lacks a co-catalyst: a) R. A. T. M. van Benthem, H. Hiemstra, G. R. Longarela, W. N. Speckamp, *Tetrahedron Lett.* **1994**, *35*, 9281 – 9284; b) M. Rönn, J.-E. Bäckvall, P. G. Andersson, *Tetrahedron Lett.* **1995**, *36*, 7749 – 7752; c) R. C. Larock, T. R. Hightower, L. A. Hasvold, K. P. Peterson, *J. Org. Chem.* **1996**, *61*, 3584 – 3585.
[10] B. A. Steinhoff, S. R. Fix, S. S. Stahl, unpublished results.
[11] a) T. Nishimura, K. Ohe, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 2645 – 2646; b) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, *64*, 6750 – 6755; c) T. Nishimura, K. Ohe, S. Uemura, *J. Org. Chem.* **2001**, *66*, 1455 – 1465.
[12] a) G. J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Science* **2000**, *287*, 1636 – 1639; b) R. Bortolo, D. Bianchi, R. D'Aloisio, C. Querci, M. Ricci, *J. Mol. Catal. A* **2000**, *153*, 25 – 29.
[13] Two groups recently reported the oxidative kinetic resolution of secondary alcohols by employing a similar catalyst system with (–)-sparteine as an asymmetric ligand: a) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2001**, *123*, 7725 – 7726; b) D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Am. Chem. Soc.* **2001**, *123*, 7475 – 7476.
[14] No palladium deposition is visible at these catalyst loadings. However, the catalyst appears to undergo irreversible deactivation over the course of the reaction. Ref. [8] presents evidence for irreversible aggregation of palladium(**0**) in the $[Pd(OAc)_2]/O_2$/DMSO system. Mechanistic studies have been initiated to probe the origin of catalyst deactivation in the present system.
[15] Allylic C–H activation followed by amination of the resulting π-allyl palladium(II) species cannot be ruled out. However, we disfavor this mechanism because several related substrates that react with similar rates cannot proceed through this pathway (Table 1).
[16] S. S. Stahl, J. L. Thorman, R. C. Nelson, M. A. Kozee, *J. Am. Chem. Soc.* **2001**, *123*, 7188 – 7189.
[17] Hydrogen peroxide is detected by an iodide/starch test upon completion of the reaction. However, manometry suggests that most of the hydrogen peroxide disproportionates into molecular oxygen and water during the course of the reaction (O_2/**2** = 0.55).
[18] This result provides preliminary evidence against a mechanism that maintains a palladium(II) oxidation state throughout the reaction (see ref. [10b]); dba = dibenzylideneacetone.
[19] Step III should exhibit a first-order dependence on [Pd], whereas catalyst inactivation should exhibit a bimolecular or higher order dependence on [Pd]. Consequently, enhanced turnover numbers and frequencies are expected at lower catalyst concentrations. For recent mechanistic characterization of the beneficial effect of reduced catalyst loading in aerobic oxidation reactions, see ref. [9]. See also, T. Rosner, J. Le Bars, A. Pfaltz, D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, *123*, 1848 – 1855.
[20] Bidentate ligands such as bipyridine are typically less effective than pyridine. S. R. Fix, S. S. Stahl, unpublished data. See also, ref. [10b].
[21] A. R. Katritzky, J. Yao, B. Yang, *J. Org. Chem.* **1999**, *64*, 6066 – 6070, and references therein.
[22] R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103 – 13159.

ZEKE Photoelectron Spectroscopy of the *cis* and *trans* Isomers of Formanilide**

Susanne Ullrich, György Tarczay, Xin Tong, Caroline E. H. Dessent, and Klaus Müller-Dethlefs*

Cationic states are involved in long-range charge transfer in polypeptides,[1] an area of intense chemical interest.[2] While a number of theoretical and time-resolved studies have contributed to our mechanistic understanding of this problem,[1] there is currently little spectroscopic information available for cationic amides.[3, 4] Basic questions regard the preference for *cis* or *trans* conformations and barrier heights for interconversion. Here we present initial results that indicate that zero electron kinetic energy (ZEKE) spectroscopy,[5, 6] a high-resolution variant of photoelectron spectroscopy, may represent a powerful technique for obtaining vibrationally resolved spectra of cationic amides and model peptides. Spectra are presented for both the *cis* and *trans* isomers of formanilide, an aromatic molecule with an amide side chain. The aromatic group provides a convenient chromophore, while significant charge delocalization occurs from the aromatic ring to the functional group in the cation, so that formanilide is a useful model system for studying the properties of cationic amides.

Local-minimum geometric structures of the neutral (S_0) and cationic (D_0) isomers of formanilide obtained from MP2(fc)/6-31G* ab initio calculations are presented in Figure 1.[7] For *trans*-formanilide, the calculations predict that the molecule

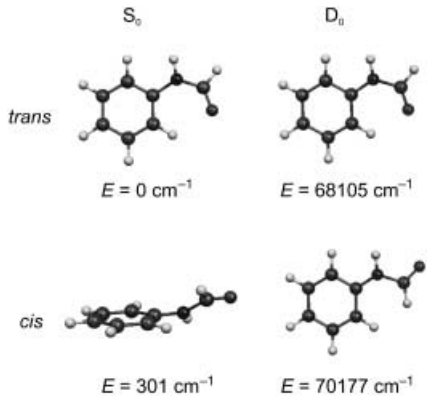


Figure 1. Optimized structures of the neutral (S_0) and cationic (D_0) isomers of formanilide at the MP2(fc)/6-31G* level of theory illustrating the ionization-induced geometry changes. Total energies are given relative to the energy of the S_0 state of *trans*-formanilide (– 399.693829 Hartree).

[*] Prof. K. Müller-Dethlefs, S. Ullrich, G. Tarczay, X. Tong, Dr. C. E. H. Dessent
Department of Chemistry
University of York
Heslington, York, YO10 5DD (UK)
Fax: (44) 1904-432-516
E-mail: kmd6@york.ac.uk

[**] This work was supported by the EPSRC (grant No. GR/L27770). C.E.H.D. thanks the Royal Society for support from a Royal Society University Research Fellowship and Prof. J. P. Simons for useful discussions. S.U. acknowledges support from the Fonds des Verbands der Chemischen Industrie and DAAD, and G.T. acknowledges support from the Hungarian Ministry of Education and the Peregrinatio II Foundation.

  1433-7851/02/4101-0166 $ 17.50+.50/0