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Synthesis of Pyrrolidines via Palladium(II)-Catalyzed Aerobic Oxidative Carboamination of Butyl Vinyl Ether and Styrenes with Allyl Tosylamides

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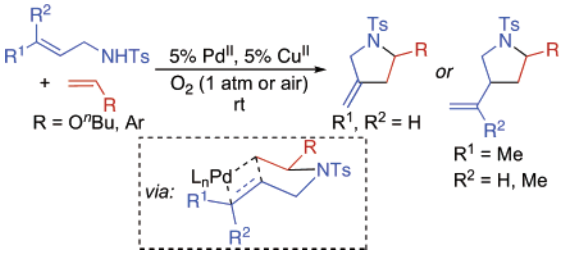
ABSTRACT



Palladium(II) catalyzes the oxidative coupling of allyl tosylamides with butyl vinyl ether and various styrene derivatives to produce 2,4-substituted pyrrolidine products at room temperature. Molecular oxygen together with a copper(II) cocatalyst mediates reoxidation of the palladium catalyst. The reactions with styrene substrates can be performed in an open flask with ambient air as the source of O_2. Several nontraditional cocatalysts, including catechol, cyclooctadiene, and methyl acrylate, have a beneficial effect on the reactions.

Palladium-catalyzed methods for the oxidation of alkenes have an extensive history dating to the discovery of the Wacker process,[1] and they find widespread use in organic synthesis for conversion of terminal alkenes to methyl ketones.[2] Although such reactions have been quite successful for the formation of carbon−oxygen bonds, analogous methods for intermolecular oxidative amination of alkenes (i.e., aza-Wacker reactions) have been identified only recently.[3−5] We have reported several Pd^{II}-catalyzed reactions that effect intermolecular C−N bond formation between alkenes and amide-type nitrogen nucleophiles (Scheme 1), including aerobic oxidative amination of terminal and cyclic

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[1] (a) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176−182. (b) Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; Kluwer: Boston, 1980. (c) Jira, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: New York, 2002; Vol. 1, pp 386-405.

[2] Takacs, J. M.; Jiang, X.-t. *Curr. Org. Chem.* **2003**, *7*, 369−396.

[3] (a) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. *Tetrahedron Lett.* **1992**, *33*, 6643−6646. (b) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996−12997. (c) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868−2869. (d) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308−7309. (e) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888−17893.

[4] Elegant studies of stoichiometric Pd-mediated amination of alkenes have been reported. Catalytic turnover is generally inhibited in these cases by the presence of 1° or 2° alkylamine substrates, which coordinate strongly to Pd^{II}. For leading references, see: (a) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335−342. (b) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415−2434.

[5] Intramolecular oxidative amination methods benefit from significant entropic advantage, and numerous examples are known. These reactions continue to be the subject of active interest. For leading references, see: (a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444−2451. (b) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 9281−9284. (c) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749−7752. (d) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584−3585. (e) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166. (f) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778−17788. (g) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130−3131.

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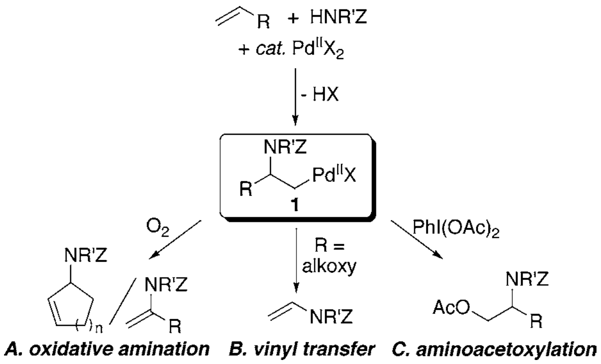
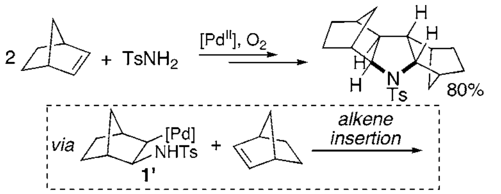
Scheme 1. Palladium(II)-Catalyzed Intermolecular C−N Bond-Forming Reactions with Alkenes[a]

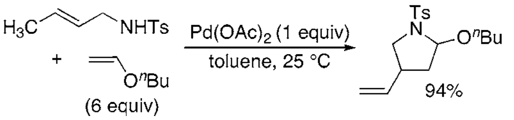


[a] HNR′Z = amide, carbamate, imide, sulfonamide.

alkenes (**A**),[3b,c,e] nonoxidative vinyl transfer from vinyl ethers (**B**),[6] and aminoacetoxylation of terminal alkenes with PhI(OAc)$_2$ as the stoichiometric oxidant (**C**).[7] Each of these reactions is thought to proceed via a common aminopalladation intermediate **1**, and the product reflects the divergent fate of this species: β-hydride elimination (**A**), β-alkoxide elimination (**B**), or oxidative cleavage of the Pd−C bond (**C**). Recent studies of the oxidative amination of norbornene revealed that the intermediate Pd−C bond can also react via alkene insertion (eq 1).[3c] The latter observation prompted us to consider whether Pd^{II}-catalyzed methods for the oxidative carboamination of alkenes could be extended to other substrates. Indeed, Oshima et al. have shown that Pd^{II} mediates stoichiometric oxidative coupling of allyl tosylamides and vinyl ethers (e.g., eq 2).[8−10] Here, we describe the development of catalytic procedures for these reactions that enable molecular oxygen to be used as the stoichiometric oxidant.[11,12] We also demonstrate that styrenes are effective reaction partners, and in the latter reactions, ambient air is an effective source of O$_2$.



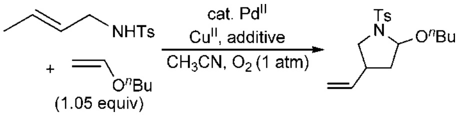
(1)



(2)

Our initial efforts focused on identifying aerobic catalytic procedures for the oxidative coupling of crotyl tosylamide and butyl vinyl ether (eq 2). Pd(OAc)$_2$ (5−10 mol %) is an effective catalyst under aerobic conditions, and improved results are obtained if cocatalytic Cu(OAc)$_2$ and 3 Å molecular sieves are also present (Table 1, entries 1−3).[13]

Table 1. Screening Results for the Pd-Catalyzed Aerobic Oxidative Coupling of Butyl Vinyl Ether with Crotyl Tosylamide[a]



entry	% catalyst	% Cu^{II}	solvent	additive	yield (%)[b]
1	10 Pd(OAc)$_2$	none	MeCN	3 Å MS	40
2	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	MeCN	none	50
3	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	MeCN	3 Å MS	63
4	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	DME	3 Å MS	29
5	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	CHCl$_3$	3 Å MS	18
6	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	DMF	3 Å MS	33
7	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	DMSO	3 Å MS	33
8	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	toluene	3 Å MS	26
9	10 (py)$_2$Pd(OAc)$_2$	10 Cu(OAc)$_2$	MeCN	3 Å MS	15
10	10 (dpp)Pd(OAc)$_2$	10 Cu(OAc)$_2$	MeCN	3 Å MS	9
11	10 (IMes)Pd(OAc)$_2$ (OH$_2$)	10 Cu(OAc)$_2$	MeCN	3 Å MS	trace
12	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	MeCN	20% TEA/ 3 Å MS	38
13	10 Pd(OAc)$_2$	10 Cu(OAc)$_2$	MeCN	20% catechol/ 3 Å MS	79
14	**5 Pd(OAc)$_2$**	**5 Cu(OAc)$_2$**	**MeCN**	**10% catechol/ 3 Å MS**	**87**[c]

[a] Substrate (0.20 mmol), butyl vinyl ether (0.21 mmol), 1 mL of MeCN, 25 °C, 24 h. [b] Yields as determined by GC. [c] Isolated yield.

Significant Pd black formation is observed in the absence of additives. Acetonitrile is the optimal solvent (entries 3−8). The use of ligands or coordinating bases, including dpp,[14] IMes, pyridine, and NEt$_3$, has a detrimental effect on the

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(6) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845−1848.

(7) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179−7181.

(8) (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809−812. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050−2054.

(9) Pd-catalyzed methods for the carboamination of alkenes are known, but they generally feature intramolecular C−N bond formation. For leading references, see: (a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1988**, *110*, 3994−4002. (b) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113-2122. (c) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906−13907. (d) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893−2901. (e) Ref 5g.

(10) For recent Cu-mediated intramolecular carboamination methods, see: (a) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573−1575. (b) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250−11251.

(11) Oshima et al. also described the oxidative coupling of allyl alcohols and vinyl ethers to produce tetrahydrofuran derivatives (ref 8). While the present work was in progress, the groups of Morken and Hosokawa reported important advances in reactions of allyl alcohols, including diastereoselective transformations and catalytic aerobic oxidation procedures, respectively. (a) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367−3370. (b) Minami, K.; Kawamura, Y.; Koga, K.; Hosokawa, T. *Org. Lett.* **2005**, *7*, 5689−5692.

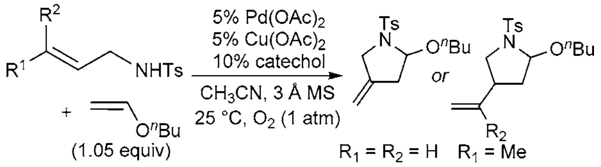
(12) Oshima-like oxidative coupling of allyl alcohols and vinyl ethers and related reactions have been applied to the synthesis of natural products. For examples, see: (a) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815−7816. (b) Kraus, G. A.; Thurston, J. *J. Am. Chem. Soc.* **1989**, *111*, 9203−9205. (c) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371−3373. (d) Trudeau, S.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5465−5468. (e) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290−7291.

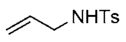
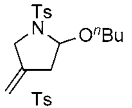
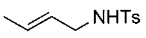
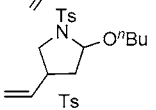
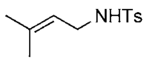
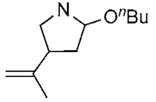
(13) For a recent study into the role of molecular sieves in palladium-catalyzed aerobic oxidation reactions, see: Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861−1868.

reaction (entries 9−12). While this work was in progress, Hosokawa reported that catechol is a beneficial cocatalyst in related reactions with allyl alcohol,[11b] and we observe a similar effect in the present reactions (entries 3 and 13). The optimal results are obtained with 5 mol % of $Pd(OAc)_2$ (entry 14).

The ability to use a near-stoichiometric quantity of butyl vinyl ether (1.05 equiv) in these reactions contrasts our other oxidative amination reactions that we have studied, which generally require excess alkene (2−6 equiv) to proceed in good yield.[3b,c,7] Application of these reaction conditions to other allyl tosylamide substrates was also successful (Table 2). The observed diastereoselectivities are similar to those observed in related reactions with allyl alcohols.[8,11]

Table 2. Pd-Catalyzed Aerobic Oxidative Coupling of Allyl Tosylamides with Butyl Vinyl Ether[a]

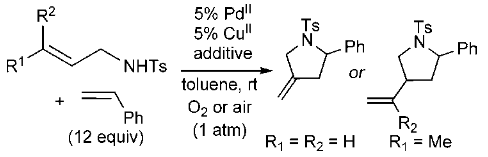


entry	allyl tosylamide	product	yield (%)[b]	dr[c]
1			76	--
2			87	1.4 : 1
3			80	1.3 : 1

[a] Substrate (1.3 mmol), butyl vinyl ether (1.4 mmol), $Pd(OAc)_2$ (0.066 mmol), $Cu(OAc)_2$ (0.066 mmol), catechol (0.13 mmol), 3 Å MS (290 mg), 6.6 mL of MeCN, 25 °C, 1 atm of O_2, 24 h. [b] Isolated yields, average of two runs. [c] dr = diastereomeric ratio.

Precedent for this class of Pd-catalyzed oxidation reactions is limited to the use of vinyl ethers.[8] In the evaluation of other alkenes, we found that styrene is also effective. The reaction requires styrene to be used in excess because it is susceptible to side reactions, such as polymerization and oxidation to acetophenone, that limit the yield if only 1 equiv is used. Results with three different allyl tosylamides (Table 3) reveal that a mixture of $Pd(OAc)_2$ and $Cu(TFA)_2$ (or $Pd(TFA)_2$ and $Cu(OAc)_2$; entries 4, 7, 12, 16, and 17) provides the highest yield of pyrrolidine product. If Pd^{II} and Cu^{II} possess the same anionic ligand (acetate or TFA), a lower yield is obtained (entries 3 and 8). In contrast to the reactions with butyl vinyl ether, toluene is the optimal solvent[15] and molecular sieves are not critical to the success of the reaction (entry 5). Crotyl tosylamide proceeds in nearly quantitative yield to the pyrrolidine product when the reaction is performed in an open flask at room temperature (i.e., with ambient air providing the source of O_2) (entry 4). With the other two tosylamides tested, significant Pd black formation and lower yields are observed under comparable conditions (entries 11 and 15). Inclusion of catechol as a cocatalyst is not beneficial (entry 14). On the basis of these results, we evaluated methyl acrylate and 1,5-cyclooctadiene (COD) as additives with the prospect that they might stabilize Pd^0 and inhibit Pd black formation.[16] Both of these additives result in improved product yields (entries 12, 13, 16, and 17).

Table 3. Screening Results for the Pd-Catalyzed Aerobic Oxidative Coupling of Styrene with Allyl Tosylamides[a]



entry	R¹	R²	catalyst	% Cu^II	additive	yield (%)[b]
1	Me	H	$Pd(OAc)_2$	none	none	29
2	Me	H	$Pd(OAc)_2$	5 $CuCl_2$	none	52
3	Me	H	$Pd(OAc)_2$	5 $Cu(OAc)_2$	none	31
4	**Me**	**H**	**$Pd(OAc)_2$**	**5 $Cu(TFA)_2$**	**none**	**97[c]**
5	Me	H	$Pd(OAc)_2$	5 $Cu(TFA)_2$	3 Å MS	92
6	Me	H	$Pd(TFA)_2$	none	none	23
7	**Me**	**H**	**$Pd(TFA)_2$**	**5 $Cu(OAc)_2$**	**none**	**98**
8	Me	H	$Pd(TFA)_2$	5 $Cu(TFA)_2$	none	72
9	Me	H	(dpp)$Pd(OAc)_2$	none	5% dpp	trace
10	Me	H	(IMes)$Pd(OAc)_2(OH_2)$	none	none	trace
11	H	H	$Pd(OAc)_2$	5 $Cu(TFA)_2$	none	28
12	**H**	**H**	**$Pd(OAc)_2$**	**5 $Cu(TFA)_2$**	**5% COD[d]**	**64[c]**
13	H	H	$Pd(OAc)_2$	5 $Cu(TFA)_2$	50% methyl acrylate	50[c]
14	H	H	$Pd(OAc)_2$	5 $Cu(TFA)_2$	10% catechol	22
15	Me	Me	$Pd(OAc)_2$	5 $Cu(TFA)_2$	none	55
16	**Me**	**Me**	**$Pd(OAc)_2$**	**5 $Cu(TFA)_2$**	**5% COD[d]**	**99**
17	**Me**	**Me**	**$Pd(OAc)_2$**	**5 $Cu(TFA)_2$**	**50% methyl acrylate**	**97[c]**

[a] Substrate (0.19 mmol), styrene (2.3 mmol), Pd^{II} (0.0094 mmol), 0.25 mL of toluene, 25 °C, 24 h. [b] Yields as determined by GC. [c] Isolated yield; reaction performed in an open flask with ambient air as the source of O_2. [d] Reaction performed at 40 °C.

These mild reaction conditions are successful with several additional styrene derivatives (Table 4). The vinylanisole-derived products (entries 3 and 4) were obtained initially as a mixture of the desired pyrrolidine and the acetophenone side product; however, treatment of this mixture with $LiAlH_4$ enables the pure pyrrolidine product to be obtained. The somewhat hindered 2-vinylanisole substrate was less reactive than the other analogues, and the best yield was obtained at a higher reaction temperature (60 °C) with the use of a pure oxygen atmosphere (rather than ambient air). No significant electronic effects are observed. Measurement of initial rates revealed that the parent styrene substrate reacts approximately

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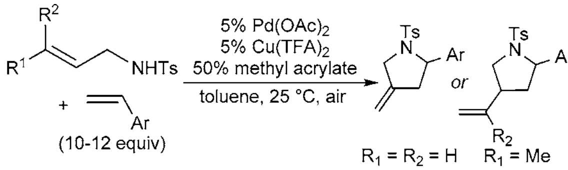
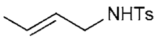
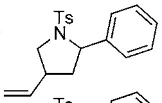
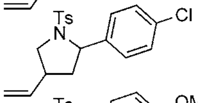
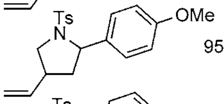
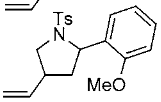
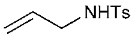
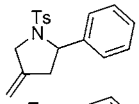
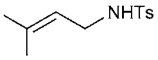
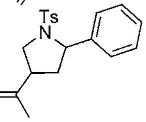
(14) Abbreviations: dpp = 4,7-diphenyl-1,10-phenanthroline, IMes = 1,3-di(2,4,6-trimethylphenyl)imidazoline-2-ylidene, COD = 1,5-cyclooctadiene, TFA = trifluoroacetate.

(15) Significantly reduced yields are observed for reactions conducted in acetonitrile.

(16) For prior examples of COD and methyl acrylate as additives in palladium-catalyzed reactions, see: (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645−2646. (b) Kuwano, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545−3547.

Table 4. Pd-Catalyzed Aerobic Oxidative Coupling of Allyl Tosylamides with Styrene Substrates[a]



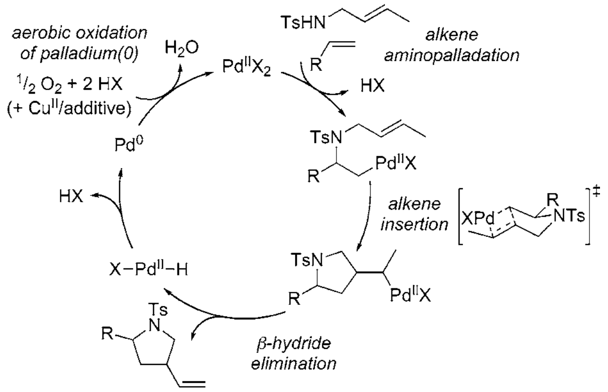
entry	substrate	product	yield (%)[b]	dr[c]
1			97	1.9 : 1
2			94	2.0 : 1
3			95[d] (68[e])	1.9 : 1
4			87[d,f] (71[e])	2.4 : 1
5			64[g]	—
6			93	1.6 : 1

[a] Allyl tosylamide (1.3 mmol), styrene (13−16 mmol), Pd(OAc)$_2$ (0.066 mmol), Cu(TFA)$_2$ (0.066 mmol), methyl acrylate (0.66 mmol), 1.8 mL of toluene, room temperature, open to air, 24 h (48 h for entry 5). [b] Isolated yields, average of two runs. [c] dr = diastereomeric ratio. [d] NMR yields, average of two runs. [e] Isolated yields after reduction of the Wacker oxidation coproduct with LiAlH$_4$, average of two runs. [f] Reaction performed at 60 °C under 1 atm of O$_2$. [g] Reaction performed at 40 °C under air with 5 mol % of COD rather than 50 mol % of methyl acrylate.

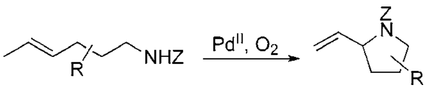
2-fold faster than either the electron-deficient *p*-chloro and the electron-rich *p*-methoxy derivatives under identical conditions. The diastereoselectivities observed in these reactions are similar to those observed with butyl vinyl ether as the substrate (cf. Table 2).

The reactions outlined above are consistent with a catalytic mechanism initiated by aminopalladation of the vinyl ether or styrene substrate (Scheme 2; cf. Scheme 1).[3,4] Exo insertion of the pendant alkene of the allyl tosylamide into the Pd−C bond forms the pyrrolidine ring, and subsequent β-hydride elimination yields the observed product.[8,11] We and others have developed numerous reactions that undergo direct dioxygen-coupled oxidation of the reduced Pd catalyst;[17] however, the reactions reported here benefit significantly from a Cu^{II} cocatalyst and other additives as well (catechol, COD, methyl acrylate). Although the precise mechanistic role of these additives remains to be elucidated, they presumably contribute to the stability of Pd^0 intermediate(s) in the reaction and/or enhance the rate of Pd^0 oxidation.[16]

Scheme 2. Proposed Catalytic Cycle for Pd^{II}-Mediated Oxidative Coupling of Allyl Tosylamides and Butyl Vinyl Ether or Styrene



Pd^{II}-catalyzed oxidation reactions for the synthesis of pyrrolidines are well-known.[5,9] In most cases, however, the reactions involve intramolecular cyclization of δ,ϵ-unsaturated amides and related substrates (e.g., eq 3), which often must be prepared via multistep syntheses. The reactions



(3)

described herein generate related products via the oxidative coupling of readily available substrates. These reactions also point toward prospects for the further development of oxidative carboamination and related Pd-catalyzed 1,2-oxidative difunctionalization reactions of alkenes.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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