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Published on Web 05/09/2006

Highly Regioselective Pd-Catalyzed Intermolecular Aminoacetoxylation of Alkenes and Evidence for *cis*-Aminopalladation and S_N2 C−O Bond Formation

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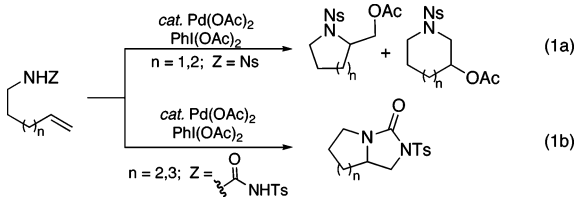
Palladium-catalyzed oxygenation of alkenes finds widespread use in organic chemistry,[1] including the production of commodity chemicals, such as acetaldehyde and vinyl acetate.[2] In contrast, related catalytic methods for intermolecular oxidative amination of alkenes (i.e., "aza-Wacker" reactions) were discovered only recently.[3,4] The latter reactions typically produce enamides via an aminopalladation/β-hydride elimination sequence (Scheme 1, top pathway). Recently, Sorensen[5] and Muñiz[6] reported that intramolecular Pd-catalyzed aminoacetoxylation and diamination of alkenes could be achieved by using $PhI(OAc)_2$ as an oxidant to trap the intermediate Pd−C bond (eqs 1a and 1b).[7] These reports build on recent reports by Sanford and co-workers, who have shown that $PhI(OAc)_2$ can oxidize Pd^{II} to Pd^{IV} to facilitate C−X bond formation (Scheme 1, bottom pathway).[8−10] Here, we report the first examples of *intermolecular* Pd-catalyzed aminoacetoxylation of alkenes. The reactions, which employ phthalimide as the nitrogen nucleophile, exhibit selectivity for terminal alkenes and are particularly effective for allyl ether substrates, which appear to benefit from chelation of the allylic oxygen atom. Mechanistic studies provided evidence for *cis*-aminopalladation of the alkene and subsequent C−O bond formation with inversion of stereochemistry. The latter is believed to arise from S_N2 nucleophilic attack of acetate on an alkyl Pd^{IV} intermediate. These reactions represent a mechanistically and stereochemically distinct pathway for vicinal difunctionalization of alkenes relative to the highly useful Os^{VIII}-catalyzed methods.[11,12]



Our initial efforts to probe the aminoacetoxylation of alkenes focused on the reactivity octene in the presence of a nitrogen nucleophile, Pd^{II} catalyst, and $PhI(OAc)_2$. Several nucleophiles used in previous studies of styrene oxidative amination[4b] were tested, including succinimide, phthalimide, pyrrolidinone, oxazolidinone, and tosylamide; however, only phthalimide proved effective. The origin of this limitation is not presently understood, but phthalimide is attractive because it serves as a useful ammonia surrogate.

Screening results for phthalimide-based aminoacetoxylation of octene (Table 1) reveal the formation of three different products in these reactions: aminoacetoxylation product **1a**, enimide **1b**, and a vicinal diacetoxylation product **1c**. No aminoacetoxylation is observed in the absence of Pd^{II} (entry 1). Among various Pd^{II} sources tested (entries 2−8), $PdCl_2(CH_3CN)_2$ was most effective; lower yields were obtained with Pd−carboxylate complexes and with the use of a strong donor carbene ligand (I^iPr). Weak nitrogen bases/donor ligands (NEt_3, pyridine) or an anionic base (OAc^-) completely inhibited the reaction. Reducing the catalyst loading to

Scheme 1. Reaction Pathways for Pd-Mediated Oxidative Amination of Alkenes

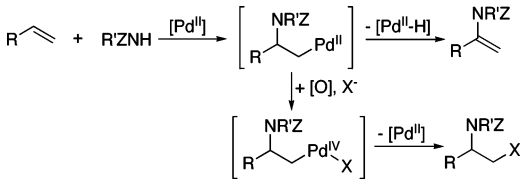
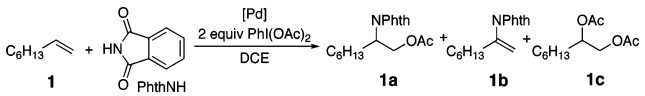


Table 1. Aminoacetoxylation of Octene: Screening Results[a]



entry	catalyst (10 mol %)	yield **1a** (**1b**/**1c**) (%)[b]
1	none	0
2	$PdCl_2(CH_3CN)_2$	52 (15/23)
3	$Pd(OAc)_2$	38 (21/29)
4	$Pd(O_2CCF_3)_2$	25 (21/21)
5	$[(I^iPr)PdCl_2]_2$[c]	19 (17/15)
6	$PdCl_2(CH_3CN)_2$/pyridine (20%)	trace
7	$PdCl_2(CH_3CN)_2/Et_3N$ (20%)	trace
8	$PdCl_2(CH_3CN)_2/Bu_4NOAc$ (1 equiv)	trace
9	$PdCl_2(CH_3CN)_2$ (5 mol % Pd)	50 (16/23)
10	**$PdCl_2(CH_3CN)_2$ (2.5 equiv $PhI(OAc)_2$)**	**60**[d] **(19/28)**
11	$PdCl_2(CH_3CN)_2$ (5 equiv $PhI(OAc)_2$)	55 (0/56)

[a] Reaction conditions: 1-octene (0.4 mmol), phthalimide (0.2 mmol), [Pd] (0.02 mmol), $PhI(OAc)_2$ (0.4 mmol), and DCE (1 mL), 80 °C, 24 h. [b] ^1H NMR yield relative to phthalimide as the limiting reagent (internal std. = 1,3,5-trimethoxybenzene); the overall yield can be >100% because byproduct **1c** does not contain phthalimide. [c] I^iPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidine. [d] Isolated yield = 55%.

5 mol % resulted in only minor yield diminution (entry 9). The best conditions featured 2.5 equiv of $PhI(OAc)_2$ (entry 10). The use of more $PhI(OAc)_2$ (5 equiv) reduced the amount of β-hydride elimination product **1b**, but increased diacetoxylation at the expense of aminoacetoxylation (entry 11). Among solvents, 1,2-dichloroethane (DCE) was significantly better than nitriles (CH_3CN, PhCN), ethers (THF, dimethoxyethane), and toluene. Overall, these results demonstrate that intermolecular aminoacetoxylation can be achieved in substantial yield for a simple unactivated alkene. Moreover, the reaction proceeds with exquisite regioselectivity; no products arising from phthalimide addition to the terminal carbon are observed. This result is noteworthy because Os-catalyzed aminohydroxylation often forms regioisomeric mixtures, often favoring the opposite regioisomer.[11,13]

In the evaluation of other alkene substrates, allyl ethers proved to be particularly effective (Table 2). Under conditions similar to those optimized for octene, allyl propyl ether undergoes regioselective aminoacetoxylation to produce **2a** in 84% yield (entry 1) together with the enimide **2b** in 16% yield. The reaction was also performed with alkene as the limiting reagent (1.5 equiv of phthalimide), and a 53% yield of **2a** was obtained.

10.1021/ja061706h CCC: $33.50

Table 2. Intermolecular Aminoacetoxylation of Alkenes Catalyzed by $PdCl_2(CH_3CN)_2$[a]

entry	alkene		product		yield (%)[b]
1	RO	R = ^{n}Pr **2**	NPhth RO OAc	**2a**	84 (78)
2		Bn **3**		**3a**	80 (75)
3		Bz **4**		**4a**	75 (72)
4		Ac **5**		**5a**	58 (53)
5	^{n}Bu O	**6**	NPhth ^{n}Bu O OAc	**6a**	47 (45)[d]
6	BnO	**7**	NPhth BnO OAc	**7a**	30
7	O	**8**	NPhth O OAc	**8a**	76 (71)
8[c]	RO	R = Bn **9**	NPhth RO OAc (±)	**9a**	78 (71)
9[c]		Bz **10**		**10a**	67 (62)
10[c]	RO Ph	R = Me **11**	NPhth RO OAc (±) Ph	**11a**	75 (74)
11[c]		Bn **12**		**12a**	68 (65)
12[c]	MeO Ar	**13** Ar = *p*-BrC_6H_4	NPhth MeO OAc (±) Ar	**13a** Ar = *p*-BrC_6H_4	65 (64)
13[c]	MeO Ph	**14**	NPhth MeO OAc (±) Ph	**14a**	73 (71)

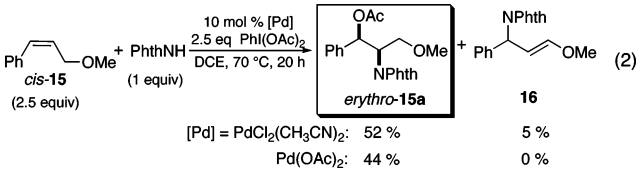
[a] Reaction conditions: alkene (0.4 mmol), phthalimide (0.2 mmol), $PdCl_2(CH_3CN)_2$ (0.02 mmol), $PhI(OAc)_2$ (0.4 mmol), and DCE (0.25 mL), 70 °C, 24 h. [b] ^{1}H NMR yield (isolated yield) relative to phthalimide. [c] Alkene (0.5 mmol), $PhI(OAc)_2$ (0.5 mmol). [d] Diacetoxylation yield = 70%.

Allyl benzyl ether **3** and allyl benzoate **4** also proceed in good yield (entries 2 and 3). The yield with allyl acetate **5** is slightly lower (entry 4); however, neither of the allylic ester substrates, **4** and **5**, yields allylic amination products. The potential benefit of a chelating allylic oxygen atom is suggested by the reduced yields of the vinyl and homoallyl ether substrates **6** and **7**, wherein the oxygen atom is one atom closer or further from the alkene (entries 5 and 6). The reaction of crotyl allyl ether **8** proceeds with high levels of chemoselectivity; aminoacetoxylation occurs exclusively at the terminal vinyl group (entry 7). In general, internal alkenes appear to be ineffective substrates. For example, crotyl benzyl ether yields a complex mixture of products, none of which appears to be the desired aminoacetoxylation product.

Very high diastereoselectivity is observed with substrates that possess an additional substituent in the allylic position, including methyl, benzyl, and aryl groups (**9**−**14**, entries 8−13). Only one diastereomeric aminoacetoxylation product is evident in the ^{1}H NMR spectrum of the products, and X-ray crystal structures of **9a** and **13a** confirm the indicated stereochemistry.[14]

With these catalytic results in hand, we turned our focus to the reaction mechanism. The mechanism and stereochemical course of the C−N and C−O bond forming steps have important implications for the future development of enantioselective transformations. The recent studies of intramolecular reactivity (eqs 1a and 1b) revealed that aminoacetoxylation generates the *anti*-addition product,[5] whereas diamination yields the *syn*-addition product.[6] In both cases, however, the authors propose a mechanism initiated by *trans*-aminopalladation of the alkene.[15]

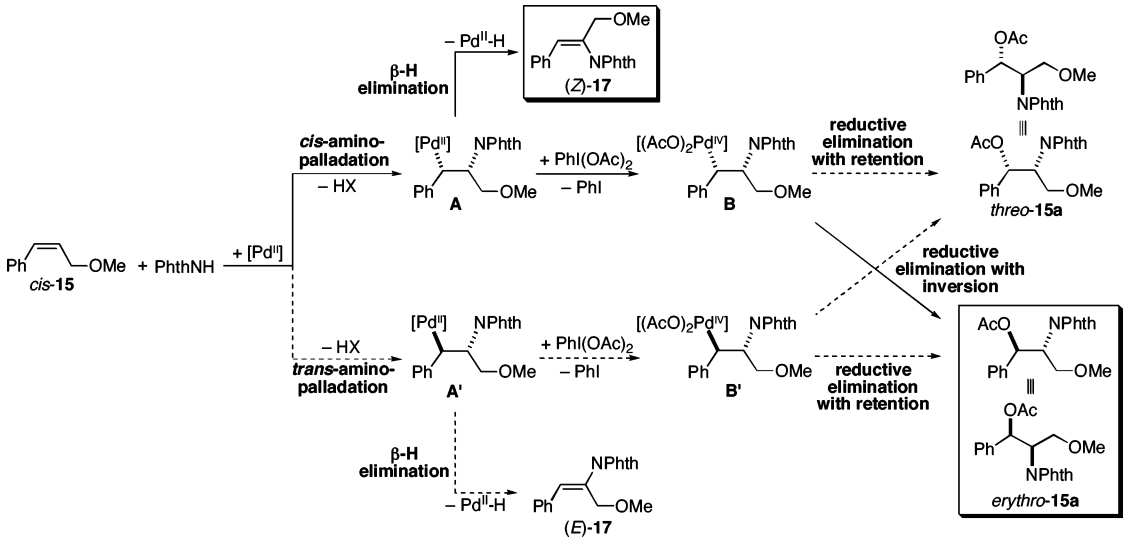
We investigated the reactivity of the cinnamyl methyl ethers, *cis*- and *trans*-**15**, under typical reaction conditions. The reaction of *cis*-**15** yields a single aminoacetoxylation product: *erythro*-**15a** (eq 2).[16] Allylic imide **16** formation (5%) and alkene isomerization into *trans*-**15** (<10%) are also observed with $PdCl_2(CH_3CN)_2$ as the catalyst. In contrast, *trans*-**15** is a very poor substrate for the reaction. Aminoacetoxylation products are formed in only trace amounts. The latter observation establishes that *cis*-**15** does not isomerize into the more stable *trans*-alkene prior to formation of *erythro*-**15a** in eq 2.



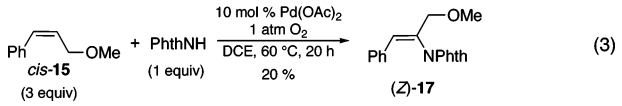
The formation of *erythro*-**15a** from *cis*-**15** reflects net *anti*-addition of phthalimide and acetate to the alkene. This stereochemical result, which is identical to that observed for the intramolecular reaction, has two possible mechanistic origins (Scheme 2): (1) *trans*-aminopalladation followed by oxidative Pd−C cleavage with retention of stereochemistry or (2) *cis*-aminopalladation followed by oxidative Pd−C cleavage with inversion of stereochemistry. Literature precedents suggest either sequence is possible.[17,18]

To distinguish between these possibilities, we investigated the reaction of *cis*-**15** under conditions that favor β-hydride elimination from the aminopalladation intermediate (eq 3; cf. Scheme 1).[3,4b] Catalyst decomposition into palladium black limits the yield under

Scheme 2. Mechanistic Explanation for the Stereochemical Outcome of Pd-Catalyzed Oxidative Amination and Aminoacetoxylation of *cis*-**15**



these conditions, but (*Z*)-**17** is the sole amination product.[14] Independent experiments demonstrate that *trans*-**15** is unreactive with either $Pd(OAc)_2$ or $PdCl_2(CH_3CN)_2$ as the catalyst. The formation of (*Z*)-**17** is explained by *cis*-aminopalladation of *cis*-**15** followed by β-hydride elimination from intermediate **A** (Scheme 2). By extension, aminoacetoxylation of *cis*-**15** is proposed to proceed via *cis*-aminopalladation followed by oxidative cleavage of the Pd−C bond with inversion of stereochemistry at carbon.



(3)

The proposed intermediacy of a Pd(IV) intermediate in this reaction (**B**, Scheme 2) finds substantial support from the recent work of Sanford and Canty, who have isolated related organopalladium(IV) products upon oxidation of Pd(II) species with $PhI(OAc)_2$ and peroxide oxidants.[8c,19] In a recent study of C−O reductive elimination from a $Pd^{IV}(Ar)(OAc)$ complex, Sanford and co-workers provide evidence for a concerted, three-centered mechanism (Figure 1A). In contrast, C−O reductive elimination from alkylplatinum(IV) species has been shown to proceed by an S_N2 mechanism.[20] The different mechanisms could arise from an intrinsic difference between Pd and Pt or a difference between the reductive elimination of M−C(aryl) versus M−C(alkyl) bonds. The present data, which provide evidence for an S_N2 mechanism (i.e., inversion of stereochemistry), support the latter hypothesis. The difference probably has a stereoelectronic origin associated with the orientation and steric accessibility of the carbon-centered orbital involved in the C−O bond-forming step.

A *cis*-aminopalladation step arising from alkene insertion into a Pd−N bond provides a rationale for the extremely high diastereoselectivity observed in the aminoacetoxylation of allylic ether substrates **9**−**14** (Table 2, entries 8−13). Coordination of the oxygen atom during the alkene insertion step orients the allylic substituent over the phthalimide group, and formation of the *syn* product is disfavored for steric reasons (Figure 2).

In summary, we have demonstrated the ability of simple Pd(II) complexes to catalyze intermolecular aminoacetoxylation of terminal alkenes. The present requirement for excess alkene substrate represents a current limitation; however, the extremely high levels of regio- and diastereoselectivity in these reactions underlie their significant potential synthetic utility, for example, in the synthesis of amino alcohols and unnatural amino acids. Also, the mechanistic insights provide a foundation for the development of enantioselective reactions.

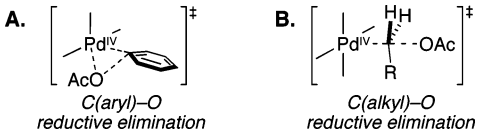


Figure 1. Mechanistic differences between C(aryl)−O (**A**) and C(alkyl)−O (**B**) reductive elimination from Pd^{IV}, which proceeds by a concerted three-centered transition state and an S_N2 pathway, respectively.

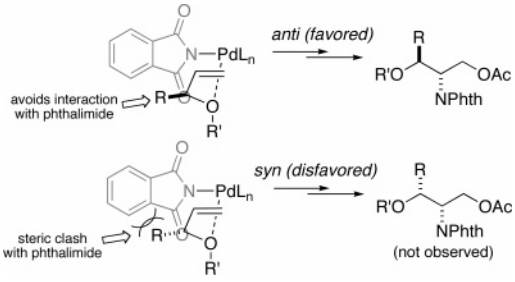


Figure 2. Stereochemical model for the diastereoselectivity observed in the aminoacetoxylation of allylic ethers possessing a substituent, R, in the allylic position.

Acknowledgment. We thank I. A. Guzei for assistance with X-ray crystallography, and L. M. Huffman for help with 1D NOESY experiments. This work was supported by the Dreyfus Foundation (Teacher-Scholar Award) and NIH (RO1 GM67173).

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

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(8) See, for example: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (c) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790−12791.
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(14) See Supporting Information for details.
(15) Sorensen et al. note that *cis*-aminopalladation of the alkene is also possible (see footnote 12 in ref 5).
(16) The aldol-based "*erythro*" designation is used for this compound in conformance with the nomenclature employed in the original characterization of this compound prepared by another method. See Supporting Information for details.
(17) Both *cis*- and *trans*-heteropalladation of alkenes are possible. See ref 7b, the following examples, and references therein: (a) Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745−7750. (b) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036−3037. (c) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778−17788. (d) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893−2901.
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JA061706H