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COMMUNICATIONS

Published on Web 05/06/2005

Palladium-Catalyzed Ring-Forming Aminoacetoxylation of Alkenes

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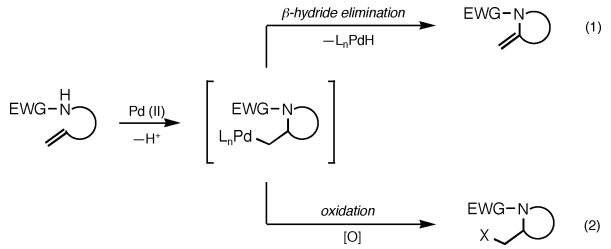
Received March 4, 2005; E-mail: ejs@princeton.edu

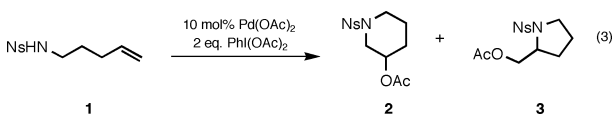
Vicinal difunctionalizations of alkenes are among the most powerful transformations known in the field of chemical synthesis.[1] One such method is the osmium-catalyzed asymmetric *cis* aminohydroxylation of alkenes,[2] yielding vicinal amino alcohols that are present in many biologically active molecules and natural products.[3] In the course of our studies in the area of complex molecule synthesis, we sought a catalytic, stereoselective, mechanistically distinct aminooxidation reaction to facilitate the construction of nitrogen-containing heterocycles and the development of new reaction types.

The palladium(II)-catalyzed addition of nitrogen nucleophiles to alkenes is a well developed process for forming C−N bonds.[4] A wide variety of nitrogen nucleophiles are known to attack the palladium(II)-activated alkene to give an alkyl palladium(II) intermediate. Although methods for the direct functionalization of alkyl palladium(II) intermediates (e.g., carbonylation[5] and halogenation[1f,g]) exist, β-hydride elimination can be a rapid process (eq 1).[4a,6] Our aim was to substitute the palladium center for acetate in the course of a mild oxidation event (eq 2, X = OAc). If successful,



this palladium-catalyzed method would permit attractive ring-forming aminoacetoxylations of alkenes. On the foundation of some recent reports showing that Pd−C σ-bonds are easily oxidized by iodine(III)-based oxidants,[7] we developed a mild method for achieving this goal. Our initial observations on this process are described below.

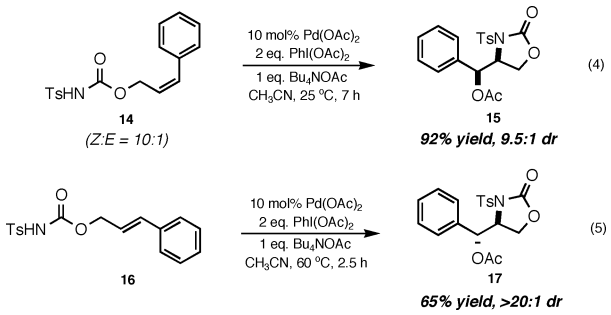
Our studies commenced with simple alkenyl nosylsulfonamide **1** (eq 3). Electron-withdrawing protecting groups were utilized



thoughout our studies to prevent poisoning of the catalyst and undesired oxidation of the substrates by hypervalent iodine. Treatment of **1** with 10 mol % $Pd(OAc)_2$ in the presence of 2.0 equiv of $PhI(OAc)_2$ and 1.0 equiv of Bu_4NOAc in CH_2Cl_2 at 25 °C for 15 min resulted in the formation of a 1.5:1 mixture of aminoacetoxylation products **2** and **3** in 72% yield. After some experimentation, the regioselectivity could be increased to 9:1 (**2**:**3**) using a 1:1 mixture of $AcOH/Ac_2O$ as solvent in 87% yield, without requiring the addition of exogenous base. Importantly, this reaction was neither air- nor moisture-sensitive, and comparable results were obtained using undistilled commercial solvents under an air atmosphere (88% yield).

Encouraged by these results, we applied the aminoacetoxylation protocol to a number of substrates (Table 1). Control experiments indicated that no aminoacetoxylation occurred in the absence of palladium, except for a slow background reaction under acidic conditions (condition C).[8] Palladium(II)-catalyzed ring-forming aminoacetoxylation of 5-hexenyl-1-nosylsulfonamide afforded a mixture of regioisomers resulting from 6-*exo* and 7-*endo* ring closures (entry 1). *N*-Tosyl amides were also effective substrates (entry 2), although this substrate displayed a high tendency for β-hydride elimination; fortunately this pathway could be suppressed by the substitution of $PdCl_2(PhCN)_2$ for $Pd(OAc)_2$ as catalyst.[9] In this case, the catalyst loading could be lowered to 1 mol %, producing the γ-lactam **6** in 65% yield. Carbamates also performed well with 5 mol % $PdCl_2(PhCN)_2$; however, minor byproducts resulting from an aminochlorination of the alkene were isolated (~10%). The allyl alcohol-derived carbamate furnished acetoxymethyl *N*-tosyl oxazolidinone **7** in 66% yield as a single regioisomer (entry 3), and the homoallyl alcohol-derived substrate underwent clean 6-*exo* closure to yield aminoacetoxylated product **8** (entry 4). $PhI(OAc)_2$ is known to oxidize tosylanilides, and 2-allyl *N*-tosylanilide was tested in order to examine its potential as a nucleophile (entry 5). Although both substrate and product were found to be susceptible to aromatic oxidation,[10] lowering the amount of oxidant to 1 equiv facilitated the difunctionalization, affording products **9** and **10** (1.9:1). 2-(1-Propenyl)cyclopentylnosylsulfonamide (entry 6) underwent cyclization to an 8:1 mixture of **11** and **12**, demonstrating the ability of the aminoacetoxylation to form fused bicyclic architectures. Further alkene substitution was permitted (entry 7), as this nosylsulfonamide with a 1,1-disubstituted alkene underwent exclusive 6-*endo* cyclization to give **13** as a single regioisomer in 80% yield.

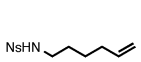
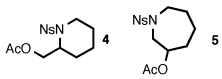
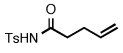
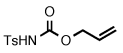
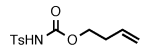
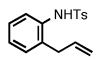
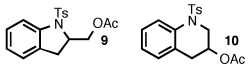
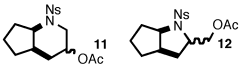
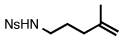
To gain insight into the mechanism of the aminoacetoxylation process, as well as to explore the diastereoselectivity of the reaction, cinnamyl alcohol-derived *N*-tosyl carbamates **14** and **16** were studied (eqs 4 and 5). Upon subjection of the predominantly *cis*



carbamate to reaction conditions involving 10 mol % $Pd(OAc)_2$ as catalyst and 1.0 equiv of Bu_4NOAc as base in CH_3CN (0.1 M), a successful aminoacetoxylation afforded 4-acetoxyphenyl *N*-tosyl

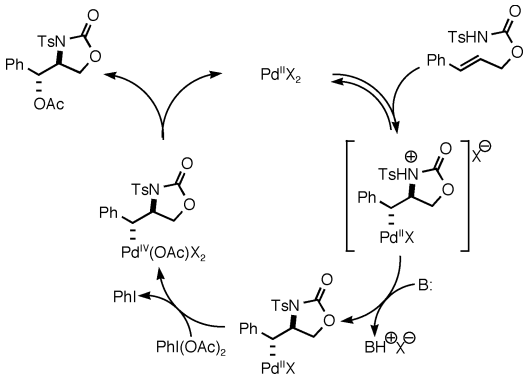
10.1021/ja051406k CCC: $30.25

Table 1. Palladium(II)-Catalyzed Aminoacetoxylation of Alkenes[a]

entry	substrate	product	conditions[b], time (h)	%yield[c]
1		 **4** **5**	A, 1	79 (1.7:1)
2		 **6**	B, 12 (1 mol% Pd)	65
3		 **7**	B, 24	66
4		 **8**	B, 12	56
5		 **9** **10**	C, 2	62[d] (1.9:1)
6		 **11** **12**	C, 36	85[e] (8:1)
7		 **13**	A, 5	80

[a] All reactions run with 1 equiv of substrate (0.2 M) and 2 equiv of $PhI(OAc)_2$ at 25 °C. All regio- and diastereoselectivities calculated by ^1H NMR. [b] Condition A: 10 mol % $Pd(OAc)_2$, 1 equiv of Bu_4NOAc, CH_2Cl_2. Condition B: 5 mol % $PdCl_2(PhCN)_2$, CH_2Cl_2. Condition C: 10 mol % $Pd(OAc)_2$, 1:1 $AcOH/Ac_2O$. [c] Isolated yields. [d] 1 equiv of $PhI(OAc)_2$ used. [e] Product **11** obtained as 2.3:1 (β: α) mixture of diastereomers.

Scheme 1. Proposed Catalytic Cycle



2-oxazolidinone in high yield (92%). We were pleased to find that this reaction also proceeded with a high level of stereocontrol (9.5:1 dr from 10:1 *Z*:*E* mixture of **14**).[11] Although requiring thermal instigation, the pure *trans* carbamate was a viable substrate as well, yielding **17** in a highly diastereoselective fashion (>20:1 dr). From these experiments, it appears that the aminoacetoxylation process is a stereoselective *trans* alkene difunctionalization, and thus a useful alternative to related *cis*-selective, metal-catalyzed alkene aminohydroxylation processes.[2]

A possible catalytic cycle based on our findings is shown in Scheme 1, although a number of details remain to be elucidated. Pd(II)-mediated reversible *trans*-aminopalladation of the alkene[12] generates a protonated intermediate that then undergoes an irreversible deprotonation step. The relative configurations of compounds **15** and **17**, the increase in reaction rate upon the addition of exogenous base, and the effect of the base on product regioselectivity provide evidence for these steps. The neutral alkyl Pd(II) intermediate could then be oxidized by $PhI(OAc)_2$ to an alkyl Pd(IV) intermediate.[13] Finally, C−O bond forming reductive elimination from the Pd(IV) center would complete the aminoacetoxylation process and regenerate the catalyst.[7]

In conclusion, we developed a mild, palladium(II)-catalyzed ring-forming aminoacetoxylation of alkenes that is applicable to a range of nitrogen nucleophiles and alkene substitution patterns. Our studies indicate the possibility for high levels of reaction regio- and stereocontrol, making this a potentially attractive method in organic synthesis. Current work is aimed at exploring the scope of the reaction with respect to both substrates and oxidants, the potential for asymmetric induction in the aminoacetoxylation process, and applications in complex molecule synthesis.

Acknowledgment. We thank Dr. Istvan Pelczer for NMR spectroscopic assistance and Prof. Martin Semmelhack for helpful discussions. This work was supported by a Bristol-Myers Squibb Unrestricted Grant in Synthetic Organic Chemistry, Merck, Princeton University, and predoctoral fellowships from the ACS/GlaxoSmithKline (E.J.A.) and Bristol Myers-Squibb (E.J.A.).

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

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(8) See Supporting Information for details on control experiments.

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(11) Relative configuration of compound **15** was determined by chemical correlation (see Supporting Information).

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(13) $Cu(OAc)_2$ (2.0 equiv), a standard oxidant for mediating Pd^0/Pd^{II} cycle catalysis, was ineffective.

JA051406K