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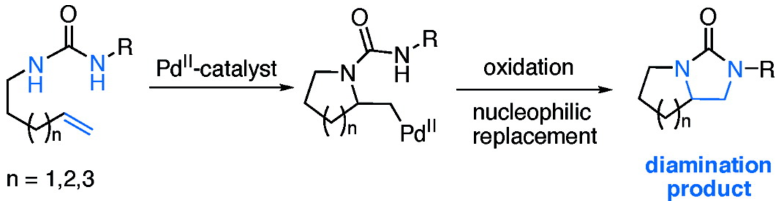
J. Am. Chem. Soc., **2005**, 127 (42), 14586-14587• DOI: 10.1021/ja055190y • Publication Date (Web): 04 October 2005



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Palladium(II)-Catalyzed Intramolecular Diamination of Unfunctionalized Alkenes

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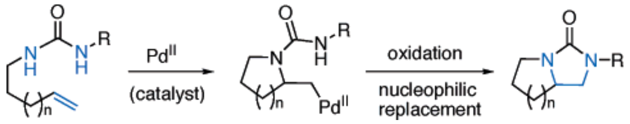
The development of efficient nitrogen transfer to carbon bonds constitutes an important endeavor in both academia and industry.[1] Such amination reactions have recently been greatly advanced through intramolecular reaction courses. Elegant examples in this area include hydroamination,[2] aminohydroxylation,[3,4] allylic amination,[5] aziridination,[6] alkane amination,[7] and aza-Wacker[8] reactions. We here describe the first realization of catalytic diamination of unfunctionalized alkenes, which relies on intramolecular reaction control.

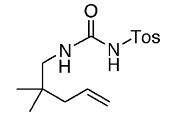
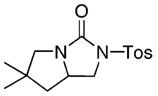
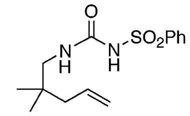
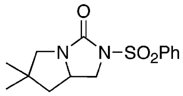
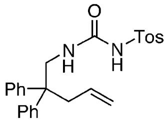
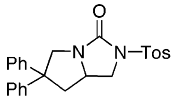
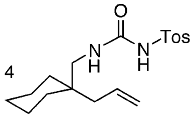
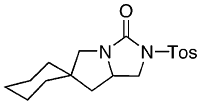
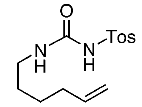
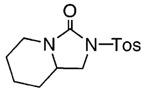
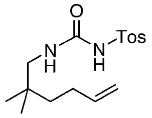
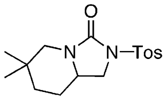
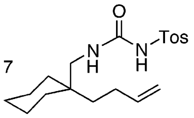
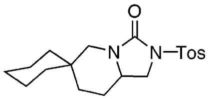
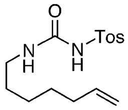
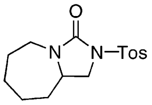
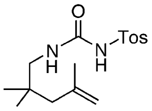
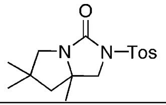
The oxidative catalytic diamination of alkenes represents an elusive reaction in modern oxidation catalysis. Starting with pioneering work by Barluenga in 1974,[9] initial investigation devised oxidation reactions that were stoichiometric in metals.[10,11] The development of an efficient catalysis is usually hampered by the fact that diamines coordinate to almost all transition metals, which results in poisoning of a potential catalyst. A pronounced example is given for imidoosmium reagents, which generate stable monomeric osmaimidazolidines.[11]

Earlier attempts by us for diamination catalysis in palladium, again, experienced the drawback of metal deactivation by the diamine products.[12] It became obvious that, without preventing the product from metal coordination, palladium catalysis would remain inefficient.[13] To this end, our initial approach started from the assumption that ω-alkenyl-substituted urea molecules should undergo cyclization in the presence of an electrophilic palladium(II) catalyst, leading to an intermediary vicinal amino pallada compound. Palladium replacement through the second amino group of the urea under oxidative conditions should then regenerate the palladium(II) catalyst and release the diamination product as a cyclic urea:



Oxidative diamination following this concept was found to take place for a range of different starting materials (Table 1). In all cases, the appropriate choice of reoxidant was crucial, and among various reoxidants tested, only the hypervalent iodine reagent PhI$(OAc)_2$ was highly efficient. With $Pd(OAc)_2$ as precatalyst and under mild conditions (CH_2Cl_2, room temperature), diamination and concomitant formation of five-, six-, and seven-membered fused rings was conveniently accomplished (Table 1). All reactions reached high to full conversion, and no compounds other than the diamination products were produced. Depending on the final ring size, three different protocols were developed. Protocol A, which is most suitable for pyrrolidine formation, employs a catalyst loading of 5 mol % and calls for a stoichiometric amount of base. The latter accelerates the reaction and leads to full conversion after 12 h (entry 1). Lowering the catalyst loading to 2 mol % requires an enhanced reaction period of up to 48 h, but does not effect the reaction selectivity. The diamination proceeds well for a variety of further substrates bearing additional substitution at the carbon skeleton (entries 2−4). Formation of the seven-membered ring annulation was slightly slower, and the reaction proceeded best with 10 mol % of palladium catalyst (Procedure C, entry 8). In contrast,

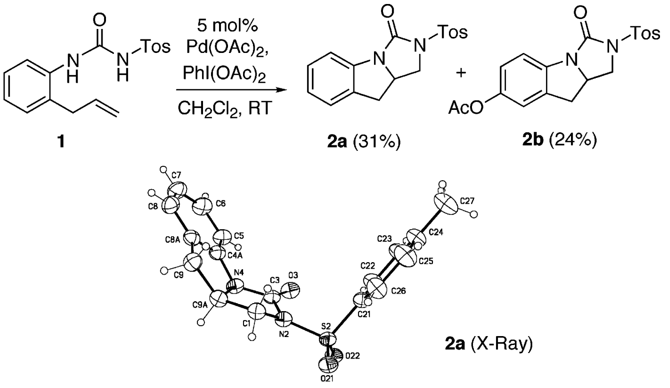
Table 1. Palladium-Catalyzed Intramolecular Diamination of Alkenes

Entry	Substrate	Procedure[a]	Product	Conversion [%][b]	Yield [%][c]
1		A		100	92
2		A		100	93
3		A		100	95
4		A		100	91
5		B		98	86
6		B		100	87
7		B		100	78
8		C		94	89
9		A		100	94

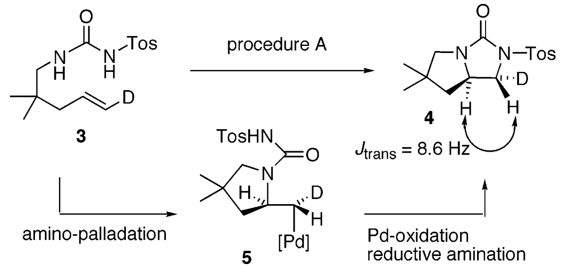
[a] Procedure A: 5 mol % of $Pd(OAc)_2$, $PhI(OAc)_2$ (2.2 equiv), NMe_4Cl/NaOAc (1 equiv), CH_2Cl_2, RT, 12 h. Procedure B: 25 mol % of $Pd(OAc)_2$, $PhI(OAc)_2$ (2.2 equiv), CH_2Cl_2, RT, 48 h. Procedure C: 10 mol % of $Pd(OAc)_2$, $PhI(OAc)_2$ (2.2 equiv), CH_2Cl_2, RT, 12 h. [b] Determined from crude ^1H NMR spectra and TLC control. [c] Given yields refer to isolated analytically pure material after column chromatography.

10.1021/ja055190y CCC: $30.25

Scheme 1. Palladium-Catalyzed Synthesis of Tricyclic Heterocycles **2a**,**b**



Scheme 2. Mechanistic Proposal



piperidine formation required a catalyst loading of 25 mol %, and a beneficial effect of base was not observed (Procedure B, entries 5−7). For all reactions, the overall conformation of the products was established from their respective NMR spectra and MS data.[14] Formation of a quaternary stereocenter was accomplished with the expected complete selectivity and in high yield (entry 9).[15]

Tricyclic heterocycles are accessible from this reaction, as well. Here, urea **1** underwent clean diamination to yield two products, **2a** and **2b**, in the absence of base (Scheme 1). The latter one is believed to derive from regioselective additional Pd-catalyzed oxidation at the arene ring.[16] Applying the conditions of Procedure A, compound **2a** is obtained as sole product (78%). It was characterized by X-ray analysis, which confirmed the expected concave surface of the tricyclic core.

To probe the underlying mechanism, diamination of selectively deuterated **3** was investigated, and the obtained diastereomerically pure product **4** showed selective deuterium incorporation. The observed coupling constant of $^3J = 8.6$ Hz between the remaining two hydrogen atoms at the urea core confirms a *trans*-arrangement of these two atoms and proves that the *E*-stereochemistry of the alkene was transferred to the product. The simplest mechanistic scenario for such a result is in agreement with our initial working hypothesis and should consist of a *trans*-selective amino-palladation to yield intermediate **5**. Finally, Pd oxidation[16] and concomitant second amination forms the cyclic urea core and displaces the palladium. This final step is obviously kinetically preferred over potentially competing β-hydride elimination.[8,17] The presence of oxidant is required, as a control reaction stoichiometric in metal was reversible, leading to recovered starting material and did not give any detectable diamination product without PhI(OAc)$_2$. Due to this result, an alternative Pd(II)/Pd(0) cycle result is less probable. Liberation of the respective diamine core was accomplished under reductive conditions (LiAlH$_4$, then HCl) and furnished the free diamine in 95% yield from nondeuterated **4**. In contrast to earlier work with preformed imidoosmium oxidants[10c,11] or the stoichiometric palladium[10a,b] and thallium[9a] diaminations, the intramolecular reactions described herein afford diamines with predictable differentiation of the nitrogen substituents.

In summary, we have described intramolecular diamination reactions of alkenes, which afford a conceptually novel synthesis of cyclic ureas and diamines, respectively. This process establishes the principle of oxidative intramolecular diamination reactions, which are truly catalytic in metal.

Acknowledgment. Financial support from the Fonds der Chemischen Industrie and the German−Israeli Foundation to K.M. is gratefully acknowledged.

Supporting Information Available: Experimental procedures, X-ray data for **2a**, and spectral characterization (^{1}H and ^{13}C NMR) for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA055190Y