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A New Method for the Synthesis of Nitrogen Heterocycles via Palladium Catalyzed Intramolecular Hydroamination of Allenes

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Abstract: The intramolecular hydroamination of certain allenes, bearing amine or sulfonyl amide groups at the terminus of the carbon chain, proceeded smoothly in the presence of catalytic amounts of palladium complex ($[(\eta^3\text{-}C_3H_5)PdCl]_2$-dppf) under weakly acidic conditions (0.15-1.0 equivalent of acetic acid) to give the corresponding 2-vinylpyrrolidines and 2-vinylpiperidines in good to high yield.

Keywords: Allenes; Cyclization; Palladium; Nitrogen heterocycles

Transition metal catalyzed addition reactions of nitrogen nucleophiles to olefinic double bonds have been regarded as one of the most useful and straightforward methods for C-N bond formation. It has been found that certain amines and amides undergo the addition reaction to unactivated C-C multiple bonds in the presence of transition metal catalysts; this is the so-called " hydroamination."[1] Most of the amination reactions are based on nucleophilic addition to the metal-activated olefins (Figure 1. Type I).[2] Recently, Marks and his co-workers reported a different type of hydroamination reaction catalyzed by organolanthanoid complexes,[1a, 3] in which the amination reaction proceeded through the insertion of the N-M bond (M = lanthanoid metals) into a carbon-carbon multiple bond (Figure 1. Type II).

Type I M = Pd $^{2+}$, Ag$^+$, Hg^{2+}, ... Type II M = organolanthanoids

Figure 1. Previous intramolecular hydroamination reaction.

Herein we report an entirely new type of the hydroamination reaction (Type III) which proceeds through the insertion of a M-H bond (M = Pd) to an allenic double bond.[4] Amines or sulfonyl amides, bearing an allene group at the terminus of the carbon chain, undergo a facile intramolecular hydroamination reaction in the presence of a catalytic amount of $[(\eta^3\text{-}C_3H_5)PdCl]_2$-dppf-$CH_3CO_2H$, giving the corresponding pyrrolidines and piperidines in good to high yields (eq. 1). The results are summarized in Table 1.

First, the cyclization of **1a**, having tosyl amide as an amine group, was investigated. The use of the catalyst system $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and dppf (1,1'-bis(diphenylphosphino)ferrocene), which proved to be the best for intramolecular hydrocarbonation,[5] required a prolonged reaction time (30 h, reflux), and gave **2a** in

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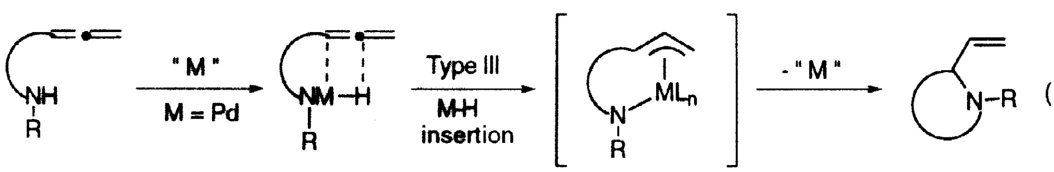
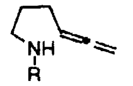
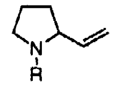
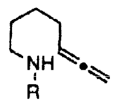
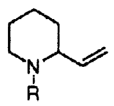
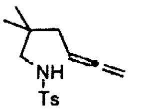
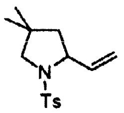
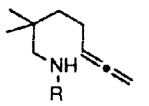
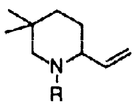
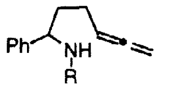
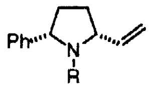
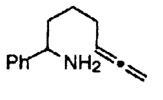
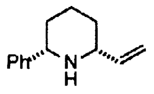


(1)

58 % yield (entry 1). Interestingly, the addition of 1 equivalent of acetic acid dramatically enhanced both yield and reaction rate (87%, 6h, entry 2).[6] Other palladium catalysts, such as $Pd(Ph_3P)_4$ and $Pd_2(dba)_3\cdot CHCl_3$ with dppf, were not effective even in the presence of acetic acid. It should be noted that

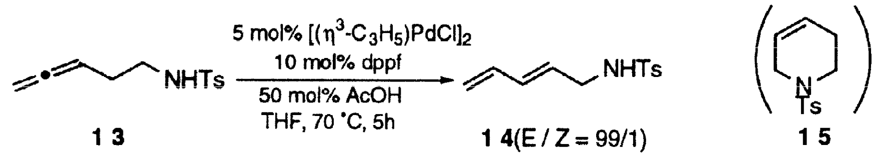
Table 1. Palladium catalyzed intramolecular hydroamination of allenes[a]

Entry	Allene	Reaction time, h	Product	Yield,[b] %
				
1[c]	**1a** R = Ts	30	**2a** R = Ts	58
2	**1a**	6	**2a**	87
3[d]	**1a**	10	**2a**	80
4	**1b** R = Tf	2	**2b** R = Tf	90
5[e]	**1c** R = Bn	4	**2c** R = Bn	60
				
6	**3a** R = Ts	10	**4a** R = Ts	41
7	**3b** R = Tf	4	**4b** R = Tf	58
				
8	**5**	5	**6**	78
				
9	**7a** R = Ts	6	**8a** R = Ts	60
10	**7b** R = Tf	1.5	**8b** R = Tf	84
				
11[e]	**9a** R = H	3	**10a** R = H	41[g] (50 : 50)
12	**9b** R = Tf	2	**10b** R = Tf	80 (94 : 6)
				
13[e]	**11**	4	**12**	52 (>95 : <5)

[a] The reactions were carried out in dilute THF solution (0.025M for the allene) in the presence of 5 mol% $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 10 mol% dppf, 100 mol% acetic acid, except where otherwise indicated. [b] Isolated yield. [c] In the absence of acetic acid. [d] 25mol% of acetic acid was used. [e] 15mol% of acetic acid was used. [g] **10a** was relatively unstable and therefore it was converted to the tosyl amide derivative. The yield refers to the isolated tosyl amides.

catalytic amounts of acetic acid (0.25 equivalent) were enough to accelerate the reaction rate (entry 3). Both triflyl amide **1b** and benzyl-protected allenic amine **1c** also gave the corresponding vinylpyrrolidines **2b** and **2c**, respectively, in good yields (entries 4 and 5). However, the use of other protecting groups, such as acetyl, trifluoroacetyl, benzyloxycarbonyl (Cbz) and 2,2,2-trichloroethyloxycarbonyl (Troc), did not give the desired cyclized products. Allenes **3**, **5**, **7**, **9** and **11** cyclized smoothly in the "5-*exo*-trig" or "6-*exo*-trig" mode, giving the corresponding vinylpyrrolidines (entries 8, 11 and 12) and vinylpiperidines (entries 6-7, 9-10 and 13). Only *exo*-cyclized products were obtained and no *endo*-cyclized product could be seen in the NMR chart of the crude mixtures. Triflyl amide **9b** gave *cis* pyrrolidine **10b** almost exclusively (entry 12),[7] although the corresponding primary amine **9a** produced a 62 : 38 mixture of pyrrolidine diastereomers (entry 11). On the other hand, primary amine **11** gave *cis* piperidine **12** as a sole product (entry 13). The *cis*-stereoselective formation of α, α'-di-substituted pyrrolidines and piperidines may be useful for the synthesis of complex natural products.

We examined the cyclization of an allenylamine having a shorter carbon chain. The reaction of **13** under the standard conditions gave 1,3-diene **14** in a moderate yield along with unidentified polymeric products, instead of affording the expected *endo*-cyclized product **15** (eq 2). The formation of the 1,3-diene suggests intervention of a π-allylpalladium intermediate, which would be produced through " hydropalladation " of **13**.[8]



(2)

The following mechanistic rationale may account for the present Pd-catalyzed cyclization of amines and amides, although it is speculative. Initially, Pd(0) catalyst would add oxidatively to acetic acid to give hydridopalladium(II) intermediate H-PdOAcL$_2$ **16**.[9] The ligand exchange between OAc of **16** and allenic amine derivative HNR$_2$ would produce another hydridopalladium species (H-PdNR$_2$L$_2$ **17**) and acetic acid. The π-allylpalladium complex would be formed through intramolecular hydropalladation of **17**,[10, 11] and subsequent reductive elimination would furnish the cyclized product.

The first palladium *catalyzed* intramolecular hydroamination was reported more than a quarter century ago.[12] More recently, the palladium *catalyzed* intramolecular hydroamination of alkynes was developed.[13] However, only limited substrates can be utilized for both reactions. Compared to alkenes and alkynes, the cyclization of allene derivatives seems to have wide applicability.

The intramolecular hydroamination of allenic amide **1a** is representative. To a solution of [(η^3-C$_3$H$_5$)PdCl]$_2$ (18 mg, 0.050 mmol) and dppf (55 mg, 0.10 mmol) in THF (30 ml) was added acetic acid (57 μl, 1.0 mmol) under argon atmosphere. The mixture was stirred for five minutes at room temperature, then a THF (10 ml) solution of **1a** (251 mg, 1.0 mmol) was added. The reaction mixture was stirred at 70 °C and reaction progress was monitored by tlc. After consumption of the starting material, the solvent was evaporated and the crude product was purified by silica gel chromatography using *n*-hexane-ethyl acetate (5 : 1) as an eluent. *N*-Tosyl-2-vinylpyrrolidine **2a** was obtained in 87% yield (219 mg).

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