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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 sulforyl amide groups at the terminus of the carbon chain, proceeded smoothly in the presence of catalytic amounts of palladium complex ($[(\eta^3\text{-}C_3\text{H}_5)\text{PdCI}]_2\text{-}dppf$) under weakly acidic conditions (0.15-1.0equivalent of acetic acid) to give the corresponding 2-vinylpyrrolidines and 2-vinylpiperidines in good to high yield. © 1998 Elsevier Science Ltd. All rights reserved.

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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." Most of the amination reactions are based on nucleophilic addition to the metal-activated olefins (Figure 1. Type I).² Recently, Marks and his coworkers 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 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 sulfortyl 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 $[(\eta^3-C_3H_5)PdCl]_2$ -dppf-CH₃CO₂H, 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 $[(\eta^3-C_3H_5)PdCl]_2$ 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

$$\begin{array}{c} & & & \\ & & & \\ & & & \\ & & & \\ &$$

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 $Pd_2(dba)_3$ ·CHCl₃ with dppf, were not effective even in the presence of acetic acid. It should be noted that

Entry	Allene	Reaction time, h	Product	Yield, ^b %
	NH R		√N ₽	
1 ^c	$1a \qquad R = Ts$	30	2a R = Ts	58
2	1a	6	2 a	87
3 ^d	1a	10	2 a	80
4	1b R = Tf	2	2b R = Tf	90
5°	1c R = Bn	4	$2c \qquad R = Bn$	60
	NH R		N R	
6	3a R = Ts	10	4a R = Ts	41
7	3b R = Tf	4	4b R = Tf	58
	NH Ts		N Ts	
8	5	5	6	78
	NH R		N R	
9	7a R = Ts	6	8a R = Ts	60
10	7b R = Tf	1.5	8 b R = Tf	84
	Ph NH		Ph ^{***} N R	
1 1 e	9a R = H	3	10a R = H	418 (50:50)
12	9b R = Tf	2	10b R = Tf	80 (94:6)
	Ph NH2 •		Phr. N.	
13 ^e	11	4	12	52 (>95:<5)

Table 1. Palladium catalyzed intramolecular hydroamination of allenes⁴

^aThe reactions were carried out in dilute THF solution (0.025M for the allene) in the presence of 5 mol% $[(\eta^3-C_3H_5)PdC1]_2$, 10 mol% dppf, 100 mol% acetic acid, except where otherwise indicated. ^bIsolated yield. ^cIn the absence of acetic acid. ⁴25mol% of acetic acid was used. ⁴15mol% of acetic acid was used. ⁴10a 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



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-PdOAcL₂ 16.⁹ The ligand exchange between OAc of 16 and allenic amine derivative HNR₂ would produce another hydridopalladium species (H-PdNR₂L₂ 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 $[(\eta^3 - C_3H_5)PdCl]_2$ (18 mg, 0.050 mmol) and dppf (55 mg, 0.10 mmol) in THF (30 ml) was added acetic acid (57 μ l, 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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REFERENCES

- For reviews of transition metal catalyzed hydroamination, see (a) Li, Y.; Marks, T. J. J. Am. Chem. Soc. 1996, 118, 9295-9306. and references cited therein. (b) Savoia, D. In Methods of Organic Chemistry (Houben-Weyl); Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; vol. E21e, pp 5356-5394. (c) Larock, R. C.; Leong, W.W. In Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 4, pp269-327.
- (a) Harding, K. E.; Tiner, T.H. In Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 4, pp 363-421. (b) Hegedus, L.S. *ibid.*, pp 551-569. (c) Orena, M. In In Methods of Organic Chemistry (Houben-Weyl); Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; vol. E21e, pp 5291-5355.
- (a) Li, Y.; Marks, T.J. J. Am. Chem Soc. 1996, 118, 707-708. (b) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gangé, M.R.; Marks, T. J. *ibid.* 1994, 116, 10241-10254.
- Palladium catalyzed intermolecular hydroaminations have been reported. See, (a) Coulson, D. R. J. Org. Chem. 1973, 38, 1483-1490. (b) Besson, L.; Goré, J.; Cazes, B. Tetrahedron Lett. 1995, 36, 3857-3860. (c) Al-Masum, M.; Meguro, M.; Yamamoto, Y. Tetrahedron Lett. 1997, 38, 6071-6074.
- 5. Meguro, M.; Kamijo, S.; Yamamoto, Y. Tetrahedron Lett. 1996, 37, 7453-7456.
- Formic acid and chloroacetic acid also exhibited similar activation effect on the reaction rate and chemical yield. However, trifluoroacetic acid and CSA did not work well.
- The 2,5-cis selectivity was observed for the Ag-mediated cyclization reaction of N-(1-phenyl-hexa-4,5dienyl)-p-toluenesulfonamide. Gallagher, T.; Jones, S. W.; Mahon, M. F.; Molloy, K. C. J. Chem. Soc., Perkin Trans. 1 1991, 2193-2198.
- About the formation of 1,3-dienes from π-allylpalladium species, see, (a) Tsuji, J. In Palladium Reagents and Catalysts; John Wiley & Sons: New York, 1995, pp 356-363. (b) Takacs, J. M.; Lawson, E. C.; Clement, F. J. Am. Chem. Soc. 1997, 117, 5956-5957. and references cited therein.
- 9. Acetic acid would enhance the rate of formation of hydridopalladium(II) species. Presumably, the direct formation of hydridopalladium(II) species from allenic amine derivatives and Pd(0) is sluggish.
- Trost and Gerusz proposed hydropalladation mechanism for the reaction of allenes with active methylene compounds: J. Am. Chem Soc. 1995, 117, 5156-5157. We also proposed the hydropalladation mechanism for the intramolecular reaction. See also ref. 5.
- Gallagher *et al.* proposed nucleophilic addition to allenes activated by arylpalladium(II) species as an alternative mechanism. However, this mechanism cannot account for the formation of 1,3-diene. Davies, I. W.; Scopes, D. I. C.; Gallagher, T. Synlett **1993**, 85-87.
- Hegedus, L. S.; McKearin, J. M. J. Am. Chem. Soc. 1982, 104, 2444-2451. See also Pugin, P.; Venanzi, L. M. J. Organomet. Chem. 1981, 214, 125-133.
- (a) Iritani, K.; Matsubara, S.; Utimoto, K. Tetrahedron Lett. 1988, 29, 1799-1802. (b) Fukuda, Y.; Matsubara, S.; Utimoto, K. J. Org. Chem. 1991, 56, 5812-5816.