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Lactam Synthesis via the Intramolecular Hydroamidation of Alkynes Catalyzed by Palladium Complexes

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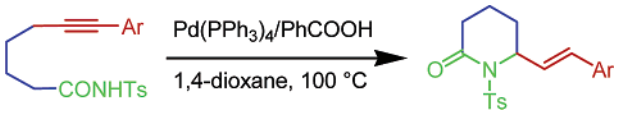
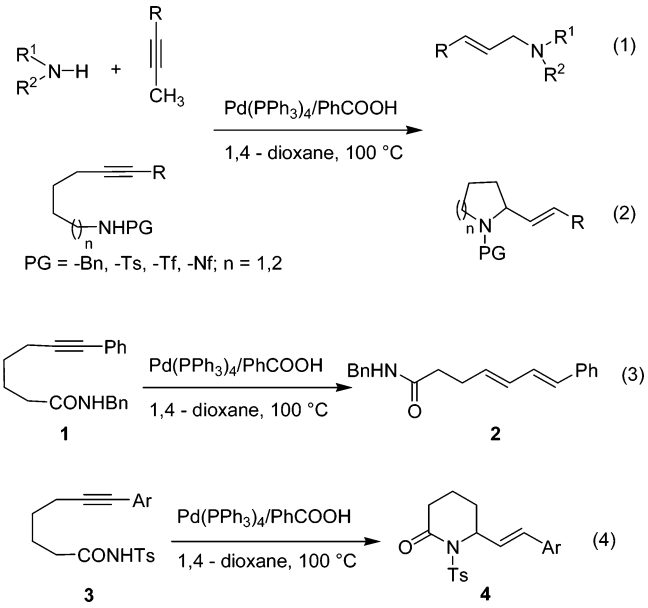
Received January 22, 2006



The palladium complexes catalyzed intramolecular hydroamidation reaction of amidoalkynes gives the corresponding lactams in good to high yields. For example, in the presence of 10 mol % of $Pd(PPh_3)_4$ and 20 mol % of PhCOOH, the reaction of the amidoalkyne **3a** in 1,4-dioxane at 100 °C proceeded smoothly to give the corresponding lactam **4a** in 92% yield.

The transition metal complex catalyzed addition of amines to activated C−C bonds, generally known as hydroamination,[1] has proven to be a valuable route for the formation of C−N bonds. Particularly noteworthy is the intramolecular cyclization of amines with tethered C−C bonds which leads to the formation of a wide variety of nitrogen heterocycles. For example, the hydroamination/cyclization of aminoalkenes,[2] aminoallenes,[3] aminodienes,[4] and aminoalkynes[5] using transition metal and lanthanide complexes provides an efficient way for synthesizing various nitrogen heterocycles. However, an analogous transformation involving the cyclization of activated C−C bonds with tethered amides has not been achieved, perhaps due to the lower nucleophilicity of amide nitrogen compared to amines.

Recently, we reported[6] an entirely new method for the hydroamination of alkynes using a $Pd(PPh_3)_4$/PhCOOH combined catalyst system. In this process, acyclic amines (via intermolecular hydroamination, eq 1) as well as cyclic amines such as piperidines and pyrrolidines (via intramolecular hydroamination, eq 2) were obtained in excellent yields. If we can extend this concept to hydroamidation, lactams can be synthesized. With this in mind, we synthesized the substrate **1** and tested for the hydroamidation reaction. Our initial research was focused on the study of solvents, concentration, and catalyst loading. However, in all cases, isomerization via β-hydride elimination mechanism[7] occurred, giving the corresponding diene **2** exclusively (eq 3). All attempts to suppress the β-hydride elimination product **2** by using $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst in combination with various ligands such as dppb, dppe, dppm, and dppf failed. After a number of attempts, we found that the *N*-tosylamides **3** undergo intramolecular hydroamidation in the presence of $Pd(PPh_3)_4$/PhCOOH catalyst in 1,4-dioxane at 100 °C to give the desired lactams **4** in good to high yields (eq 4). The key for this success was to use a tosyl group on amide nitrogen.



After finding the key role of tosyl group for obtaining the lactams by suppressing the formation of the β-hydride elimination product, we screened various metal catalysts in order to search the best one.[8] The results are summarized in Table 1. As anticipated, the reaction of **3a** in the presence of 10 mol % of $Pd(PPh_3)_4$ in benzene, without addition of carboxylic acids, did not give the desired product at all (entry 1). After addition of 20% benzoic acid,[9] the reaction became facile, and **4a** was isolated in 91% yield as the *E*-isomer (entry 2). Similar to our previous observations, no formation of the *Z*-isomer was observed as judged by the ^1H NMR spectrum of the crude reaction mixture. The use of acetic acid, instead of benzoic acid,

(1) For a review, see: (a) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703. (b) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104−114. For a general review, see: (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198.

(2) (a) Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933−2935. (b) Tian, S.; Arredondo, V. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 2568−2570. (c) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983−8988. (d) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737−1739. (e) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367−391.

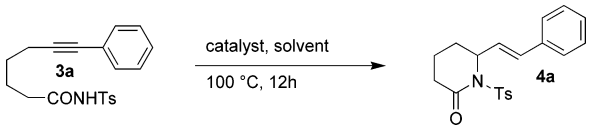
(3) (a) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871−4872. (b) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421−5424.

(4) (a) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878−15892. (b) Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 7886−7887.

(5) (a) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956−11963. (b) Bytschkov, I.; Doye, S. *Tetrahedron Lett.* **2002**, *43*, 3715−3718. (c) Muller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170−183. (e) Fairfax, D.; Stein, M.; Livinghouse, T.; Jensen, M. *Organometallics* **1997**, *16*, 1523−1525. (f) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295−9306. For a general review on organolanthanide-catalyzed hydroamination, see: (g) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673−686. For a general review on group IV metal complex catalyzed hydroamination, see: (h) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935−946.

10.1021/jo060142x CCC: $33.50
Published on Web 03/29/2006

TABLE 1. Catalyst Optimization for Hydroamidation of 3a



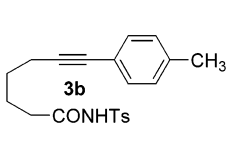
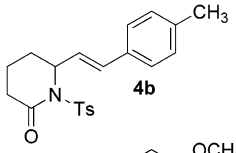
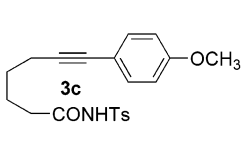
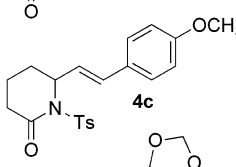
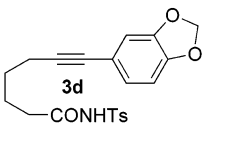
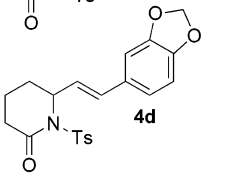
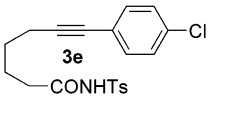
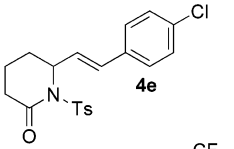
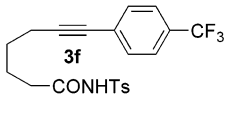
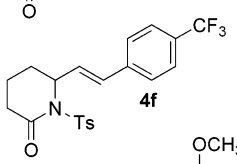
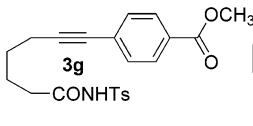
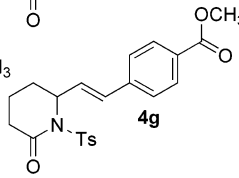
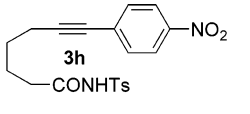
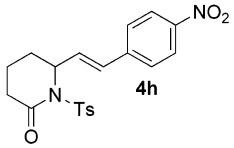
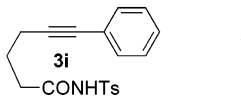
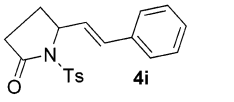
entry	catalyst	additive	solvent	yield[b] (%)
1	10% $Pd(PPh_3)_4$		benzene	0[c]
2	10% $Pd(PPh_3)_4$	20% PhCOOH	benzene	93 (91)[d]
3	10% $Pd(PPh_3)_4$	20% CH_3COOH	benzene	72
4	10% $Pd(PPh_3)_4$	20% H_2O	benzene	63
5	10% $Pd(PPh_3)_4$	20% MeOH	benzene	52
6	10% $Pd(PPh_3)_4$	10% PPh_3	benzene	14[e]
7	**10% $Pd(PPh_3)_4$**	**20% PhCOOH**	**1,4-dioxane**	**94 (92)[d]**
8	10% $Pd(PPh_3)_4$	20% PhCOOH	toluene	45
9	10% $Pd(PPh_3)_4$	20% PhCOOH	THF	46
10	10% $Pd(PPh_3)_4$	20% PhCOOH	CH_3CN	76
11	10% $Pd(PPh_3)_4$	20% PhCOOH	CH_2Cl_2	84
12	5% $Pd(PPh_3)_4$	20% PhCOOH	1,4-dioxane	61

[a] The reactions of **3a** (0.3 mmol) in the presence of metal catalysts and additives were carried out at 100 °C in benzene (0.2 M) for 12 h. [b] Yields were determined by ^1H NMR spectroscopy with dibromomethaneas in internal standard. [c] The starting material was observed by TLC. [d] Isolated yield is shown in parentheses. [e] The reaction mixture was heated for 100 h.

provided **4a** in lower yield (entry 3). We then examined other proton sources, H_2O (63%) and MeOH (52%); however, the yields were not superior to those obtained with carboxylic acid additives (entries 4 and 5). Rather surprisingly, the use of PPh_3 as an additive did not work well for the present reaction (entry 6).[6c] Various solvents such as 1,4-dioxane, toluene, THF, acetonitrile, and CH_2Cl_2 were examined, but we found that 1,4-dioxane (92%) gave the best result (entries 7−11). Decreasing the amount of catalyst resulted in lower yields (entry 12).

With optimized conditions in hand, the hydroamidation was explored using a variety of amidoalkynes **3** containing either electron-donating or electron-withdrawing groups in the aromatic ring. The results are summarized in Table 2. Treatment of **3b**, having a methyl group at the para position in the aromatic ring

TABLE 2. Palladium-Catalyzed Hydroamidation of Various Amidoalkynes[a]

entry	substrate (**3**)	product (**4**)	yield (%)[b]
1			71
2			70
3			77
4			88
5			81
6			86
7			87
8			0[c]

[a] The reactions of **3** (0.3 mmol) in the presence of $Pd(PPh_3)_4$ (10 mol %) and benzoic acid (20 mol %) were carried out at 100 °C in 1,4-dioxane (0.2 M) for 12 h. [b] Isolated yields. [c] The starting material recovered.

with respect to alkyne, with $Pd(PPh_3)_4$ under the standard conditions gave the corresponding hydroamidation product **4b** in 71% yield (entry 1). In a similar manner, the reaction of the amidoalkynes **3c** and **3d**, having an electron-donating group at the aromatic ring, also proceeded smoothly to afford the products **4c** and **4d** in 70 and 77% yields, respectively (entries 2 and 3). The chloro group was tolerated under the present reaction conditions, allowing us to use the substrate **3e** which on cyclization afforded **4e** in 88% yield (entry 4). Substrates containing electron-withdrawing groups at the aromatic nucleus proved very good for the present reaction. Thus, the substrates **3f**, **3g**, and **3h**, having $-CF_3$, −COOMe, and $-NO_2$ groups at the para position in the aromatic ring, gave **4f**, **4g**, and **4h**, respectively, in excellent yields (entries 5−7). The five-membered lactam **4i** was not obtained from **3i** under the present reaction conditions (entry 8). We attempted various reaction

(6) (a) Kadota, I.; Shibuya, A.; Lutete, M. L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570−4571. (b) Lutete, M. L.; Kadota, I.; Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347−357. (c) Bajracharya, G. B.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4883−4886. (d) Patil, N. T.; Wu, H.; Kadota, I.; Yamamoto, Y**.** *J. Org. Chem.* **2004**, *69*, 8745−8750. (e) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2101−2103. (f) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622−1623. For other references related to this chemistry, see: (f) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262−10263. (g) Patil, N. T.; Kadota, I.; Shibuya, A.; Gyoung Y. S.; Yamamoto, Y. *Adv. Synth. Catal.* **2004**, *346*, 800−804. (h) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *19*, 6478−6481. (i) Patil, N. T.; Wu, H.; Kadota, I.; Yamamoto, Y**.** *J. Org. Chem.* **2004**, *69*, 8745−8750. (j) Kadota, I.; Lutete, M. L.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207−6210. (k) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Can. J. Chem.* **2005**, *83*, 569−573. (l) Patil, N. T.; Khan, N. F.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 8497−8499. (m) Zhang, W.; Haight, A. R.; Hsu, M. C. *Tetrahedron Lett.* **2002**, *43*, 6575−6578.

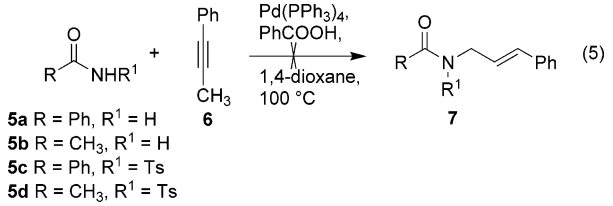
(7) For the formation of 1,3-dienes from π-allylpalladium species, see: (a) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *117*, 55956-5957. (b) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301−2303.

(8) This includes $Pt(PPh_3)_4$, $Ni(PPh_3)_4$, $RhH(PPh_3)_4$, $RHCl(PPh_3)_3$, $Ni(CO)_2(PPh_3)_2$, $RuHCl(CO)PPh_3)_2$, and $RuH_2(CO)(PPh_3)_3$. Only $Pd(PPh_3)_4$ was found to be effective.

(9) Enhancement of reaction rate by the use of a Pd(0)/carboxylic acid combined catalytic system is also observed by others; see: (a) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161−3163 (b) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438−4439. For a review, see: (c) Trost, B. M. *Chem. Eur. J.* **1998**, *4*, 2405−2412.

conditions such as heating the reaction mixture without solvent or increasing the amount of palladium catalyst and reaction time. Unfortunately, none of the conditions gave the product **4i**.

With success in developing the intramolecular hydroamidation process, we next turned our attention toward the intermolecular hydroamidation reaction. The reactions of 1-phenyl-1-propyne **6** with either of the amides **5a**−**d** in the presence of 10 mol % of $Pd(PPh_3)_4$ and 40 mol % of PhCOOH were examined under the standard conditions. However, in all cases, the reactions did not proceed to give product **7** (eq 5).



The mechanism of the intramolecular hydroamidation reaction is presumably similar to that of the hydroamination reaction reported previously and is shown in Figure 1.[6a] Hydropalladation[10] of the alkyne **3a** with the hydridopalladium species **9**, generated from Pd(0) and benzoic acid, produces the vinylpalladium species **8**, which gives the substituted phenylallene **10** on β-elimination.[11] Subsequent hydropalladation of the allene **10** with **9** gives the π-allylpalladium species **11**. Intramolecular nucleophilic substitution in the π-allylpalladium complex **11** gives the product **4a** along with the hydridopalladium species **9**.

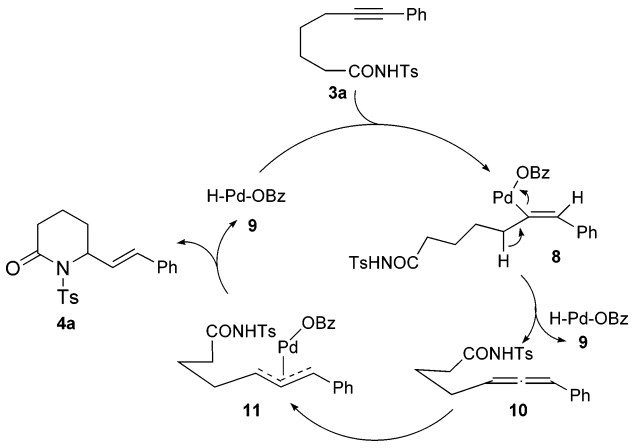


FIGURE 1. Plausible mechanism for the hydroamidation reaction.

As mentioned above, the basicity of nitrogen atom is very important for the amide cyclization reaction to proceed. The amido alkyne **1** gave the diene **2**, as shown in eq 3, instead of giving the desired lactam. The reason for the formation of diene can be well accounted for on the basis of the transition state described in Figure 2. The π-allylpalladium complex **12** would undergo β-hydride elimination due to the assistance of more basic nitrogen, which abstracts a hydrogen β to the π-allylpalladium group leading to the formation of diene **2**.[7] On the contrary, **11** generated from **3** undergoes ligand exchange at the palladium atom (path **B**) rather than β-hydride elimination (path **A**) as the nitrogen of **11** becomes less basic due to the presence of two electron-withdrawing groups (Figure 3). Perhaps the nitrogen atom of **11** possesses nucleophilicity enough to attack the palladium atom in the π-allyl complex **11**, although it is decreased by the presence of the two electron-withdrawing groups.

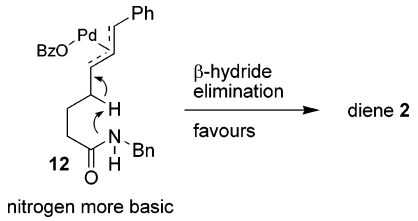


FIGURE 2. Explanation for the formation of diene **2**.

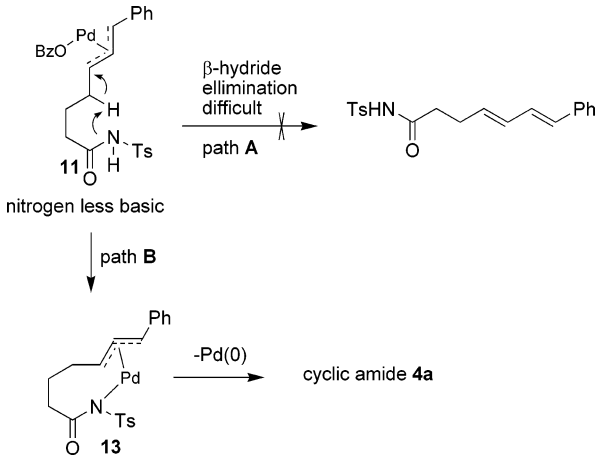


FIGURE 3. Explanation for the formation of the cyclic amide **4**.

In summary, we have developed the $Pd(PPh_3)_4$-catalyzed intramolecular hydroamidation reaction of the amido alkynes **3**. This process allows the facile and efficient construction of six-membered lactams **4** in an atom-economical manner. Although the reaction reported herein is limited for the synthesis of six-membered lactams, we think that the absence of any other comparable synthetic protocols for such transformations justifies the importance of our findings.

Experimental Section

General Procedure for Synthesis of Lactams. To a 5 mL screw-capped vial equipped with a magnetic stirring bar were added the amidoalkyne **3a** (106 mg, 0.3 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol), benzoic acid (7.5 mg, 0.06 mmol), and 1,4-dioxane (1.5 mL). After the mixture was stirred for 12 h at 100 °C, TLC was taken in order to confirm whole disappearance of the starting material. The solvent was removed under reduced pressure, and the residue was purified by short silica gel column with eluent (hexane/ethyl acetate, 9:1) to give **4a** (98.0 mg) in 92% yield.

Supporting Information Available: Experimental details, characterization data, and ^{1}H NMR spectra of newly synthesized compounds **1**, **2**, **3a**−**i**, and **4a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161−3163.
(11) (a) Sheng, H.; Lin, S.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 4893−4894. (b) Lu, X.; Ji, J.; Ma, D.; Shen, W. *J. Org. Chem.* **1991**, *56*, 5774−5778.