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Palladium-Catalyzed Intramolecular Cyanoamidation of Alkynyl and Alkenyl Cyanoformamides

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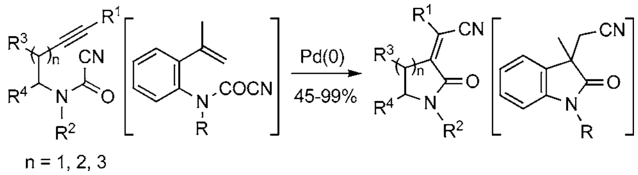
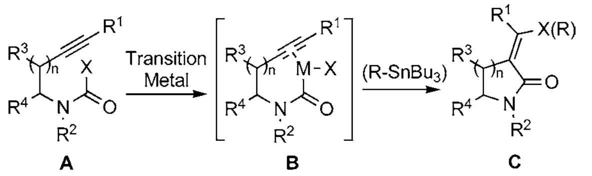
ABSTRACT



The five- to seven-membered α-alkylidene lactams were prepared in 45–99% yield by the palladium-catalyzed cyanoamidation of alkynyl cyanoformamides. The reaction proceeded exclusively in a 5-exo mode, giving the corresponding (*Z*)-alkenes as major products. The reaction was also applied to 1,1-disubstituted alkenes to afford oxindoles bearing a quaternary carbon center.

Transition-metal-catalyzed carbonylative cyclization of unsaturated amines with use of carbon monoxide is a powerful tool for the synthesis of lactams and various heterocyclic compounds.[1] Recent progress in this research area has demonstrated that these compounds can be synthesized without carbon monoxide through the use of well-designed substrates.[2] Grigg et al. explored a palladium-catalyzed cyclization-anion capture protocol for the synthesis of α-alkylidene oxindoles from alkynyl carbamoyl chlorides (Scheme 1, X = Cl, R^1 = H).[3a] Kambe and co-workers reported the palladium-catalyzed intramolecular thio- and seleno-carbamoylation of appropriate alkynes (X = SPh and SePh).[3b] Recently, our group also reported the rhodium-catalyzed intramolecular hydroamidation of alkynyl formamides (X = H) to afford α-alkylidene-γ-lactams.[4] However, these methods have not been applied to the synthesis of tetrasubstituted alkene derivatives with all carbon substituents. This prompted us to investigate the transition-metal-catalyzed intramolecular cyanoamidation of alkynes **A** into lactams **C** (X = CN). Such nitriles **C** obtained by this method would be versatile building blocks in organic synthesis and are seen in many natural products, pharmaceuticals, and organic materials.[5] Although direct activation of the C−C single bond by transition metals (**A** → **B**) and subsequent

Scheme 1. Lactam Synthesis by Transition-Metal Catalysts



X = Cl (*ref* 3a, n = 1), SePh, SPh (*ref* 3b, n = 0, 2, 3),
H (*ref* 4, n = 1), CN (this work, n = 1, 2, 3)

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(1) For recent reviews see: (a) El Ali, B.; Alper, H. *Synlett* **2000**, 161. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127 and references therein. For recent examples, see: (c) Costa, M.; Cà, N. D.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 4607. (d) Dong, C.; Alper, H. *Tetrahedron*: *Asymmetry* **2004**, *15*, 35. (e) Granito, C.; Troisi, L.; Ronzini, L. *Heterocycles* **2004**, *63*, 1027. (f) Ma, S.; Wu, B.; Jiang, X. *J. Org. Chem.* **2005**, *70*, 2588.

(2) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.

(3) (a) Fielding, M. R.; Grigg, R.; Urch, C. J. *Chem. Commun.* **2000**, 2239. (b) Toyofuku, M.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 9706.

(4) Kobayashi, Y.; Kamisaki, H.; Yanada, K.; Yanada, R.; Takemoto, Y. *Tetrahedron Lett.* **2005**, *46*, 7549.

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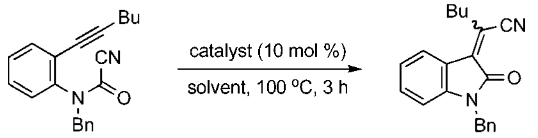
addition of the metal complex to the C−C unsaturated bond (**B** → **C**) should be of great synthetic value because such a reaction provides a simultaneous installation of two C−C bonds onto the C−C triple bond with perfect atom economy, only a few reports are available.[6] We report here a concise synthesis of α-alkylidene lactams by the palladium-catalyzed intramolecular cyanoamidation of alkynyl cyanoformamides. To the best of our knowledge, this is the first report of transition-metal-catalyzed carbonylative cyclization using C−C bond activation.[7]

We first investigated the reaction conditions for the intramolecular cyanoamidation of cyanoformamide **1a**. Representative results are summarized in Table 1. Although we carried out the reaction of **1a** with $Rh_4(CO)_{12}$ at 130 °C,[4] the desired product **2a** could not be obtained (entry 1). Likewise other metal complexes such as $Ru_3(CO)_{12}$, $Pt(PPh_3)_4$, $Ni(PPh_3)_4$, and $RhCl(PPh_3)_3$ were totally ineffective. After further experiments on cyclization, we found that $Pd(PPh_3)_4$ was an effective catalyst for the cyanoamidation, and the desired α-alkylidene lactams **2a** were obtained in 97% yield as a mixture of (*E*)- and (*Z*)-isomers (entry 2).[8] In contrast, when the reaction was performed with $Pd(acac)_2$ in the presence of PPh_3 (4 equiv) instead of $Pd(PPh_3)_4$, the yield of **2a** decreased to 39% (entry 3). Similarly, the use of other phosphine ligands only resulted in unsatisfactory results (entries 4 and 5). We next examined the effect of the solvent on the chemical yield. Among the solvents examined, toluene and xylene gave good results in terms of chemical yield and the ratio of *Z*/*E* isomers (entries 2 and 6). When a polar solvent such as DMF was used, both the chemical yield and the *Z*/*E* ratio decreased (entry 7).

Table 1. Survey of Intramolecular Cyanoamidation of **1a**



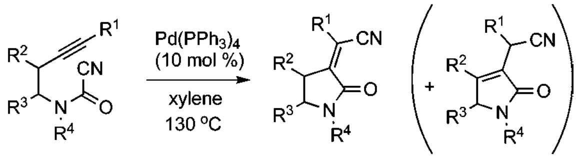
1a **2a**

entry[a]	catalyst	solvent	yield (%)	*Z*/*E* ratio
1	$Rh_4(CO)_{12}$	toluene	0	–
2	$Pd(PPh_3)_4$	toluene	97	73/27
3	$Pd(acac)_2/4PPh_3$	toluene	39	*b*
4	$Pd(acac)_2/4PBu^n_3$	toluene	0	–
5	$Pd(acac)_2/2dppb^c$	toluene	17	*b*
6[d]	$Pd(PPh_3)_4$	xylene	97	69/31
7	$Pd(PPh_3)_4$	DMF	71	21/79

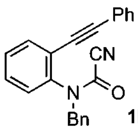
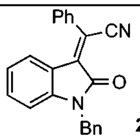
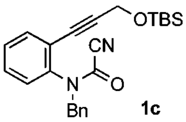
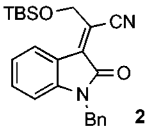
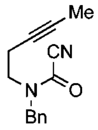
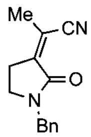
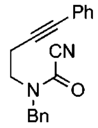
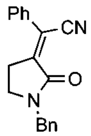
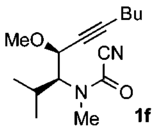
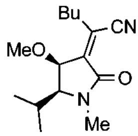
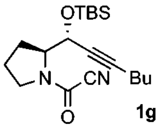
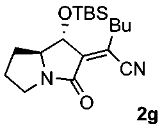
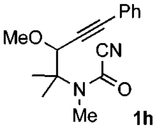
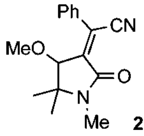
[a] All reactions were carried out with **1a** (0.158 mmol) and catalyst (10 mol %) in solvent (1.5 mL) under an argon atmosphere. [b] In each case, a trace amount of *E*-isomer was obtained. [c] dppb = 1,4-bis(diphenylphosphino)butane. [d] Carried out at 130 °C.

Having established the optimum reaction conditions, we next investigated the cyanoamidation of several alkynyl cyanoformanilides (**1b**,**c**) and alkynyl cyanoformamides (**1d**−**h**) (Table 2). The palladium-catalyzed reaction of formanilides **1b**,**c**, which have different substituents such as

Table 2. Pd-Catalyzed Cyanoamidation of Alkynes **1b**−**h**



1b-h **2b-h** **3e, f**

entry[a]	substrate	time (h)	product	yield of 2/3 (%)
1	 **1b**	8	 **2b**	45[b]
2	 **1c**	8	 **2c**	57[b]
3	 **1d**	1	 **2d**	84
4	 **1e**	1	 **2e**	77[c]
5	 **1f**	4	 **2f**	99[d]
6	 **1g**	1	 **2g**	77
7	 **1h**	4	 **2h**	84

[a] All reactions were carried out under an argon atmosphere. [b] In each case, a trace amount of *E*-isomer of **2b** or **2c** was detected. [c] Products were obtained as a mixture of **2e** (38%) and **3e** (39%). [d] Products were obtained as a mixture of **2f** (68%) and **3f** (31%).

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[5] (a) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597. (b) Greenham, N. C.; Moratti, S. C.; Bradley, D. D. C.; Friend, R. H.; Holmes, A. B. *Nature* **1993**, *365*, 628.

[6] (a) Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629. (b) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (c) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639. Palladium- and nickel-catalyzed intramolecular cyanoboration of alkynes, see; (d) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358.

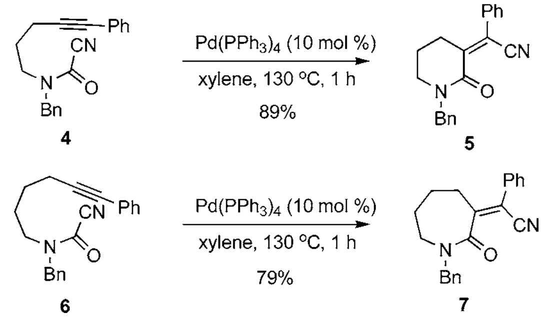
[7] For a recent review on C−C bond activation, see: (a) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. For recent examples of C−CN bonds activation, see: (b) Taw, F. L.; Mueller, A. H.; Bergman, R. G.; Brookhart, M. *J. Am. Chem. Soc.* **2005**, *125*, 9808 and references therin.

[8] The stereochemistry of the products was determined by the NOE experiments of their ^1H NMR experiments, and it was already reported that *E/Z* isomerization of sevaral α-alkylideneoxindoles easily occurs in polar solvents, see: Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588.

Ph and CH_2OTBS as an alkynyl side chain, proceeded slowly even at 130 °C, and gave the corresponding oxindoles **2b** and **2c** in respective yields of 45% and 57% (entries 1 and 2). In contrast to these results, the same reaction of acyclic cyanoformamides **1d** took place smoothly to furnish the desired lactam **2d** in 84% yield as a single isomer (entry 3). In the case of cyanoformamide **1e** having a phenyl group, the corresponding cyclized adduct **2e** and the isomerized product **3e** were obtained as a 1/1 mixture in a combined yield of 77% (entry 4). The product **3e** was probably derived from **2e** via 1,3-migration of the C4 proton.[9] The reaction of cyanoformamides **1f**,**g**, which were easily prepared from L-valine and L-proline, also occurred smoothly to provide the lactam **2f** and bicyclic lactam **2g** in good yields (entries 5 and 6). In addition, the cyclization of α,α-disubstituted amino acid derivative **1h** similarly afforded **2h** in 84% yield (entry 7). These results suggest that the Pd-catalyzed carbonylative cyclization of nonaromatic substrates **1d**−**h** proceeds exclusively in a 5-*exo* mode and that the substituents have little effect on this cyclization.

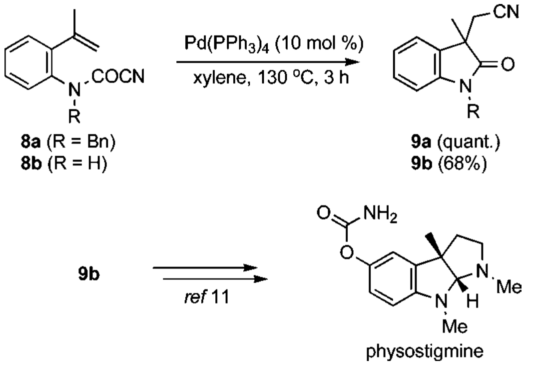
We further examined the scope and limitations of the palladium-catalyzed intramolecular cyanoamidation. For this purpose, this protocol was next applied to the cyclization of cyanoformamides **4** and **6** possessing alkyl chains of different lengths (Scheme 2). As expected, cyanoformamide **4** was successfully cyclized in the presence of 10 mol % of Pd$(PPh_3)_4$. The reaction regio- and stereoselectively gave six-membered lactam **5** in 89% yield. The stereochemistry of **5** was determined by NOE experiment. Furthermore, by the same treatment of **6** as **4**, the corresponding seven-membered lactam **7** was obtained in good yield as a single isomer.

Scheme 2. Application to the Synthesis of Six- and Seven-Membered Lactams



To expand the utility of this reaction, the intramolecular cyanoamidation of 1,1-disubstituted alkenes **8a**,**b** was next examined (Scheme 3). The reaction of **8a** proceeded cleanly with perfect regioselectivity to afford the cyclized adduct **9a**, which had a quaternary carbon center, in excellent yield. The presence of a protecting group was not critical, since N−H cyanoformamide **8b** was similarly converted into its lactam **9b** in 68% yield.[10] The obtained adduct **9b** was a key intermediate for the total synthesis of physostigmine,[11] which possesses a core structure of pyrrolo[2,3-*b*]indole alkaloids. Therefore, this cyclization may be a novel method for the preparation of related alkaloids.[12]

Scheme 3. The Cyclization of 1,1-Disubstituted Alkenes **8a**,**b**



In summary, we have developed a novel method for the synthesis of five- to seven-membered α-alkylidene lactams by the palladium-catalyzed intramolecular cyanoamidation of alkynyl and alkenyl cyanoformamides. Further detailed investigations into the synthetic and mechanistic aspects of this cyclization are underway in this laboratory.

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

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[9] Treatment of the isolated **2e** under the same reaction conditions afforded **3e** in 38% yield along with recovery of the starting material **2e** (47%).

[10] In contrast to this result, the same reaction of the corresponding alkynes led to a complex mixture.

[11] (a) Marales-Ríos, M. S.; Bucìo, M. A.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 881. (b) Julian, P. L.; Pikl, J.; Boggess, D. *J. Am. Chem. Soc.* **1934**, *56*, 1797. (c) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705 and references therein.

[12] (a) Kawasaki, T.; Terashima, R.; Sakaguchi, K.; Sekiguchi, K.; Sakamoto, M. *Tetrahedron Lett.* **1996**, *37*, 7525. (b) Kawasaki, T.; Ogawa, A.; Takashima, Y.; Sakamoto, M. *Tetrahedron Lett.* **2003**, *44*, 1591. (c) Kawasaki, T.; Ogawa, A.; Terashima, R.; Saheki, T.; Ban, N.; Sekiguchi, H.; Sakaguchi, K.; Sakamoto, M. *J. Org. Chem.* **2005**, *70*, 2957.