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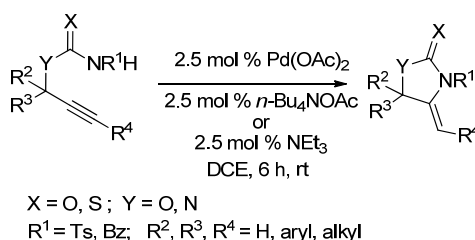
Palladium-Catalyzed Intramolecular Hydroamination of Propargylic Carbamates and Carbamothioates

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ABSTRACT



An efficient and simple methodology was developed for the synthesis of oxazolidinones, oxazolidinones, imidazolidinones, imidazolidinones from the corresponding propargylic starting materials using Pd(OAc)₂ and *n*-Bu₄NOAc as catalysts in DCE at room temperature.

Oxazolidinone and their derivatives constitute an important class of heterocyclic compounds that are versatile intermediates in organic synthesis.¹ They have been widely used in both the pharmaceutical² and agricultural³ industry as they show a diverse range of biological activities. Oxazolidinone derivatives can act as inhibitors, sigma receptors, and antibiotics.⁴ Because of the extensive utility of oxazolidinones, numerous methods

for their synthesis have been developed. The most common way of preparing oxazolidinones involves the reaction of an amino alcohol with phosgene or chloroformate as carbonyl precursor.⁵ Oxazolidinones can also be synthesized starting from propargylic alcohols, amines and CO₂ as carbonyl precursor in the presence of metal salts,⁶ phosphines⁷ or ionic liquids.⁸ In addition, cyclization of propargylic carbamates is a feasible alternative and ranks high amongst the methods to synthesize oxazolidinones.⁹

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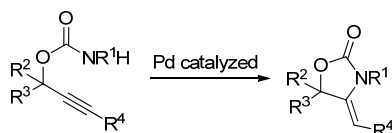
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In the 1990's, Tamaru and Murai reported on a copper-catalyzed cyclization of propargylic carbamates.¹⁰ Later on, Gagosz and Schmalz independently discovered gold-catalyzed cyclizations of propargylic carbamates.¹¹ In 2007, Chandrasekaran and coworkers reported LiOH-catalyzed cyclizations of carbamates.¹² Recently, Kang and coworkers found that *N*-heterocyclic carbenes catalyze a domino cyclization of propargylic alcohols and benzoyl isocyanates,¹³ and Looper and coworkers reported on a rhodium-catalyzed hydroamination of propargyl guanidines.¹⁴ Lei and Lu have also reported a related palladium-catalyzed tandem intramolecular amidopalladation of alkynes, followed by insertion of an alkene.¹⁵

All the above protocols for the cyclization of propargylic carbamates have some limitations. In most of the reactions it is necessary to employ strong base such as potassium *t*-butoxide, and furthermore, the procedures require long reaction times and excess catalyst loading.¹⁰ When LiOH was employed as catalyst for the cyclization,¹² the tosylcarbamate was easily hydrolyzed. The solvent used in the latter reaction was dimethylformamide, which is difficult to remove from the reaction mixture in large scale reactions.

As part of our continuous research on palladium-catalyzed reactions,¹⁶ one objective was to find robust synthetic procedures allowing for carbon-carbon and carbon-heteroatom bond forming reactions. In this communication, we wish to describe the successful development of a novel palladium(II)-catalyzed cyclization of propargyl carbamates to oxazolidinones (Scheme 1).

Scheme 1. Palladium-catalyzed cyclization of propargyl carbamates to oxazolidinones



¹⁰ (a) Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1990**, *31*, 4887; (b) Tamaru, Y.; Kimura, M.; Tanaka, S.; Kure, S.; Yoshida, Z. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2838. (c) Kouichi, O.; Toshihisa, I.; Naoto, C.; Yoshikane, K.; Murai, S. *J. Org. Chem.* **1991**, *51*, 2267.

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¹² (d) Ramesh, R.; Chandrasekaran, Y.; Megha, R.; Chandrasekaran, S. *Tetrahedron* **2007**, *63*, 9153.

¹³ Kyoung, A. J.; Muchchintala, M.; Eunyong, Y.; Yun, Y. L.; Hoseop, Y.; Kang, E. J. *J. Org. Chem.* **2012**, *77*, 2924

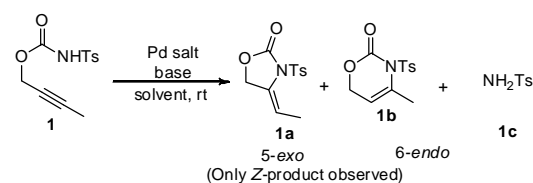
¹⁴ Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 684.

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¹⁶ (a) For a review on palladium-catalyzed oxidative carbocyclizations see: Deng, Y.; Persson, A. K. Å.; Bäckvall, J. E. *Chem. Eur. J.* **2012**, *18*, 11498. (b) Deng, Y.; Bartholomeyzik, T.; Bäckvall, J. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 6283. (c) Deng, Y.; Bäckvall, J. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 3217. (d) Jiang, M.; Jiang, T.; Bäckvall, J. E. *Org. Lett.* **2012**, *14*, 3538. (e) Deng, Y.; Bartholomeyzik, T.; Persson, A. K. Å.; Sun, J.; Bäckvall, J. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 2703. (f) Jiang, T.; Persson, A. K. Å.; Bäckvall, J. E. *Org. Lett.* **2011**, *13*, 5838. (g) Persson, A. K. Å.; Jiang, T.; Johnson, M. T.; Bäckvall, J. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 6155. (h) Persson, A. K. Å.; Bäckvall, J. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 4624. (i) Franzen, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2003**, *125*, 6056.

The propargylic carbamates were easily prepared by the condensation of a propargylic alcohol with equimolar amounts of tosylisocyanate (TsNCO) in THF and were used as such with no further purification. For the cyclization studies but-2-yn-1-yl tosylcarbamate **1** was employed as model substrate. Initially, 5 mol % of Pd(OAc)₂ and 5 mol % of NaOAc were used in THF at room temperature, and under these conditions the reaction provided 40% of 5-exo product **1a**, 5 % of 6-endo product **1b** and 25% of hydrolyzed starting material measured as tosylamide **1c** (Table 1).

Table 1. Effect of bases, solvents and palladium salts.^a



entry	Pd salt	base	solvent	time h	product (yield) ^b		
					1a	1b	1c
1	Pd(OAc) ₂	NaOAc	THF	24	40	5	25
2	"	CsOAc	"	24	40	5	28
3	"	Ba(OAc) ₂	"	24	No reaction		
4	"	NaHCO ₃	"	24	No reaction		
5	"	NEt ₃	"	24	25	3	40
6	"	Hünig's base	"	24	25	3	40
7	"	<i>n</i> -Bu ₄ NOAc	"	6	70	7	20
8	PdCl ₂	"	"	24	16	-	10
9	Pd(PPh ₃) ₄	"	"	24	12	-	8
10	Pd(acac) ₂	"	"	24	45	4	12
11	Pd(TFA) ₂	"	"	6	68	7	18
12	Pd(OAc) ₂	"	DCE	2	93	6	-
13	"	"	dioxane	12	65	4	20
14	"	"	PhCH ₃	12	60	4	5
15	"	"	CH ₃ CN	12	55	3	20
16	"	"	CHCl ₃	12	90	7	-
17	"	"	EtOAc	12	58	5	18
18 ^c	"	"	DCE	6	93	5	-
19 ^d	"	"	DCE	36	85	5	-

^a Reaction conditions: **1** (0.5 mmol), Palladium salt (5 mol %), base (5 mol %), solvent 1 mL. ^b ¹H NMR yield (Methyl tert-butyl ether used as internal standard). ^c 2.5 mol % Pd(OAc)₂ and 2.5 mol % *n*-Bu₄NOAc. ^d 1 mol % Pd(OAc)₂ and 1 mol % *n*-Bu₄NOAc

Several bases, palladium salts, and solvents were then screened with the objective to increase the efficiency of the cyclization reactions, and the results are summarized in Table 1. In the screening of various bases the desired cyclic product was less predominant and the hydrolyzed product was formed to a large extent. With some bases (entries 3 and 4) no reaction took place. However, when *n*-Bu₄NOAc (5 mol %) was used as base, the desired oxazolidinone **1a** was obtained in 70 % yield. The reaction was also run with additional palladium salts including PdCl₂, Pd(acac)₂, and Pd(TFA)₂. Comparable results were

obtained for Pd(TFA)₂ and Pd(OAc)₂, and for the further solvent optimization we choose Pd(OAc)₂ since it is less expensive than Pd(TFA)₂ (entries 12-17, Table 1). During the solvent optimization studies, we observed complete conversion of starting material in 2 hours with no hydrolysis of **1** when DCE was used as solvent. The reaction resulted in 93% of 5-exo cyclic product **1a** (only (*Z*)-isomer) and 6% of the 6-endo cyclic product **1b**.

Having obtained good product selectivity, the catalyst loading was next optimized. When the amounts of Pd(OAc)₂ and *n*-Bu₄NOAc were decreased from 5 mol % each to 2.5 mol % each, the reaction took 6 hours to reach full conversion of the carbamate (entry 18). A further reduction of catalyst loading to 1 mol % required very long reaction times (36 h) for complete conversion (entry 19).

After optimizing the reaction conditions for the cyclization of carbamate **1**, the scope of the palladium-catalyzed cyclization with other carbamates was studied and the results are summarized in Table 2. Variation of the substituent on the acetylene (R³) in **1** to hydrogen, ethyl, *n*-propyl, or phenyl (entries 2-5) did not affect the rate of the cyclization reaction and the carbamate products were formed in excellent yields and selectivity. We then studied the effect of a monosubstituent at the propargylic position of the carbamates (R¹ = substituent, R² = H) and it was found that the cyclization reaction proceeded smoothly to furnish the corresponding oxazolidinone products in high yields (entries 6-10). Disubstitution at the propargylic position (R², R³) resulted in an efficient cyclization reaction and gave good yields in all cases (entries 11-13) except for one substrate (**14**), which has a vinyl group at the 1-position (entry 14). The spiro propargylic carbamates were also cyclized and afforded the desired spirooxazolidinone in 86% yield (entry 15). We applied this protocol successfully to the cyclization of but-3-ynyl carbamate **16** to the corresponding 4-methylene-3-tosyl-1,3-oxazinan-2-one (**16a**) under the same condition with a longer reaction time (entry 16). Several of these alkylidinoxazolidinones are important starting materials in oxidative Heck couplings with arylboroxines.¹⁷

After having obtained successful reaction conditions for the cyclization of propargylic carbamates to oxazolidinones, we investigated the possibility of using the same protocol for the synthesis of oxazolidinones, imidazolidinones, and imidazolidinones from benzoylthiocarbamate, benzoylthioureas, and tosylureas, respectively.

The benzoylthiocarbamates **17-19** were prepared in situ from the corresponding propargylic alcohols and thioisocyanate. The cyclization of thiocarbamates **17-19** to the corresponding oxazolidinones was carried out with 2.5 mol % Pd(OAc)₂ and 2.5 mol % *n*-Bu₄NOAc (entries 1-3, Table 3). Thiocarbamates with internal alkynes (entries 1-3) gave cyclized product in good yield. Thiourea compound **20** smoothly cyclized under the same

Table 2. Synthesis of tosylloxazolidinones.^a

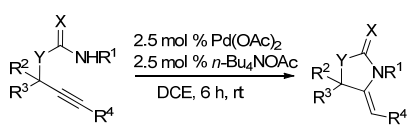
entry	substrate	product	yield (%)
1			93
2			90
3			92
4			94
5			92
6			88
7			86
8			88
9			90
10			87
11			90
12			88
13			82
14			50
15			86
16 ^b			90

^a Reaction conditions: 2.5 mol % Pd(OAc)₂ and 2.5 mol % *n*-Bu₄NOAc in DCE at rt for 6 h. ^b Reaction time 24 h.

¹⁷ Alamsetti, S. K.; Persson, A. K. Å.; Jiang, T.; Bäckvall, J. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 13745.

reaction condition and gave spiroimidazolidinone **20a** in 80% yield. Cyclization of tosylurea compound **21** afforded imidazolidinone **21a** as major product and internal olefin as minor product (90:10) after 6 h (entry 5). Tosylurea compound **22** cyclized smoothly and gave the corresponding spirocyclic product **22a** in 80% yield.

Table 3. Synthesis of oxazolidinones, imidazolidinones, and imidazolidinones.^a



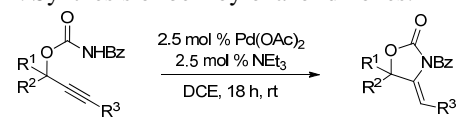
entry	substrate	product	yield(%)
1			79
2			68
3			75
4			80
5			85
6			80

^a Reaction conditions: as in Table 1.

Although the cyclization of benzoylthiocarbamates worked well with 2.5 mol % Pd(OAc)₂ and 2.5 mol % *n*-Bu₄NOAc, our efforts to cyclize benzoylcarbamates to the corresponding oxazolidinones under the same reaction conditions were unsuccessful. However, when *n*-Bu₄NOAc was replaced by triethylamine, the reaction went smoothly. Under these conditions benzoylcarbamates with terminal and internal alkyne moieties successfully cyclized to the corresponding oxazolidinones (Table 4, entries 1-3). Also, Benzoylcarbamate **26** cyclized to the corresponding spirocyclic oxazolidinone **26a**.

Regarding the mechanism, we believe that the reaction proceeds through an overall *trans*-amidopalladation of the alkyne, followed by protodepalladation of the alkenyl-Pd intermediated with retention of configuration (Scheme 2).

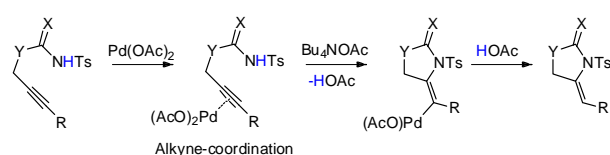
Table 4. Synthesis of benzoyloxazolidinones.^a



entry	substrate	product	yield(%)
1			68
2			70
3			71
4			73

^a Reaction conditions: 2.5 mol % of Pd(OAc)₂ and 2.5 mol % of Et₃N in DCE at room temperature for 18 h.

Scheme 2. Plausible palladium-catalyzed cyclization mechanism.



In summary we have developed an efficient and experimentally simple catalytic procedure for the formation of cyclic enamides relying on 2.5 mol % Pd(OAc)₂ and 2.5 mol % *n*-Bu₄NOAc as catalysts in DCE at room temperature with good to excellent yields starting from inexpensive and commercially available propargylic alcohols and isocyanate. The protocol was extended to the synthesis of oxazolidinones, imidazolidinones, and imidazolidinones from the corresponding starting materials in good yields. We also cyclized benzoylcarbamate to the corresponding cyclic compounds using 2.5 mol % Pd(OAc)₂ along with 2.5 mol % NEt₃ in DCE at room temperature.

Acknowledgment. Financial support from the Swedish Research Council and the European Research Council (ERC AdG 247014) is gratefully acknowledged.

Supporting Information Available. Experimental procedures and characterization data, including copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the internet at <http://pubs.acs.org>.