ORGANIC
LETTERS

2007
Vol. 9, No. 7
1191−1193

Highly Functionalized and Stereocontrolled Syntheses of 2-(2-Methylenecycloalkyl)-furan Derivatives by Pd-Catalyzed Cycloreduction

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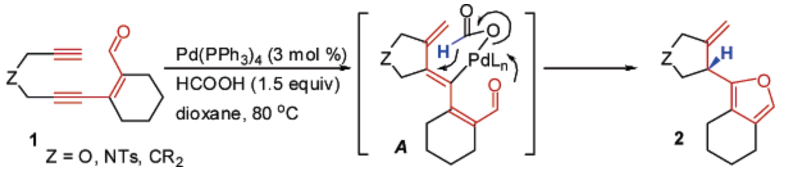
Received December 10, 2006

ABSTRACT



We have discovered a new method employing Pd-catalyzed cycloreduction of conjugated enynals 1 bearing an alkyne unit leading to the corresponding 2-(2-methylenecycloalkyl)-furans 2a–j and a related compound 7 in good to excellent yields.

Pd-catalyzed cycloreduction of enynes and enediynes gives various polycyclic compounds in a very convenient single step.[1] A few years ago, we reported Pd-catalyzed cycloreductions of enediynes leading to [*m*,5,*n*]-tricyclic compounds[2] and we could synthesize (±)-ceratopicanol by using this method as a key step.[3] This reaction proceeded with high levels of stereoselectivities leading to concave-shaped triquinane skeletons accompanying a significant increase in structural complexity. Extension of this method to 1,*n*-diynes could provide a successful formation of 1,2-bismethylenecycloalkane derivatives which are the same compounds from Pd-catalyzed cycloisomerization of the corresponding enynes. A major advantage in diyne cycloreduction is in the formation of a stable alkenylpalladium intermediate, and enyne cycloisomerization forms the alkylpalladiums labile for β-elimination. Such an increase in stability of the alkenylpalladiums could prompt us to further explore new reactions.[4] Herein, we report functionalized and stereocontrolled syntheses of 2-(2-methylenecyclopentyl)-furans by a Pd-catalyzed cycloreduction method. Furans have attracted increasing attention as synthetic target compounds due to their widespread occurrence in nature and due to the wide range of biological activities.[5]

We assumed that the alkenylpalladium species could have oxophilicity for the carbonyl oxygen in an appropriate

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[1] For reviews, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (b) Lu, X.; Zhu, G.; Wang, Z.; Ma, S.; Ji, J.; Zhang, Z. *Pure Appl. Chem.* **1997**, *69*, 553.

[2] (a) Oh, C. H.; Rhim, C. Y.; Kang, J. H.; Kim, A.; Park, B. S.; Seo, S. *Tetrahedron Lett.* **1996**, *37*, 8875. (b) Oh, C. H.; Rhim, C. Y.; Jung, H. H.; Jung, S. H. *Bull. Korean Chem. Soc.* **1999**, *20*, 643. For a related enyne cycloreduction: (c) Oh, C. H.; Jung, H. H.; Kim, J. S.; Cho, S. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 752.

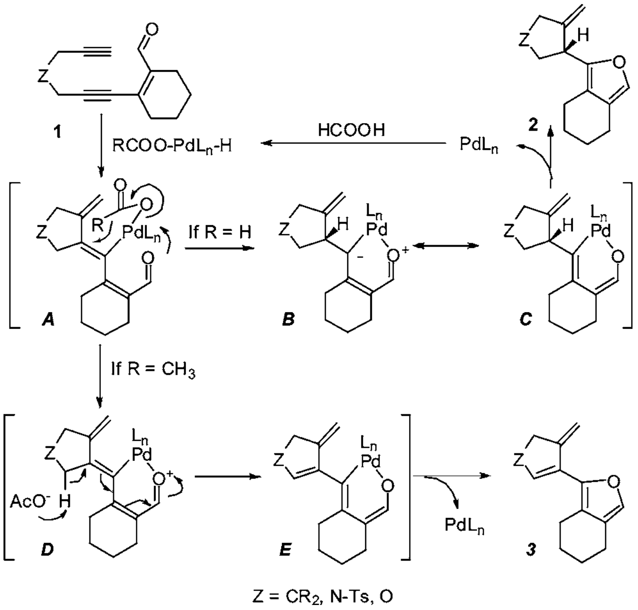
[3] Oh, C. H.; Rhim, C. Y.; Kim, M.; Park, D. I.; Gupta, A. K. *Synlett* **2005**, 2694.

[4] (a) Tsuji, J. *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*; John Wiley: Chichester, 1995. (b) Soderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12. (c) Heck, R. F. *Palladium reagents in Organic Synthesis*; Academic Press: New York, 1985. (d) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; VCH: Weinheim, 1988.

[5] (a) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (c) Bach, T.; Krüger, L. *Eur. J. Org. Chem.* **1999**, *1999*, 2045. (d) Marshall, J. A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962. (e) Batna, A.; Spiteller, G. *Lipids* **1994**, *29*, 397. For reviews, see: (f) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, Germany, 1995; pp 231−242. (g) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon Press: Oxford, 2002; Vol. 14, pp 139−179.

10.1021/ol0629871 CCC: $37.00

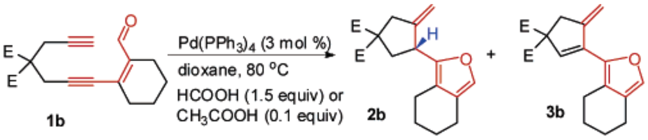
Scheme 1



position similar to carbopalladation (Scheme 1). Terminal or activated triple bonds are known to undergo facile hydropalladation with a HPdOCOH species, generated in situ by mixing Pd compounds with formic acid, to form the vinylpalladium species which undergoes carbopalladation with the alkyne unit to form the intermediate **A**.[6] The carbonyl oxygen could attack the palladium nucleus to release CO_2 and subsequently to transfer hydride to the indicated carbon in **B** from the sterically less-hindered face.[7] Electron delocalization to **C** followed by reductive elimination could result in the formation of the furan **2b** and PdL$_n$ for the next catalytic cycle.

Our preliminary results are summarized in Table 1. Initially, we attempted Pd-catalyzed cycloisomerizations of **1b** in the presence of acetic acid and triethylsilane as an initiator and a reductant, respectively, but this resulted in decomposition (entry 1). When 1.5 equiv of formic acid was employed with palladium catalysts, **1b** was cleanly converted into **2b** as a major route (entries 2−4).

Table 1. Cyclizations of **1b** under Various Conditions



	catalysts (3 mol %)	additive (equiv)	solvent, temp (°C), time (h)	products (% yield)
1	$Pd(PPh_3)_4$	AcOH (0.1) Et_3SiH (1.5)	dioxane, 80, 4	dec
2	**$Pd(PPh_3)_4$**	**HCOOH (1.5)**	**dioxane, 80, 4**	**2b (90)**
3	$Pd(OAc)_2/PPh_3$	HCOOH (1.5)	dioxane, 80, 4	**2b** (68)
4	$PdCl_2(PPh_3)_2$	HCOOH (1.5)	dioxane, 80, 4	**2b** (36)
5	$Pd(PPh_3)_4$	AcOH (0.1)	dioxane, 80, 4	**3b** (45)
6	$Pd(PPh_3)_4$	AcOH (0.1)	toluene, 80, 4	**3b** (26)
7	$Pd(PPh_3)_4$	AcOH (0.1)	EDC, 80, 4	nr

Even with a catalytic amount of acetic acid, the furan derivative **3b** was isolated in moderate yield when $Pd(PPh_3)_4$ was employed as a catalyst in dioxane (entry 5).[8] This reaction was less efficient in toluene and did not occur in 1,2-dichloroethane (EDC) (entries 6 and 7). Mechanistically, the intermediate **A** ($R = CH_3$) might undergo cyclization to the oxypalladacycle **D**, releasing an acetate anion, and deprotonation of **D** to **E** by an acetate anion followed by reductive elimination to the product **3b**. Attempting selective hydrogenation of **3b** toward the conditions in entry 2 failed. Even in a gram-scale reaction, we could convert **1b** to the 2-(2-methylenecyclopentyl)-furan derivative **2b** in 90% yield.

Our conditions were tested for several substrates prepared by using known methods (Figure 1 and Table 2).[9] Overall, all substrates **1a−j** were successfully transformed to the corresponding furan derivatives **2a−j** in high to excellent yields. Looking closely, the substrate **1c** bearing a seven-membered ring tether was superior to **1b** bearing a six-

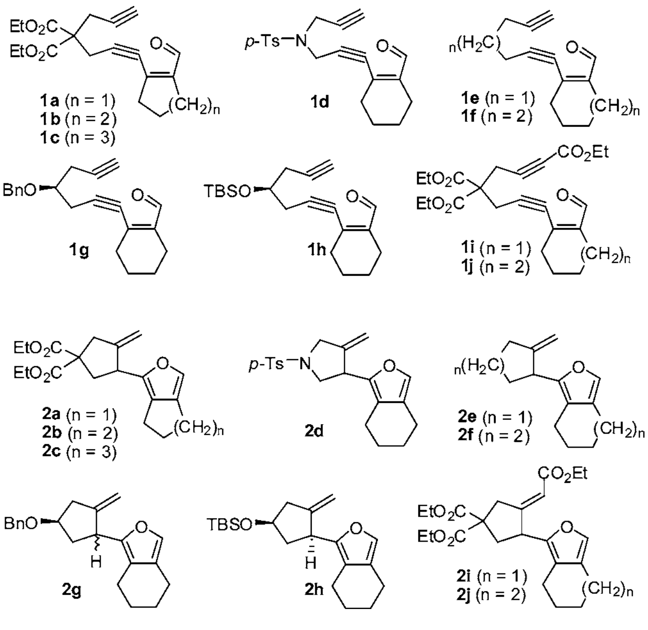


Figure 1. Structures of enediynals and their cycloreduction products.

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(6) For reviews, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.

(7) Such H transfer to the β-carbon of the Pd intermediate has not been reported. We thought that the carbonyl oxygen could attack the Pd, and then concomitant electron migration might lead to H transfer to the β-carbon and further delocalization to the palladacycle **C** in Scheme 1. To prove this mechanism, we employed deuterated formic acid (DCOOD) and isolated the deuterated product **2f-*d*$_2$**.

(8) (a) Uno, T.; Wakayanagi, S.; Sonoda, Y.; Yamamoto, K. *Synlett* **2003**, 1997. (b) Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146. (c) Oh, C. H.; Kim, A.; Rhim, C. Y.; Kang, J. H.; Park, B. S. *Bull. Korean Chem. Soc.* **1996**, *17*, 879.

(9) (a) Sonogashira, K.; Tohda, Y.; Nobue, R. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Bekele, T.; Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 8471.

Table 2. Cycloreductions of **1** to Furans **2** under Pd Catalysis

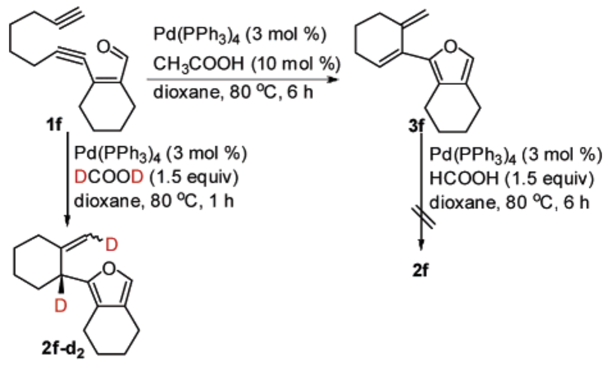
entry	compd	*n*	temp (°C)	time (h)	% yield
1	**1a**	1	70	0.5	77
2	**1b**	2	80	0.5	90
3	**1c**	3	70	0.5	96
4	**1d**		80	2.0	83
5	**1e**	1	80	1.0	66
6	**1f**	2	80	1.0	61
7	**1g**		80	0.5	67
8	**1h**		80	1.0	68
9	**1i**	1	70	2.0	40
10	**1j**	2	70	3.0	54

membered ring. The substrate **1a** with a five-membered ring also afforded the corresponding furan **2a** along with a small amount of uncharacterized byproducts. A substrate **1d** bearing a nitrogen tether underwent this cycloreduction to **2d** without any problem. This implied that the present reaction could apply to the substrates without possessing *gem*-dialkyl groups. Thus, two substrates, **1e** and **1f**, with no *gem*-diesters were converted into the corresponding furan derivatives **2e** and **2f**.

Note that the present method exhibited excellent stereoselectivity depending on the size of the protecting groups. Although a benzyl-protected substrate **1g** afforded the furan derivative **2g** (cis/trans = 3:1) in 67% yield, TBS-protected **1h** afforded the furan **2h** in 68% yield with only the cis configuration without any detectable amount of trans isomer in its crude NMR spectrum.[10] Introduction of an ethoxycarbonyl group at the terminal alkyne is interesting because it might show better reactivity toward Pd catalysts, and the resultant products could be converted into other valuable compounds. Two substrates, **1i** and **1j**, under our conditions were cycloreduced into **2i** and **2j** in 40% and 54% yields, respectively.

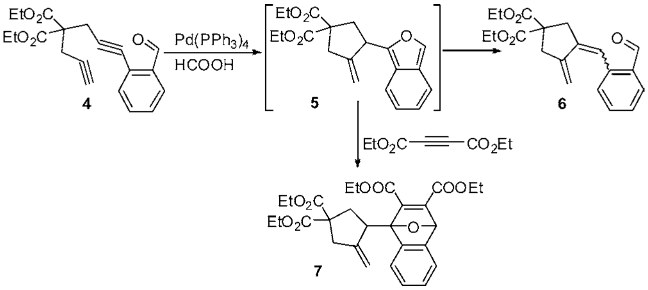
To gain more mechanistic insight, we carried out two experiments (Scheme 2). First, **1f** was cyclized under Pd–AcOH catalytic conditions to **3f** nicely, but reduction of **3f** to **2f**, upon exposure of **3f** to the present conditions, did not occur. Second, when deuterated formic acid was employed under our conditions, deuterated product **2f-*d*$_2$** was isolated in 66% yield, although the deuterium position at the methylene was mixed.[11] These two experiments strongly support our proposed mechanism in Scheme 1.

Scheme 2



Finally, we tried to apply our method to **4** tethered to an aromatic aldehyde (Scheme 3). This reaction worked successfully to afford the corresponding isobenzofuran **5**, but isolation was unsuccessful due to its instability.[12] The isolated product from this reaction was the diene **6** which was formed presumably by acid-catalyzed decomposition of **5** upon exposure to silica gel.[13] Evidence of formation of the isobenzofuran **5** was found by a trapping experiment done by reacting with diethyl acetylene dicarboxylate to produce **7** in 45% yield.[14]

Scheme 3



In conclusion, we have discovered a new method employing Pd-catalyzed cycloreduction of conjugated enynals **1** bearing an alkyne unit leading to the corresponding 2-(2-methylenecycloalkyl)-furans **2a**–**j** in good to excellent yields, respectively. Because of the broad application of furans in medicinal, synthetic, and material chemistry fields, a convenient and atom-economical method for their synthesis should generate great interest from organic synthetic chemists.

Acknowledgment. We wish to acknowledge the financial support of the Center for Molecular Design and Synthesis (CMDS) and BK21.

Supporting Information Available: Characterization of new compounds **2a**–**j**, **2f-*d*$_2$**, and **7** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] A NOE experiment of **2h** clearly indicated two protons in the cyclopentane ring in a cis relationship. See Supporting Information.

[11] The mixed geometric D-incorporation at the terminal alkyne might imply a stepwise hydropalladation, and the fixed orientation at the cyclohexane ring would occur via our proposed mechanism (Scheme 1).

[12] (a) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc*. **2006**, *128*, 12376. (b) Chan, S. H.; Yick, C. Y.; Wong, H. N. C. *Tetrahedron* **2002**, *58*, 9413.

[13] Any proton source might protonate at the oxygen atom of **4** to **4**-H$^+$ and then rearrange to **5**.

[14] For the chemistry of isobenzofurans, see: (a) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (b) Ghorai, B. K.; Jiang, D.; Herndon, J. W. *Org. Lett.* **2003**, *5*, 4261.