J|A|C|S COMMUNICATIONS

Published on Web 12/20/2007

Microwave-Assisted Palladium(0)-Catalyzed Alkylative Cyclization of Allenyl Aldehydes Leading to 3-Substituted 3-Cycloalken-1-ols

Hirokazu Tsukamoto,* Tomotaka Matsumoto, and Yoshinori Kondo

Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki-aza aoba 6-3, Aoba-ku, Sendai 980-8578, Japan

Received August 13, 2007; E-mail: hirokazu@mail.pharm.tohoku.ac.jp

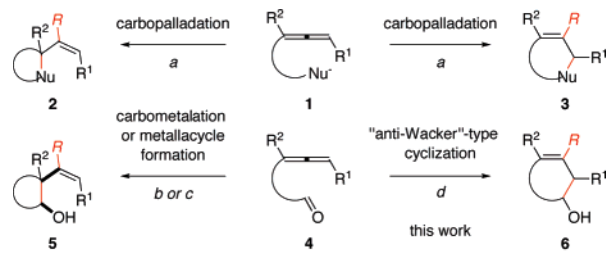
Transition-metal-catalyzed cyclization of functionalized allenes serves as a powerful one-step method to prepare carbo- and heterocycles containing highly substituted olefin groups,[1−3] which should be useful intermediates for natural and pharmaceutical product synthesis. Palladium(0) catalysts with organic halides have been often employed for the cyclization reactions, most of which proceed through carbopalladation of the allene moiety and are focused on the arylative ones of allenes **1** bearing a nucleophilic functionality leading to *exo*- or *endo*-olefin-containing cyclic compounds **2** and **3**.[1] Furthermore, addition of reducing metals to the above reaction conditions allows cyclization of allenes **4** bearing an electrophilic carbonyl group leading to *exo*-alkenyl-containing homoallylic cycloalkanols **5**.[2] However, its counterpart process leading to *endo*-olefin-containing homoallylic alcohols **6** has never been developed[3] because in situ assembled η^1-allylmetal generated by the carbopalladation and subsequent transmetalation could not form a six-membered cyclic transition state with the intramolecular carbonyl group.[4] In addition, alkylative cyclization employing nickel(0) catalysts and organozinc reagents[5] should not be applicable to transformation of allenyl aldehydes **4** into **6** owing to oxidative addition forming a metallacycle composed of Ni^0 and **4**.[6,7] Herein, we disclose a Pd^0-catalyzed alkylative, arylative, alkenylative, alkynylative, and borative cyclization reaction of **4** based not on carbopalladation but on our original “anti-Wacker”-type cyclization[8] to provide homoallylic alcohols **6** (Scheme 1).

At first, we examined the arylative cyclization of allenyl aldehyde **4a** under the best reaction conditions for that of alkynals[8] (1.5 equiv of **7A**, 2 mol % of $Pd(PPh_3)_4$, MeOH, 65 °C). As compared with the alkynal cyclization, the reaction rate is faster and gives 3-cyclohexenol **6aA** in lower yield along with a considerable amount of hydroarylated product **8aA** (Table 1, entry 1).[9] The formation of **8aA** can be reduced by increasing the reaction temperature to 80 °C and completely suppressed by microwave irradiation[10,11] (entries 2 and 3). Importantly, no reaction takes place in the absence of the palladium catalyst.

Arylboronic acids with electron-donating or -withdrawing groups serve as nucleophiles, and electron-rich boronic acids give higher yields than their electron-deficient counterparts (entries 3−12). These cyclization reactions also occur with heteroaryl- and alkenylboronic acids **7K−N** (entries 13−16). Trialkylboranes **7O**,**P** possessing β-hydrogens participate in this process without undergoing competitive β-hydride elimination (entries 17 and 18). Furthermore, a combination of terminal alkyne and catalytic amount of CuI serves as an alkynylmetal and provides enyne alcohol **6aQ** in good yield (entry 19).[12] Remarkably, use of an excess bis(pinacolato)diboron (**7R**) leads to exclusive formation of borated alcohol **6aR** prior to dimerization with **4a** (entry 20).

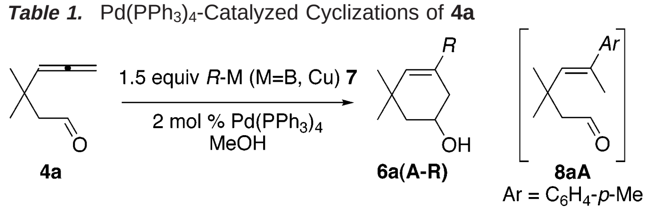
Next, the arylative cyclization reactions of other allenes **4b−g** with **7C** were examined (Table 2). 1,1-Disubstituted allene aldehyde **4b** affords tetrasubstituted alkene containing 3-cyclohexenol **6bC** in high yield (entry 1). Axial chirality of 1,3-disubstituted allene **4c** can be transferred into cyclized product **6cC**, which informs us about the reaction mechanism mentioned below (entry 2). Allenyl ketone **4d** requires higher temperature and longer time but provides tertiary homoallylic alcohol **6dC** in good yield (entry 3). In contrast to alkynal cyclization, allenyl aldehydes **4e** and **4f** containing

Scheme 1. Alkylative Cyclization of Functionalized Allenes **1** and **4**



[a] R-X, cat. Pd^0. [b] R-X, $(Bu_3Sn)_2$ or In, cat. Pd^0 [c] R-Zn, cat. Ni^0. [d] R-B or R-Cu, cat. Pd^0-PPh_3

Table 1. $Pd(PPh_3)_4$-Catalyzed Cyclizations of **4a**

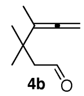
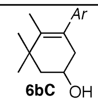
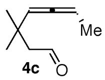
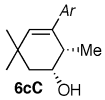
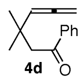
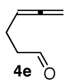
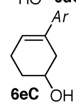
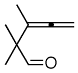
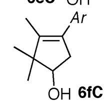
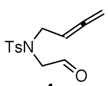
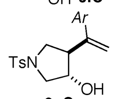


entry[a]	7	6	yield (%)
1	*p*-Me-C_6H_4-$B(OH)_2$ **7A**	**6aA**	54 (24)[b]
2	**7A**	**6aA**	69 (10)[b]
3	**7A**	**6aA**	86 (trace)[b]
4	*p*-Me_2N-C_6H_4-$B(OH)_2$ **7B**	**6aB**	90
5	*p*-MeO-C_6H_4-$B(OH)_2$ **7C**	**6aC**	quant.
6	C_6H_5-$B(OH)_2$ **7D**	**6aD**	84
7	*p*-Cl-C_6H_4-$B(OH)_2$ **7E**	**6aE**	85
8	*p*-OHC-C_6H_4-$B(OH)_2$ **7F**	**6aF**	80
9	*o*-OHC-C_6H_4-$B(OH)_2$ **7G**	**6aG**	82
10	*p*-F_3C-C_6H_4-$B(OH)_2$ **7H**	**6aH**	78
11	*p*-NC-C_6H_4-$B(OH)_2$ **7I**	**6aI**	88
12	*m*-NO_2-C_6H_4-$B(OH)_2$ **7J**	**6aJ**	65
13	2-furan-$B(OH)_2$ **7K**	**6aK**	94
14	3-furan-$B(OH)_2$ **7L**	**6aL**	93
15	*trans*-propenyl-$B(OH)_2$ **7M**	**6aM**	82
16	*cis*-propenyl-$B(OH)_2$ **7N**	**6aN**	79[c]
17[d]	Et_3B **7O**	**6aO**	quant.
18[d]	octyl-9-BBN **7P**	**6aP**	80
19[d,e]	PhCCH-cat. CuI **7Q**	**6aQ**	78
20[d,f]	$(BPin)_2$ **7R**	**6aR**	85

[a] Reaction at 65 °C (entry 1) and 80 °C (entry 2) for 1 h with oil bath heating, and at 80 °C for 10 min with microwave irradiation (entries 3−20). [b] **8aA** is also obtained in the yields shown in parentheses. [c] Small amount of **6aM** is contained. [d] Reaction with 2 equiv of nucleophiles. [e] Reaction with 4 mol % of $Pd(PPh_3)_4$ and 4 mol % of CuI. [f] Pin = pinacolato.

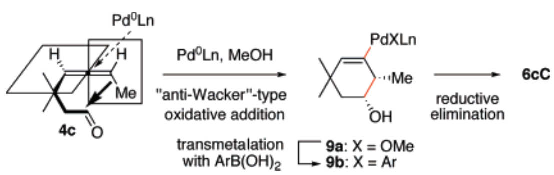
10.1021/ja076080p CCC: $40.75

Table 2. Pd(PPh_3)$_4$-Catalyzed Arylative Cyclizations of **4b**−**g**[a]

entry	4	6[b]	time (min)	yield (%)
1	 **4b**	 **6bC**	20	89
2[c]	 **4c**	 **6cC**	10	74[e] (92% ee)
3[d]	 **4d**	 **6dC**	90	70
4	 **4e**	 **6eC**	10	78
5	 **4f**	 **6fC**	20	72
6	 **4g**	 **6gC**	20	23[f]

[a] Reaction with 1.5 equiv of **7C** and 2 mol % of catalyst at 80 °C under microwave irradiation. [b] Ar = C_6H_4-*p*-OMe. [c] Reaction with 5 mol % of catalyst. [d] Reaction at 100 °C. [e] Small amount of *anti*-isomer (epimer at C-1, 91% ee) is contained. [f] The *syn*-isomer is also obtained in 8% yield.

Scheme 2. Possible Mechanism for the Arylative Cyclization of **4c**



conformationally more flexible methylene and shorter tethers also undergo efficient cyclization reactions (entries 4 and 5). However, this catalytic system is less suitable for the cyclization of allenyl aldehyde **4g** with a longer tether than the previously reported ones[2,5] (entry 6).

The high efficiency of chirality transfer from the starting optically active **4c** to **6cC** (Table 2, entry 2)[13] supports *trans*-specific addition of **7C** to the aldehyde across the distal allene π-system, which would result from an intramolecular electrophilic addition of the carbonyl group in **4c** to the allene coordinated by electron-rich Pd^0 (anti-Wacker-type oxidative addition)[8,15] and concomitant transmetalation with **7C** followed by reductive elimination (Scheme 2). It is worth noting that both regiochemistry and stereochemistry of addition of the catalyst and the carbonyl to the allene moiety are opposite to those of the Ni^0-catalyzed allene aldehyde coupling reported by Jamison.[7]

In summary, we have developed an efficient synthetic method for 3-substituted 3-cyclohexenols and -cyclopentenol from allene carbonyl compounds. Microwave irradiation turns out to increase not only the reaction rate but also the product yield and to suppress formation of hydroarylation byproducts observed in the same catalytic system.[9] In addition to sp^2- and sp^3-carbonucleophiles, sp-carbon and boron nucleophiles also participate in this process. We also obtain proof of the reaction mechanism involving not carbopalladation but anti-Wacker-type cyclization. Cyclic homoallylic alcohols generated in these reactions should be versatile intermediates in carbocycle synthesis since they contain a rich array of preparatively important functional groups. Studies expanding the scope of the cyclization process are underway.

Acknowledgment. This work was partly supported by a Grant-in-Aid from the Japan Society for Promotion of Sciences (No. 18790003) and Banyu Pharmaceutical Co. Ltd. Award in Synthetic Organic Chemistry, Japan.

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

References

(1) Reviews on transition-metal-catalyzed cyclization of allenes: (a) Ma, S. *Pure Appl. Chem.* **2006**, *78*, 197−208. (b) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701−712. (c) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12−21. (d) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067−3125. (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590−3593. (f) Yamamoto, Y.; Radhakrishman, U. *Chem. Soc. Rev.* **1999**, *28*, 199−207. (g) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111. (h) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387−391.

(2) Palladium(0)-catalyzed arylative cyclization with aryl iodides and distannane or In: (a) Ha, Y.-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143−1146. (b) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376−4379. See also silylative and stannylative cyclization: (c) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343−345. (d) Yu, C.-M.; Youn, J.; Lee, M.-K. *Org. Lett.* **2005**, *7*, 3733−3736.

(3) An indirect method based on silaboration of allenyl aldehyde followed by Lewis acid promoted cyclization and subsequent cross-coupling reaction with aryl bromides was reported. Ohmura, T.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2006**, *128*, 13682−13683.

(4) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793.

(5) (a) Montgomery, J.; Song, M. *Org. Lett.* **2002**, *4*, 4009−4011. (b) Song, M.; Montgomery, J. *Tetrahedron* **2005**, *61*, 11440−11448. (c) Kang, S.-K.; Yoon, S.-K. *Chem. Commun.* **2002**, 2634−2635.

(6) In fact, Ni^0 catalyst resulted in formation of **6aD** in poor yield. Reaction conditions for Pd^{2+}- or Rh^{1+}-catalyzed intermolecular coupling reaction of allenes, aldehydes, and arylboronic acids based on carbometalation as follows were also unsuitable for the formation of **6aD**: (a) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221−2224. (b) Hopkins, C. D.; Guan, L.; Malinakova, H. C. *J. Org. Chem.* **2005**, *70*, 6848−6862. (c) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2006**, *8*, 5971−5974. (d) Bai, T.; Ma, S.; Jia, G. *Tetrahedron* **2007**, *63*, 6210−6215.

(7) (a) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 7320−7321. (b) Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2005**, *61*, 11405−11417. (c) Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 11350−11359.

(8) (a) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406−1407. (b) Tsukamoto, H.; Ueno, T.; Kondo, Y. *Org. Lett.* **2007**, *9*, 3033−3036.

(9) Palladium(0)-catalyzed hydroarylation and hydroalkynylation of allenes: (a) Oh, C. H.; Ahn, T. W.; Reddy, V. R. *Chem. Commun.* **2003**, 2622−2623. (b) Ma, S.; Jiao, N.; Ye, L. *Chem.—Eur. J.* **2003**, *9*, 6049−6056. (c) Qian, R.; Guo, H.; Liao, Y.; Guo, Y.; Ma, S. *Angew. Chem., Int. Ed.* **2005**, *42*, 4771−4774. (d) Bruyere, D.; Grigg, R.; Hinsley, J.; Hussain, R. K.; Korn, S.; Orgaz De La Cierva, C.; Sridharan, V.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 8669−8672.

(10) Recent reviews on microwave-assisted organic synthesis: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284. (b) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164−178.

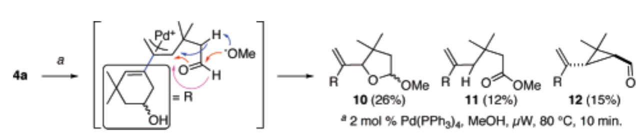
(11) We also observed that employment of arylboronic esters led to exclusive formation of **6aA**. In situ formation of methyl arylboronate might be accelerated by microwave irradiation.

(12) Use of alkynylboronic esters resulted in protonation of the esters.

(13) In addition to this result, no competitive addition to the formyl group in **7F** (Table 1, entry 9),[14] no reductive cyclization using **7O,P** (Table 1, entries 17 and 18), and less efficiency and *anti* selectivity of the cyclization of **4g** (Table 2, entry 6) would also exclude the carbopalladation pathway.

(14) Grigg reported Pd^0-catalyzed coupling reaction of 2-haloaryl aldehydes with external allene: (a) Anwar, U.; Grigg, R.; Rasparini, M.; Savic, V.; Sridharan, V. *Chem. Commun.* **2000**, 645−646. (b) Gai, X.; Grigg, R.; Collard, S.; Muir, J. E. *Chem. Commun.* **2002**, 1765−1766.

(15) Reaction of **4a** in MeOH without nucleophiles gives 3-cyclohexenols **10**−**12**, which would result from carbopalladation of **4a** with a cyclic alkenylpalladium intermediate such as **9a**.



JA076080P