ORGANIC LETTERS
2008
Vol. 10, No. 13
2633−2636

A New Five-Membered Ring Forming Process Based on Palladium(0)-Catalyzed Arylative Cyclization of Allenyl Enones

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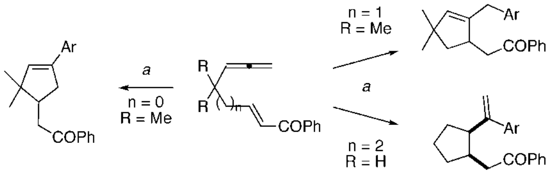
Received March 6, 2008

ABSTRACT



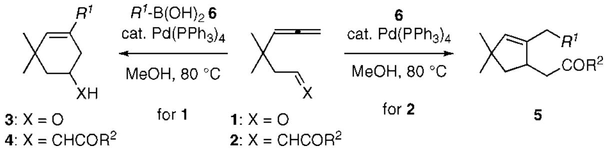
[a] Ar-B(OH)$_2$, cat. Pd^0-PPh$_3$ or P(c-Hex)$_3$, MeOH, 80 °C

A palladium(0)/monophosphine catalyst promotes a novel arylative cyclization reaction of C1-, C2-, and C3-tethered allenyl enones with arylboronic acids to produce five-membered ring containing products. The regioselectivity of the process, associated with aryl group introduction into the allene moiety, depends on the length of the tether. This finding suggests that the cyclization reaction does not proceed through a carbopalladation pathway but rather via a route involving palladacycle-forming or “anti-Wacker”-type oxidative addition to the Pd^0 catalyst.

Transition-metal-catalyzed carbocyclization reactions of functionalized allenes serve as powerful one-step methods to prepare carbocycle and heterocycle containing, highly substituted alkenes,[1–6] which are potentially useful intermediates in the synthesis of natural and pharmaceutically interesting substances.

We recently developed a new process for the synthesis of 3-substituted 3-cyclohexen-1-ols **3** that relys on Pd^0/monophosphine-catalyzed alkylative cyclization of allene−aldehydes **1** with organoboron reagents **6** (Scheme 1, left).[2a]

Scheme 1. Pd^0-Catalyzed Alkylative Cyclization of Allene−Aldehydes and −Enones



Initial circumstantial evidence suggested that the cyclization reaction proceeds through a pathway involving (1) intramolecular electrophilic addition of the carbonyl group in **1** to the allene, coordinated to electron-rich Pd^0 (so-called “anti-

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(1) Reviews on transition-metal-catalyzed cyclizations 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. (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) Pd-catalyzed cyclizations of allene−aldehydes: (a) Tsukamoto, H.; Matsumoto, T.; Kondo, Y. *J. Am. Chem. Soc.* **2008**, *130*, 388–389. (b) Tsukamoto, H.; Matsumoto, T.; Kondo, Y. *Org. Lett.* **2008**, *10*, 1047–1050. (c) Ha, Y.-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143–1146. (d) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376–4379. (e) Yu, C.-M.; Youn, J.; Lee, M.-K. *Org. Lett.* **2005**, *7*, 3733–3736.

(3) Ni-catalyzed cyclizations of allene-aldehydes: (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.

10.1021/ol800509z CCC: $40.75

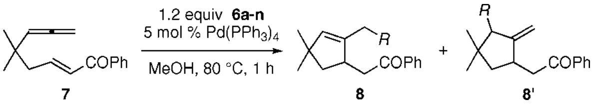
Wacker”-type oxidative addition),[7] (2) concomitant transmetalation with the organoboron reagent, and (3) reductive elimination. However, due to the similar regioselectivity associated with carbopalladation,[1,2b–d,8] it is difficult to rule out a mechanism for this process that involves sequential insertion of the allene and carbonyl moiety into the carbon−palladium(II) bond.[9–11]

Fortunately, during the course of studies designed to uncover the origin of the “anti-Wacker”-type oxidative addition, we discovered that this catalytic system promotes a cyclization reaction of the allene−enone **2** that follows a different regiochemical course to provide the cyclopentene **5** rather than cyclohexene **4** (Scheme 1, right).

Below, we describe the results of an investigation of the effects of the length of tethers on the different regiochemical modes of cyclization seen in Pd^0/monophosphine-catalyzed arylative cyclization reactions of allene-containing electron-deficient alkenes. The findings suggest that the regiochemical course of the carbocyclization process can be rationalized by invoking palladacycle-forming or “anti-Wacker”-type oxidative addition to the Pd^0 catalyst. To the best of our knowledge, the carbocyclization reactions of 1,2,5- and 1,2,6-trienes desribed in this report are the first examples of metal-catalyzed cyclization reactions of this type.[12]

The arylative cyclization of (2*E*)-5,5-dimethyl-1-phenyl-2,6,7-octatrien-1-one (**7**), using a slight excess of phenylboronic acid (**6a**), takes place in the presence of 5 mol % of $Pd(PPh_3)_4$ at 80 °C to provide cyclopentene **8a** in good yield (Table 1, entry 1). In contrast to related allene−aldehyde cyclizations,[2a] the use of methanol as solvent and microwave irradiation are not essential for this process (e.g., 1,4-dioxane can be used as solvent) (entries 1 and 2). Importantly, the reaction does not take place in the absence of the palladium catalyst or in the presence of $Pd(OAc)_2(dppe)$ as a Pd^{2+} source.

Table 1. Arylative, Alkenylative, and Reductive Cyclization of **7**



entry	6	product	yield (%)
1	$C_6H_5B(OH)_2$ **6a**	**8a**	68
2[a,b]	**6a**	**8a**	61
3	*p*-MeO-$C_6H_4B(OH)_2$ **6b**	**8b**	62
4	*p*-Me-$C_6H_4B(OH)_2$ **6c**	**8c**	70
5	*o*-Me-$C_6H_4B(OH)_2$ **6d**	**8d**	68
6[b]	*m*-Me-$C_6H_4B(OH)_2$ **6e**	**8e**	76
7	*p*-F-$C_6H_4B(OH)_2$ **6f**	**8f**	77
8	*p*-Cl-$C_6H_4B(OH)_2$ **6g**	**8g**	75
9	*p*-Ac-$C_6H_4B(OH)_2$ **6h**	**8h**	69
10[b]	*p*-OHC-$C_6H_4B(OH)_2$ **6i**	**8i**	75
11[b]	*m*-NO_2-$C_6H_4B(OH)_2$ **6j**	**8j**	70
12	(*E*)-PhCH═CHB(OH)$_2$ **6k**	**8k**	80
13	3-thiophene-B(OH)$_2$ **6l**	**8l**	80
14[c]	2-thiophene-B(OH)$_2$ **6m**	**8m**	25[d]
15[e]	Et_3B **6n**	**8n, 8′n** (R = H)	54[f](1:1)[g]

[a] Reaction in 1,4-dioxane. [b] Reaction for 2 h. [c] Reaction for 6 h. [d] **8′n** (R = H) and **8o** (R = OMe) were also obtained in 11% and 29% yields, respectively. [e] 1.6 equiv of **6n** was used. [f] **8o** was also obtained in 24% yield. [g] The ratio was determined by ^1H NMR.

Arylboronic acids containing electron-donating (entries 3−6) or -withdrawing groups (entries 7−11) serve as nucleophiles in this process, as exemplified by the formation of **8b**−**j** in high yields. Alkenylative cyclization also occurs with **7** to provide 1,4-diene **8k** (entry 12). However, the two nucleophiles 2-thiopheneboronic acid and triethylborane display different behavior in contrast with that of other substrates for the allene-aldehyde cyclization. For example, cyclization reaction of **7** with 2-thiopheneboronic acid (**6m**) is sluggish, even though its isomer **6l** reacts in a normal fashion (entries 13 and 14).[13] Also, triethylborane (**6n**), possessing β-hydrogens, does not undergo ethylative cyclization but rather produces the reduction products **8n** and **8′n** (R = H) as a 1:1 mixture (entry 15).

Reaction of the 1,1-disubtituted allene−enone **9** leads to formation of the tetrasubstituted alkene containing cyclopentene **18** (Table 2, entry 1). Use of a PdCp(η^3-allyl)/P(*c*-Hex)$_3$ combination[7b] in place of $Pd(PPh_3)_4$ promotes conversion of the 1,3-disubstituted allene **10** to cyclized product **19** as a mixture of diastereomers (entry 2). The aldehyde and methyl ketone appended alkenes **11** and **12**, as well as the phenyl ketone analogue **7**, undergo $Pd(PPh_3)_4$-catalyzed cyclization to produce the corresponding products **20** and

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(4) Pd-catalyzed cyclizations of 1,2,7-trienes: (a) Zhu, G.; Zhang, Z. *Org. Lett.* **2004**, *6*, 4041–4047. (b) Doi, T.; Yanagisawa, A.; Nakanishi, S.; Yamamoto, K.; Takahashi, T. *J. Org. Chem.* **1996**, *61*, 2602–2603. (c) Doi, T.; Yanagisawa, A.; Yamamoto, K.; Takahashi, T. *Chem. Lett.* **1996**, 1085–1086. (d) Doi, T.; Takasaki, M.; Nakanishi, S.; Yanagisawa, A.; Yamamoto, K.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2929–2935. (e) Ohno, H.; Miyamura, K.; Mizutani, T.; Kadoh, Y.; Takeoka, Y.; Hamaguchi, H.; Tanaka, T. *Chem. Eur. J.* **2005**, *11*, 3728–3741.

(5) Ni-catalyzed cyclizations of 1,2,7-trienes: Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139−11143.

(6) Pd-catalyzed cyclizations of allene−ynecarboxylate: (a) Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Tetrahedron Lett.* **2005**, *46*, 2247–2250. (b) Oh, C. H.; Park, D. I.; Jung, S. H.; Reddy, V. R.; Gupta, A. K.; Kim, Y. M. *Synlett* **2005**, 2092–2094.

(7) (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.

(8) Pd-catalyzed intermolecular coupling reactions of allenes, aldehydes, and arylboronic acids based on carbopalladation: (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.

(9) Arylpalladium(II) species, formed by oxidative addition of arylboronic acid to palladium(0), are proposed to be intermediates in the Pd^0-catalyzed carbonylations of the boronic acids. (a) Ohe, T.; Ohe, K.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1988**, *344*, C5−C7. (b) Cho, C. S.; Ohe, T.; Uemura, S. *J. Organomet. Chem.* **1995**, *496*, 221–226.

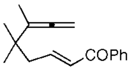
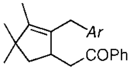
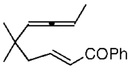
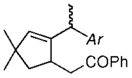
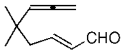
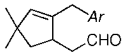
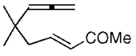
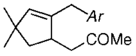
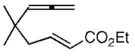
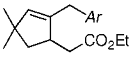
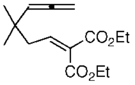
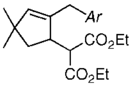
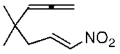
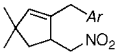
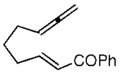
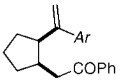
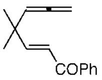
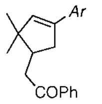
(10) The only example of the opposite regioselectivity of intermolecuar carbopalladation is seen in reactions of allenes substituted with sulfones. (a) Fu, C.; Ma, S. *Org. Lett.* **2005**, *7*, 1605–1607. The opposite regioselectivity of intramolecular carbopalladation of allenes is reported in the following. (b) Grigg, R.; Rasul, R.; Redpath, J.; Wilson, D. *Tetrahedron Lett.* **1996**, *37*, 4609–4612. (c) Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. *Helv. Chim. Acta* **1997**, *80*, 623–639, See also ref 4a–d.

(11) Pd^{2+}−diphosphine catalysts that are applicable to the carbopalladation pathway do not promote the reactions described herein. Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *9*, 4227–4230, See also ref 2b.

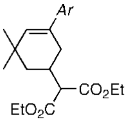
(12) There is only one example of allylmetalation of a 1,2,6-triene. Nishikawa, T.; Shinokubo, H.; Ohshima, K. *Org. Lett.* **2003**, *5*, 4623–4626.

(13) Organoboron reagents **6m**,**n** do not serve as good nucleophiles in direct cross-coupling reactions with allylic alcohols. (a) Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2003**, 1200–1201. The 2-thienyl group is used as dummy ligand in the Hiyama cross-coupling reaction. (b) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, 138–139.

Table 2. Arylative Cyclization of Trienes **9**−**17** with **6c**[a]

entry	substrate	product	time (h)	yield (%)
1	 **9**	 **18**	1	61
2	 **10** (racemic)	 **19** (dr = 1.1 : 1)	1	64
3	 **11**	 **20**	1	60
4	 **12**	 **21**	1	67
5	 **13**	 **22**	2	54
6	 **14**	 **23**	1	52[c]
7[b]	 **15**	 **24**	16	62[d]
8	 **16**	 **25**	1	57[e]
9	 **17**	 **26**	16	66

[a] Reaction with 1.2 equiv of **6c** and 5 mol % of catalyst in MeOH at 80 °C. Pd(PPh$_3$)$_4$ (entries 1, 3, 4, 9) or PdCp(η^3-C$_3$H$_5$)-P(c-Hex)$_3$ (1:3) (entries 2, 5−8) was used as the catalyst. Ar = C$_6$H$_4$-p-Me. [b] Reaction in 1,4-dioxane in place of MeOH. [c] Cyclohexene **27** was also obtained in 9% yield. [d] Cyclohexene **28** was also obtained in 6% yield. [e] Small amount of the trans isomer was observed.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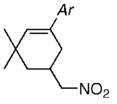
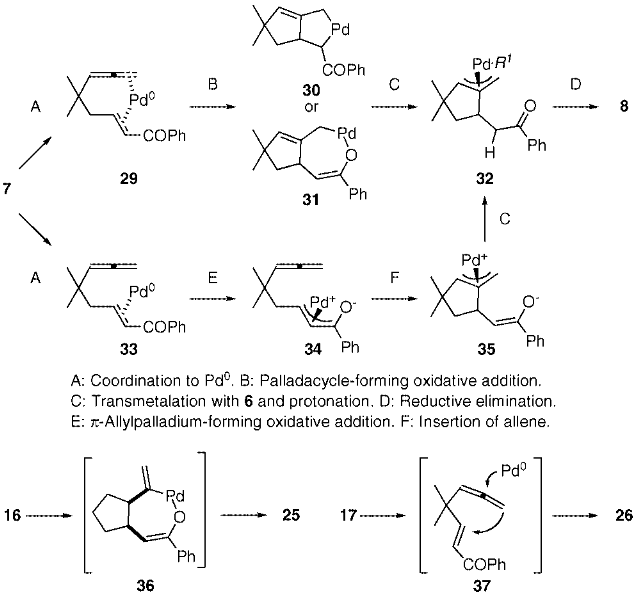

28

21 (entries 3 and 4). Again, the Pd^0 catalyst ligated with P(c-Hex)$_3$, a more σ-donating phosphine, is a more effective catalyst for the arylative cyclization of less electron-withdrawing ester-substituted alkene **13** (entry 5). Cyclization reactions of the malonate **14** and nitro alkene **15** produce major amounts of the respective cyclopentenes **23** and **24** along with minor quantities of the corresponding cylohexenes **27** and **28** (entries 6 and 7).[14]

The effects of tether length on the cyclization process were examined. Pd/P(c-Hex)$_3$-catalyzed reaction of the 1,2,7-triene **16** provides the cis-fused cyclopentane **25** containing an *exo* (1-aryl)ethenyl group (entry 8). On the other hand, 1,2,5-triene **17** undergoes cyclization in the presence of Pd(PPh$_3$)$_4$ to afford cyclopentene **26**, in which the aryl group and β-carbon of the enone are connected to the respective central sp- and terminal sp^2-carbons of the allene (entry 9).

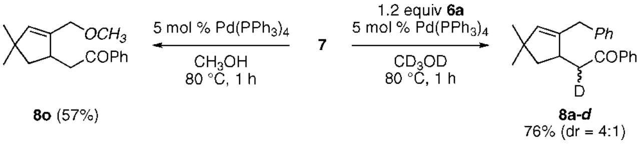
Scheme 2. Possible Mechanism for the Arylative Cyclization of **7**, **16**, and **17**



A: Coordination to Pd^0. B: Palladacycle-forming oxidative addition.
C: Transmetalation with **6** and protonation. D: Reductive elimination.
E: π-Allylpalladium-forming oxidative addition. F: Insertion of allene.

A plausible mechanism for the arylative cyclization of allenyl enone **7** is displayed in Scheme 2. In this pathway, the catalytic cycle is initiated by coordination and oxidative addition of both the allene and enone moieties in **7** to Pd^0 to form either [3,3,0]- or [3,5,0]bicyclic palladacycles **30** and **31** (Scheme 2, top). Transmetalation and protonation with the boronic acid **6**, taking place in either order, followed by reductive elimination of **32** at the less hindered allylic carbon regenerates the Pd^0 catalyst along with the cyclization product **8**.

Scheme 3. Cyclization of **7** in CD$_3$OD and in the absence of **6a**



Formation of methyl ether **8o** in reactions performed in the absence of nucleophiles (Scheme 3, left) and incorporation of a deuterium into the α-position of phenyl ketone in **8a** in the reaction carried out in methanol-d_4 (Scheme 3, right) gives support to the mechanism for formation of **30** and **31**.[15]

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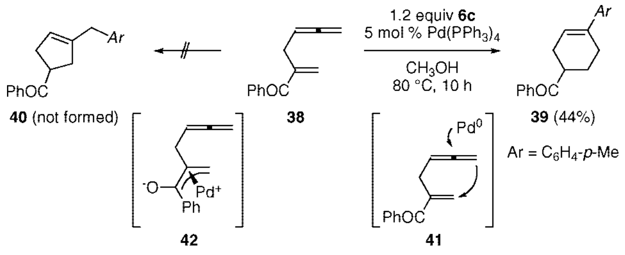
(14) In contrast to those promoted by Pd/P(c-Hex)$_3$, Pd(PPh$_3$)$_4$-catalyzed cyclizations of **14** and **15** provide cyclohexenes **27** and **28** as major products along with minor amounts of cyclopentenes **23** and **24**. These electron-deficient alkenes should not form π-complexes readily with the Pd^0 catalyst that are ligated with less-σ-donating PPh$_3$.

At this time, it is not possible to rule out an alternative mechanism involving formation of π-allylpalladium **34** via oxidative addition of the enone moiety in **7** to Pd^0 followed by insertion of the allene to generate intermediate **32** (Scheme 2, middle).[16] However, reaction of 1,2,5-triene **38**, containing an internal enone, does not afford cyclopentene **40** by way of intramolecular allene insertion of π-allylpalladium **42**. Rather, cyclohexene **39** is generated through an "anti-Wacker"-type 6-endo cyclization (Scheme 4).[17] The different behavior of organoboron reagents **6m**,**n** in reactions of allene−aldehydes versus allene−enones (Table 1, entries 14 and 15) reflects the participation of different palladium intermediates, i.e., σ-alkenyl- versus π-allylpalladium species, respectively.[18]

Scheme 4. Arylative Cyclization of 1,2,5-Trienes **38**



The change from "anti-Wacker"-type oxidative addition to palladacycle-forming addition is the consequence of the much higher tendency for Pd^0 catalysts to form π-complexes with electron-deficient alkenes rather than with the carbonyl group. Palladacycle formation would be slowed by both methyl substitution at the terminal allene carbon and the presence of a less potent electron-withdrawing group at the alkene. In contrast, the formation of palladacycles would be promoted by the use of more σ-donating P(*c*-Hex)$_3$ ligands in place of PPh$_3$ (Table 2, entries 2 and 5−7). The cyclization of 1,2,7-triene **16** would proceed through the alkenylpalladium intermediate **36**, containing a cis-fused cyclopentane ring, and provide the cis addition product **25** in contrast to trans-selective cyclization of 5,6-dienals[2a] (Table 2, entry 8, and Scheme 2, bottom, left). On the other hand, "anti-Wacker"-type cyclization would dominate in reaction of 1,2,5-triene **17**, which, owing to the presence of a short tether, cannot form a palladacycle (Table 2, entry 9, and Scheme 2, bottom, right).

In summary, the studies described above have led to the development of a Pd^0-catalyzed arylative cyclization reaction of allenyl enones with arylboronic acids that form five-membered ring products. The cyclization reactions proceed through pathways involving palladacycle-forming or "anti-Wacker"-type oxidative additions to the Pd^0 catalyst, the relative efficiencies of which depend on the tether length in the allenyl enones. The results of this study also suggest that "anti-Wacker"-type oxidative additions observed in the allene-aldehyde cyclization originate from the low tendency for the Pd^0 catalyst to form π-complexes with carbonyl groups. Finally, the five-membered ring products generated in these reactions should be versatile intermediates in carbocycle synthesis since they contain a rich array of preparatively important functional groups. Studies of transformations of the functionalized cyclic compounds 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.

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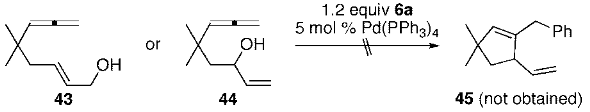
[15] We also demomstrated that the reaction conditions did not transform **8a** into **8a**−***d***.

[16] It is reported that the oxidative addition of enone to the Pd^0 occurs in the presence of strong Brønsted or Lewis acid. (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944–1950. (b) Ogoshi, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2003**, *125*, 9020–9021. See also: (c) Hanzawa, Y.; Yabe, M.; Oka, Y.; Taguchi, T. *Org. Lett.* **2002**, *4*, 4061–4063. (d) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5055–5508.

[17] We also observed that 1,2,6-triene **43** containing an allylic alcohol or its regioisomer **44** did not afford the cyclization product **45** through a π-allylpalladium intermediate.[13a]



[18] The difference results from the slower reductive elimination from π-allylpalladium(II) than that from σ-alkenylpalladium(II). β-Hydrogen elimination prior to reductive elmination would promote reductive cyclization of **7**, leading to the formation of **8n** and **8′n.**