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Palladium-Catalyzed Approach to Stereodefined Ten-Membered Cycles from 1,5-Bisallenes

Jiajia Cheng,[†] Xuefeng Jiang,[†] and Shengming Ma*[,†,‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China, and Shanghai Key Laboratory of Green Chemistry and Chemical Process Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, P. R. China

masm@sioc.ac.cn

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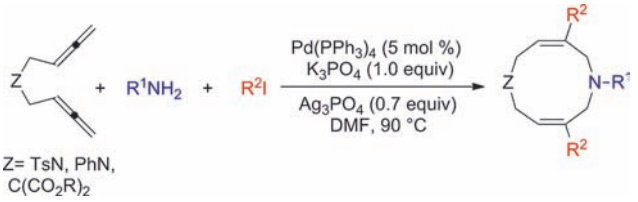
ABSTRACT



A three-component Pd(0)-catalyzed reaction of 1,5-bisallenes with organic halides in the presence of primary amines was observed to afford stereodefined not readily available ten-membered cyclic compounds highly chemo- and regioselectively. A mechanism involving two π-allylic palladium intermediates was proposed to account for the observed regio- and stereoselectivity.

Most of the biologically active molecules are cyclic compounds.[1] However, medium-sized heterocycles including ten-membered compounds are difficult to prepare due to entropic and enthalpic reasons.[2] Known methods always require very special techniques, such as highly diluted solutions.[3] Thus, new methodologies for the efficient synthesis of this medium-sized heterocycle are highly desirable.

On the other hand, transition-metal-catalyzed reactions of functionalized allenes have become one of the most important tools for the synthesis of some biologically important systems.[4] With the development of multicomponent reactions (MCRs), which have become efficient synthetic methods to create complex molecules,[5] novel multicomponent reactions involving allenes as substrates

[†] Chinese Academy of Sciences.
[‡] East China Normal University.

(1) For reviews, see: (a) Majhi, T. P.; Achari, B.; Chattopadhyay, P. *Heterocycles* **2007**, *71*, 1011. (b) Dietrich, B.; Viout, P.; Lehn, J. M. *Macrocyclic Chemistry*; VCH: Weinheim, 1993. (c) Weber, E.; Vögtle, F. *Macrocycles*; Springer: Berlin, 1992. (d) Evans, P. A.; Holmes, B. *Tetrahedron* **1991**, *47*, 9131.

(2) For related reviews, see: (a) Shiina, I. *Chem. Rev.* **2007**, *107*, 239. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(3) For reviews, see: (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (b) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. (c) Parker, D. *Macrocycle synthesis: A practical approach*; Oxford Univ. Press: Oxford, 1996. Selected examples: (a) Kitagaki, S.; Teramoto, S.; Mukai, C. *Org. Lett.* **2007**, *9*, 2549. (b) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749. (c) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (d) Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656.

(4) For reviews, see: (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (b) Marshall, J. *Chem. Rev.* **2000**, *100*, 3163. (c) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735. (d) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133. (e) Kim, H.; Williams, L. J. *Curr. Opin. Drug Disc.* **2008**, *11*, 870. (f) Back, T. G.; Clary, K. N.; Gao, D. *Chem. Rev.* **2010**, *110*, 4498. (g) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau., A. *Chem. Rev.* **2011**, *111*, 1954. (h) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.

(5) For reviews on multicomponent reactions: see: (a) Alba, A.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (b) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.

(6) For selected reports on Pd-catalyzed three-component reactions of allenes, see: (a) Yang, F. Y.; Wu, M. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2000**, *122*, 7122. (b) Ma, S.; J, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4737. (c) Huang, T. H.; Chang, H. M.; Wu, M. Y.; Cheng, C. H. *J. Org. Chem.* **2002**, *67*, 99. (d) Shu, W.; Jia, G.; Ma, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 2788.

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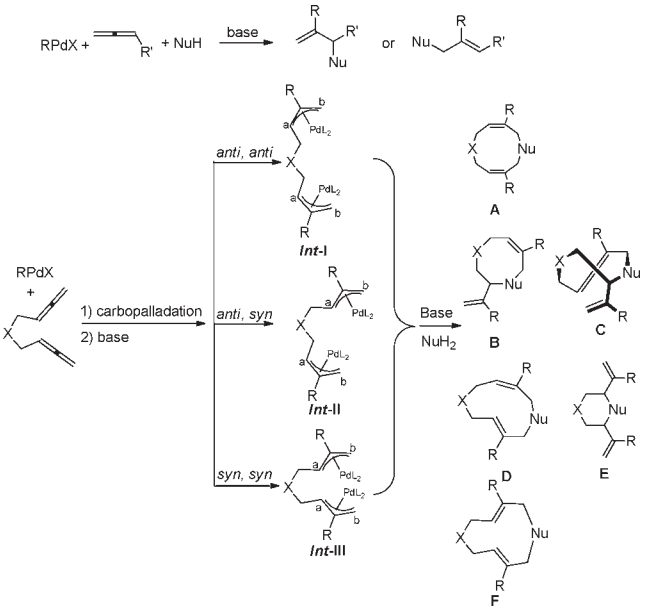
to construct complex structures have attracted much attention.[6]

Pd-catalyzed carbopalladation of allenes may afford the π-allylic palladium species which would react with a nucleophile to form the allylation product.[7,8] Based on this, we envisioned that the carbopalladation of 1,5-bisallenes may afford two π-allylic Pd intermediates, which may be trapped by a NuH_2-type of nucleophile sequentially to give cyclic products.[9] Nontheless, there are three types of intermediates and each one has four reaction sites which may lead to six types of products **A** to **F** (Scheme 1). It should be mentioned that most of the known reports on the trapping of two π-allylic metal species by a NuH_2-type of nucleophile are prone to form 5- or 6-membered cyclic compounds.[10] Thus, in this reaction the control of regio- and stereoselectivity would be a formidable challenge. Of particular interest is the possible selective formation of the ten-membered products **A**. Herein, we wish to disclose our recent observation of the three-component cyclization for the highly regioselective synthesis of ten-membered heterocycles with two stereodefined C=C bonds.

Our initial work began with the cyclization of bis(2,3-butadienyl)tosylamide **1a** with phenyl iodide **2a** in the presence of benzylamine **3a** as the NuH_2-type of nucleophiles. When the reaction was carried out in *N*,*N*-dimethylformamide (DMF) at 90 °C catalyzed by 5 mol % $Pd(PPh_3)_4$ in the presence of 4.0 equiv of K_2CO_3, surprisingly, the ten-membered cycloalkene **4a** was obtained in 35% yield exclusively (Table 1, entry 1)! The structure and configuration of the C=C bond was unambiguously established by its X-ray diffraction study (Figure 1).[11] It is worth noting that other **B**–**F** types of regio- and

Scheme 1. Possible Reaction Pathways for Carbopalladation of Allenes and Bisallenes



stereoisomers were not observed, indicating that this reaction is highly regio- and stereoselective. The solvent effect was examined with $Pd(PPh_3)_4$ as the catalyst, and DMF was found to be the best for the reaction (Table 1, entries 1–5). No better results were observed by using catalyst

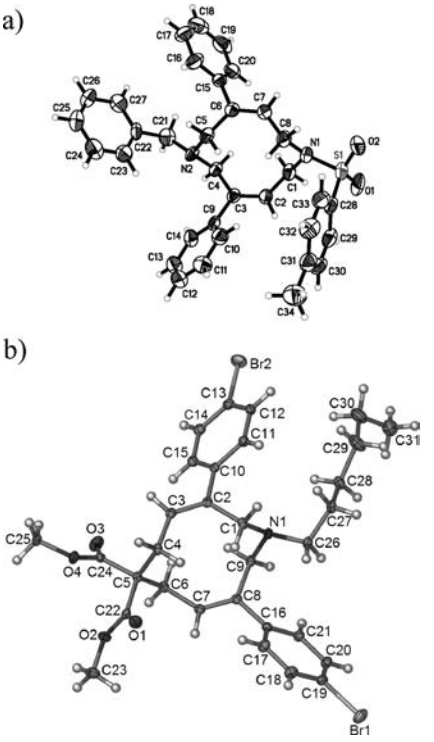


Figure 1. ORTEP drawings of (a) **4a** and (b) **4u**.

(7) For related reviews, see: (a) Shaw, B. L.; Stringer, A. J. *Inorg. Chim. Acta Rev.* **1973**, *7*, 1. (b) Otsuka, S.; Nakamura, A. *Adv. Organomet. Chem.* **1976**, *14*, 245. (c) Bowden, F. L.; Giles, R. *Coord. Chem. Rev.* **1976**, *20*, 81. (d) Jones, W. M.; Klosin, J. *Adv. Organomet. Chem.* **1998**, *42*, 147. (e) Bai, T.; Ma, S.; Jia, G. *Coord. Chem. Rev.* **2009**, *253*, 423.

(8) For a seminal report on the synthesis of medium-sized rings by Pd-catalyzed allylic substitution, see: (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867. For related reviews, see:(b) Trost, B. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 1173. (c) Trost, B. M. *ACS Adv. Chem. Ser.* **1992**, *230*, 463.

(9) For a highlight of 1,5-bisallenes, see: Chen, G.; Jiang, X.; Fu, C.; Ma, S. *Chem. Lett.* **2010**, *39*, 78.

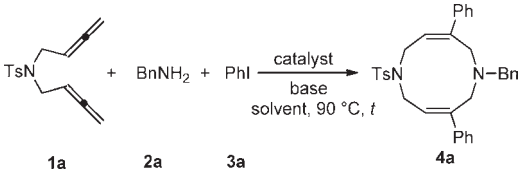
(10) For selected examples of π-allyllic palladium, see: (a) Huang, Y.; Lu, X. *Tetrahedron Lett.* **1988**, *29*, 5663. For selected examples of π-allyllic iridium, see:(b) Miyabe, H.; Yoshida, K.; Kobayashi, Y.; Matsumura, A.; Takemoto, Y. *Synlett* **2003**, 1031. (c) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239.

(11) Crystal data for **4a**. $C_{34}H_{34}N_2O_2S$, MW = 534.69, monoclinic, space group *Pbca*, final R indices [$I > 2\sigma(I)$], $R_1 = 0.0697$, $wR_2 = 0.1677$, R indices (all data) $R_1 = 0.1590$, $wR_2 = 0.1999$, $a = 13.1485(16)$ Å, $b = 16.858(2)$ Å, $c = 25.981(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 5758.7(12)$ Å^3, $T = 293$ K, $Z = 8$, reflections collected/unique: 28914/5349 ($R_{int} = 0.1070$), number of observations [$I > 2\sigma(I)$] 2161, parameters:354. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 831646).

(12) Crystal data for **4u**. $C_{31}H_{37}Br_2NO_4$, MW = 647.44, monoclinic, space group *Pbca*, final R indices [$I > 2\sigma(I)$], $R_1 = 0.0388$, $wR_2 = 0.0840$, R indices (all data) R1 = 0.0589, wR2 = 0.0939, $a = 15.4711(9)$ Å, $b = 9.7718(6)$ Å, $c = 39.174(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 5922.3(6)$ Å^3, $T = 173$ K, $Z = 8$, reflections collected/unique: 64554/5205 ($R_{int} = 0.0637$), number of observations [$I > 2\sigma(I)$] 4012, parameters:343. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 831645).

systems of $Pd(dba)_2$/phosphorus or a nitrogen containing ligand (Table 1, entries 6–7). A $Pd(dba)_2$/*N*-heterocyclic carbene (NHC) ligand catalyst system failed to catalyze the reaction (Table 1, entry 8). When the same reaction was carried out with Ag_3PO_4 as the halide scavenger, the yield of **4a** was very similar (36%) (Table 1, entry 9). Then, the reaction was tested with different bases, such as K_2CO_3, Cs_2CO_3, K_3PO_4, and Na_3PO_4. Among them K_3PO_4 was shown to be the best with **4a** being isolated in 43% yield (Table 1, entries 13–16). Thus, $Pd(PPh_3)_4$ (5 mol %), Ag_3PO_4 (0.7 equiv), and K_3PO_4 (1 equiv) in DMF at 90 °C were defined as the optimized reaction conditions for further study. Based on the NMR analysis of the crude reaction mixture formed under the optimized conditions before separation, only one stereoisomer was formed.

Table 1. Optimization of the Reaction Conditions for the Pd-Catalyzed Three-Component Cyclization of **1a** with $BnNH_2$ and PhI[a]

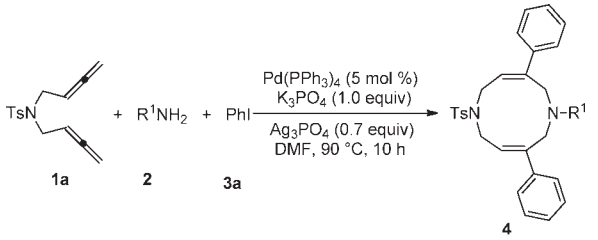


entry	catalyst	base or additive	solvent/*t* (h)	yield (%)[b]	**1a** (%)[c]
1	$Pd(PPh_3)_4$	K_2CO_3	DMF/10	35	0
2	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN[d]/16.5	28	30
3	$Pd(PPh_3)_4$	K_2CO_3	THF[d]/10	n.d.	48
4	$Pd(PPh_3)_4$	K_2CO_3	toluene/17	n.d.	60
5	$Pd(PPh_3)_4$	K_2CO_3	dioxane/22	n.d.	45
6	$Pd(dba)_2$/L[e]	K_2CO_3	DMF/10	n.d.	0
7	$Pd(dba)_2/PPh_3$	K_2CO_3	DMF/10	17	0
8	$Pd(dba)_2$/IPr[f]	K_2CO_3	DMF/10	n.d.	0
9	$Pd(PPh_3)_4$	Ag_3PO_4[i]	DMF/10	36	0
10	$Pd(PPh_3)_4$	Ag_2CO_3[g]	DMF/10	n.d.	25
11	$Pd(PPh_3)_4$	$AgNO_3$[h]	DMF/10	n.d.	0
12	$Pd(PPh_3)_4$	AgOAc[h]	DMF/10	n.d.	0
13	$Pd(PPh_3)_4$	K_2CO_3[i]	DMF/10.5	28	0
14	$Pd(PPh_3)_4$	Cs_2CO_3[i]	DMF/10	n.d.	0
15	$Pd(PPh_3)_4$	K_3PO_4[i]	DMF/10	45 (43[j])	0
16	$Pd(PPh_3)_4$	Na_3PO_4[i]	DMF/10	32	0

[a] The reaction was carried out using **1a** (0.1 M), $BnNH_2$ (1.0 equiv), PhI (3.0 equiv), base (1.0 equiv), additive (0.7 equiv), palladium complex (5 mol %), and ligand (10 mol %) at 90 °C. [b] Determined by ^1H NMR analysis with mesitylene as the internal standard. n.d. = not detected. [c] **1a** recovered after the reaction. [d] The reaction was conducted under reflux. [e] L = 2,2′-bipyridine. [f] 6 mol % IPr was added. IPr = 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene. [g] 1.0 equiv of silver salt was added to the reaction mixture. [h] 2.0 equiv of silver salt was added to the reaction mixture. [i] 0.7 equiv of Ag_3PO_4 was added. [j] Isolated yield.

With the optimized conditions in hand, we turned to examine the substrate scope of the reaction. We first studied the cyclization reaction of bisallene **1a** with different amines under the optimized reaction conditions (Table 2). The reaction is obviously influenced by the structures of amines: substituted benzylamine with an electron-donating group at the phenyl moiety gave poorer results than benzylamine (Table 2, entry 2). Aliphatic amines gave better results. In addition, the following issues should be noted: (1) The yields of these reactions range from 35% to 62%; (2) phenethylamine (Table 2, entry 6) may also be used to afford the corresponding ten-membered rings with an excellent stereoselectivity.

Table 2. $Pd(PPh_3)_4$-Catalyzed Coupling Cyclization of **1a** with Different Amines under Standard Conditions[a]



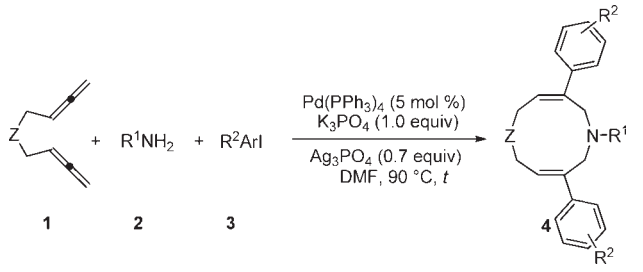
entry	R^1NH_2	yield of **4** (%)[b]
1	Bn (**2a**)	43 (**4a**)
2	*p*-$MeOC_6H_4CH_2$ (**2b**)	35 (**4b**)
3	*n*-C_4H_9 (**2c**)	49 (**4c**)[c]
4	*n*-C_6H_{13} (**2d**)	62 (**4d**)
5	cyclopropyl (**2e**)	48 (**4e**)[c]
6	$C_6H_4CH_2CH_2$ (**2f**)	56 (**4f**)

[a] The reaction was conducted using **1a** (0.1 M), R^1NH_2 (1.0 equiv), PhI (3.0 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (1.0 equiv), and Ag_3PO_4 (0.7 equiv) in DMF at 90 °C. [b] Yield of isolated product. [c] Amine (2.0 equiv) was used.

The scope of this reaction of differently tethered 1,5-bisallenes **1** with different phenyl iodides to give ten-membered rings has also been demonstrated (Table 3). The phenyl ring in the aryl iodide could be substituted by 4-Me, 3-Me (Table 3, entries 1–2), 4-Cl (Table 3, entry 4), *p*/*m*-Br (Table 3, entries 5–6), and the aryl group (Table 3, entry 10). Polysubstituted phenyl iodides are also suitable for this MCR process (Table 3, entry 3). Phenyl iodides with electron-withdrawing and -donating substituents on the phenyl ring are all good substrates (Table 3, entries 7–9). The reaction also proceeded smoothly with other aliphatic amines (Table 3, entries 11 and 12). Moreover, with differently tethered bisallene as the substrates, a ten-membered ring was obtained in moderate yields (Table 3, entries 13–15). The structure and configuration of the C=C bonds of **4u** were further confirmed by an X-ray diffraction study (Figure 1).[12] Finally, it is easy to conduct the reaction to afford **4d** in 62% yield in a gram scale (Scheme 2).

The high regio- and stereoselectivity of this reaction may be explained as follows: Carbopalladation of one of the two allene groups in the substrate would favor the formation of π-allylic Pd intermediate *anti*-**7** due to the steric interaction of the phenyl group R and the

Table 3. $Pd(PPh_3)_4$-Catalyzed Cyclization of **1** with Amines and Organic Halides under Standard Conditions[a]



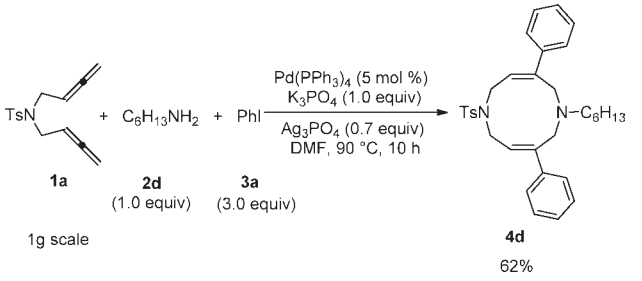
entry	Z	R^1NH_2/R^2ArI	t (h)	yield of **4**(%)[b]
1	TsN (**1a**)	n-C_6H_{13} (**2d**)/4-Me (**3b**)	16	50 (**4g**)
2	TsN (**1a**)	n-C_6H_{13} (**2d**)/3-Me (**3c**)	10	53 (**4h**)
3	TsN (**1a**)	n-C_6H_{13}(**2d**)/3,4-Me_2 (**3d**)	10	61 (**4i**)
4	TsN (**1a**)	n-C_6H_{13} (**2d**)/4-Cl (**3e**)	10	59 (**4j**)
5	TsN (**1a**)	n-C_6H_{13} (**2d**)/4-Br (**3f**)	10	51 (**4k**)
6	TsN (**1a**)	n-C_6H_{13} (**2d**)/3-Br (**3g**)	10	54 (**4l**)
7	TsN (**1a**)	n-C_6H_{13} (**2d**)/4-F (**3h**)	10	61 (**4m**)
8	TsN (**1a**)	n-C_6H_{13} (**2d**)/4-EtOOC (**3i**)	10	51 (**4n**)
9	TsN (**1a**)	n-C_6H_{13} (**2d**)/4-MeO (**3j**)	10	44 (**4o**)
10	TsN (**1a**)	n-C_6H_{13} (**2d**)/4-C_6H_5 (**3k**)	9.5	42 (**4p**)
11	TsN (**1a**)	n-C_4H_9 (**2c**)/4-Br (**3f**)	10	54 (**4q**)[c]
12	TsN (**1a**)	Bn (**2a**)/4-Br (**3f**)	8	45 (**4r**)
13	PhN (**1b**)	n-C_6H_{13} (**2d**)/4-EtOOC (**3i**)	10	38 (**4s**)
14	X (**1c**)[d]	n-C_6H_{13} (**2d**)/H (**3a**)	10	33 (**4t**)
15	X (**1c**)[d]	n-C_6H_{13} (**2d**)/4-Br (**3f**)	10	40 (**4u**)

[a] The reaction was conducted at 90 °C in DMF with **1** (c = 0.1 M), R^1NH_2 (1.0 equiv), R^2ArI (3.0 equiv), K_3PO_4 (1.0 equiv), and Ag_3PO_4 (0.7 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %) at indicated time. [b] Yield of isolated product. [c] Amine (2.0 equiv) was used. [d] X = $C(CO_2Me)_2$.

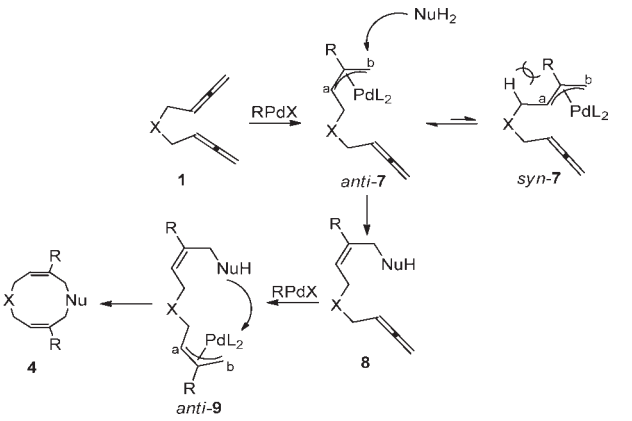
substituent containing the other allene group in *syn*-**7**. The regioselective intermolecular allylation of *anti*-**7** would lead to the formation of intermediate **8**. Then carbopalladation of the second allene moiety in the substrate would favor the formation of π-allylic Pd intermediate *anti*-**9**. The regioselective intramolecular allylic substitution of *anti*-**9** would lead to the formation of the ten-membered product **4** (Scheme 3).

In conclusion, we have developed a highly efficient methodology for the synthesis of challenging ten-membered rings from 1,5-bisallenes, amines, and organic halides. As a result of the challenge often encountered in the synthesis of ten-membered rings, this Pd(0)-catalyzed three-component coupling cyclization reaction is highly

Scheme 2. 1-g Scale Reaction of **1a**



Scheme 3. Rationale for the Selectivity Observed



regio- and stereoselective, which involves two π-allylic Pd intermediates and utilizes primary amines as dinucleophiles. Further studies in this area including the scope of the bisallenes and other NuH_2-types of nucleophiles are being pursued in our laboratory.

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