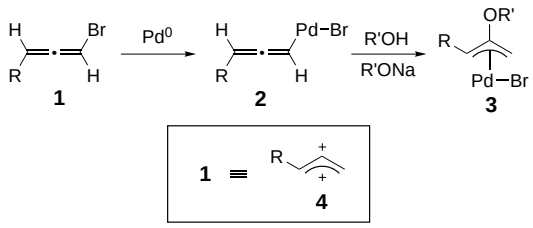
Medium-Sized Heterocycles

Bromoallenes as Synthetic Equivalents of Allyl Dications: Synthesis of Medium-Sized Nitrogen Heterocycles through the Cyclization of Bromoallenes in the Presence of a Palladium(0) Catalyst and an Alcohol**

*Hiroaki Ohno, Hisao Hamaguchi, Miyo Ohata, and Tetsuaki Tanaka**

Medium-sized nitrogen heterocycles (7- to 12-membered rings) are an extremely important class of compounds, which occur in a wide range of natural and non-natural products.[1] In particular, seven- and eight-membered nitrogen heterocycles are constituents of a number of compounds with interesting pharmacological properties.[2,3] Cyclization to medium-sized heterocycles is often slow and is hampered by the unfavorable enthalpies (strain in medium rings) and entropies (probability of the chain ends meeting) of the reaction. Accordingly, the construction of medium-sized heterocycles is a popular challenge for synthetic chemists.[4,5]

Currently, the reactivity of bromoallenes is attracting much interest as a result of their interesting chemical properties associated with their cumulated double bonds and bromine substituent.[6–8] In contrast, as far as we are aware, ring-forming reactions of bromoallenes have scarcely been studied.[9] This Communication is based on a new finding that the bromoallene **1** can act as allyl dication equivalent **4** when treated with palladium(0) in an alcohol solvent, presumably by the mechanism shown in Scheme 1.[10] Although similar types of reaction are often observed with propargylic carbonates in the presence of a palladium catalyst and a soft nucleophile such as active methylene, aryl alcohols,



Scheme 1. Bromoallenes as allyl dication equivalents.

[*] Prof. Dr. T. Tanaka, Dr. H. Ohno, H. Hamaguchi, M. Ohata
Graduate School of Pharmaceutical Sciences, Osaka University
1-6 Yamadaoka, Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-8214
E-mail: t-tanaka@phs.osaka-u.ac.jp

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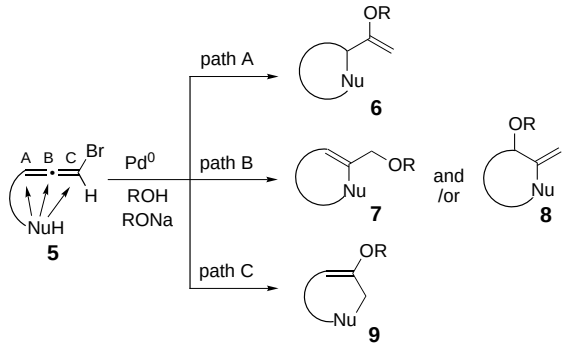
or amides,[10,11] the reaction of allenic substrates and the synthesis of eight-membered rings are unprecedented.

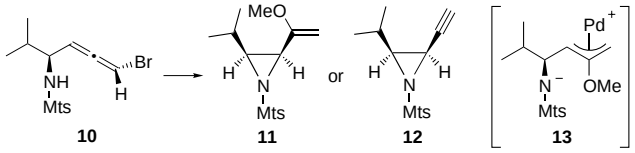
Utilizing this chemistry, we expected that various heterocyclic medium-sized rings could be formed through the intramolecular attack of an appropriate nucleophilic functionality such as an oxygen or nitrogen nucleophile. This sequence can lead to different products depending on whether the intramolecular nucleophilic attack takes place at the proximal (path A), central (path B), or distal (path C) position of the allenyl moiety (Scheme 2). Furthermore, in path B, the regioselectivity of the attack of an external nucleophile would make prediction of the product complicated. Herein we describe a highly regioselective method for the synthesis of heterocyclic medium-sized rings containing nitrogen atoms, through the palladium(0)-catalyzed cyclization of bromoallenes.[12]



Scheme 2. Synthesis of medium-sized rings by palladium(0)-catalyzed cyclization of bromoallenes.

In an initial experiment, we found that the reaction of bromoallene **10**, which bears a protected amino group at the α position, with $[Pd(PPh_3)_4]$ and NaOMe in MeOH provided 2,3-*cis*-2-(1-methoxy)vinylaziridine **11** stereoselectively (Table 1, entry 1). Considering that an N-activated 3-alkyl-2-vinylaziridine can be easily equilibrated with a palladium(0) catalyst via a π-allyl palladium complex to give predominantly the more stable 2,3-*cis* isomer,[13] this result strongly suggests the formation in the reaction of an intermediate π-allyl palladium complex **13**, which bears a methoxy group on the central carbon atom. This cyclization did not proceed in the absence of a palladium catalyst (Table 1, entry 2). When the reaction was carried out in THF in the presence or absence of palladium (Table 1, entries 3 and 4), *cis*-2-ethynylaziridine **12** was obtained as a single isomer, consistent with the results of our previous study.[9]

Table 1: Aziridination of bromoallene **10** in the presence of a palladium catalyst.[a]



Entry	$[Pd(PPh_3)_4]$ [mol %]	Solvent	*t* [h]	Product[b]	Yield [%][c]
1	10	MeOH	6	**11** (96:4)	81
2	–	MeOH	6	–	–
3	10	THF	5.5	**12** (>99:1)	82
4	–	THF	6	**12** (>99:1)	69[d]

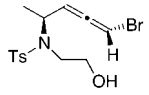
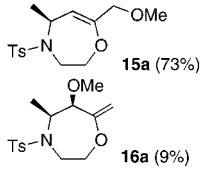
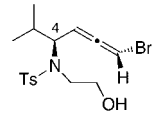
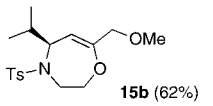
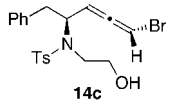
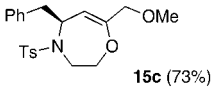
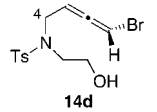
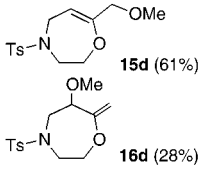
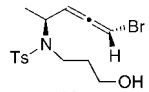
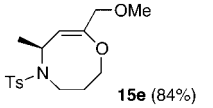
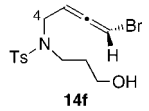
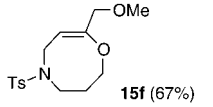
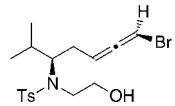
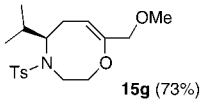
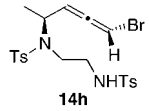
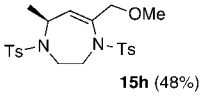
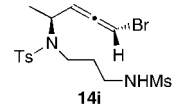
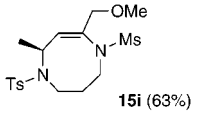
[a] Reactions were carried out at 25 °C in THF or MeOH with diastereomerically pure bromoallene **10** and NaOMe (1.2 equiv) in the presence or absence of $[Pd(PPh_3)_4]$. [b] Ratios were determined by ^{1}H NMR (300 MHz). [c] Yields of isolated products. [d] 30% of **10** was recovered. Mts = 2,4,6-trimethylphenylsulfonyl.

Next, according to the working hypothesis depicted in Scheme 2, we investigated the synthesis of medium-sized heterocycles through the cyclization of bromoallenes in the presence of a palladium catalyst. To investigate the effect of axial chirality on the cyclization reaction, diastereomerically pure (*S*,a*S*)-bromoallenes **14a–i** were prepared from known intermediates.[9] The results of the cyclization reactions are summarized in Table 2. Bromoallene **14a**, which bears an oxygen functionality, was treated with NaOMe (1.5 equiv) in MeOH in the presence of $[Pd(PPh_3)_4]$ (5 mol %) to afford the seven-membered ring **15a** (73%) and a small amount of its regioisomer **16a** (9%; Table 2, entry 1). In contrast, bromoallenes **14b** and **14c** with a bulkier substituent at C4 gave the seven-membered rings **15b** and **15c**, respectively, as the only isolable isomers. When bromoallene **14d**, which lacks a substituent at C4, was used, a considerable amount of regioisomer **16d** was isolated (28%; Table 2, entry 4). These results clearly demonstrate that the regioselectivity of the second nucleophilic attack is controlled by the steric size of the substituent at C4 of the bromoallenes. Next, similar reactions were conducted with bromoallenes **14e–g** (Table 2, entries 5–7), which bear a five-atom tether between the allenyl and hydroxy groups. In contrast to what was observed for the formation of seven-membered rings by this method, reaction of bromoallenes **14e–g** gave the eight-membered rings **15e–g** as the only isolable isomers, irrespective of the substituent at C4. Furthermore, bromoallenes **14h** and **14i**, which bear nitrogen functionalities, also gave the corresponding seven-membered ring **15h** and eight-membered ring **15i**, respectively, as a single isomer (Table 2, entries 8 and 9). These results show that the intramolecular nucleophilic attack takes place at the central position of the allenyl moiety (path B in Scheme 2) and, in most cases, the regioselectivity of the attack of methoxide is extremely high.

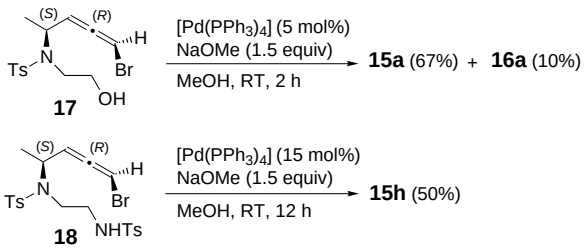
As shown in Scheme 3, the reaction of bromoallene (*S*,a*R*)-**17** also gave 1,4-oxazepine derivative **15a** (67%) along with **16a** (10%), a comparable result to the reaction of bromoallene (*S*,a*S*)-**14a** (Table 1, entry 1). Similarly, (*S*,a*R*)-**18** was cyclized into 1,4-diazepine derivative **15h** under identical reaction conditions in 50% yield (compare Table 1, entry 8). Based on these results, as both the *S*,a*S* and *S*,a*R* bromoallenes undergo the described transformation to provide the same products, a diastereomeric mixture of bromoallenes can be used directly in these reactions.

In analogy to this work, other alcohols can be used instead of MeOH in the cyclization reaction (Scheme 4). For example, bromoallene **14c** was treated with a preformed mixture of NaH (1.5 equiv) and EtOH/THF (1:1) in the presence of $[Pd(PPh_3)_4]$ (10 mol %) to afford the seven-membered ring **19** (60%). Similarly, the reaction of bromoallene **14a** with

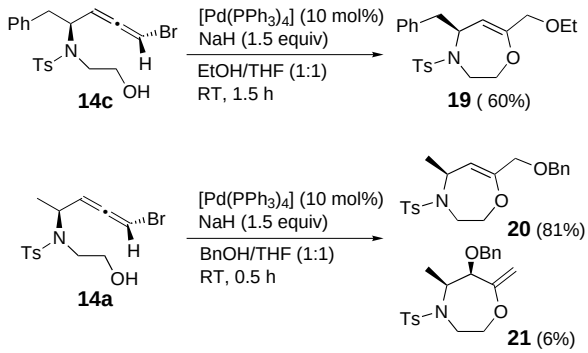
Table 2: Synthesis of medium-sized nitrogen heterocycles by cyclization of bromoallenes.[a]

Entry	Substrate	$[Pd(PPh_3)_4]$ [mol%]	t [h]	Product (Yield [%])[c]
1	 **14a**	5	3	 **15a** (73%) **16a** (9%)
2	 **14b**	5	6	 **15b** (62%)
3	 **14c**	10	3.5	 **15c** (73%)
4	 **14d**	10	6	 **15d** (61%) **16d** (28%)
5	 **14e**	5	6	 **15e** (84%)
6	 **14f**	10	11	 **15f** (67%)
7	 **14g**	10	3[b]	 **15g** (73%)
8	 **14h**	10	10	 **15h** (48%)
9	 **14i**	10	12	 **15i** (63%)

[a] Reactions were carried out at 25 °C in MeOH with diastereomerically pure bromoallenes, $[Pd(PPh_3)_4]$ (5–10 mol%), and NaOMe (1.5 equiv). [b] The reaction was conducted at 50 °C. [c] Yields of isolated products.



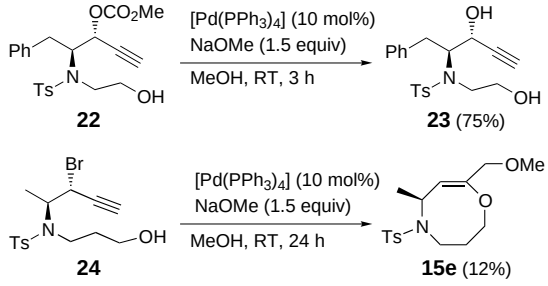
Scheme 3. Reaction of *S*,a*R* bromoallenes.



Scheme 4. Cyclizations with other alcohols as the second nucleophile.

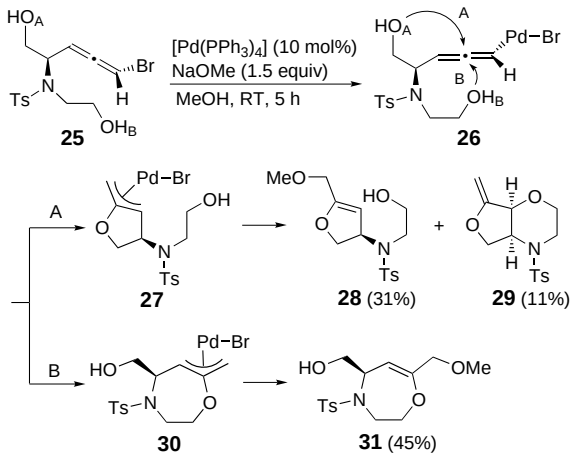
BnOH gave the seven-membered rings **20** (81%) and **21** (6%).

Propargylic carbonates are well-known to undergo a similar type of palladium-catalyzed transformation.[10,11] To investigate the possibility of using propargylic substrates as medium-sized-ring precursors, propargylic carbonate **22** was exposed to identical reaction conditions to those employed above (Scheme 5). However, only solvolysis of the carbonate **22** occurred and the diol **23** was obtained. Similarly, treatment of propargyl bromide **24**, which was found to be relatively unstable, with NaOMe in MeOH in the presence of $[Pd(PPh_3)_4]$ yielded only a small amount of the desired cyclized product **15e** (12% yield).[14] These results suggest that the efficient palladium(0)-catalyzed cyclization to form medium-sized rings is a reaction characteristic of bromoallenes.



Scheme 5. Reaction of a propargylic carbonate and of a propargylic bromide under identical reaction conditions.

Finally, we investigated the reaction of bromoallene **25**, which bears two oxygen functionalities and has two possible reaction pathways open to it (Scheme 6). If the hydroxy group A (OH_A) attacks the central position of the allene in allenyl palladium(II) bromide **26** (path A), **28** and/or **29** will be produced via the intermediate **27**. In contrast, reaction of OH_B in **26** (path B) would lead to the seven-membered ring **31**. Interestingly, exposure of **25** to the palladium-catalyzed cyclization conditions gave a mixture of **28** (31% yield), **29** (11%), and **31** (45%). This result clearly shows that the bromoallenes cyclize into seven-membered heterocycles as easily as they do into five-membered rings, even in cases in



Scheme 6. Cyclization of bromoallene **25** bearing two oxygen functionalities.

which the resulting seven-membered heterocycle (such as **31**) contains two heteroatoms.

In conclusion, we have developed a novel synthesis of medium-sized heterocycles through the cyclization of bromoallenes that bear an oxygen or nitrogen functionality in the presence of a palladium(0) catalyst and an alcohol. In many cases, this reaction proceeds with high regioselectivity and affords the products in good to high yields. This is the first example that demonstrates the synthesis of medium-sized rings through the cyclization of haloallenes, and is a reaction that provides a very useful method for the synthesis of seven- or eight-membered heterocycles.

Experimental Section

General procedure: A solution of bromoallene **14a** (54 mg, 0.15 mmol) in MeOH (1 mL) was added to a stirred mixture of NaOMe (12.2 mg, 0.225 mmol) and $[Pd(PPh_3)_4]$ (8.7 mg, 7.5 μmol) in MeOH (1 mL) under a nitrogen atmosphere at room temperature, and the mixture was stirred for 3 h at this temperature. Concentration under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with *n*-hexane/EtOAc (3:1) to give, in order of elution, **16a** (4.4 mg, 9%) and **15a** (34.1 mg, 73%) as colorless oils. **15a**: $[\alpha]_D^{25} = +24.7$ ($c = 1.00$, $CHCl_3$); IR (KBr): $\tilde{\nu} =$ 1674 (C=C–O), 1331 cm^{-1} (NSO_2); ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 1.28 (d, $J = 7.0$ Hz, 3H; CCH_3), 2.41 (s, 3H; $PhCH_3$), 3.24 (s, 3H; OCH_3), 3.48 (ddd, $J = 14.5$, 6.0, 2.5 Hz, 1H; CH_aH_b), 3.56 (d, $J =$ 12.5 Hz, 1H; $MeOCH_aH_b$), 3.60 (d, $J = 12.5$ Hz, 1H; $MeOCH_aH_b$), 3.91 (ddd, $J = 12.5$, 6.0, 3.0 Hz, 1H; CH_aH_b), 4.04 (ddd, $J = 14.5$, 7.0, 3.0 Hz, 1H; CH_aH_b), 4.14 (ddd, $J = 12.5$, 7.0, 2.5 Hz, 1H; CH_aH_b), 4.68 (qd, $J = 7.0$, 6.5 Hz, 1H; CHMe), 4.86 (d, $J = 6.5$ Hz, 1H; C=CH), 7.26–7.27 (m, 2H; Ph), 7.68–7.70 ppm (m, 2H; Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.3$, 21.4, 45.0, 50.2, 58.0, 71.0, 73.0, 108.0, 127.1 (2C), 129.5 (2C), 137.7, 143.1, 154.5 ppm; MS (FAB): *m*/*z* (%): 312 [*M*H$^+$] (71), 296 (100); HRMS (FAB): calcd for $C_{15}H_{22}NO_4S$ (*M*H$^+$): 312.1270; found: 312.1274. **16a**: $[\alpha]_D^{28} = +46.8$ ($c = 0.49$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 1635$ (C=C), 1346 cm^{-1} (NSO_2); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.22$ (d, $J = 6.5$ Hz, 3H; CCH_3), 2.43 (s, 3H; $PhCH_3$), 3.18 (ddd, $J = 13.0$, 5.0, 3.5 Hz, 1H; CH_aH_b), 3.46 (ddd, $J =$ 13.0, 8.5, 3.0 Hz, 1H; CH_aH_b), 3.53 (s, 3H; OCH_3), 3.67 (ddd, $J = 11.5$, 5.0, 3.0 Hz, 1H; CH_aH_b), 3.83–3.88 (m, 2H; CHMe and CHOMe), 3.90 (ddd, $J = 11.5$, 8.5, 3.5 Hz, 1H; CH_aH_b), 4.22 (d, $J = 2.5$ Hz, 1H; C=CH_aH_b), 4.40 (d, $J = 2.5$ Hz, 1H; C=CH_aH_b), 7.30–7.32 (m, 2H; Ph), 7.67–7.69 ppm (m, 2H; Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 15.6, 21.5, 42.5, 50.9, 55.0, 62.8, 79.1, 85.4, 127.4 (2C), 129.7 (2C), 136.4, 143.4, 158.6 ppm; MS (FAB): *m*/*z* (%): 312 [*M*H$^+$] (24), 136 (100); HRMS (FAB): calcd for $C_{15}H_{22}NO_4S$ (*M*H$^+$): 312.1270; found: 312.1286.

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Keywords: allenes · cyclization · heterocycles · palladium

[1] For a recent review, see: P. A. Evans, A. B. Holmes, *Tetrahedron* **1991**, *47*, 9131–9166.

[2] For selected examples of seven-membered nitrogen heterocycles, see: a) T. Duong, R. H. Prager, J. M. Tippett, A. D. Ward, D. I. Kerr, *Aust. J. Chem.* **1976**, *29*, 2667–2682; b) C. Boros, S. M. Hamilton, B. Katz, P. Kulanthaivel, *J. Antibiot.* **1994**, *47*, 1010–1016; c) Y. Ishihara, K. Hirai, M. Miyamoto, G. Goto, *J. Med. Chem.* **1994**, *37*, 2292–2299; d) F. Morís-Varas, X.-H. Qian, C.-H. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7647–7652; e) G. L. Grunewald, V. H. Dahanukar, P. Ching, K. R. Criscione, *J. Med. Chem.* **1996**, *39*, 3539–3546.

[3] For selected examples of eight-membered nitrogen heterocycles, see: a) B. Basil, E. C. J. Coffee, D. L. Gell, D. R. Maxwell, D. J. Sheffield, K. R. H. Wooldridge, *J. Med. Chem.* **1970**, *13*, 403–406; b) D. L. Klayman, J. P. Scovill, J. F. Bartosevich, C. J. Mason, *J. Med. Chem.* **1979**, *22*, 1367–1373; c) E. Vedejs, R. J. Galante, P. G. Goekjian, *J. Am. Chem. Soc.* **1998**, *120*, 3613–3622, and references therein.

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