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Palladium(0)-Catalyzed Stereoselective Cyclization of Allenenes: Divergent Synthesis of Pyrrolidines and 3-Azabicyclo[3.1.0]hexanes from Single Allenenes

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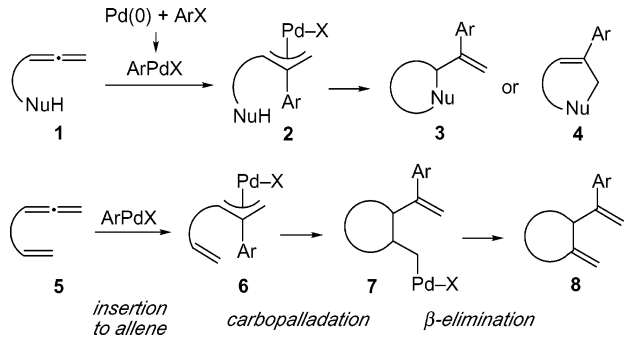
Abstract: Two novel palladium(0)-catalyzed cyclizations of allenenes are described. Treatment of allenenes such as *N*-(1-alkyl-2,3-butadienyl)-*N*-allylsulfonamide with an aryl halide and K_2CO_3 in the presence of a catalytic amount of $Pd(PPh_3)_4$ in dioxane affords 2,3-*cis*-pyrrolidines in a stereoselective manner. In sharp contrast, cyclization of the same allenenes using catalytic $Pd_2(dba)_3$·$CHCl_3$ in the presence of allyl methyl carbonate in CH_3CN leads to stereoselective formation of a 3-azabicyclo[3.1.0]hexane framework in moderate yields.

Allenes are an important class of compounds with unique reactivities due to the existence of two orthogonal π-bonds. In particular, in recent years transition-metal-catalyzed cyclizations are becoming one attractive approach for the construction of heterocycles.[1] Allenes of the type **1**, which bears a nucleophilic moiety such as a nitrogen or oxygen-containing functional group, undergo a variety of palladium(0)-catalyzed cyclizations to form cyclic products **3** or **4** (Scheme 1).[2,3] In sharp contrast, palladium(0)-catalyzed reactions of allenes that contain an additional multiple bond have scarcely been studied until recently, despite their potential versatility in organic synthesis. We expected that cyclization of allenenes **5** would provide a useful approach to carbo- and heterocycles such as **8**.

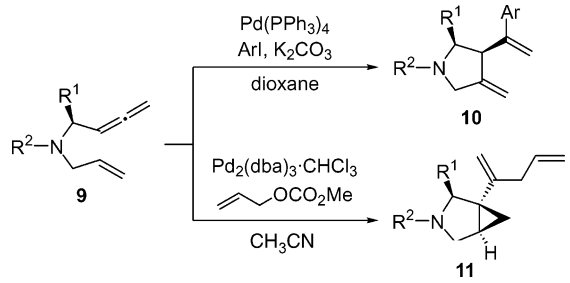
Recently, Kang and co-workers reported that bisallenes form five-membered rings on treatment with silylstannane and palladium(0).[4] Independently, RajanBabu and co-workers observed stannylsilylation of allenynes under similar reaction conditions followed by carbocyclization of the resulting allylstannanes.[5] Palladium(II)-catalyzed oxidative cyclization of allene-substituted alkenes and palladium(0)-catalyzed cyclization of allenes bearing an allyl ester moiety were reported by Bäckvall.[6] Although some cyclizations of allenes with an additional multiple bond such as Pauson−Khand-type reactions[7] and cycloadditions[8] were reported, palladium(0)-catalyzed cyclization as shown in Scheme 1 is unknown as far as we are aware. In the course of this study, we found an unusual intramolecular cyclopropanation of the allenic moiety with a double bond catalyzed by palladium(0). In this paper, we describe full details of our study which enables an efficient synthesis of both 2,3-*cis*-pyrrolidines **10** and 3-azabicyclo[3.1.0]hexanes **11** by the palladium(0)-catalyzed cyclization of the same allenenes **9** (Scheme 2).[9]

With a view to synthesizing nitrogen heterocycles, we prepared allenenes **17** through the diethylzinc-mediated reductive synthesis of amino allenes catalyzed by palladium(0),[10] starting from (*S*)-amino acid-derived amino alcohols **12**. A typical synthetic procedure is shown in Scheme 3. Brominated α,*β*-enoates **13a**−**c** were readily

SCHEME 1



SCHEME 2



(1) For recent reviews, see: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067−3125. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590−3593.

(2) For pioneering works, see: (a) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615−2617. (b) Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85. For a recent review, see: (c) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12−21.

(3) For some recent examples, see: (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992−2993. (b) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943−7944. (c) Kang, S. K.; Kim, K.-J. *Org. Lett.* **2001**, *3*, 511−514. (d) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904−4914. (e) Ohno, H. *Yakugaku Zasshi* **2001**, *121*, 733−741. (f) Hiroi, K.; Hiratsuka, Y.; Watanabe, K.; Abe, I.; Kato, F.; Hiroi, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1351−1353.

(4) Kang, S.-K.; Baik, T.-G.; Kulak, A. N.; Ha, Y.-H.; Lim, Y.; Park, J. *J. Am. Chem. Soc.* **2000**, *122*, 11529−11530.

(5) Shin, S.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2001**, *123*, 8416−8417.

(6) (a) Löfstedt, J.; Franzén, J.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8015−8025. (b) Franzén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2002**, *124*, 11246−11247. (c) Franzén, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 6056−6057.

(7) (a) Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535−6545. (b) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755−1758.

(8) (a) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844. (b) Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395−405 and references therein.

(9) For preliminary communications, see: (a) Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2647−2650. (b) Ohno, H.; Takeoka, Y.; Miyamura, K.; Kadoh, Y.; Tanaka, T. *Org. Lett.* **2003**, *5*, 4763−4766.

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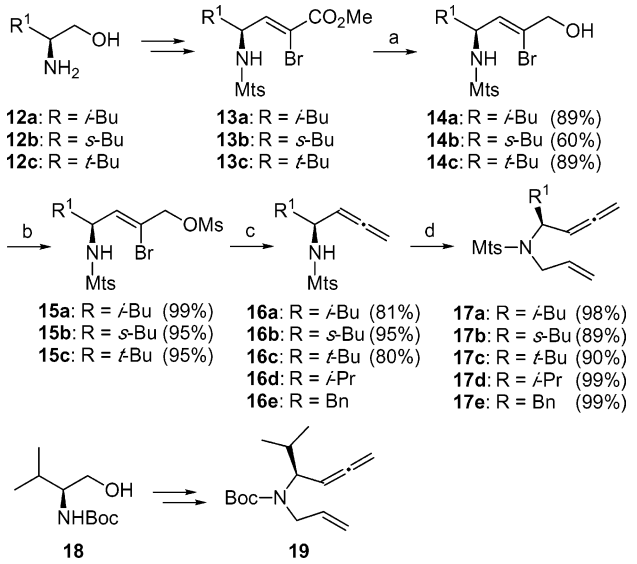
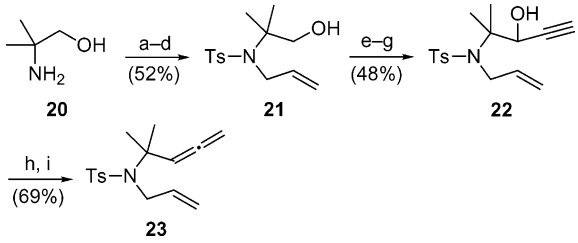
SCHEME 3 [a]



[a] Reagents: (a) DIBAL-H; (b) MsCl, Et_3N; (c) Et_2Zn, cat. $Pd(PPh_3)_4$; (d) NaH, allyl bromide. Mts = 2,4,6-trimethylphenylsulfonyl.

SCHEME 4 [a]

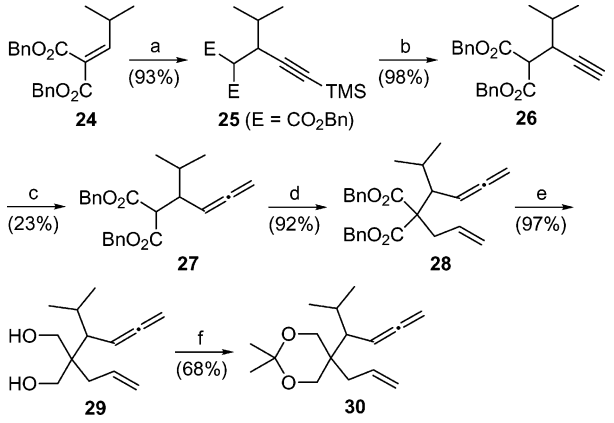


[a] Reagents: (a) TsCl, Et_3N; (b) TBSCl, imidazole; (c) NaH, allyl bromide; (d) TBAF; (e) $(COCl)_2$, DMSO, then $(i\text{-}Pr)_2NEt$; (f) TMS-acetylene, *n*-BuLi; (g) NaOMe, MeOH; (h) MsCl, Et_3N; (i) $LiAlH_4$, $AlCl_3$.

prepared from amino alcohols **12** (see the Supporting Information). Reduction of **13** with DIBAL-H afforded allylic alcohols **14a**−**c**, which were then treated with MsCl and Et_3N. Reaction of the resulting mesylates **15a**−**c** with Et_2Zn and a catalytic amount of $Pd(PPh_3)_4$ in THF[10] gave allenes **16a**−**c** in high yields. Other known amino allenes **16d** and **16e** were also prepared in a similar manner according to the literature.[10] Allylation of the protected amino group of **16** gave the requisite allenenes **17a**−**e** in high yields. Similarly, *N*-Boc derivative **19** was readily synthesized from *N*-Boc-(*S*)-valinol (see the Supporting Information).

Allenene **23** bearing a geminal dimethyl group was synthesized from 2-amino-2-methyl-1-propanol **20** as shown in Scheme 4. Tosylation followed by allylation of the amino group by the standard procedure afforded **21**, which was converted into the corresponding propargyl alcohol **22**. Hydride reduction of the corresponding mesylate with $LiAlH_4$ and $AlCl_3$[11] afforded allenene **23** with a geminal dimethyl group. It should be noted that

SCHEME 5 [a]



[a] Reagents: (a) TMS-acetylene, EtMgBr, CuCl; (b) TBAF; (c) $(HCHO)_n$, $(i\text{-}Pr)_2NH$, CuBr; (d) NaH, allyl bromide; (e) $LiAlH_4$; (f) TsOH, 2,2-dimethoxypropane, MS 4A. TBAF = tetrabutylammonium fluoride.

preparation of **23** by way of Et_2Zn-mediated reductive allene synthesis was not possible because of a difficulty in preparation of the substrate: Wittig olefination of the corresponding aldehyde led to recovery of the starting material. Furthermore, reaction of the propargyl alcohol **22** with *o*-nitrobenzenesulfonylhydrazine (NBSH) under Mitsunobu conditions (Myers' method)[12] only gave an unidentified byproduct.

To investigate the effect of the protected amino group on the cyclization, we prepared allenenes **28** and **30**, which are carbocycle precursors, through the Crabbé reaction[13] (Scheme 5). Copper-catalyzed 1,4-addition of trimethylsilylacetylide to dibenzyl (isopropylidene)malonate **24** afforded **25** in 93% yield. Deprotection of the trimethylsilyl group followed by the Crabbé reaction[13] of the resulting terminal acetylene **26** gave allene **27** although in low yield. The allene **27** was then treated with NaH and allyl bromide in DMF to give **28**, the ester groups of which were reduced with $LiAlH_4$ and protected to afford acetonide **30** (Scheme 5).

In an initial experiment, we investigated the palladium(0)-catalyzed cyclization of the allenene **17d** and found that the carbocyclization of allenenes and subsequent β-hydride elimination proceeds efficiently upon treatment with iodobenzene (7 equiv) and K_2CO_3 (7 equiv) in the presence of a catalytic amount of $Pd(PPh_3)_4$ (Table 1). Reaction of **17d** in refluxing dioxane provided the 2,3-*cis*-pyrrolidine **31a** in 85% yield as the sole isolable product (Table 1, entry 1). Decreased loading of iodobenzene (2 equiv) and K_2CO_3 (2 equiv) lowered the yield to 60% (entry 2). Although the reaction in CH_3CN gave 61% yield of **31a**, other polar solvents such as DMSO and DMF were less effective (entries 4 and 5). From these results, dioxane was found to be the solvent of choice for the pyrrolidine formation from allenenes. Whereas the use of 4-iodoanisole (entry 6) and 4-iodotoluene (entry 7) as the aryl halide gave comparable

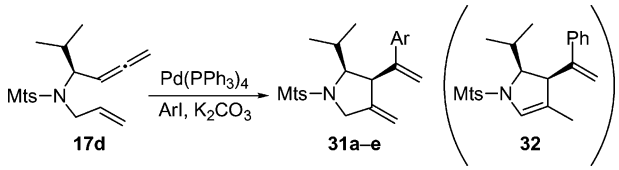
(10) (a) Ohno, H.; Toda, A.; Oishi, S.; Tanaka, T.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 5131−5134. (b) Ohno, H.; Miyamura, K.; Tanaka, T.; Oishi, S.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **2002**, *67*, 1359−1367.

(11) (a) Claesson, A.; Olsson, L.-I. *J. Am. Chem. Soc.* **1979**, *101*, 7302−7311. See also, (b) Borden, W. T.; Corey, E. J. *Tetrahedron Lett.* **1969**, *10*, 313−316.

(12) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492−4493.

(13) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747−751.

TABLE 1. Optimization of Reaction Conditions for Stereoselective Synthesis of 2,3-*cis*-Pyrrolidines 31a[a]



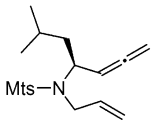
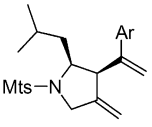
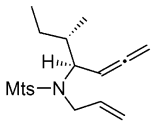
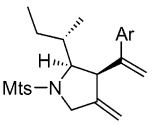
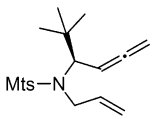
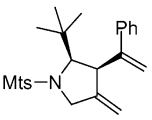
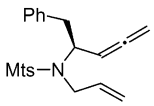
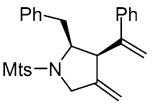
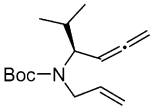
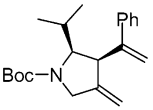
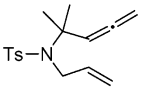
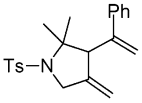
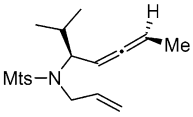
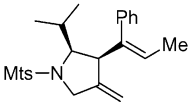
entry	solvent	ArI (equiv)	*T* (°C)	time (h)	product (yield, %)[b]
1	dioxane	PhI (7)	reflux	5	**31a** (85)
2	dioxane	PhI (2)	reflux	4.5	**31a** (60)
3	CH_3CN	PhI (7)	reflux	5	**31a** (61)
4[c]	DMSO	PhI (7)	100	3.5	**31a** (28)
					32 (3)
5	DMF	PhI (7)	100	4	**31a** (50)
					32 (6)
6	dioxane	4-MeOPhI (2)	reflux	3	**31b** (60)
7	dioxane	4-MePhI (2)	reflux	8	**31c** (56)
8	dioxane	4-NO_2PhI (2)	reflux	11	**31d** (36)
9	dioxane	1-naphthyl-I (2)	reflux	8	**31e** (25)

[a] All reactions were carried out in the presence of $Pd(PPh_3)_4$ (10 mol %), PhI (2 or 7 equiv), and K_2CO_3 (1 equiv to ArI). [b] Yields of isolated products. The 2,3-trans isomers of **31** were not observed (2,3-cis/trans = >98:2). [c] Other unidentified products were also isolated.

results to iodobenzene, only 36% of the pyrrolidine **31d** was obtained when the reaction was carried out with the electron-poor 1-iodo-4-nitrobenzene (entry 8). Reaction with sterically congested 1-iodonaphthalene gave pyrrolidine **31e** in only 25% yield (entry 9), presumably due to the lower reactivity of the iodide.[14]

Next, reaction of various amino allene-derived allenenes was investigated. The results are summarized in Table 2. While the allenene **17a** bearing an isobutyl group required prolonged reaction time for the complete consumption of the starting materials (24−30 h, entries 1 and 2), the allenene **17b** with a *sec*-butyl group yielded the pyrrolidines **34** in shorter reaction time (4−6.5 h, entries 3 and 4) similar to **17d** (Table 1). Therefore, the substituent α to the allene was found to be extremely important for the efficiency of the cyclization.[15] Similarly, the allenene **17c** with a bulky *tert*-butyl group (entry 5) was more reactive than **17e** having a smaller benzyl group (entry 6). We speculate that the bulky α substituent stabilizes the conformation required for the carbocyclization. The allenene **19**, the amino group of which is protected by a Boc group, afforded *N*-Boc-pyrrolidine derivative **37** although in relatively low yield (41%, entry 7). As we expected, a geminal dimethyl group of **23** assists the cyclization to **38** (entry 8); however, this reaction requires 20 h for the complete conversion. Thus, efficacy of cyclization depends on a subtle balance between the bulkiness of the substituent and the reactivity. Internal allene **39**, which was prepared by allylation of the known amino allene[16] (see the Supporting Information), was also cyclized into the five-membered ring **40** in 59% yield. In this case, 10% of the starting allenene **39** was recovered. The observed (*Z*)-geometry of the double bond

TABLE 2. Stereoselective Formation of Various 2,3-*cis*-Pyrrolidines[a]

entry	allenene	ArI	time (h)	product (yield[b])
1[c]	 **17a**	PhI	24	 **33a**: Ar = Ph (46%)
2	**17a**	4-MeOPhI	30	**33b**: Ar = 4-MeOPh (50%)
3	 **17b**	PhI	6.5	 **34a**: Ar = Ph (64%)
4	**17b**	4-MeOPhI	4	**34b**: Ar = 4-MeOPh (55%)
5	 **17c**	PhI	5	 **35** (61%)
6	 **17e**	PhI	24	 **36** (58%)
7	 **19**	PhI	20	 **37** (41%)
8	 **23**	PhI	20	 **38** (59%)
9	 **39**	PhI	13	 **40** (59%)

[a] All reactions were carried out in the presence of $Pd(PPh_3)_4$ (10 mol %), PhI (2 equiv), and K_2CO_3 (2 equiv) unless otherwise stated. [b] Yields of isolated products. [c] Increased amounts of ArI (4 equiv) and K_2CO_3 (4 equiv) were used.

of **40** will be a consequence of thermodynamic preference for the *syn*-π-allylpalladium(II) intermediate over other isomers.[1a,3d]

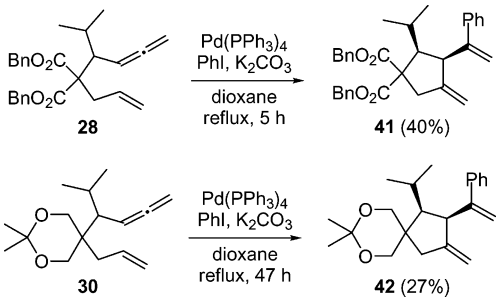
As shown in Scheme 6, the cis-selective carbocyclization of allenenes **28** and **30** to form methylidene cyclopentanes **41** and **42** was also possible; however, yields of **41** and **42** were lower (40% and 27%, respectively). It has been proven that a nitrogen atom substituted by an

(14) Similarly, the reaction of **17d** with sterically congested 2-iodotoluene gave a mixture of unidentified products, and the desired arylated pyrrolidine was not isolated.

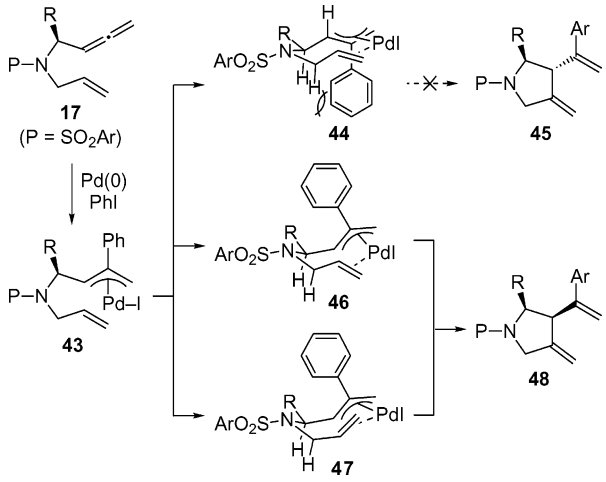
(15) The reaction of the unsubstituted allenene led to a complex mixture of unidentified products.

(16) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 349−352. (b) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811−2820. For preparation of 2-ethynylaziridines, see: (c) Ohno, H.; Toda, A.; Fujii, N.; Ibuka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3929−3933. (d) Ohno, H.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2949−2962.

SCHEME 6



SCHEME 7

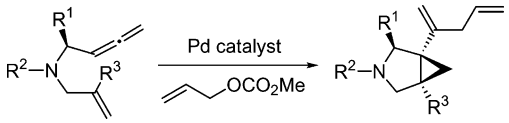


arylsulfonyl group (Table 1, entry 2) stabilizes the required conformation for the allenene cyclization more effectively than carbamate (Table 2, entry 7) or a carbon atom having a geminal substituent (Scheme 6).

In all cases examined, 2,3-*trans*-pyrrolidine could not be isolated from the reaction mixture. The observed 2,3-cis selectivity in the pyrrolidine formation can be rationalized as shown in Scheme 7. If the intermediate **43** underwent carbocyclization via the conformation **44**, the 2,3-*trans*-pyrrolidine **45** would be formed. However, an unfavorable steric interaction between pseudoaxial protons and the phenyl group in **44** does exist to destabilize this conformer. Thus, the ring-formation would proceed preferentially from the more abundant conformers **46** and/or **47**, and β-hydride elimination of the resulting alkylpalladium(II) yields the *cis*-pyrrolidine **48** as a single isomer.

During the course of this study, we unexpectedly found that 3-azabicyclo[3.1.0]hexanes can be stereoselectively constructed from allenenes by simply changing the reaction conditions. As shown in Table 3, treatment of allenene **17a** with allyl carbonate (6 equiv)[17] in the presence of a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ in CH_3CN at 80 °C afforded 3-azabicyclo[3.1.0]hexane **50a** in 35% yield (entry 1). Although the formation of small rings including cyclopropanes[18] by intramolecular nucleophilic attack onto the allenic moiety is well documented,[3] direct synthesis of bicyclic cyclopropanes by the reaction of allenes with an additional multiple bond is unprecedented. Similarly, the allenene **17e** having a benzyl group gave relatively low yields of the bicyclic cyclopropane **50e** (entry 5). In contrast, the isoleucine derivative **17b** (entry 2) and the valine derivatives **17d** (entry 4) and **49c** (entry 9) which bear a branched alkyl group on the α-position, afforded 3-azabicyclo[3.1.0]hexanes in better yields (57−64%). However, sterically too congested allenenes **17c** (entry 3) and **23** (entry 6) were less reactive. These results clearly show that the presence of an appropriate substituent at the α-position to the allenic moiety is extremely important for the successful conversion. Two possible reaction mechanisms for the palladium(0)-catalyzed cyclopropanation of allenenes were already proposed in the preliminary communication.[9b,19]

TABLE 3. Stereoselective Formation of 3-Azabicyclo[3.1.0]hexanes[a]



entry	allenene	R^1	R^2	R^3	time (h)	product (yield, %)[b]
1	**17a**	*i*-Bu	Mts	H	24	**50a** (35)
2	**17b**	*s*-Bu	Mts	H	7	**50b** (57)
3	**17c**	*t*-Bu	Mts	H	24	**50c** (16)[c]
4	**17d**	*i*-Pr	Mts	H	5	**50d** (64)
5	**17e**	Bn	Mts	H	6	**50e** (18)
6	**23**	Me_2	Ts	H	60	**51** (24)[d]
7	**49a**	*i*-Bu	Mts	Me	24	**52a** (36)
8	**49b**	*s*-Bu	Mts	Me	24	**52b** (39)
9	**49c**	*i*-Pr	Mts	Me	7	**52c** (59)

[a] All reactions were carried out with $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol %) and allyl carbonate (6 equiv) in CH_3CN. [b] Yields of isolated products. [c] Isomerized internal alkyne was obtained (40%). [d] The starting allenene **23** was recovered (29%).

In conclusion, we have developed two different palladium(0)-catalyzed cyclizations leading to substituted pyrrolidines and 3-azabicyclo[3.1.0]hexanes using the same allenenes. These results clearly demonstrate that allenenes are extremely useful substrates for palladium-catalyzed cyclization to heterocycles. Furthermore, the latter reaction is a first example of palladium-catalyzed cyclopropanation of allenes with a double bond, which shows a novel reactivity of allenes.

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Supporting Information Available: Synthetic procedure and characterization for all products, NOE experiment for the determination of relative configurations, as well as ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Decreased loading of the allyl carbonate (2 equiv) lowered the yields. It is presumably due to the side reaction of allylpalladium(II) intermediate with another molecule of the allyl carbonate.

(18) Ma, S.; Jiao, N.; Zhao, S.; Hou, J. *J. Org. Chem.* **2002**, *67*, 2837−2847.

(19) The reason the present reaction conditions promote the cyclopropanation reaction instead of the Oppolzer cyclization leading to **10** (Scheme 2) is not understood. Assuming that the methoxide which is generated by the reaction of allyl carbonate with palladium(0) might assist the present cyclopropanation, we investigated reaction of the allenene **17d** with iodobenzene or phenyl triflate and catalytic $Pd_2(dba)_3{\cdot}CHCl_3$ in CH_3CN in the presence of NaOMe. However, unchanged starting allenene **17d** was recovered in both cases. The reaction in AcOH using the Oppolzer's conditions afforded unidentified products and no cyclopropane was obtained.