Review

Development of Useful Reactions Involving Tandem Cyclizations Based on the Novel Reactivities of Allenic Compounds

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This review highlights author's recent study on allenic compounds. In the first section, organocopper-mediated ring-opening reaction of ethynylaziridines and palladium-catalyzed reductive synthesis of allenes including those which are not accessible by other means, are described. In the second section, palladium-catalyzed stereoselective cyclization of allenes and tandem reaction leading to aziridines, pyrrolidines, benzoisoindoles, and cyclopropanes are presented. The final section presents aziridination and medium-ring formation by intramolecular reaction of bromoallenes, which are scarcely investigated until quite recently. The latter reaction is based on our recent discovery that bromoallenes can act as allylic dication equivalents in the presence of a palladium catalyst and alcohol.

Key words allene; palladium; heterocycle; aziridine; medium-sized ring; tandem reaction

1. Introduction

Allene is a versatile functionality which serves as either a nucleophile or an electrophile and also as a precursor for cycloaddition reactions.[2—7)] This multi-reactivity and existence of two orthogonal π-bonds attract considerable attention of organic chemists. In particular, a series of excellent results in the field of transition-metal catalyzed reaction of allenes are now being produced.[8—10)] Introduction of an additional functionality to allenes makes them a multifunctional chiral C-3 unit which can be potentially applied to novel tandem reactions. This review presents our recent study of allene chemistry, including 1) synthesis of allenes, 2) palladium-catalyzed cyclization of allenes including tandem cyclization, and 3) cyclization of bromoallenes to aziridines and medium-sized heterocycles.

2. Synthesis of Allenes

2.1. Stereoselective Synthesis of Chiral Amino Allenes by Organocopper-Mediated *anti*-*S*$_N$2′-Substitution Reaction of Chiral Ethynylaziridines[11,12)] Among various substituted allenes, amino allenes are versatile building blocks for constructing azacycles. However, a scan of the literature has revealed a surprising paucity of methods that facilitate the synthesis of chiral internal allenes bearing a nitrogen functionality separated from the allenic carbon atom only by one carbon atom.[13)] The author planned to synthesize chiral amino allenes by organocopper-mediated ring-opening reaction of ethynylaziridines.

The stereochemical course of organocopper-mediated *S*$_N$2′ substitution of propargylic compounds has been well documented[14,15)]: they usually undergo highly stereoselective *anti*-facial reactions; *i.e.*, the *S*$_N$2′ displacement generally proceeds *anti* to the leaving group. The organocopper-mediated ring-opening reaction of propargylic epoxides also affords the corresponding hydroxy allenes in a highly regio- and *anti*-*S*$_N$2′-selective manner.[16)] Interestingly, it has been reported by Alexakis *et al.* that the *S*$_N$2′ displacement of the propargylic epoxides or ethers can lead to either *anti* or *syn* products, depending on the reaction conditions or copper reagents used.[17,18)] It is of considerable interest to determine whether chiral ethynylaziridines can be transformed diastereoselectively into chiral amino allenes by the reaction with organocopper reagents.

The requisite *N*-arylsulfonylated 2,3-*trans*- and 2,3-*cis*-3-alkyl-2-ethynylaziridines **1** and **3**, respectively, with high optical purities (>98% ee) were prepared in a straightforward manner from natural α-amino acids following our recently published procedures.[19,20)] Although the reaction of ethynylaziridines **1** with Gilman-type reagent, $R_2CuLi \cdot nLiX$ (X=Cl or Br) or $R_2CuLi \cdot LiCN \cdot nLiX$ afforded a mixture of products including *syn*- and *anti*-*S*$_N$2′ products, and reduction product. In contrast, it was found that organocyanocuprates, $RCu(CN)M \cdot nLiX$ (M=Li or MgBr, X=Cl or Br), are the reagent of choice for the ring-opening reaction, giving excellent isolated yields of the corresponding *anti*-*S*$_N$2′ products (Chart 1). For example, exposure of **1** to $MeCu(CN)Li \cdot 2LiCl$, *i*-$PrCu(CN)MgBr \cdot 2LiCl$, *n*-$BuCu(CN)Li \cdot 2LiCl$, or *n*-$Bu_3SnCu(CN)Li \cdot 2LiCl$ yields the corresponding ring-opened products **2a**—**d** in high yields. The 2,3-*trans*-isomer **3** also gave exclusively the *anti*-*S*$_N$2′ products **4**. In all cases examined, regio- or stereoisomeric products were not detected in the reaction mixture.

The stereochemical course of the ring-opening reaction of ethynylaziridines is shown in Chart 2. Similar to other related

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substitution of propargylic compounds, the reaction of aziridines generally proceeds *anti* to the leaving nitrogen atom.

2.2. Synthesis of Allenes from Allylic Alcohol Derivatives Bearing a Bromine Atom Using a Palladium(0)/Diethylzinc System[21,22] In the course of the author's recent study involving synthesis of ethynylaziridines,[19,20] it was found that the allylic mesylates having a bromine atom on the central carbon can be converted into the allenes on treatment with diethylzinc in the presence of a palladium(0) catalyst. Although there have been some reports describing related synthesis of allenes,[23—25] no systematic investigation involving the synthesis of allenes from such class of compounds has been carried out, and a catalytic synthesis of allenes from such substrates is unknown. As described above (Section 2.1), internal allenes (1,3-disubstituted allenes) bearing an *N*-protected amino group could be readily synthesized from ethynylaziridines by treatment with organocopper reagents[11,12]; however, preparation of monosubstituted allenes without contaminating the corresponding acetylene by the use of organocopper chemistry has proven to be quite difficult. Although reliable synthetic methods of terminal allenes have been already developed, some of these are unsuitable for the synthesis of allenes bearing a nitrogen functionality.[26—28] The potential utility of the synthesis of allenes by a palladium(0)/diethylzinc system, especially for the synthesis of terminal allenes bearing an amino group, led us to a detailed investigation of this reaction.

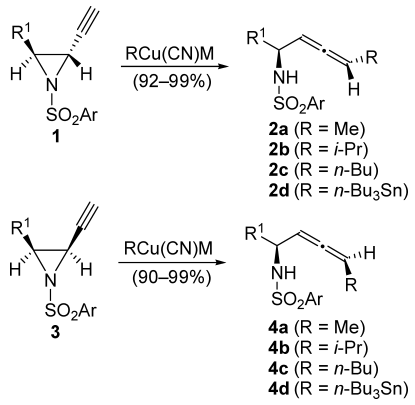

Chart 1. Synthesis of α-Amino Allenes by Ring-Opening Reaction of 2-Ethynylaziridines

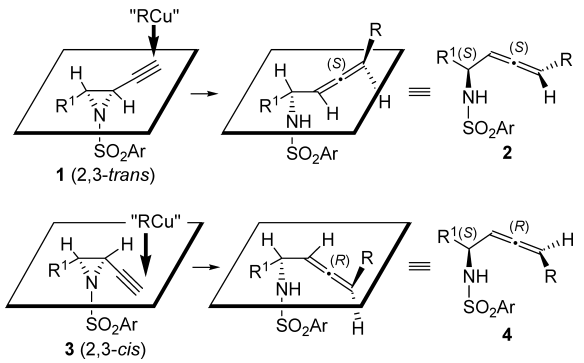

Chart 2. Stereochemical Course of the Ring-Opening Reaction of 2-Ethynylaziridines

First, various substrates bearing an amino group for the palladium-catalyzed reduction was examined. As shown in Fig. 1, both the (*Z*)- and (*E*)-mesylates **5** and **6** were converted into the corresponding α-amino allenes **7**—**10** in good to high yields by exposure to $Pd(PPh_3)_4$ (10 mol%) and Et_2Zn (2 eq) in THF for 20 to 60 min. Similarly, β-amino allene **11** and γ-amino allenes **12** and **13** were obtained in good yields from the corresponding mesylates.

To expand the synthetic utility of the reaction, the synthesis of various alkyl and aryl allenes lacking an amino group was investigated. Monoalkyl allenes **14** was synthesized in good yield from (*Z*)- or (*E*)-mesylates. Similarly, bis(mesylate)s were converted into the bis(allene) **15**. This allene synthesis is also applicable to the conversion of secondary alcohol derivatives into the corresponding internal allenes such as **16** and **18**. It should be noted that synthesis of the mesylates **5** having an aryl group at the C-1 or C-3 position (R^1 or R^2=Ar) was quite difficult, presumably due to the conjugated system. Accordingly, the reaction of the corresponding acetates and trichloroacetates was investigated in such cases. When using the acetate for the synthesis of aryl allene **17**, the reaction proceeded quite slowly at room temperature, and prolonged reaction time was required. In contrast, when using the trichloroacetate, the reaction was completed at room temperature within 30 min, and 69% of the aryl allene **17** was obtained. From these observations, it is obvious that this allene synthesis is useful for the synthesis of allenes bearing aminoalkyl, alkyl, and aryl group(s) including terminal, internal, and bis(allene)s. In all cases, no acetylenic compounds were detected.

Next, the influence of the stereochemistry of the mesyloxy group, on the axial chirality of the resulting allenes, was in-

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Hiroaki Ohno

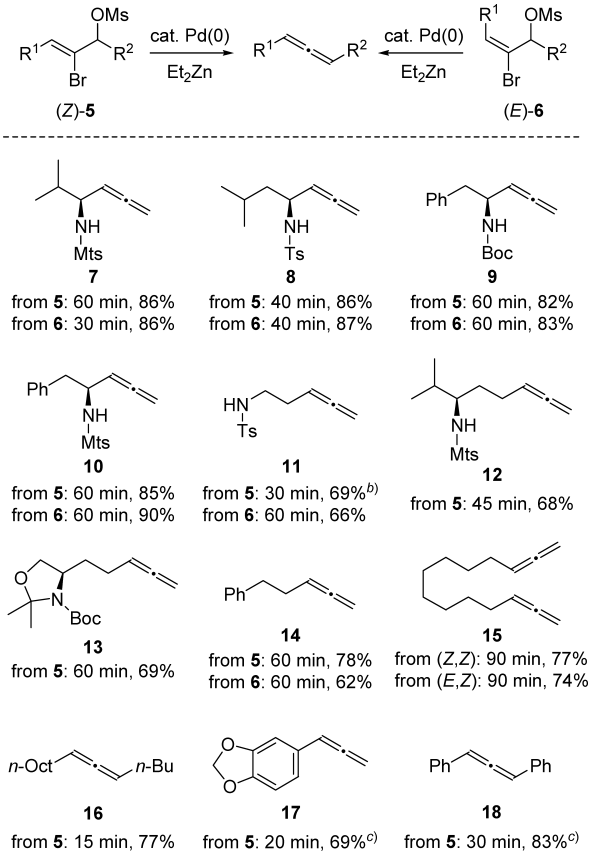


Fig. 1. Synthesis of Allenes Using a Palladium(0)/Diethylzinc System[a)]

a) Reactions were carried out in THF at room temperature under argon using $Pd(PPh_3)_4$ (10 mol%) and Et_2Zn (2 eq), unless otherwise stated. *b*) 4 mol% of $Pd(PPh_3)_4$ was used. *c*) Since preparation of the mesylates was difficult, the corresponding trichloroacetates were used. Mts=2,4,6-trimethylphenylsulfonyl.

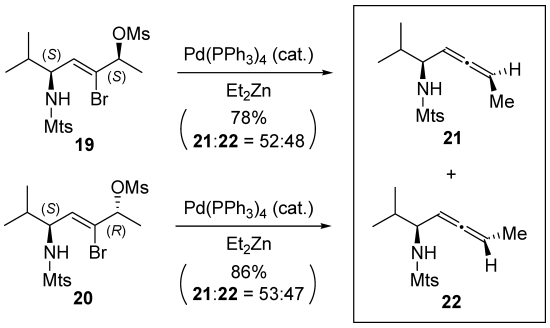


Chart 3. Formation of Allenes from the Mesylates **19** and **20**

vestigated. As shown in Chart 3, the reaction of the (*S*,*S*)-mesylate **19** with Et_2Zn in the presence of catalytic $Pd(PPh_3)_4$ afforded a mixture of amino allenes **21** and **22** in 78% yield (**21** : **22**=52 : 48). Similarly, the (*S*,*R*)-mesylate **20** also gave an almost equimolar mixture of **21** and **22** (86% yield, **21** : **22**=53 : 47). Accordingly, it is apparent that the chirality of the substrates is not reflected to the axial chirality of the resulting allenes.

These results can be rationalized as follows (Chart 4): oxidative addition of **23** to palladium(0) will afford η^3-allylpalladium(II) intermediate **24** with inversion of configuration. While *syn*-1,2-elimination of palladium(II) bromide from **26** would give (*R*)-**27**, elimination from **29** would give (*S*)-**27**. Since an almost 1 : 1 mixture of **21** and **22** was obtained from

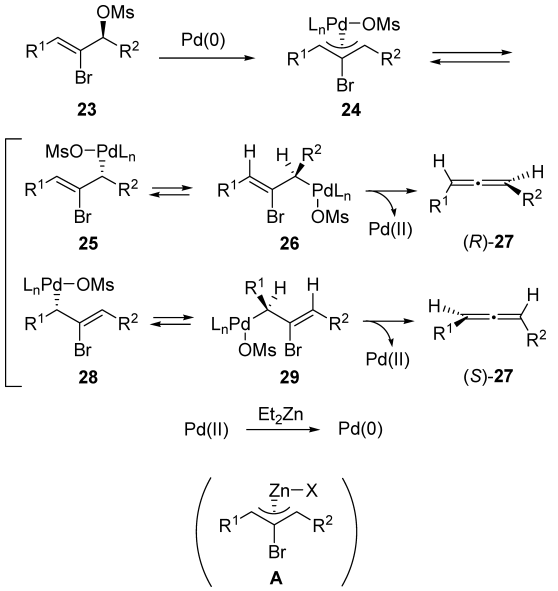


Chart 4. Stereochemical Course of the Reductive Allene Synthesis from Mesylates

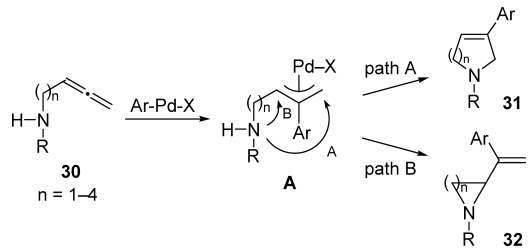


Chart 5. Cyclization of Amino Allenes

either **19** or **20** (Chart 3), the author speculates that both **26** and **29** are competent intermediates in the reaction. The generated palladium(II) species would be converted into palladium(0) by the action of Et_2Zn, which is well accepted in the literature.[29)] Although Et_2Zn is not essential when 1 eq of $Pd(PPh_3)_4$ was employed, another mechanism *via* transmetallation of the η^3-allylpalladium(II) intermediate with diethylzinc to form **A** cannot be ruled out.[30,31)]

3. Palladium-Catalyzed Cyclization of Allenes

3.1. Stereoselective Synthesis of 2-Alkenylaziridines and 2-Alkenylazetidines by Palladium-Catalyzed Intramolecular Amination of α- and β-Amino Allenes[32—34)]

Transition metal-catalyzed cyclization of allenes bearing a (pro-)nucleophilic functionality such as oxygen, nitrogen, and carbon has attracted much attention in recent years.[35,36)] Particularly, cyclization of amino allenes using such metals as Pd(0 or II),[37—45)] Ag(I),[46—50)] and organolanthanides[51)] has become quite useful methodology for the synthesis of five- or six-membered azacycles, and several groups have applied such cyclization to the total synthesis of natural products.[52—54)] It is well documented that cyclization of amino allene **30** with a one- or two-carbon tether between the allene and the nitrogen atom (n=1 or 2) yields five- or six-membered azacycles **31** (n=1 or 2) selectively by path A (Chart 5), while an amino allene bearing a longer carbon tether (n=3 or 4) also affords five- or six-membered rings **32** (n=3

or 4) *via* path B. In contrast, ring-closure of amino allenes bearing a shorter carbon chain (n=1 or 2) yielding three- or four-membered azacycles (path B) was unprecedented.[55—59] Recent development of aziridine and azetidine chemistry prompted us to synthesize these compounds bearing a wide variety of alkenyl groups *via* cyclization of amino allenes.[60—63] It was of great interest to determine whether amino allenes can be cyclized into strained aziridines and azetidines using a transition-metal-based catalytic system and whether the axial chirality of the amino allenes influences the chemo- and stereoselectivity of the cyclization process.

Amino allenes were prepared by use of the organocopper-mediated ring-opening reaction of chiral ethynylaziridines as already described in Section 2.1. First, the cyclization of α-amino allenes under various reaction conditions was investigated. To the author's initial disappointment, exposure of **33a** and **34a** to the known reaction conditions [$Pd(PPh_3)_4$, K_2CO_3, and iodobenzene in DMF][39] afforded undesired five-membered rings **35a** and **36a**, respectively, although in a stereoselective manner (Chart 6). Other known cyclization using Ag(I) again resulted in the formation of a five-membered ring as the sole isolable product.

After considerable unsuccessful experimentation, the expected aziridine formation was realized when the palladium(0)-catalyzed cyclizations were conducted in 1,4-dioxane. The results are summarized in Table 1. Typically, a dioxane solution of the amino allene **33a**, iodobenzene, K_2CO_3, and a catalytic amount of $Pd(PPh_3)_4$ (4 mol%) was refluxed yielding 2,3-*cis*- and 2,3-*trans*-2-alkenylaziridines **37a** and **38a** in an 82 : 18 ratio in a good combined yield (80%, entry 1). Arylation takes place on the central carbon of the allenic moiety, in the same manner as is described in the previous cyclization of amino allenes. Similarly, by using *p*-iodotoluene instead of iodobenzene, the expected aziridines **37e** and **38e** were obtained (entries 5, 10).

The previous studies on the alkenylaziridines by the author's group revealed that 2,3-*cis*-2-alkenylaziridines are relatively more stable than their 2,3-*trans*-isomers, and that 2,3-*trans*-isomers can be easily isomerized into their *cis*-isomers upon treatment with palladium(0), *via* η^3-allylpalladium(II) intermediates.[64—67] However, it has been proven that upon exposure of the 2,3-*trans*-2-alkenylaziridines of the type **38** having a methyl substituent on the double bond to the cyclization conditions, isomerization to the *cis* isomer **37** was observed only to a small extent. This is presumably due to the lower reactivity of alkenylaziridines **37**/**38** having a highly substituted vinyl group toward palladium(0), and palladium(0) hence reacts with iodobenzene preferably to form phenylpalladium(II) iodide. Accordingly, the stereoselective formation of alkenylaziridines **37** and **38** (Table 1) would be mainly controlled kinetically.

A plausible rationale for the stereoselectivities of the aziridination reaction of internal amino allenes is depicted in Chart 7. Phenylpalladium(II) iodide, formed *in situ* from iodobenzene and Pd(0), would generate η^3-allylpalladium complexes by the reaction with (*S*,a*S*)-**33** approaching from the less hindered face. Predominant formation of the complex **39** (path A) over **40** (path B) can be expected due to the relatively small steric repulsion of phenylpalladium(II) iodide with a methyl group than with an aminomethyl group (R_L). The *cis*-*E*-alkenylaziridine **37** would be formed as a

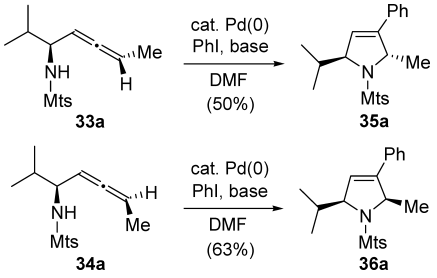
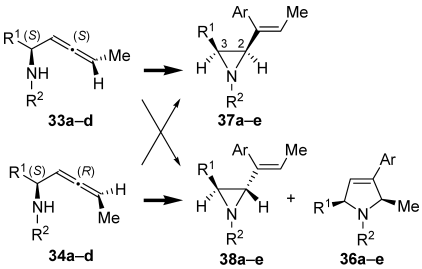


Chart 6. Formation of Five-Membered Rings from α-Amino Allenes

Table 1. Palladium(0)-Catalyzed Aziridination of the α-Amino Allenes **33** and **34**[a]



a: R^1 = *i*-Pr, R^2 = Mts, Ar = Ph
b: R^1 = Bn, R^2 = Mts, Ar = Ph
c: R^1 = Bn, R^2 = Mtr, Ar = Ph
d: R^1 = $TBSOCH_2$, R^2 = Mts, Ar = Ph
e: R^1 = *i*-Pr, R^2 = Mts, Ar = 4-MePh

Entry	Allene	ArI	Product ratio[b]	Yield[c] (%)
1	**33a**	PhI	**37a** : **38a**=82 : 18	80
2	**33b**	PhI	**37b** : **38b**=85 : 15	79
3	**33c**	PhI	**37c** : **38c**=80 : 20	79
4	**33d**	PhI	**37d** : **38d**=72 : 28	74
5	**33a**	4-MePhI	**37e** : **38e**=91 : 9	64
6	**34a**	PhI	**37a** : **38a** : **36a**=2 : 90 : 8	79
7	**34b**	PhI	**37b** : **38b** : **36b**=17 : 67 : 16	73
8	**34c**	PhI	**37c** : **38c** : **36c**=17 : 78 : 5	77
9	**34d**	PhI	**37d** : **38d** : **36d**=23 : 64 : 13	71
10	**34a**	4-MePhI	**37e** : **38e** : **36e**=12 : 85 : 3	44

a) All reactions were carried out in 1,4-dioxane under reflux using $Pd(PPh_3)_4$ (4—20 mol%), K_2CO_3 (4 eq), and ArI (4 eq). *b*) Ratios were determined by ^{1}H-NMR (270 MHz) or isolation of the products. *c*) Isolated yields. Mtr=4-methoxy-2,3,6-trimethylphenylsulfonyl.

major product by the intramolecular nucleophilic attack of the nitrogen onto the stable *syn*-η^3-allylpalladium complex **41** derived from **39**[68] *via* η^3–η^1–η^3 mechanism, reproducing palladium(0). Formation of the minor *trans*-*E*-alkenylaziridine **38** can be rationalized by path B, in that the allylpalladium complex **40** is isomerized into stable **42**, followed by cyclization. The predominant formation of the *trans*-(*E*)-alkenylaziridine **38** from (*S*,a*R*)-**34** can be explained in a similar manner. The significant effect of the solvent on the regioselectivity of the reaction was not rationalized at the present stage of the authors' understandings.

Next, cyclization of β-amino allenes for the synthesis of alkenylazetidines was investigated. Considering the results of the palladium-catalyzed cyclization of α-amino allenes, the author anticipated that the choice of 1,4-dioxane would also be suitable for the cyclization of β-amino allenes. Treatment of the β-amino allene **43a** with iodobenzene, K_2CO_3, and catalytic $Pd(PPh_3)_4$ in dioxane yielded an isomeric mixture of

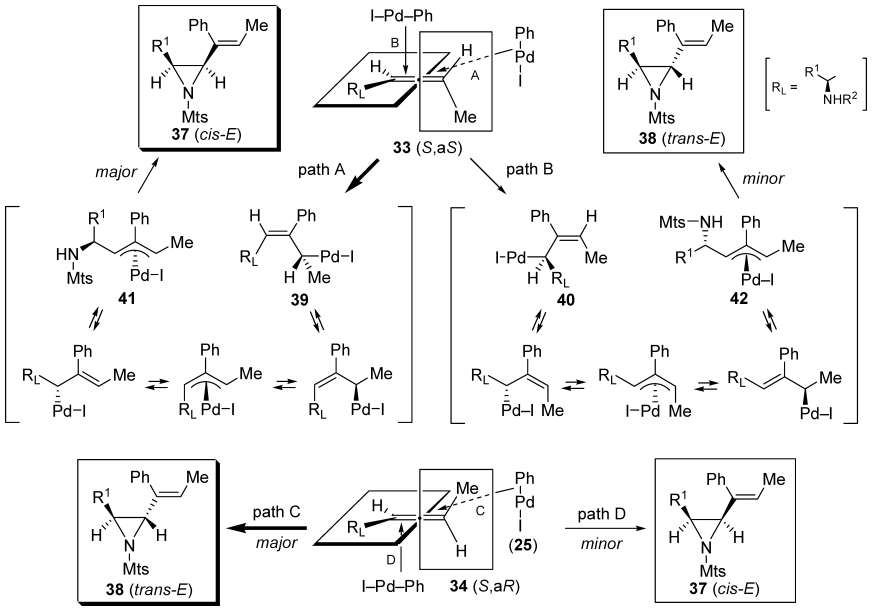
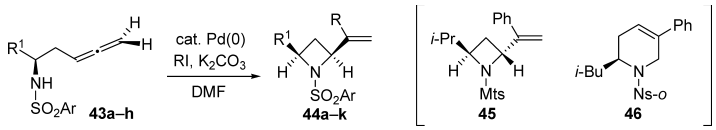


Chart 7. One Plausible Rationale for the Stereoselective Aziridination of **33** and **34**

Table 2. Palladium(0)-Catalyzed Azetidine Synthesis from β-Amino Allenes[a)]



Entry	Allene	R^1	R^2	RI	Reaction time (h)	Product ratio[b)]	Yield[c)] (%)
1[d)]	**43a**	*i*-Pr	Mts	PhI	4	**44a** : **45** = 82 : 18	91
2	**43a**	*i*-Pr	Mts	PhI	2	**44a** = 100	98
3	**43b**	*i*-Bu	Mts	PhI	3.5	**44b** = 100	84
4	**43c**	*i*-Bu	Ts	PhI	3	**44c** = 100	89
5	**43d**	*i*-Bu	*o*-Ns[e)]	PhI	0.75	**44d** : **46** = 62 : 38	87
6	**43e**	Bn	Ts	PhI	1	**44e** = 100	89
7	**43f**	$TBSOCH_2$	Mts	PhI	1.5	**44f** = 100	53
8	**43g**	$MeO_2C(CH_2)_2$	Mts	PhI	1	**44g** = 100	67
9	**43h**	$MeO_2C(CH_2)_2$	Mtr	PhI	1.5	**44h** = 100	73
10	**43b**	*i*-Bu	Mts	3-NO_2PhI	1	**44i** = 100	22
11	**43b**	*i*-Bu	Mts	PhCH=CHBr	0.75	**44j** = 100	68
12	**43e**	Bn	Ts	4-MePhI	1.5	**44k** = 100	81

a) All reactions were carried out in DMF at 70 °C using $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (4 eq), and RI (4 eq) unless otherwise stated. *b*) Ratios were determined by ^{1}H-NMR (270 MHz) or isolation of the products. *c*) Combined isolated yields. *d*) Reaction was conducted in 1,4-dioxane under reflux. *e*) *o*-Ns=2-nitrophenylsulfonyl.

2,4-*cis*- and 2,4-*trans*-3-alkyl-2-alkenylazetidines **44a** and **45** (82 : 18; Table 2, entry 1), while in DMF, unexpectedly, 2,4-*cis*-isomer **44a** was afforded exclusively (entry 2). Similar results were obtained using other β-amino allenes **43** bearing a variety of alkyl (isobutyl, benzyl, siloxymethyl, or methoxycarbonylethyl group) and *N*-protecting groups (Mts, Ts, Mtr), yielding the 2,4-*cis*-4-alkyl-2-alkenylazetidines **44** in good to excellent yields. However, the amino allene **43d** bearing a *o*-nitrophenylsulfonyl (*o*-Ns) group gave a considerable amount of the six-membered ring **46** along with the desired azetidine **44d** (**44d** : **46** = 62 : 38; entry 5), in analogy with the results by Hiemstra reported almost at the same time.[56)] Other aryl- or alkenyl groups such as a 3-nitrophenyl, (*E*)-styryl, or 4-methylphenyl group can also be introduced on the double bond of the alkenylazetidines (entries 10—12).

Chart 8 shows a plausible pathway for the preferable formation of 2,4-*cis*-2-alkenylazetidine **44** over its 2,4-*trans* isomer **45**. The two η^3-allylpalladium complexes **47** and **49**, which would be generated by the reaction of β-amino allene **43** with R–Pd–X, are expected to be interconvertible *via* a η^3–η^1–η^3 mechanism. Since unfavorable steric interaction between the arylsulfonyl and allyl groups in **51** or arylsulfonyl and R^1 groups in **52** would destabilize these conformers, predominant formation of 2,4-*cis*-azetidine **44** *via* the conformer **50** is readily understood. In addition, the predominant formation of 2,4-*cis*-azetidines would also be influenced by palladium(0)-catalyzed isomerization.[69)]

3.2. Palladium(0)-Catalyzed Cyclization of Allenenes Including Tandem Cyclization[70—72)] Allenes of general type **53**, which bears a nucleophilic moiety such as a nitrogen or oxygen-containing functional group, are a well-known class of compounds that undergo a variety of palladium(0)-

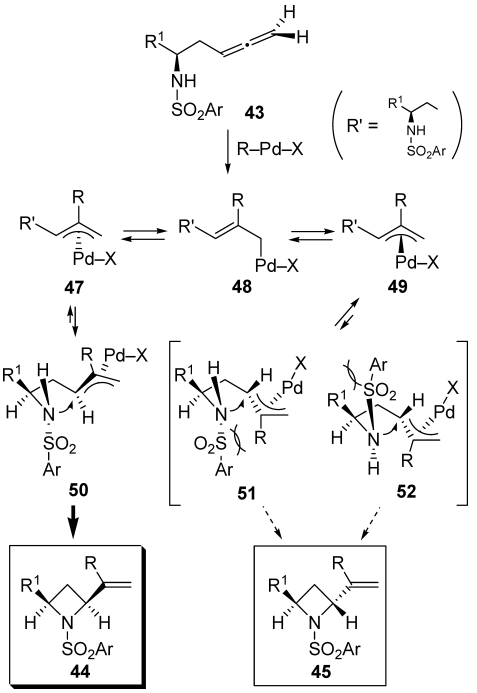


Chart 8. Palladium-Catalyzed Stereoselective Formation of 2,4-*cis*-Azetidine **44**

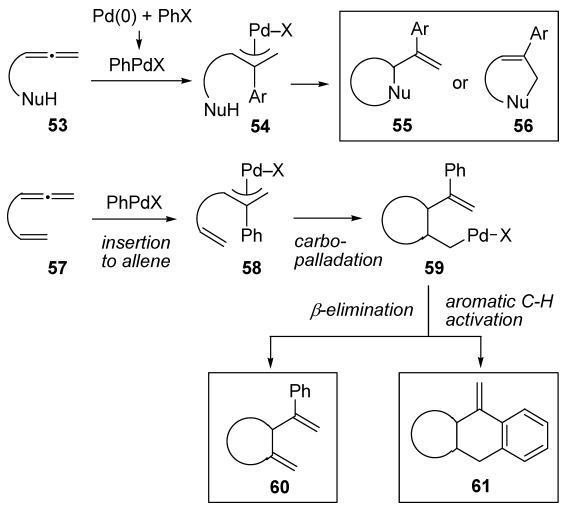


Chart 9. Palladium(0)-Catalyzed Cyclization of Allenes

catalyzed cyclizations to form cyclic products **55** or **56** (Chart 9).[37—45] In sharp contrast, however, palladium-catalyzed reactions of allenes that contain an additional multiple bond have scarcely been studied. Recently, cyclizations of bisallenes on treatment with silylstannane and palladium(0) were independently reported by two research groups.[73,74] 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.[75,76] Oh and co-workers reported cyclization of allenynes in the presence of a palladium catalyst and organic acid.[77,78] However, palladium(0)-catalyzed tandem cyclization of an allene that contains an additional multiple bond has scarcely been investigated.[79,80]

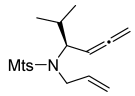
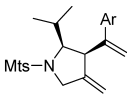
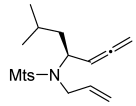
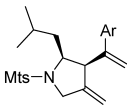
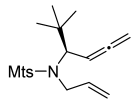
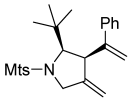
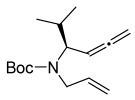
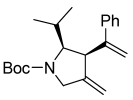
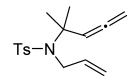
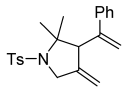
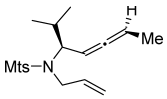
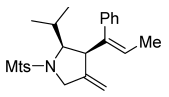
In analogy with the reaction of the allenes **53**, which terminates with the intramolecular nucleophilic attack of the η^3-allylpalladium(II) intermediate by a nucleophile, the allenene **57** could undergo a tandem cyclization of the type shown in Chart 9 under similar conditions. Thus, the η^3-allylpalladium(II) intermediate **58**, formed by the reaction of the allenene **57** with phenylpalladium(II) halide, would be converted into the intermediate **59** by carbocyclization.[81,82] If β-hydride elimination then predominated, a monocyclic product **60** would be produced. However, further cyclization onto the aromatic ring through C–H activation would lead to a tricyclic product such as **61** in a single step.

Palladium-catalyzed C–H activation of an aromatic group has received considerable attention in recent years. Particularly, tandem carbon–carbon bond formations through this process are useful in that complex molecules can be directly obtained in a single operation. Although palladium-catalyzed mono-cyclization onto an aryl ring forming two,[83,84] three,[85—87] or four carbon–carbon bonds[88,89] in one-pot manner are well documented, the tandem reaction involving a bis-cyclization process is extremely rare.[90—93] Tandem carbon–carbon bond formation including C–H activation of aromatic rings using allenic compounds is unknown.

In an initial experiment, the palladium(0)-catalyzed cyclization of the allenene **62**—**67** was investigated and found that the carbocyclization of allenenes and subsequent β-hydride elimination proceeds efficiently upon treatment with iodobenzene and K_2CO_3 in the presence of a catalytic amount of $Pd(PPh_3)_4$ (Table 3). Reaction of **62** in refluxing dioxane provided the 2,3-*cis*-pyrrolidine **68a** in 60% yield as the sole isolable product (Table 3, entry 1). Although the reaction in CH_3CN gave a similar result, other polar solvents such as DMSO and DMF were less effective. The use of 4-iodoanisole (entry 2) and 4-iodotoluene (entry 3) as the aryl halide gave comparable results to iodobenzene. The allenene **63** bearing an isobutyl group required prolonged reaction time for the complete consumption of the starting materials (24—30 h, entries 4, 5). Therefore, the substituent α to the allene was found to be extremely important for the efficiency of the cyclization. The allenene **65**, the amino group of which is protected by a Boc group, afforded *N*-Boc-pyrrolidine derivative **71** although in relatively low yield (41%, entry 7). A geminal dimethyl group of **66** assists the cyclization to **72** (entry 8); however, this reaction requires 20 h for the complete conversion. Internal allene **67** was also cyclized into the five-membered ring **73** in 59% yield. The observed (*Z*)-geometry of the double bond of **73** will be a consequence of thermodynamic preference for the *syn*-η^3-allylpalladium(II) intermediate over other isomers.[68]

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 Chart 10. Insertion of phenylpalladium iodide to the allenic moiety of **74** would give a η^3-allylpalladium(II) intermediate **75**. If the intermediate **75** underwent carbocyclization *via* the conformation **76**, the 2,3-*trans*-pyrrolidine **79** would be formed. However, an unfavorable steric interaction between pseudo-axial protons and the phenyl group in **76** does exist to destabilize this conformer. Thus, the ring-formation would proceed preferentially from the more abundant conformers **77** and/or **78**, and β-hydride elimination of the resulting alkylpalladium(II) yields the *cis*-pyrrolidine **80** as a single isomer.

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

Entry	Allene	ArI	Time (h)	Product (yield[b)])
				
1	**62**	PhI	5	**68a**: Ar=Ph (60%)
2	**62**	4-MeOPhI	3	**68b**:Ar=4-MeOPh (60%)
3	**62**	4-MePhI	8	**68c**: Ar=4-MePh (56%)
				
4[c)]	**63**	PhI	24	**69a**: Ar=Ph (46%)
5	**63**	4-MeOPhI	30	**69b**: Ar=4-MeOPh (50%)
6	 **64**	PhI	5	 **70** (61%)
7	 **65**	PhI	20	 **71** (41%)
8	 **66**	PhI	20	 **72** (59%)
9	 **67**	PhI	13	 **73** (58%)

a) All reactions were carried out in the presence of $Pd(PPh_3)_4$ (10 mol%), PhI (2 eq), and K_2CO_3 (2 eq) in dioxane unless otherwise stated. *b*) Isolated yields. *c*) Increased amounts of ArI (4 eq) and K_2CO_3 (4 eq) were used.

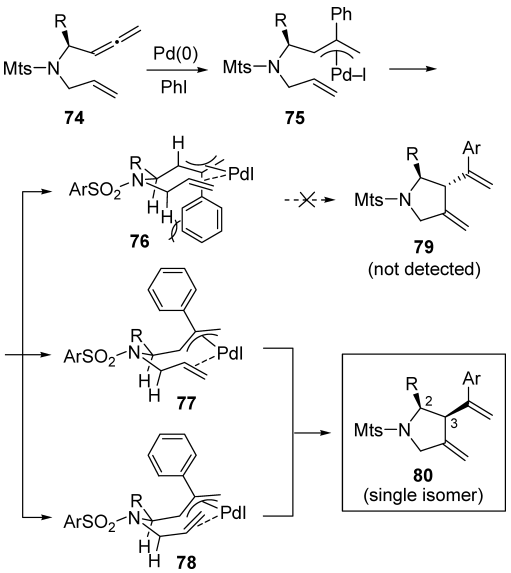


Chart 10. Stereoselective Formation of 2,3-*cis*-Pyrrolidines **80**

Next, inhibition of the β-hydride elimination was investigated in order to promote the desired tandem cyclization. The author expected that the replacement of the β-hydrogen

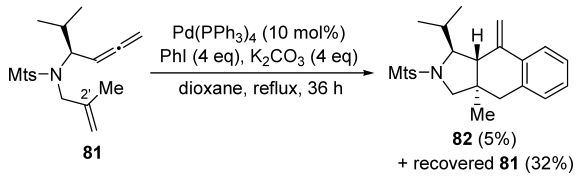


Chart 11. Palladium(0)-Catalyzed Tandem Cyclization of 2′-Methylated Allenene **81**

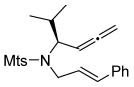
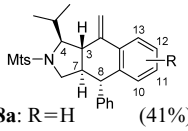
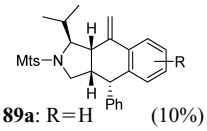
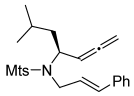
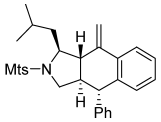
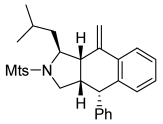
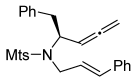
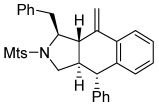
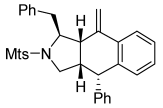
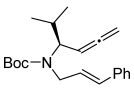
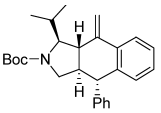
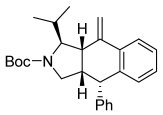
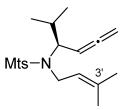
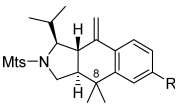
atom with an alkyl group would suppress the β-hydride elimination and allow another cyclization step. However, introduction of a methyl group at the 2′-position dramatically decreased the reactivity of the allenene, and the desired tricyclic product **82** was obtained from the 2′-methylated allenene **81** in just 5% yield after 36 h (Chart 11). However, this result clearly shows that inhibition of the β-hydride elimination does promote the desired tandem cyclization onto an aryl group by C–H activation.

Next, the cyclization of allenenes **83**—**86** bearing a phenyl substituent at the 3′-position was investigated since the introduction of a substituent at the olefin terminus might impede the required arrangement of the palladium center relative to the hydrogen atom for β-hydride elimination to occur.[94—96)] To the author's delight, the allenene **83** reacted with iodobenzene, K_2CO_3, and a catalytic amount of palladium(0) in dioxane to give a separable diastereomeric mixture of the benzoisoindole derivatives **88a** and **89a** in moderate yields (41%, 10%, respectively; Table 4, entry 1). This is the first example of a successful palladium(0)-catalyzed tandem cyclization of allenenes. Introduction of an electron-donating substituent such as methyl and methoxy group at the 4-position of iodobenzene increased the reaction rate and slightly improved the combined yields of the tricyclic products (entries 2, 3). However, the reaction with 2-iodoanisole (entry 4) gave lower yields of the desired benzoisoindoles **88d** (36%) and **89d** (2%), presumably due to the steric hindrance of the 2-anisyl group. Similarly, other *N*-cinnamylamino allenes **84**—**86** also reacted to afford the expected tricyclic products (entries 5—7). Substituents other than a phenyl group at the olefin terminus can also promote the tandem cyclization (entries 8, 9).

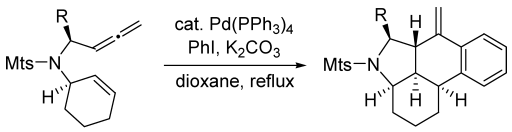
In order to examine the scope of the tandem cyclization as a useful synthetic method of various polycyclic compounds, the reaction of the *N*-cyclohexenyl derivatives **97** (Chart 12) was investigated. Treatment of **97** under the standard cyclization conditions led to formation of the desired tetracyclic compounds **98** in 49—61% yield as a single isomer. It is noteworthy that three stereogenic centers are newly created with complete stereoselectivity. These results clearly demonstrate the utility of this tandem cyclization as a novel method for the synthesis of complex heterocycles.

Three possible mechanistic pathways for the final C–H activation are shown in Chart 13. (1) Intramolecular oxidative addition of an aromatic C–H bond of **99** to palladium(II) to form palladium(IV) intermediate **100**,[97—99)] which gives the benzoisoindole **103** on loss of HI and subsequent reductive elimination (path A). (2) Carbopalladation onto the aryl group in **99** would give the palladium(II) intermediate **101**, in which the β-hydrogen has an *anti*-configuration to the palladium atom. In most cases, the subsequent β-hydride elimination proceeds with the *syn*-stereochemistry.[95,96)] Accord-

Table 4. Palladium(0)-Catalyzed Tandem Cyclization of Allenenes with Iodobenzene Derivatives[a)]

Entry	Substrate	ArI	Reaction time (h)	Product (yield[b)])	
					
1	**83**	PhI	7.5	**88a**: R=H (41%)	**89a**: R=H (10%)
2		4-MePhI	7	**88b**: R=11-Me (37%)	**89b**: R=Me (18%)
3		4-MeOPhI	3.5	**88c**: R=11-OMe (36%)	**89c**: R=OMe (20%)
4		2-MeOPhI	10	**88d**: R=13-OMe (36%)	**89d**: R=13-OMe (2%)
5[c)]	 **84**	PhI	29	 **90** (21%)	 **91** (14%)
6	 **85**	PhI	23	 **92** (30%)	 **93** (24%)
7	 **86**	PhI	30	 **94** (16%)	 **95** (35%)
					
8[c)]	**87**	PhI	28	**96a**: R=H (42%)	
9		4-MeOPhI	30	**96b**: R=OMe (45%)	

a) Unless otherwise stated, reactions were carried out with $Pd(PPh_3)_4$ (10 mol%), ArI (2 eq), and K_2CO_3 (2 eq) in dioxane under reflux. *b*) Isolated yields. *c*) Increased amounts of ArI (4 eq) and K_2CO_3 (4 eq) were used.



97a: R = *i*-Pr
97b: R = *i*-Bu
97c: R = *s*-Bu

98a: R = *i*-Pr (49%)
98b: R = *i*-Bu (51%)
98c: R = *s*-Bu (61%)

Chart 12. Palladium(0)-Catalyzed Tandem Cyclization of **97**

ingly, the rearomatization to **103** might proceed through a facile stereomutation furnishing the required *syn*-elimination,[100,101)] presumably by the η^3–η^1–η^3 mechanism of the allylpalladium(II) species.[102)] Also, the *anti*-elimination might be one rationalization for the rearomatization of **101**.[103—105)] Alternatively, (3) electrophilic attack of the aromatic carbon onto the palladium(II) intermediate **99** would give a cationic intermediate **102**, deprotonation of which and subsequent reductive elimination would afford **103** (path C).[106—108)] At the present stage of the author's understanding, it is difficult to determine which is the most favorable reaction course in this reaction, as well as in related reactions.[109—112)]

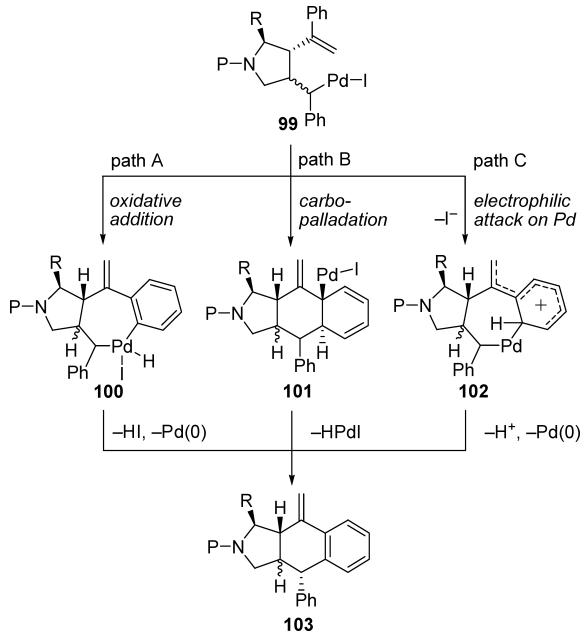


Chart 13. Possible Reaction Pathways for the C–H Functionalization

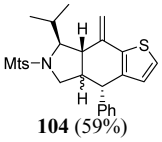
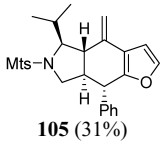
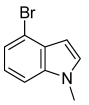
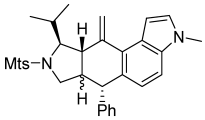
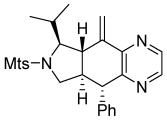
Finally, direct synthesis of tri- or tetracyclic heterocycles using the tandem cyclization with heteroaromatic halides was investigated (Table 5). The reaction of the allenene **83** with 2-bromothiophene yielded tricyclic products **104** in 59% combined isolated yields (entry 1). The cyclization using 3-bromofuran afforded tricyclic furan **105** as a single isolable diastereomer (entry 2). The relatively low yield (31%) is due to instability of **105**. Furthermore, it was found that bicyclic heteroaryl halides are good partners for the tandem cycliza-

tion of the allenene **83** (entry 3). Although we suffered from lower reactivity of chloropyrazine in the reaction with **83**, this problem has been overcome by using iodopyrazine (entry 4) to give **107** in 62% yield.

3.3. Novel Synthesis of 3-Azabicyclo[3.1.0]hexanes by Unusual Palladium(0)-Catalyzed Cyclopropanation of Allenenes[71,113] 3-Azabicyclo[3.1.0]hexane is a basic structure of biologically active natural products[114] such as CC-1065, duocarmycin, and indolizomycin, and also a framework of a pharmacologically important class of compounds such as 3,4-methanoprolines,[115,116] poly-L-proline type II peptide mimetics,[117] and conformationally rigid analogues of [1,4′-bipiperidine]-4′-carboxamides (Fig. 2).[118] Moreover, heterocyclic compounds with this ring system are known as useful intermediates for cyclopropane amino acids such as conformationally restricted analogues of L-glutamate[119] and γ-aminobutyric acid (GABA).[120,121] Therefore, stereoselective construction of a nonracemic 3-azabicyclo[3.1.0]hexane framework is an attractive research subject for organic chemists. However, catalytic synthesis of 3-azabicyclo[3.1.0]hexanes is relatively rare.[122—126]

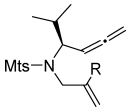
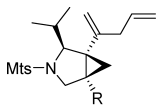
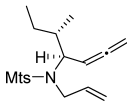
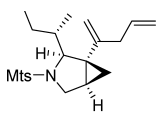
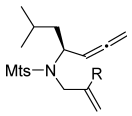
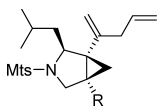
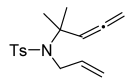
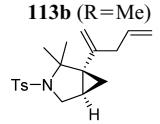
During the course of the study on tandem cyclization of allenenes (Section 3.2), it was found that 3-azabicyclo[3.1.0]hexanes can be directly constructed from allenenes by simply changing the reaction conditions (Table 6). Although the reaction of allenene **62** with allyl carbonate and catalytic $Pd(PPh_3)_4$ or $[(\eta^3\text{-}C_3H_5)PdCl]_2$ in CH_3CN led to recovery of the starting material, it was found that treatment of **62** with allyl carbonate in the presence of a catalytic amount of $Pd_2(dba)_3\cdot HCl_3$ in CH_3CN at 80 °C afforded 3-azabicyclo[3.1.0]hexane **111a** in 64% yield (entry 1). Although the

Table 5. Palladium(0)-Catalyzed Tandem Cyclization of Allenene **83** with Heteroaryl Halides[a]

Entry	ArX	Time (h)	Product (yield)[b]
1		8	 **104** (59%) *trans* : *cis* = 80 : 20
2		5	 **105** (31%)
3		12	 **106** (49%) *trans* : *cis* = 89 : 11
4		8	 **107** (62%)

a) All reactions were carried out using allenene **63** in the presence of $Pd(PPh_3)_4$ (10 mol%), ArI (2 eq), and K_2CO_3 (2 eq) in dioxane under reflux. *b*) Isolated yields.

Table 6. Synthesis of 3-Azabicyclo[3.1.0]hexanes from Allenenes[a]

Entry	Allenene	Time (h)	Product	Yield[b]
1	 **62** (R = H)	5 h	 **111a** (R = H)	64
2	**108** (R = Me)	7 h	**111b** (R = Me)	59
3	 **109**	7 h	 **112**	57
4	 **63** (R = H)	24 h	 **113a** (R = H)	35
5	**110** (R = Me)	24 h	**113b** (R = Me)	36
6	 **66**	60 h	 **114**	24[c]

a) All reactions were carried out with $Pd_2(dba)_3\cdot CHCl_3$ (10 mol%) and allyl carbonate (6 eq) in CH_3CN. *b*) Isolated yields. *c*) The starting allenene **66** was recovered (29%).

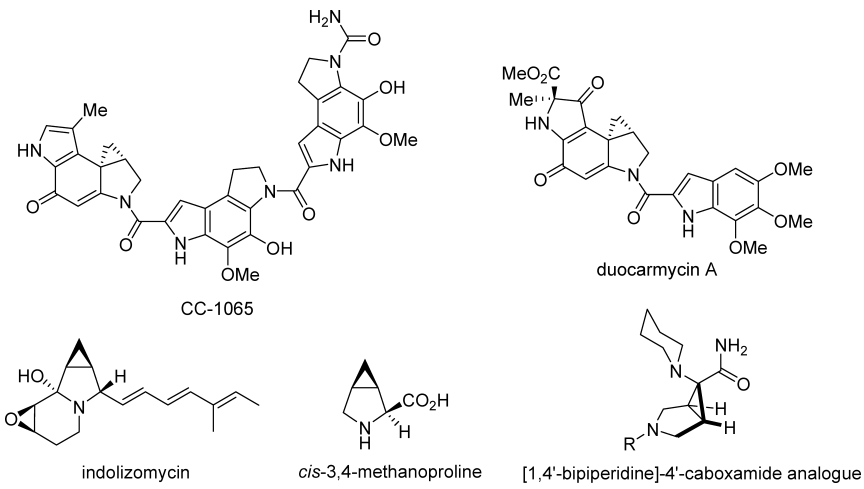


Fig. 2. Representative Pharmacologically Important Compounds Having a 3-Azabicyclo[3.1.0]hexane Framework

formation of small rings, including cyclopropanes,[58,59] by intramolecular nucleophilic attack onto the allenic moiety is well documented,[32—34,55—57] direct synthesis of bicyclic cyclopropanes by the reaction of allenes with an additional multiple bond is unprecedented. Similarly, the reaction of allenenes **108** and **109** under the identical reaction conditions gave **111b** and **112** in 57—59% yields. In contrast, allenenes **63** and **110** having an isobutyl group (entries 4, 5) and **66** having a geminal dimethyl group (entry 6) gave relatively low yields of the bicyclic cyclopropanes **113a**, **b**, and **114**, respectively. These results clearly show that the presence of an appropriate sterically-congested substituent at the α-position to the allenic moiety, which would assist and not interfere in the cyclization, is extremely important for the successful conversion. In fact, the corresponding allenene without the α-substituent was completely inert to the reaction conditions. In all cases, a cyclized product of the type **80** (Chart 10) was not isolated, and the cyclopropanation reaction proceeded in a stereoselective manner.

Although the reaction mechanism of this cyclopropanation is not understood, this reaction clearly demonstrates a novel reactivity of allenes with a palladium(0) catalyst. Chart 14 shows two explanations of the reaction leading to the bicyclic cyclopropanes **119**. Reaction of allenene **115** with η^3-allylpalladium(II) methoxide, derived from allyl carbonate and palladium(0), gives the allylated η^3-allylpalladium(II) intermediate **116**. If deprotonation of **116** predominates to form a palladium carbene intermediate **117** (path A), stereoselective formation of the cyclopropane **119** is readily understood.[127] However, to the best of the author's knowledge, generation of a palladium carbene species from η^3-allylpalladium(II) methoxide is unprecedented. If the intramolecular carbopalladation of **116** *via* **120** predominates (path B), alkylpalladium intermediate **121** would be formed.[128] Although isomerization of the double bond of **121** to **122** is necessary, this pathway also enables the stereoselective formation of bicyclic cyclopropane **119**. The reason why the present reaction conditions promote the cyclopropanation reaction instead of the Oppolzer cyclization leading to **80** (Chart 10) is unclear.

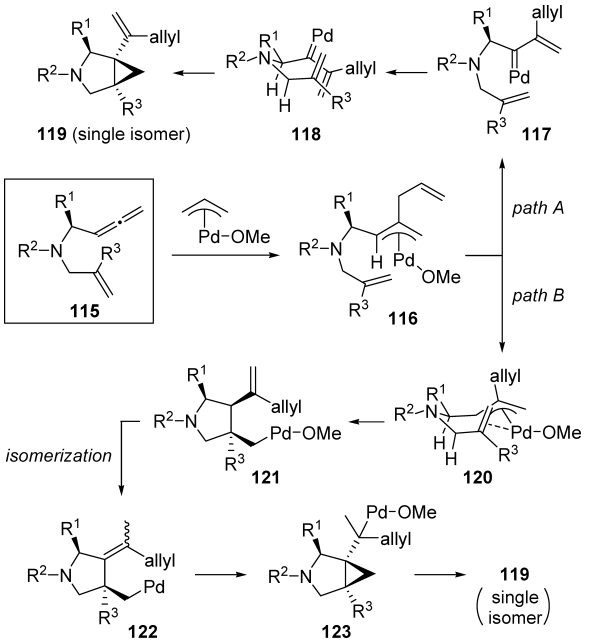


Chart 14. Explanations of the Cyclization of Allenenes Leading to the Bicyclic Cyclopropanes

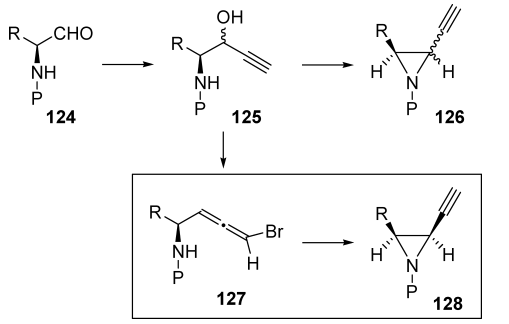
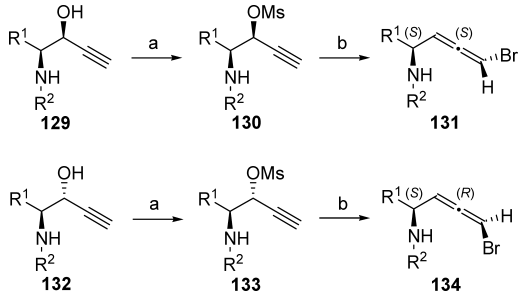


Chart 15. Aziridination of Bromoallenes

4. Cyclization of Bromoallenes

4.1. A Highly *cis*-Selective Synthesis of 2-Ethynylaziridines by Intramolecular Amination of Chiral Bromoallenes[129,130] Reactions of bromoallenes have attracted much interest in recent years, because of their cumulated double bonds and high reactivity.[131] These reactions involve organocopper-mediated substitutions,[132,133] palladium-catalyzed cross-coupling reactions,[134] and the formation of nucleophilic allenylmetal reagents.[135] Among them, the organocopper-mediated substitution of bromoallenes is extremely useful in that the substitution of propargylic oxygen by an alkyl group can be carried out with overall retention of configuration[136]: both the bromination of propargyl esters with CuBr/LiBr[137,138] and alkylation of the resulting bromoallenes by organocopper reagents proceed with inversion of configuration.[139] In contrast, the reaction of bromoallenes with nitrogen nucleophiles is relatively limited. Although the intermolecular amination of racemic bromoallenes has been already reported,[140—142] an intramolecular reaction and a stereochemical course of the amination toward chiral bromoallenes were unprecedented.

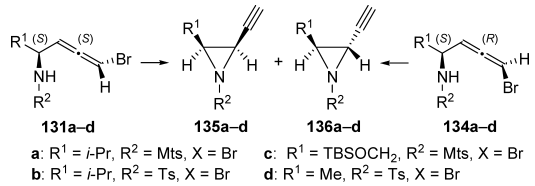
In connection with a research program directed toward the reactions of 2-ethynylaziridines both as carbon electrophiles (Section 2.1)[11,12] and nucleophiles,[143,144] our group required a reliable synthetic method of chiral 2-ethynylaziridines in a stereoselective manner. Ethynylaziridines can be synthesized by the reaction of *N*-tosylimines with sulfonium ylide,[145] reaction of lithium acetylides[146] or allenylzincs[147] with imines, or the Mitsunobu reaction of amino alcohols bearing an ethynyl group[20]; however, the stereoselective synthesis of enantiopure 2-ethynylaziridines is still difficult. Apparently, one of the simplest methods for the synthesis of enantiopure ethynylaziridines **126** is the Mitsunobu reaction of the propargyl alcohol **125** (Chart 15), which in turn could be readily prepared from amino aldehydes **124** derived from α-amino acids. However, a highly diastereoselective synthesis of either *syn*- or *anti*-**125** by the reaction of amino aldehydes with metal acetylides has proven to be difficult, with the exception of some examples.[148—150] Since aziridination under the Mitsunobu conditions proceeds with inversion of configuration, a mixture of 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines **126** is always obtained from a diastereomixture of **125**.



Reagents and Conditions: (a) MsCl, Et_3N, THF, −78 to −40 °C; (b) CuBr·DMS, LiBr, THF, 25 or 50 °C.

Chart 16. Preparation of Bromoallenes Bearing a Protected Amino Group

Table 7. NaH-Mediated Aziridination of Bromoallenes in DMF[a)]



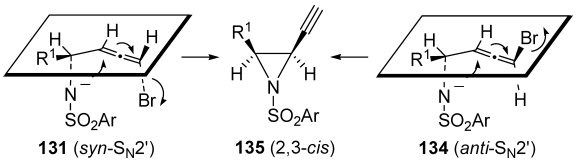
a: R^1 = *i*-Pr, R^2 = Mts, X = Br **c**: R^1 = $TBSOCH_2$, R^2 = Mts, X = Br
b: R^1 = *i*-Pr, R^2 = Ts, X = Br **d**: R^1 = Me, R^2 = Ts, X = Br

Entry	Allene	Time (min)	Ratio[b)] *cis* : *trans*	Yield[c)]
1	**131a**	60	**135a** : **136a** = 82 : 18	93%
2	**131b**	60	**135b** : **136b** = 88 : 12	99%
3	**131c**	60	**135c** : **136c** = 79 : 21	76%
4	**131d**[d)]	180	**135d** : **136d** = 91 : 9	85%
5	**134a**	30	**135a** : **136a** = >99 : 1	99%
6	**134b**	30	**135b** : **136b** = >99 : 1	84%
7	**134c**	30[e)]	**135c** : **136c** = 92 : 8	91%
8	**134d**[d)]	240	**135d** : **136d** = 93 : 7	76%

a) Reactions were carried out with NaH (1.2 or 1.3 eq) at 25 °C in DMF unless otherwise stated. *b*) Ratios were determined by ^{1}H-NMR or isolation of the products. *c*) Combined isolated yields. *d*) Diastereomixture of the bromoallenes was used (96 : 4 for **131d** and 97 : 3 for **134d**). *e*) Reaction was conducted at 50 °C.

To establish a stereoselective synthetic method of chiral 2-ethynylaziridines **126**, the author planned an aziridination of bromoallenes **127** bearing a protected amino group, which would be readily prepared from the propargyl alcohol **125** (Chart 15). The (*S*,a*S*)-bromoallenes **131** bearing a protected amino group were synthesized from *syn*-amino alcohols **129**[151)] in high yields (Chart 16). Thus, mesylation of **129** by the standard method gave **130**, which was then converted into the desired bromoallenes **131** by treatment with CuBr·DMS/LiBr.[137,138)] Similarly, (*S*,a*R*)-**134** were synthesized from the *anti*-amino alcohols **132**.[151)]

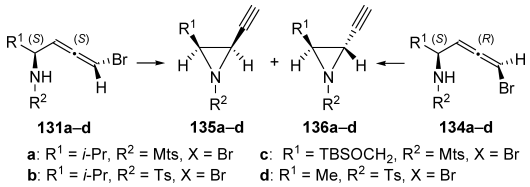
The intramolecular amination of the bromoallenes bearing an (*N*-Boc)amino group showed poor stereoselectivities (*cis* : *trans* = 60 : 40—41 : 59) under various reaction conditions. In contrast, the reaction of *N*-arylsulfonylated amino allenes showed good to high 2,3-*cis* selectivity. The results are summarized in Table 7. NaH-mediated reaction of **131a** in DMF afforded 2,3-*cis*-aziridines **135a** in 82 : 18 ratio and high yield (93%, entry 1). Similarly, other (*S*,a*S*)-bromoallenes **131b**—**d** yielded mixtures of 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines in which the *cis*-isomers **135** predominated (79 : 21—91 : 9, entries 2—4). Interestingly, the highest 2,3-*cis* selectivity was observed in the reaction of bromoallene **131d** bearing the smallest substituent (R^1 = Me) at C-4 (91 : 9, entry 4). Furthermore, upon the treatment of (*S*,a*R*)-bromoallenes **134a**—**d** with NaH/DMF (entries 5—8), 2,3-*cis*-aziridines **135a**—**d** were obtained in higher selectivities (>92 : 8). When the allenes **134a** and **134b** bearing an isopropyl group were used (entries 5, 6), only the *cis*-isomers **135a** and **135b** were obtained. From these observations, the aziridination of the (*S*,a*S*)-bromoallenes **131** with NaH/DMF proceeds in a *syn*-S_N2' manner, while an *anti*-S_N2' pathway predominates in the reaction of the (*S*,a*R*)-allenes **134** (Chart 17). These results suggest that the described method would provide 2,3-*cis*-2-ethynylaziridines **128** stereoselectively from a mixture of *syn*- and *anti*-amino alcohols **125** (Chart 15).



131 (*syn*-S_N2') **135** (2,3-*cis*) **134** (*anti*-S_N2')

Chart 17. Stereochemical Course of the NaH-Mediated Aziridination of **131** and **134** in DMF

Table 8. NaH-Mediated Aziridination of Bromoallenes in THF[a)]



a: R^1 = *i*-Pr, R^2 = Mts, X = Br **c**: R^1 = $TBSOCH_2$, R^2 = Mts, X = Br
b: R^1 = *i*-Pr, R^2 = Ts, X = Br **d**: R^1 = Me, R^2 = Ts, X = Br

Entry	Allene	Time (h)	Ratio[b)] (*cis* : *trans*)	Yield[c)]
1	**131a**	4	**135a** : **136a** = >99 : 1	84%
2	**131b**	17	**135b** : **136b** = >99 : 1	99%
3	**131c**	5[d)]	**135c** : **136c** = >99 : 1	48%[e)]
4	**131d**	48	**135d** : **136d** = >99 : 1	77%
5	**134a**	1[d)]	**135a** : **136a** = 26 : 74	92%

a) Reactions were carried out at 25 °C using NaH (1.2 or 1.3 eq) in THF unless otherwise stated. *b*) Ratios were determined by ^{1}H-NMR or isolation of the products. *c*) Combined isolated yields. *d*) The reaction was conducted at 50 °C. *e*) Desilylated bromoallene (30%) was isolated.

These experimental results have been rationalized by the B3LYP density functional calculations together with the 6—31+G(d) basis set and the Onsager solvation model, conducted by Prof. Dr. Kaori Ando (University of Ryukyus). The transition structures for *cis*-aziridine formation of both (4*S*,a*R*)- and (4*S*,a*S*)-bromoallenes in DMF are favored over the corresponding *trans* transition structures by 4.35 and 1.41 kcal/mol, respectively. Furthermore, detailed analysis of the transition states in a gas phase predicted that a less polar solvent would give higher *cis* selectivities for (4*S*,a*S*)-bromoallenes. Accordingly, the reaction of **131** with NaH in a less polar solvent was next investigated. The results are summarized in Table 8. As expected, NaH-mediated cyclization of **131a** in THF afforded only 2,3-*cis*-aziridine **135a** as a single isomer (entry 1). Similarly, other (*S*,a*S*)-bromoallenes **131b**—**d** gave satisfactory results (entries 2—4). A relatively low yield of the *cis*-aziridine **135c** (48%, entry 3) in the reaction of the bromoallene **131c** bearing a siloxymethyl group is due to the desilylation of **131c** under the basic reaction conditions (30% of the desilylated bromoallene was isolated). In

sharp contrast, treatment of (*S*,a*R*)-**134a** yielded the *trans*-aziridine **136** in moderate selectivity (entry 5). These results are in good agreement with the computational investigation by Prof. Ando.[130)]

4.2. Palladium(0)-Catalyzed Synthesis of Medium-Sized Heterocycles by Using Bromoallenes as Allyl Dication Equivalents[152—154)] Medium-sized heterocycles are an extremely important class of compounds, the structural units of which are commonly found within the framework of a variety of natural products.[155)] In particular, seven- and eight-membered heterocycles are constituents of a number of compounds with interesting pharmacological properties.[156—160)] The abundance of medium rings bearing oxygen or nitrogen atom(s) in medicinally interesting compounds continues to ensure that they are important synthetic targets for organic chemists. Synthetic routes to medium-ring heterocycles involving direct ring closure are often slow and hampered by unfavorable enthalpies (the strain in many medium rings) and entropies (probability of the chain ends meeting) of the reaction. Today, the most powerful methodology for the synthesis of medium-sized rings is the ring-closing metathesis (RCM)[161)] that sometimes requires high dilution conditions for successful conversion and often involves generation of byproducts such as ethylene.

In the course of our examination of the aziridination reaction of bromoallenes (Section 4.1),[129,130)] it was found that the reaction of bromoallene **131a** with $Pd(PPh_3)_4$ and NaOMe in MeOH provided 2,3-*cis*-2-(1-methoxy)vinylaziridine **138** stereoselectively (Chart 18). This result strongly suggests the formation of η^3-allylpalladium complex **137** bearing a methoxy group on the central carbon. Namely, bromoallene **139** can act as an allyl dication equivalent **140** when treated with palladium(0) in an alcoholic solvent. Although similar types of reaction are often observed in propargylic carbonates with a palladium catalyst and soft nucleophiles such as active methylene, aryl alcohols or amide,[162—166)] the reaction of allenic substrates and the synthesis of eight-membered rings are unprecedented.

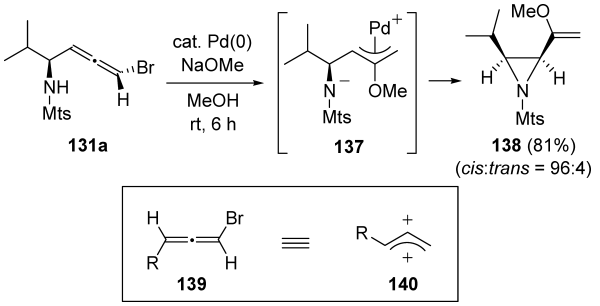


Chart 18. Bromoallenes as Allyl Dication Equivalents

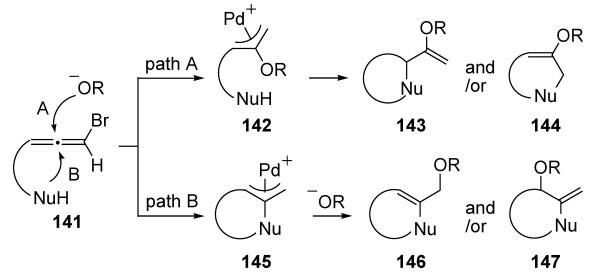


Chart 19. Regioselectivity of Palladium(0)-Catalyzed Cyclization of Bromoallenes

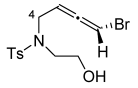
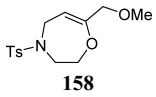
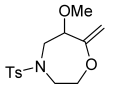
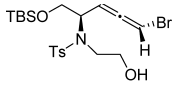
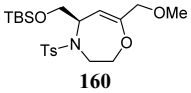
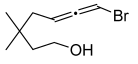
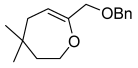
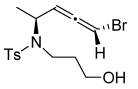
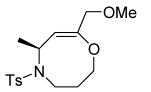
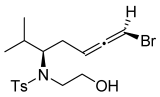
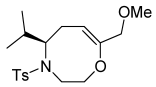
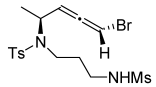
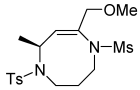
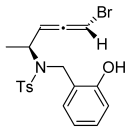
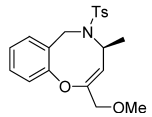
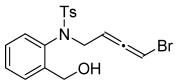
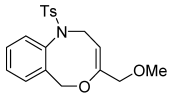
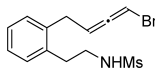
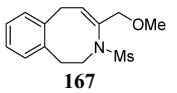
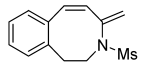
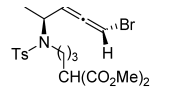
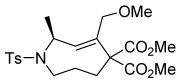
Utilizing this chemistry, the author expected that various heterocyclic medium rings could be formed *via* intramolecular attack of an appropriate functionality such as an oxygen, a nitrogen or an active methylene nucleophile (Chart 19). If the intermolecular nucleophilic attack at the central carbon atom of the allene moiety of **141** predominates over the intramolecular reaction (path A), cyclized products **143** and/or **144** would be obtained. On the other hand, if the intramolecular nucleophilic attack takes place predominantly, cyclization at the central carbon atom of the allenic moiety would proceed to give **146** and/or **147**.

According to the working hypothesis depicted in Chart 19, the synthesis of medium-sized heterocycles through the cyclization of bromoallenes in the presence of a palladium catalyst was investigated. To investigate the effect of the axial chirality on the cyclization reaction, diastereomerically pure bromoallenes were prepared. The results of the cyclization with bromoallenes **148**—**157** are summarized in Table 9. Bromoallene **148**, which bears an oxygen functionality, was treated with NaOMe (1.5 eq) in MeOH in the presence of $Pd(PPh_3)_4$ (5 mol%) to afford the seven-membered ring **158** (61%) along with its regioisomer **159** (28%, entry 1). In contrast, bromoallenes **149** with a bulkier substituent at C-4 gave the seven-membered ring **160** as the only isolable isomers. These results clearly demonstrated that the regioselectivity of the second nucleophilic attack is controlled by the steric size of the substituent at C-4 of the bromoallenes. Other alcohols could be analogously used instead of MeOH for the present cyclization reaction. For example, bromoallene **150** was treated with a preformed mixture of NaH (1.5 eq) and BnOH–THF (1 : 3) in the presence of $Pd(PPh_3)_4$ (5 mol%) to afford the tetrahydrooxepine derivative **161** having a benzyloxy group (72%). Next, similar reactions were conducted with bromoallenes **151** and **152** (entries 4, 5), which bears a five-atom tether between the allenyl and hydroxyl groups. The reaction of these bromoallenes gave the eight-membered rings **162** and **163** as the sole isolable isomers. Furthermore, bromoallenes **153** with a nitrogen functionality, also gave the corresponding eight-membered ring **164** as a single isomer (entry 6).

The synthesis of benzo-annulated medium-sized heterocycles, which are the basic structures of pharmacologically important compounds,[167)] was next investigated. The palladium(0)-catalyzed cyclization of bromoallene **154** in MeOH gave benzo[*b*]-1,5-oxazocine **165** in low yield (15%). In contrast, when the reaction was conducted in a mixed solvent of MeOH/THF (1 : 1), the cyclized product **165** was obtained in a better yield (57%; entry 7). Similarly, the reaction of the bromoallene **155** gave benzo[*c*]-1,5-oxazocine **166** under the same reaction conditions in high yield (82%; entry 8). Interestingly, when the amino allene **156** was used (entry 9), a methoxylated benzo[*d*]azocine derivative **167** was obtained as a major product (60% yield) along with a small amount of β-elimination product **168** (5% yield), which was formed by β-hydride elimination of the η^3-allylpalladium(II) intermediate of the type **145** (Chart 19). This is presumably due to the relatively acidic nature of the β-hydrogen at the benzylic position.

In sharp contrast to the reaction of the bromoallenes hav-

Table 9. NaH-Mediated Aziridination of Bromoallenes in THF[a)]

Entry	Substrate	Conditions	Product	Yield[b)]
1	 **148**	MeOH rt, 6 h	 **158**	61
			 **159**	28
2	 **149**	MeOH rt, 4.5 h	 **160**	74
3	 **150**	BnOH/THF (1 : 3) rt, 5 h	 **161**	72
4	 **151**	MeOH rt, 6 h	 **162**	84
5	 **152**	MeOH 50 °C, 3 h	 **163**	73
6	 **153**	MeOH rt,12 h	 **164**	63
7	 **154**	MeOH/THF (1 : 1) rt, 4 h	 **165**	57
8	 **155**	MeOH/THF (1 : 1) rt, 5 h	 **166**	82
9	 **156**	MeOH/THF (1 : 1) rt, 4 h	 **167**	60
			 **168**	5
10	 **157**	MeOH 50 °C, 3 h[c)]	 **169**	56

a) Reactions were carried out at with diastereomerically pure bromoallenes, $Pd(PPh_3)_4$ (5—10 mol%), and NaOMe or NaH (1.5 eq) unless otherwise stated. *b*) Isolated yields. *c*) 20 mol% of $Pd(PPh_3)_4$ was used.

ing an oxygen or nitrogen nucleophile affording *cis*-rings exclusively, bromoallene **157** having an active methylene nucleophile gave eight-membered rings **169** with *trans*-configuration (56% yield, entry 10).[168] This allene is found to be less reactive than those having an oxygen or nitrogen nucleophile, presumably due to the steric hindrance. The results shown in Table 9 revealed that the intramolecular nucleophilic attack takes place at the central position of the allenic moiety (path B in Chart 19) and, in most cases, the regioselectivity of the attack of methoxide is extremely high. It should be clearly noted that both the (*S*,a*S*)- and (*S*,a*R*)-bromoallenes equally undergo the present transformation to give the same products, which means that a diastereomeric mixture of bromoallenes can be directly employed for preparative use.

A possible reaction course is shown in Chart 20. Oxidative addition of bromoallene **170** to Pd(0) gives η^1-allenylpalladium complex **171**, which is in a state of equilibrium with η^3-propargylpalladium complex **172**.[169,170] The first intramolecular nucleophilic addition occurs to the central carbon of η^3-propargylpalladium complex **172** to produce a palladacyclobutene **173**.[171] This is followed by protonation by MeOH to generate η^3-allylpalladium complex **174**. In many cases, the methoxide attacks the terminal carbon to give **175** because of the steric repulsion with the R substituent. When the R substituent is effectively smaller, a considerable amount of the adduct **176** is obtained by the attack of methoxide to the internal carbon of η^3-allylpalladium complex **174**. Kurosawa, Ogoshi, and co-workers recently reported that a polar solvent shifts the equilibrium between η^1-allenyl- and η^3-propargylpalladium complexes toward the latter which is a reactive intermediate for the central attack.[172,173] Although the exact reason for the observed central attack in the presence of a monodentate ligand and an alcohol is unclear, the polar alcoholic solvent might promote the central attack by shifting the equilibrium toward the η^3-propargylpalladium complex **172**. An alcoholic solvent will also promote the reaction by protonation of the palladacyclobutene intermediate **173**.

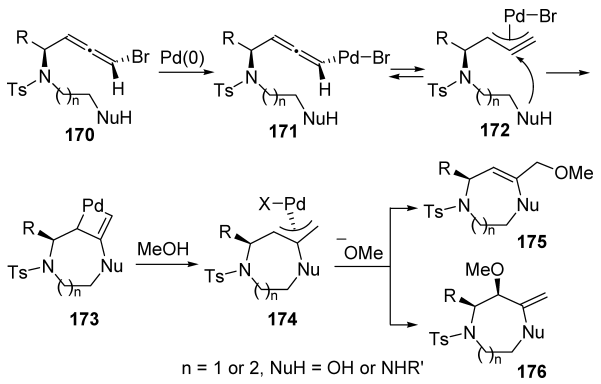


Chart 20. Possible Reaction Course

5. Conclusion

As presented here, our group have developed several useful transformations of allenic substrates mainly for the synthesis of heterocyclic compounds including aziridines, azetidines, pyrrolidines, benzoisoindoles, 3-azabicyclo-[3.1.0]hexanes, and various medium-sized heterocycles. Dur-

ing the course of this study, our group have established two reliable synthetic methods of allenes. Although space restriction does not permit a detailed description, our group developed some other interesting novel reactions such as (1) stereoselective synthesis of 1,3-amino alcohols *via* allenylindium reagents using 2-ethynylaziridines as chiral carbon nucleophiles,[143,144] (2) samarium(II)-mediated radical cyclization onto an aromatic group,[174—178] (3) synthesis and isomerization of vinylaziridines and their application to the stereoselective synthesis of (*E*)-alkene dipeptide isosteres.[64—67,179,180] The author hopes the presented reactions based on the novel reactivities of allenes will facilitate further development of allene chemistry[181—183] and application to synthesis of pharmacologically important compounds from this class of compounds.

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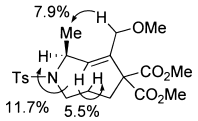

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