Angewandte Chemie

Cyclization Reactions

Bromoallenes as Allyl Dication Equivalents in the Absence of Palladium(0): Synthesis of Bicyclic Sulfamides by Tandem Cyclization of Bromoallenes**

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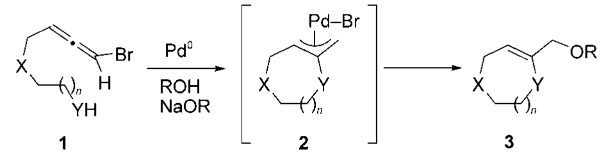
Reactions of bromoallenes have attracted much interest in recent years because of the interesting chemical properties associated with their cumulated double bonds and bromine atom.[1] However, except for our recent study on ring-forming reactions,[2,3] all the reactions of bromoallenes reported to date are intermolecular reactions, such as organocopper-mediated substitutions,[4] palladium-catalyzed cross-coupling reactions,[5] and formation of allenyl–metal reagents.[6] Recently, we found that bromoallenes can act as allyl dication equivalents in the presence of palladium(0), which is an extremely useful process for the synthesis of medium-sized heterocycles (Scheme 1).[3] Thus, reaction of bromoallene **1** with sodium alkoxide in the presence of a palladium(0) catalyst and alcohol affords the (η^3-allyl)palladium(II) intermediate **2** by intramolecular nucleophilic attack at the central carbon atom of the allenic moiety. A second nucleophilic reaction with alkoxide provides **3** in good to high yields. In light of this chemistry, we expected that bicyclic compounds **6** could be formed by tandem cyclization of the bromoallene **4** via (η^3-allyl)palladium(II) intermediate **5** (Scheme 2).



Scheme 1. Palladium(0)-catalyzed medium-ring formation from bromoallenes.

In the field of medicinal chemistry, a sulfamide is one of the most important structural motifs that exist in many pharmaceutically useful compounds. For example, some sulfamides, including cyclic ones, are known to be effective HIV[7] and serine protease inhibitors,[8] and as both agonists

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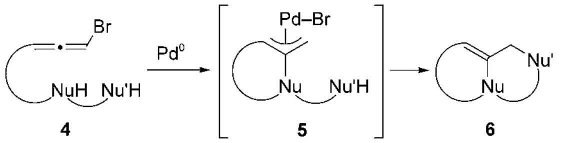
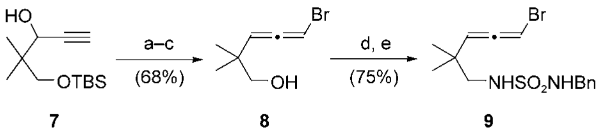


Scheme 2. Synthesis of bicyclic heterocycles.

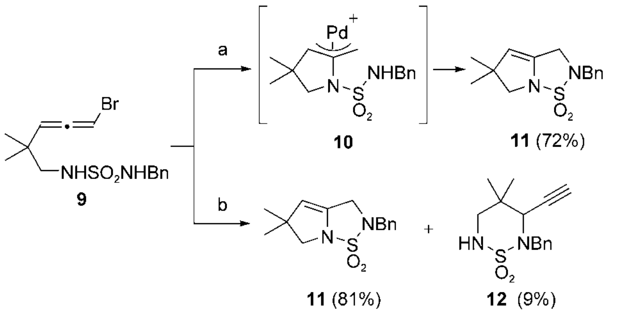
and antagonists of serotonin[9] and histamine receptors.[10] Furthermore, cyclic sulfamides have also been used as effective chiral auxiliaries in asymmetric aldol reactions.[11] However, most of the reported methods for the synthesis of sulfamides rely on the reaction of diamines with sulfuryl chloride or the sulfamide $H_2NSO_2NH_2$ under drastic reaction conditions.[12] Accordingly, we planned a novel synthesis of bicyclic sulfamides by tandem cyclization of bromoallenes. We describe here a highly regioselective construction of cyclic sulfamides with a bicyclo[3.3.0]octane skeleton from bromoallenes containing a sulfamide moiety as nucleophile, and show that some bromoallenes can act as allyl dication equivalents *even in the absence of palladium(0).*

To investigate the synthesis of bicyclic sulfamides by tandem cyclization of bromoallenes, as depicted in Scheme 2, the bromoallene **9** bearing a sulfamide moiety as nucleophile was prepared from propargyl alcohol **7**[13] as shown in Scheme 3. Thus, treatment of **7** with MsCl and Et_3N gave the corresponding mesylate, which was then converted into the bromoallenol **8** by treatment with $CuBr{\cdot}SMe_2/LiBr$[14] followed by desilylation. Condensation of **8** with BocNH-SO_2NHBn[15] under the Mitsunobu conditions gave the corresponding *N*-Boc bromoallene, the Boc group of which was removed by treatment with 3 N HCl to afford the desired bromoallene **9** bearing two nitrogen nucleophiles.



Scheme 3. Synthesis of bromoallene **9** bearing a sulfamide group: a) MsCl, Et_3N; b) $CuBr{\cdot}SMe_2$, LiBr; c) 1% HCl/EtOH; d) BocNH-SO_2NHBn, PPh_3, diethylazodicarboxylate (DEAD); e) 3 N HCl, EtOAc.

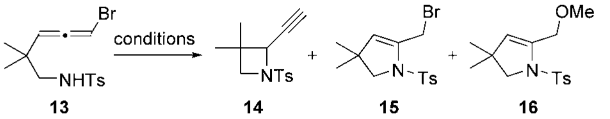
We next investigated the tandem cyclization of the bromoallene **9** in the presence of palladium(0). To realize the desired cyclization, selective addition of the internal sulfamide nitrogen to the central allenic carbon, followed by preferential reaction of the terminal sulfamide nitrogen over that of alkoxide, is essential. Fortunately, cyclization of the bromoallene **9** gave the bicyclic sulfamide **11** (72% yield) as the only isolable product (Scheme 4), presumably via the intermediate **10**. Surprisingly, the same reaction also proceeded in the absence of palladium(0) to afford **11** in better yield (81%) along with a small amount of the six-membered-ring product **12** (9%), although the required reaction time was longer. These results demonstrate that bromoallene **9** can act as an allyl dication equivalent in the absence of palladium(0). However, it should be clearly noted that, in the medium-ring formation,[3] the palladium catalyst is essential for successful conversion.[16] Thus, the reaction of bromoallenes as an allyl dication in the absence of a palladium catalyst can be applied to highly reactive bromoallenes which easily form cyclized products, such as five-membered rings.



Scheme 4. Synthesis of bicyclic sulfamide **11** in the presence or absence of palladium(0): a) $[Pd(PPh_3)_4]$ (10 mol%), NaH (2.5 equiv), MeOH, 60°C, 11.5 h; b) NaH (2.5 equiv), MeOH, 60°C, 16 h.

Next, we investigated the effect of the solvent on the palladium-free reaction using bromoallene **13**. The results are summarized in Table 1. Treatment of bromoallene **13** with NaH in DMF gave the azetidine **14** as the major product[17] and a small amount of dihydropyrrole **15** containing a bromomethyl group (Table 1, entry 1). Similar results were obtained when using NaOMe as the base in DMF or THF (Table 1, entries 2 and 4). Although the reaction of **13** with NaH in MeOH at room temperature gave **15** in low yield (8%; Table 1, entry 5), the reaction at 60°C gave dihydropyrrole **16**, which contains a methoxymethyl group, in high yield (94%; Table 1, entry 6). From these observations, it can clearly be seen that bromoallenes can effectively act as allyl dication equivalents in an alcoholic solvent in the absence of palladium(0).

Table 1: Cyclization of bromoallene **13** in the absence of palladium(0).[a]

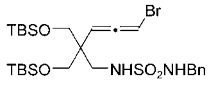
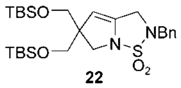
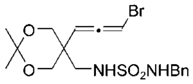
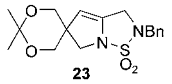
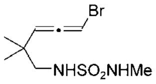
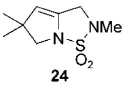
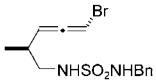
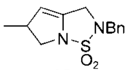
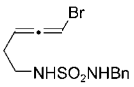
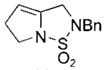


Entry	Solvent	*T*	*t* [h]	Product (yield[b] [%])
1	DMF[c]	room temp	0.5	**14** (76) and **15** (13)
2	DMF[d]	room temp	0.5	**14** (77) and **16** (7)
3	THF[d]	room temp	1.5	no reaction
4	THF[d]	50°C	2.5	**14** (48) and **15** (16)
5	MeOH[c]	room temp	20	**15** (8)[e]
6	MeOH[c]	60°C	7	**16** (94)

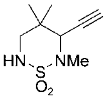
[a] Reactions were carried out with NaH (1.5 equiv) or NaOMe (1.5 equiv) as base in the absence of $[Pd(PPh_3)_4]$. [b] Yields of isolated products. [c] NaH was used as base. [d] NaOMe was used as base. [e] 71% of **13** was recovered.

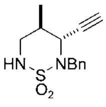
We next investigated the tandem cyclization reaction with other bromoallenes, which were prepared from the corresponding bromoallenols by a similar procedure to that shown in Scheme 3. The results of these cyclizations are summarized in Table 2. As we expected, treatment of the bromoallene **17**, which contains a protected diol, gave the bicyclic sulfamide **22** in 91 % yield (Table 2, entry 1). Similarly, the bromoallene **18** was converted into the tricyclic sulfamide **23** in 89 % yield (Table 2, entry 2). Bicyclic sulfamides **24** and **25** were obtained as the major products from the reaction of bromoallenes **19**, which has a methyl group on the terminal nitrogen, or racemic **20**, which has a single methyl substituent on the carbon between the allenyl and sulfamide groups (Table 2, entries 3 and 4). When the bromoallene **21**, which contains an unsubstituted carbon tether, was used, bicyclic sulfamide **26** was isolated (50 %) along with a considerable amount of the six-membered-ring product **29** (24 %; Table 2, entry 5).

Table 2: Synthesis of bicyclic sulfamide in the absence of palladium(0).[a]

Entry	Substrate	Time [h]	Product	Yield [%][b]
1	 **17**	4.5	 **22**	91
2	 **18**	6	 **23**	89
3	 **19**	12	 **24**	65[c]
4	 **(±)-20**	10	 **25**	57[d]
5	 **21**	12	 **26**	50[e]

[a] Reactions were carried out with NaH (2.5 equiv) in MeOH at 60 °C. [b] Yields of isolated products. [c] Six-membered-ring product **27** was obtained in 10 % yield as a minor product. [d] Six-membered-ring products **28a** and **28b** were obtained in 9 % and 5 % yield, respectively. [e] Six-membered-ring product **29** was obtained in 24 % yield.


27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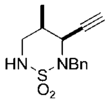
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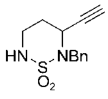
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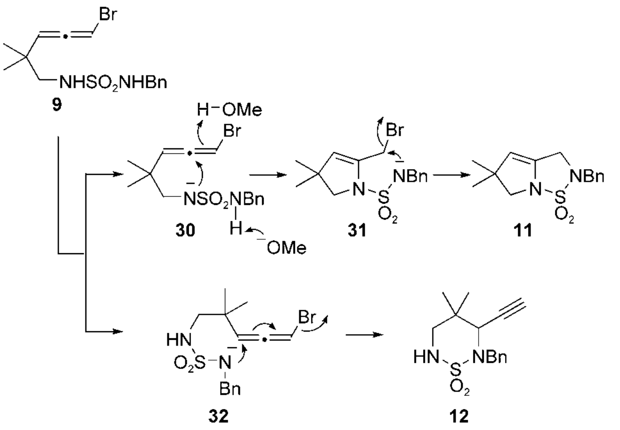
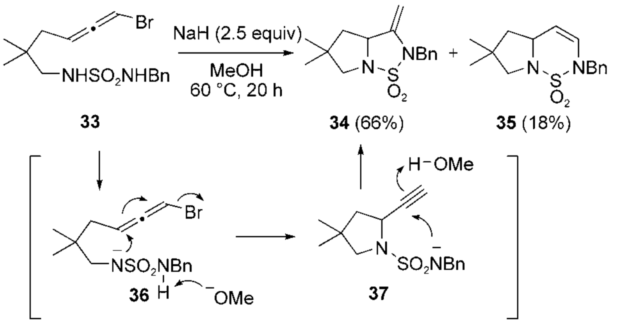
Possible reaction courses are shown in Scheme 5. In the tandem cyclization, the first intramolecular nucleophilic attack takes place at the central carbon atom of bromoallene **30** and is followed by protonation by MeOH to produce intermediate **31** bearing a bromomethyl group. The second intramolecular nucleophilic addition affords the bicyclic sulfamide **11**. This reaction pathway via the intermediate **31** is supported by the experimental results shown in Table 1: NaH-mediated cyclization of the bromoallene **13**, which contains a tosylamide group, in MeOH at room temperature (Table 1, entry 5), yielded the dihydropyrrole **15** (8 %), which contains a bromomethyl group, along with a considerable amount of the starting bromoallene **13** (71 %). In contrast, the same reaction at higher temperature (Table 1, entry 6) gave the methoxymethyl derivative **16**, which is produced by the nucleophilic substitution of **15** with methoxide. Formation of the six-membered-ring product **12** can be rationalized by an S_N2'-type intramolecular attack by the terminal nitrogen.


Scheme 5. Possible reaction courses.

Finally, we investigated the synthesis of cyclic sulfamides from bromoallene **33**, which has a three-atom tether between the sulfamide and bromoallene (Scheme 6). Interestingly, the first cyclization occurs regioselectively at the allenic carbon close to the sulfamide group to give **34** (66 %) and **35** (18 %). Pyrrolidine **37** is considered to be a plausible intermediate, formed by S_N2'-type intramolecular amination of **36**.[18] This is followed by *exo*- or *endo*-cyclization to afford **34** or **35**, respectively. This result reveals that the base-induced cyclization of bromoallenes in MeOH in the absence of palladium(0) favors five-membered-ring formation, which is in striking contrast to the palladium(0)-catalyzed reaction.[3]



Scheme 6. Reaction of bromoallene **33**, which has a three-atom tether between the sulfamide and bromoallene.

In conclusion, we have developed a novel synthesis of cyclic sulfamides containing a bicyclo[3.3.0]octane skeleton from bromoallenes having a sulfamide moiety as nucleophiles. Although the palladium-free cyclization reaction is limited to the reaction of relatively reactive substrates, we have demonstrated for the first time that bromoallenes can act as allyl dication equivalents *even in the absence of palladium(0)*, and that the intramolecular reaction with two nucleophiles enables the direct formation of bicycles by tandem cyclization. These cyclizations are extremely useful for the synthesis of bicyclic sulfamides and could extend the potential application of sulfamides as new pharmaceutically useful agents in medicinal chemistry.

Experimental Section

General procedure for the cyclization of bromoallenes in the absence of palladium(0). Reaction of **9** (Scheme 4): NaH (60% suspension in mineral oil; 12 mg, 0.3 mmol) was added to MeOH (0.5 mL) at room temperature under nitrogen, and the mixture was stirred for 10 min at this temperature. A solution of the bromoallene **9** (43.1 mg, 0.12 mmol) in MeOH (0.7 mL) was added at room temperature to the stirred mixture, which was stirred for 16 h at 60 °C. Concentration under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with *n*-hexane/EtOAc (3:1) to give, in order of elution, **11** (27 mg, 81%) and **12** (3.5 mg, 9%). **11**: colorless solid; m.p. 48 °C; IR (KBr): $\tilde{\nu} = 1682$ (C=C–N), 1317 cm^{-1} (NSO_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.21$ (s, 6H; 2 × CMe), 3.32 (s, 2H; CH_2), 3.73 (d, $J = 1.5$ Hz, 2H; CH_2), 4.32 (s, 2H; CH_2Ph), 4.79 (t, $J = 1.5$ Hz, 1H; C=CH), 7.30–7.37 ppm (m, 5H; Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 27.5$ (2C), 46.1, 48.4, 51.6, 59.2, 111.6, 128.1, 128.4 (2C), 128.7 (2C), 134.7, 136.3 ppm; MS (FAB) *m/z* (%): 279 (89) [MH^+], 91 (100); HRMS (FAB) calcd. for $C_{14}H_{19}N_2O_2S$ [MH^+]: 279.1167; found 279.1169. **12**: colorless crystals; m.p. 118 °C (*n*-hexane/EtOAc); IR (KBr): $\tilde{\nu} = 3284$ ($NHSO_2$), 2114 (C≡C), 1336 cm^{-1} (NSO_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.05$ (s, 3H; CMe), 1.08 (s, 3H; CMe), 2.56 (d, $J = 2.4$ Hz, 1H; C≡CH), 2.94 (ddd, $J = 14.4, 5.4, 1.8$ Hz, 1H; CH_aH_b), 3.56 (dd, $J = 2.4, 1.8$ Hz, 1H; CH-C≡CH), 3.64 (dd, $J = 14.4, 10.8$ Hz, 1H; CH_aH_b), 4.09 (d, $J = 14.1$ Hz, 1H; $PhCH_aH_b$), 4.70–4.76 (m, 1H; NH), 4.78 (d, $J = 14.1$ Hz, 1H; $PhCH_aH_b$), 7.28–7.39 ppm (m, 5H; Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.16$, 23.22, 33.7, 49.4, 52.4, 59.5, 77.0, 77.1, 127.9, 128.6 (2C), 128.9 (2C), 135.2 ppm; elemental analysis calcd (%) for $C_{14}H_{18}N_2O_2S$: C 60.40, H 6.52, N 10.06; found: C 60.19, H 6.52, N 10.00.

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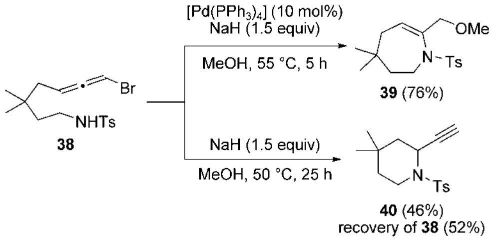
of the bromoallene **38** with NaH in MeOH in the absence of $[Pd(PPh_3)_4]$ gave the six-membered-ring product **40** in 46 % yield



by an S_N2'-type, intramolecular nucleophilic attack on the proximal carbon of the allene moiety .

[17] We have already reported the formation of azetidines by NaH-mediated intramolecular amination of bromoallenes: see, ref. [2b].

[18] To determine the intermediate of this tandem cyclization reaction, we investigated the stepwise reaction of the bromoallene **33**. Treatment of the bromoallene **33** with NaH in DMF gave the pyrrolidine **37** in 86 % yield. Reaction of **37** under the same reaction conditions as the one-pot reaction afforded the *exo*-cyclized product **34** (67 %) and *endo*-cyclized product **35** (20 %) in essentially the same product ratio. Related five-membered-ring formation by intramolecular amination of a carbon–carbon triple bond has been reported, see: a) Y. Tamaru, M. Kimura, S. Tanaka, S. Kure, Z. Yoshida, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2838–2849; b) P. A. Jacobi, H. L. Brielmann, S. I. Hauck, *J. Org. Chem.* **1996**, *61*, 5013–5023; c) M. M. Cid, D. Domínguez, L. Castedo, E. M. Vázquez-López, *Tetrahedron* **1999**, *55*, 5599–5610.