CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000653

VIP

Synthesis of Fused and Linked Bicyclic Nitrogen Heterocycles by Palladium-Catalyzed Domino Cyclization of Propargyl Bromides

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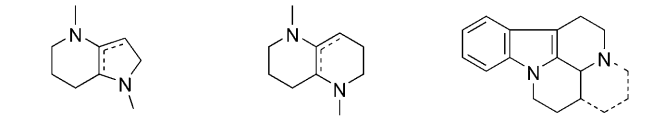
Abstract: The palladium(0)-catalyzed direct construction of bicyclic heterocycles is described. Treatment of propargyl bromides that have nucleophilic functional groups connected by two or three carbon atoms with catalytic [Pd(PPh_3)$_4$] affords bis-cyclization products in good yields. The desired bicyclic heterocycles can be obtained selectively when using substrates with appropriate nucleophilic groups. We also describe the reaction of a 2-alkynylazetidine derivative with a catalytic amount of [Pd(PPh_3)$_4$] under base-free conditions, which affords the same fused heterocycles as the corresponding propargyl bromides.

Keywords: cyclization · domino reactions · heterocycles · palladium · propargylic compounds

Introduction

Development of useful druglike templates is an important subject in drug discovery. Although polycyclic structures fused by a 1,2-diamine motif are found in many biologically active alkaloids,[1] this type of structure has not been widely used as a scaffold for biologically active compounds. Potential scaffolds that have seen little use include the bicyclic structures of the pyrrolo[3,2-*b*]pyridines **A** and 1,5-naphthyridines **B** (Scheme 1).[2] In contrast, the β-carboline derivatives **C** have been more widely applied.[3] The minimal use of these bicyclic structures is partly due to the absence of reliable methods for their construction. In our previous work, we found that bromoallenes **D** could act as allyl dication equivalents **E** in the presence of a palladium(0) catalyst and alcohol. These were extremely useful for the synthesis of medium-sized heterocycles **3**[4] and bicyclic sulfamides **6**[5] (Scheme 2).



Scheme 1. Bicyclic heterocycles with 1,2-diamine fusion motif.

Based on this dual reactivity of bromoallenes, we planned a direct construction of bicyclic structures **A** and **B** by domino cyclization of the allenyl/propargyl bromides **7**/**8** containing nucleophilic functional groups on each terminal carbon (Scheme 3). This cyclization would proceed through formation of η^3-propargylpalladium **9** by palladation of the bromides **7**/**8**. Subsequent nucleophilic attack on the central carbon of **9** would lead to the η^3-allylpalladium intermediates **10** and/or **11**. A second nucleophilic cyclization at the distal or proximal carbon atom of the intermediates **10** and **11** would provide the corresponding four fused or linked bicyclic compounds **12**–**15**. Apparently, regioselectivity in the first and second cyclizations (path A vs. B, C vs. D, and E vs. F) is key to success with this strategy.

Tsuji and co-workers originally developed palladium-catalyzed domino reactions of propargylic compounds.[6,7] It is

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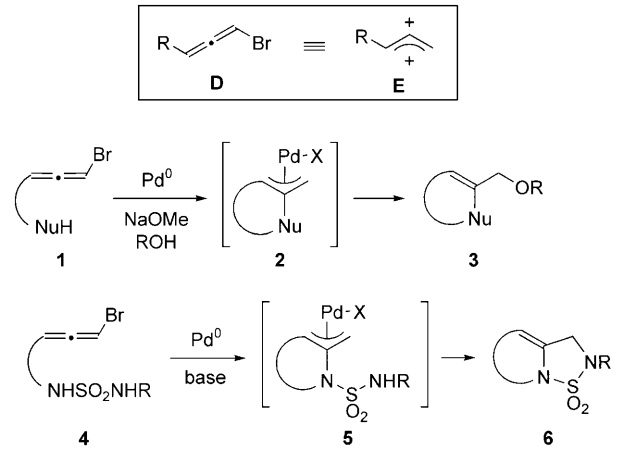
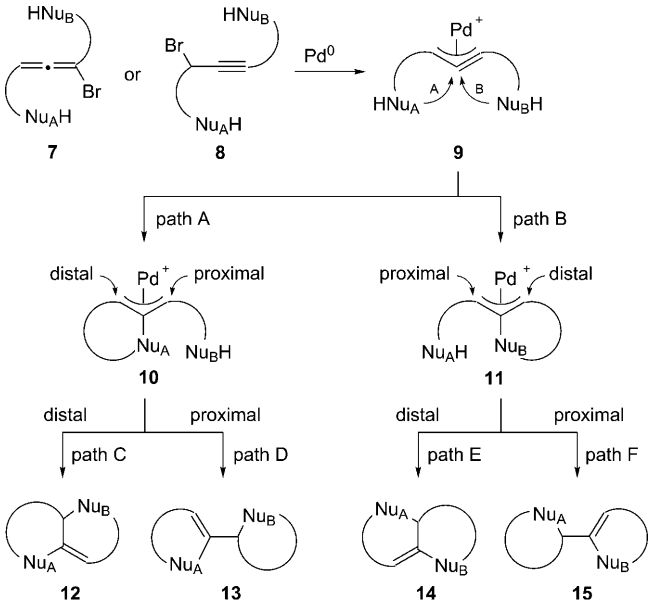
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000653.



Scheme 2. Palladium(0)-catalyzed construction of medium-ring heterocycles and bicyclic sulfamides by using bromoallenes as allyl dication equivalents.

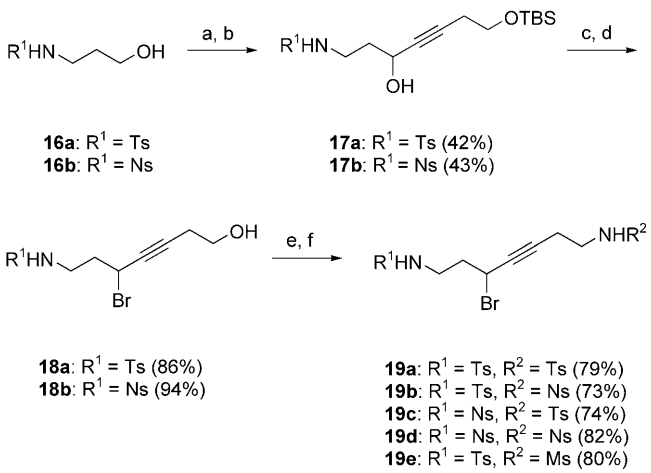


Scheme 3. Reaction courses of palladium(0)-catalyzed domino cyclization of allenyl/propargyl bromides **7** and **8**.

widely documented that these reactions provide a powerful approach for construction of heterocyclic frameworks by combination of inter- and intramolecular nucleophilic attacks.[6,8,9] In contrast, there is no precedent for the direct construction of bicyclic heterocycles through intramolecular domino cyclizations of propargylic compounds. In the present study, we report full details of our investigation into direct construction of pyrrolo[3,2-*b*]pyridines **A** and 1,5-naphthyridines **B** by palladium-catalyzed domino cyclization of propargyl bromides that have two nucleophilic moieties.[10] We also investigated the treatment of a 2-alkynylazetidine derivative with a catalytic amount of palladium(0), and found that under base-free conditions it affords the same fused heterocycle as the corresponding propargyl bromide.

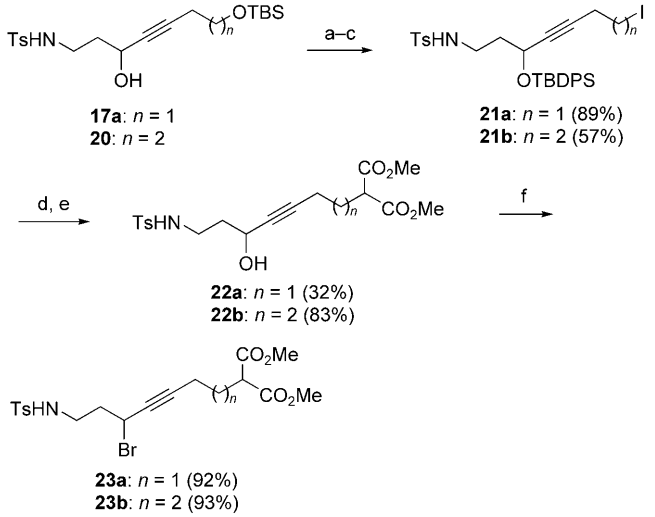
Results and Discussion

Synthesis of propargyl bromides that have nucleophilic functional groups: Because efficient chemoselective synthesis of 1,3-disubstituted bromoallenes of type **7** with conventional methods has proven to be difficult,[11] we focused on the domino reaction of propargyl bromides **8**. The representative propargyl bromides **18** and **19** that have nitrogen and oxygen nucleophiles for the domino cyclization were readily prepared as described below (Scheme 4). Oxidation of N-protected 3-aminopropan-1-ols **16** to the aldehydes with PCC (PCC = pyridinium chlorochromate) followed by addition of acetylide derived from protected but-3-yn-1-ol afforded propargyl alcohols **17**. Bromination with CBr_4 and PPh_3 in the presence of imidazole and subsequent removal of the silyl group with 1% HCl/EtOH provided the propargyl bromides **18**. Introduction of a sulfonamide group by a Mitsunobu reaction with *N*-Boc sulfonamide followed by cleavage of the Boc group with 3 N HBr/EtOAc afforded the desired propargyl bromides **19a–e**. Other propargyl bromides that have nitrogen or oxygen nucleophiles on each terminal carbon were prepared in a straightforward manner by a similar protocol (see the Supporting Information).



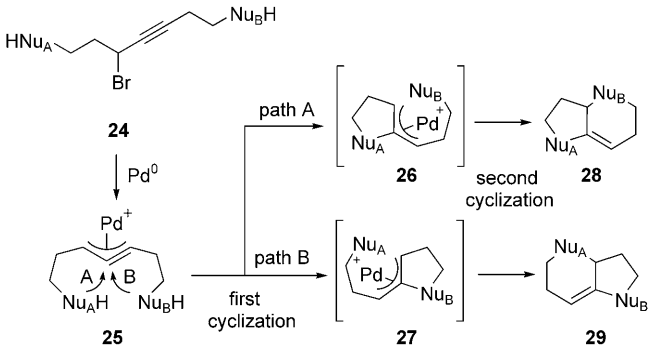
Scheme 4. Synthesis of propargyl bromides **18** and **19** that have nitrogen or oxygen nucleophiles. Reagents: a) PCC, molecular sieves (MS; 4 Å), CH_2Cl_2, 0 °C; b) $HC{\equiv}C(CH_2)_2OTBS$, *n*BuLi, THF, −78 °C; c) CBr_4, PPh_3, imidazole, THF, RT; d) 1% HCl/EtOH, RT; e) R^2NHBoc, DEAD, PPh_3, THF, RT; and f) 3 N HBr/EtOAc, 70 °C. Abbreviations: TBS = *tert*-butyldimethylsilyl; DEAD = diethyl azodicarboxylate.

The malonate derivatives **23** were synthesized from propargyl alcohols **17a** and **20** as shown in Scheme 5. The iodides **21** were produced after silylation of a secondary hydroxy group, desilylation of the primary hydroxy group with dilute HCl, and iodination with I_2 and PPh_3 in the presence of imidazole. Treatment of **21** with sodium dimethyl malonate and cleavage of the silyl ether with TBAF provided propargyl alcohols **22**. Finally, bromination of **22** with CBr_4 and PPh_3 gave the desired propargyl bromides **23**.



Scheme 5. Synthesis of propargyl bromides **23** that have carbon and nitrogen nucleophiles. Reagents: a) TBDPSCl, imidazole, THF, RT; b) 1% HCl/EtOH, RT; c) I_2, PPh_3, imidazole, THF, RT; d) NaH, $CH_2(CO_2Me)_2$, DMF, RT; e) TBAF, THF, RT; and f) CBr_4, PPh_3, imidazole, THF, RT. Abbreviations: TBDPS = *tert*-butyldiphenylsilyl; TBAF = tetrabutylammonium fluoride.

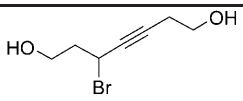
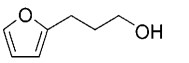
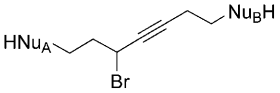
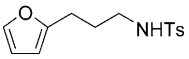
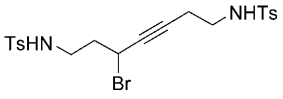
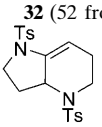
Reaction of propargyl bromides that have nucleophilic groups tethered by two carbon atoms: We first investigated the domino cyclization of propargyl bromides of type **24** with the nucleophiles connected by two carbon atoms (Scheme 6). In this reaction, highly symmetrical η^3-propargylpalladium complex **25** will be formed as the intermediate.[12] Therefore, use of the substrates in which two nucleophiles are the same ($Nu_A = Nu_B$) would avoid the regioselectivity issue during the first cyclization (path A vs. B). Furthermore, the regioselectivity of the first cyclization is expected to be controlled by the relative reactivity of the two nucleophiles (Nu_A and Nu_B). Otherwise, we can estimate the reactivity difference of a nucleophilic group depending on its location. The second cyclization on the distal carbon of the η^3-allylpalladium complex **26** or **27** would afford the fused bicyclic products **28** or **29**, respectively.



Scheme 6. Reaction courses of propargyl bromides **24** with nucleophiles connected by two carbon atoms.

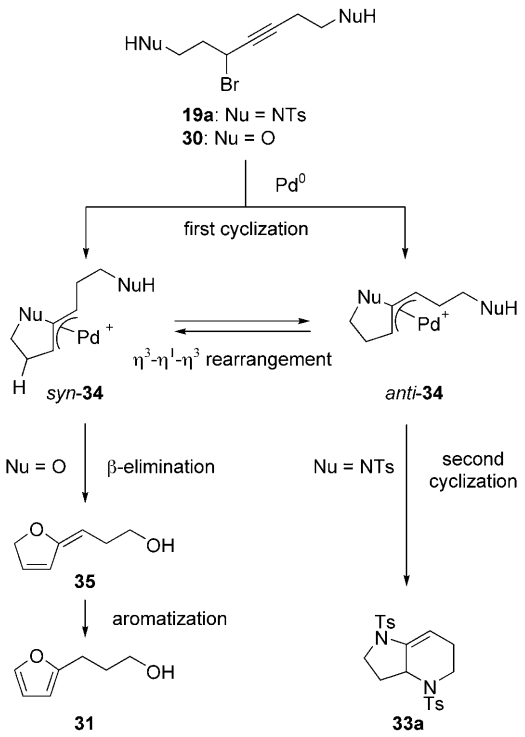
We initially investigated the domino cyclization with propargyl bromide **30** that has two hydroxy groups (Table 1, entry 1). Contrary to our expectations, furan derivative **31** was obtained in 62% yield under standard conditions for the formation of bicyclic sulfamides from bromoallenes ([$Pd(PPh_3)_4$], NaH, MeOH, 60°C).[5] Likewise, the reaction of propargyl bromides **18a** and **18c** that have hydroxy and tosylamide nucleophilic groups afforded the furan **32** in moderate yields (64 and 52%; Table 1, entries 2 and 3, respectively). These results demonstrate that the hydroxy group of **18** and **30** is more reactive than the tosylamide group in the first cyclization, and that a more reactive nucleophilic group promotes the first cyclization irrespective of its location. These results are consistent with our hypothesis. In other words, both Nu_A and Nu_B with appropriate carbon tethers in the palladium complex **25** (Scheme 6) can react with the central carbon of the propargylic moiety. Encouragingly, when the bis-tosylamide **19a** was employed, the desired domino cyclization proceeded to provide the fused bis-cyclization product **33a** in 89% yield (Table 1, entry 4).[13] Other palladium sources and ligands have proven to be ineffective for the desired reaction (Table 1, entries 5–7).

Table 1. Reaction of propargyl bromides that have oxygen and/or nitrogen nucleophiles.[a]

Entry	Substrate	*t* [h]	Product (Yield [%])[b]
1	 **30**	4.5	 **31** (62)
2	 **18a**: Nu_A = NTs, Nu_B = O	3.5	 **32** (64 from **18a**)
3	**18c**: Nu_A = O, Nu_B = NTs	4.5	**32** (52 from **18c**)
	 **19a**		 **33a**
	Pd source		
4	[$Pd(PPh_3)_4$]	0.5	89
5[c]	[$Pd_2(dba)_3$·$CHCl_3$]	16	0
6[c,d]	[$Pd_2(dba)_3$·$CHCl_3$], DPPF	12	0
7	[$Pd(OAc)_2$]	3	trace

[a] All reactions were carried out with [$Pd(PPh_3)_4$] (5 mol%) and NaH (2.5 equiv) in MeOH at 60°C. [b] Yields of isolated products. [c] [$Pd_2(dba)_3$·$CHCl_3$] (2.5 mol%) was used. [d] DPPF (5 mol%) was used.

Proposed reaction mechanisms for the formation of furan **31** and bis-cyclization product **33a** are shown in Scheme 7. Oxidative addition of propargyl bromides **19a** or **30** to palladium(0) would result in η^3-propargylpalladium complexes. Subsequent nucleophilic attack onto the central carbon atoms of these complexes would produce η^3-allylpalladiums *syn*-**34** and *anti*-**34**, which are in equilibrium.[14] For the second cyclization to proceed and afford a fused ring, it is necessary to form *anti*-**34**, which has the nucleophilic group

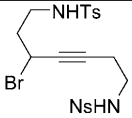
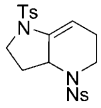
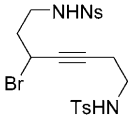
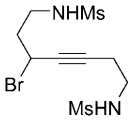
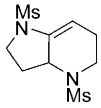
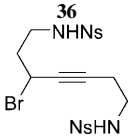
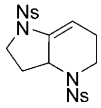
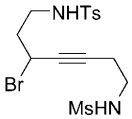
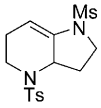
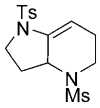
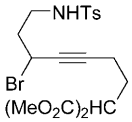
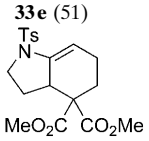


Scheme 7. Plausible reaction mechanisms for the formation of furan **31** and bicyclic product **33a**.

located in proximity to the distal carbon of the η^3-allylpalladium moiety. Although *syn*-**34** would usually be more stable than *anti*-**34**,[15] it is an inappropriate isomer for the second cyclization at the distal position. Accordingly, the reaction of propargyl bromide **30** that has two hydroxy groups undergoes β-hydride elimination from *syn*-**34** (Nu = O) followed by aromatization of diene **35** to produce furan **31**. Formation of furan **32** from **18** can be explained in a similar manner. In sharp contrast, the propargyl bromide **19a** that has two tosylamide groups will form η^3-allylpalladium complexes *syn*- and *anti*-**34** with a sterically congested Nu group (Nu = NTs), which would destabilize *syn*-**34**. Thus, formation of the desired product **33a** from the bis-tosylamide derivative **19a** can be rationalized by the assistance of the tosylamide group in the five-membered ring.

Next, we investigated the reactivity of several nucleophilic groups in the domino cyclization. The results are summarized in Table 2. The propargyl bromide **19b** that has nosyl- and tosylamide groups afforded bicyclic product **33b** in 79% yield, in which the tosylamide group was incorporated into the five-membered ring (Table 2, entry 1). Similarly, the same bicyclic product **33b** was formed in 87% yield from the regioisomeric propargyl bromide **19c** (Table 2, entry 2). These results show that the tosylamide group participates in the first cyclization to form a five-membered ring, which is followed by the second cyclization by the nosylamide, irrespective of their location. Propargyl bromides **36** and **19d** that have bis-mesyl or bis-nosylamide groups were also efficiently converted into the corresponding bicyclic products

Table 2. Palladium-catalyzed formation of fused bicyclic heterocycles.[a]

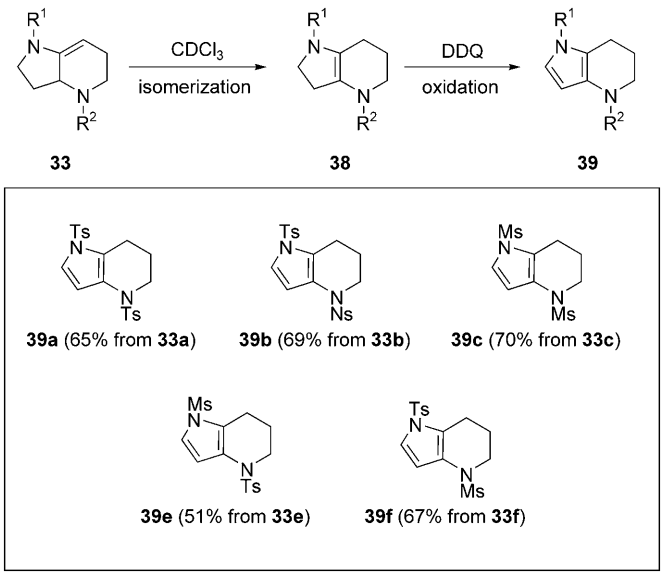
Entry	Substrate	*t* [min]	Product (Yield [%])[b]
1	 **19b**	5	 **33b** (79)
2	 **19c**	5	**33b** (87)
3	 **36**	45	 **33c** (68)
4	 **19d**	5	 **33d** (91)
5	 **19e**	45	 **33e** (51)  **33f** (16)
6	 **23a**	30	 **37** (78)

[a] All reactions were carried out with $[Pd(PPh_3)_4]$ (5 mol%) and NaH (2.5 equiv) in MeOH at 60°C. [b] Yields of isolated products.

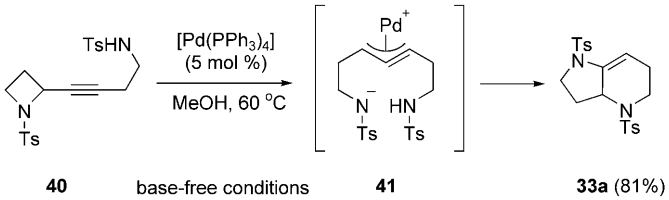
33c (68%) and **33d** (91%), respectively (Table 2, entries 3 and 4). When propargyl bromide **19e** that has tosyl- and mesylamide groups was utilized, the first cyclization by the mesylamide group preferentially proceeded to afford **33e** as a major product (**33e**: 51%; **33f**: 16%; Table 2, entry 5).[16] When using the malonate derivative **23a**, the first cyclization by the tosylamide group and the second cyclization by the malonate moiety selectively proceeded to afford **37** in 78% yield (Table 2, entry 6).

The bis-cyclization products can be easily converted into the pyrrole derivatives. For example, the desired fused pyrroles **39a–f** were obtained in moderate yields (51–70%) through isomerization of **33** in $CDCl_3$ followed by DDQ-mediated (DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone) oxidation except for **33d** (Scheme 8).[17,18]

Next, the domino reaction of the 2-alkynylazetidine derivative **40** was examined (Scheme 9). As we expected, the desired domino reaction through ring-expansion of **40** was facilitated with catalytic $[Pd(PPh_3)_4]$ in MeOH to produce bicyclic product **33a** in 81% yield. Because aza-anionic intermediate **41** will be directly formed from **40**, the reaction proceeded under base-free conditions.



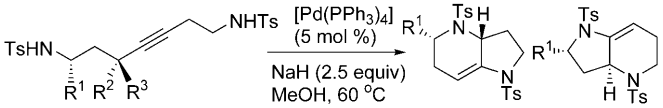
Scheme 8. Synthesis of fused pyrrole derivatives **39a–f**.



Scheme 9. Ring-expansion and domino cyclization of 2-alkynylazetidine **40**.

We then investigated the stereochemical courses of the domino cyclization by using propargyl bromides *syn*- and *anti*-**42** that have an alkyl group (Me or *i*Pr) on the carbon substituted by a tosylamide group (Table 3). When the reaction of propargyl bromide *syn*-**42a** was conducted under standard conditions, the first nucleophilic attack by the less-hindered nitrogen atom proceeded in moderate selectivity to afford bis-cyclization product **43a** as a major product (**43a**: 52%; **44a**: 13%; Table 3, entry 1). Similarly, propargyl bromide *syn*-**42b** that has a bulkier alkyl group (*i*Pr) afforded the corresponding bicyclic products (**43b**: 57%; **44b**: 10%; Table 3, entry 2). Interestingly, the reaction of *anti*-**42a** afforded the bicyclic products **43a** and **44a** (**43a**: 42%; **44a**: 22%; Table 3, entry 3), which are the same products as from *syn*-**42a**. These results clearly demonstrate that the stereochemistry of the substrates was not reflected in that of the product. Remarkably, when the propargyl bromide *anti*-**42b** was employed, the first cyclization by a more congested nitrogen atom preferentially proceeded to afford the bicyclic product **44b** as a major isomer (**43b**: 21%; **44b**: 49%; Table 3, entry 4). The unambiguous structure assignments for **33d**, **43b**, and **44b** were confirmed by X-ray analysis (Figure 1).[19,20] Interestingly, the bulkier isopropyl group of

Table 3. Domino cyclization of propargyl bromides *syn*- and *anti*-**42**.[a]



Entry	Substrate	t [min]	Product (Yield [%])[b]	
1	*syn*-**42a**: R^1 = Me	30	**43a** (52)	**44a** (13)
2	*syn*-**42b**: R^1 = *i*Pr	45	**43b** (57)	**44b** (10)
3	*anti*-**42a**: R^1 = Me	30	**43a** (42)	**44a** (22)
4	*anti*-**42b**: R^1 = *i*Pr	30	**43b** (21)	**44b** (49)

[a] All reactions were carried out with $[Pd(PPh_3)_4]$ (5 mol%) and NaH (2.5 equiv). [b] Yields were determined by using NMR spectroscopy.

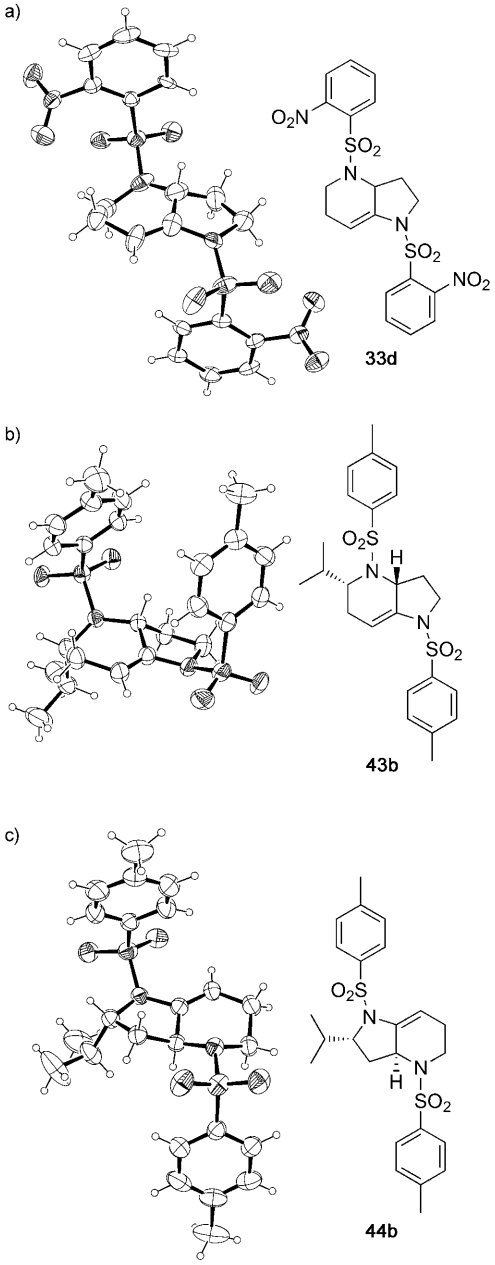
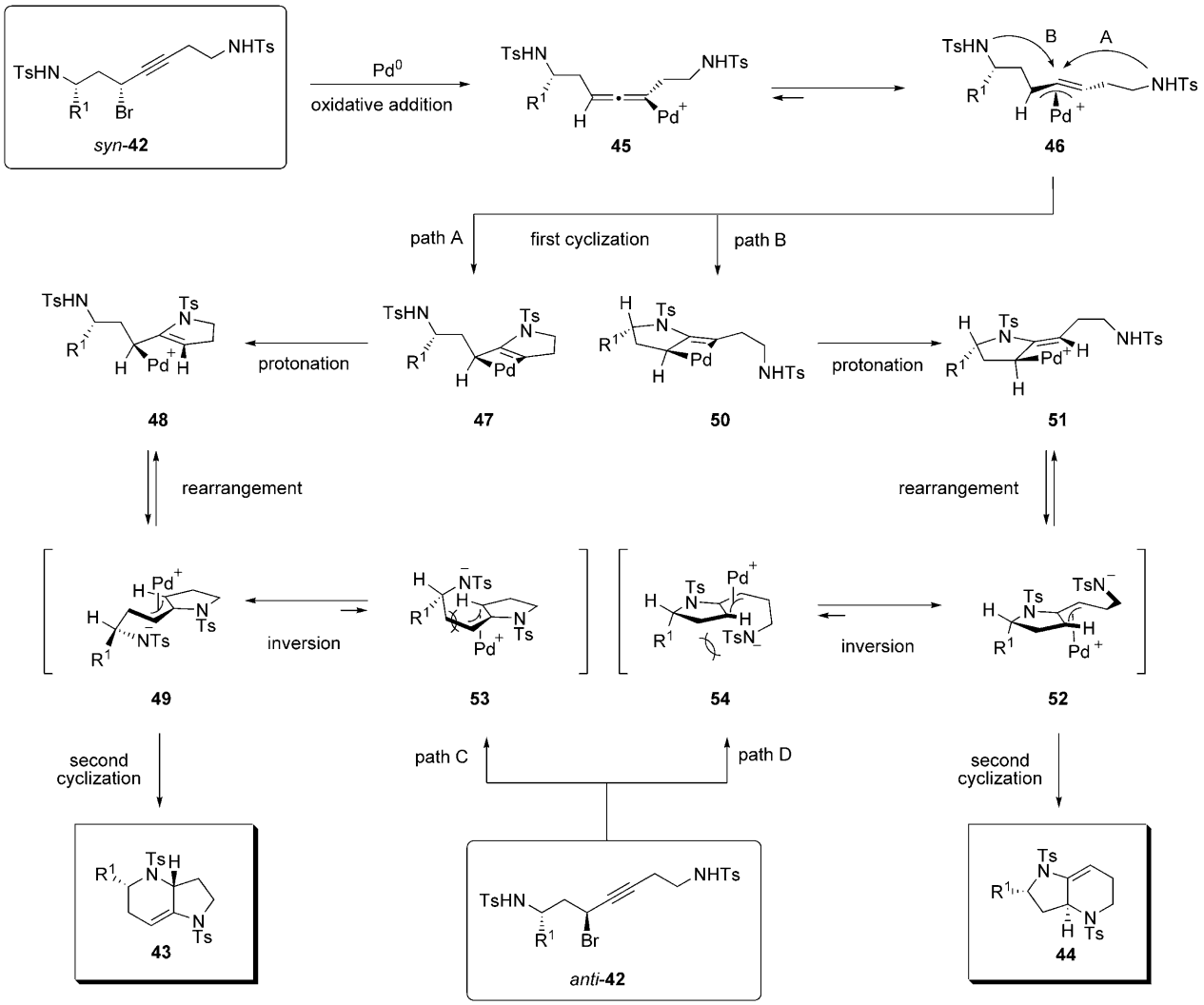


Figure 1. The crystal structures of a) **33d**, b) **43b**, and c) **44b**. Ellipsoids are shown at the 30% probability level.

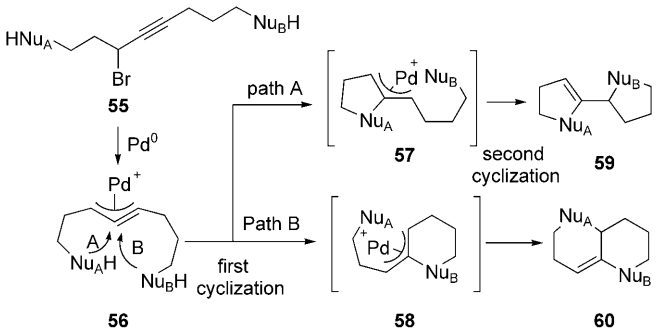
43b and **44b** was located in the pseudoaxial position, presumably due to steric repulsion between oxygen atoms of the sulfonyl group and the isopropyl group.

Based on these results, plausible stereochemical courses of the domino cyclization of propargyl bromides *syn*- and *anti*-**42** are shown in Scheme 10. Stereoselective *anti*-S_N2' attack of palladium(0) onto *syn*-**42** would provide the allenylpalladium complex **45**,[21] which will be followed by transformation into η^3-propargylpalladium complex **46**. The first cyclization by the less-hindered nitrogen atom would produce a fused palladacyclobutene intermediate **47** (path A).[22] Protonation of **47** leads to the η^3-allylpalladium complex **48**, which is in equilibrium with **49**. The second *anti*-cyclization by the more hindered nitrogen atom of **49** would give the major isomer **43** in a stereoselective manner.[23] The first cyclization by the more hindered nitrogen atom will form the minor isomer **44** in a similar pathway via palladacycle (**50**) formation (path B), protonation to give **51**, and the *anti*-type second cyclization of **52**. The fact that *anti*-**42** affords the same isomeric products **43** and **44** indicates that inversion of the configuration occurs during these steps. One possible explanation is that unfavorable steric repulsions around the alkyl group in η^3-allylpalladium complexes **53** and **54**, which will be produced from *anti*-**42** through path C and path D in a similar manner to the reaction of *syn*-**42**, might interfere the *anti*-nucleophilic attack of the nitrogen nucleophile. Therefore, inversion of the configuration of **53** and **54** would be promoted to afford the intermediates **49** and **52**, respectively, the same complexes as derived from *syn*-**42**.

Reaction of propargyl bromides that have a nucleophilic group connected by three carbon atoms: Finally, we investigated the domino cyclization of the propargyl bromides **55** having a longer carbon tether between the Nu_BH group and propargyl moiety (Scheme 11). In this case, η^3-propargylpalladium complex **56** would be formed. Thus, two types of η^3-allylpalladium complexes **57** and/or **58** can be produced in the first cyclization (path A vs. path B). The second cyclization of the resulting η^3-allylpalladium complex **57** will pro-



Scheme 10. Stereochemical courses of the domino reaction of propargyl bromides *syn*- and *anti*-**42**.



Scheme 11. Reaction courses of propargyl bromides **55**.

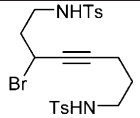
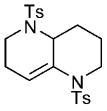
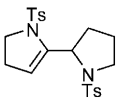
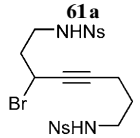
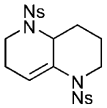
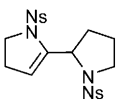
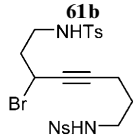
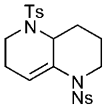
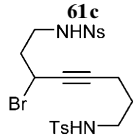
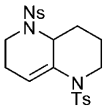
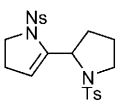
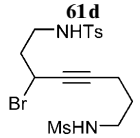
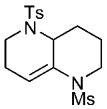
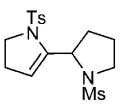
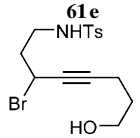
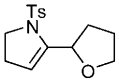
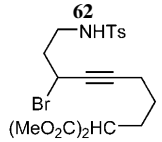
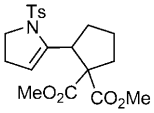
vide the linked bicyclic product **59**, whereas the intermediate **58** will form a 6,6-fused bicyclic product **60**.

First, the domino cyclization of the propargyl bromides having various nucleophilic groups was examined. The results are summarized in Table 4. Reaction of propargyl bromides **61a** and **61b** that have bis-tosyl or bis-nosylamide group favored six-membered ring formation in the first cyclization to afford the corresponding fused bicyclic product **63a** (70%) and **63b** (74%), respectively, in good yields (Table 4, entries 1 and 2).[24] Interestingly, when the propargyl bromide **61c** that has nosyl- and tosylamide groups on each terminus was employed, fused bicyclic heterocycle **63c** was obtained as the sole isomer in 73% yield (Table 4, entry 3). This product may result from the predominant six-membered ring formation by the nosylamide group over five-membered ring formation by the tosylamide group. The regioisomeric propargyl bromide **61d**, which has a nosylamide group on the carbon close to the bromine atom, also resulted in formation of the same type of 6,6-fused bicyclic product **63d** with somewhat decreased selectively (**63d**: 67%; **64d**: 15%; Table 4, entry 4). The reaction of propargyl bromide **61e** that has mesyl- and tosylamide groups afforded the fused bicyclic product **63e** (39%) and the linked bicyclic heterocycle **64e** (21%), which shows relatively lower reactivity of the mesylamide group in the first cyclization (Table 4, entry 5). From these observations, the first cyclization of the diamine derivatives generally favors six-membered ring formation, in which the selectivity depends on the relative reactivity of the nitrogen functionality. In sharp contrast, amino alcohol derivative **62** selectively afforded linked bis-cyclization product **65** in 72% yield (Table 4, entry 6). In a similar manner, malonate derivative **23b** exclusively produced linked bicyclic product **66** in 60% yield (Table 4, entry 7). Therefore, the regioselectivity of the first cyclization is controlled by a subtle balance of the nucleophilicity of the functional group and ring size of the cyclization.

Conclusion

In conclusion, we have developed a palladium(0)-catalyzed novel domino cyclization of propargyl bromides that has nucleophilic functionalities on each terminal carbon. In many cases, when using substrates with appropriate nucleophiles and carbon tethers, this reaction selectively provides the desired bicyclic heterocycles. The 2-alkynylazetidine derivative also provides the same bicyclic compound through a ring-expansion reaction under base-free conditions. This strategy could provide a convenient approach to the development of druglike templates such as pyrrolo[3,2-*b*]pyridines and 1,5-naphthyridines.

Table 4. Palladium(0)-catalyzed formation of fused and linked bicyclic heterocycles.[a]

Entry	Substrate	*t* [min]	Product (Yield [%])[b]	
1	 **61a**	35	 **63a** (70)	 **64a** (13)
2	 **61b**	45	 **63b** (74)	 **64b** (5)
3	 **61c**	40	 **63c** (73)	
4	 **61d**	35	 **63d** (67)	 **64d** (15)
5	 **61e**	20	 **63e** (39)	 **64e** (21)
6	 **62**	90	 **65** (72)	
7	 **23b**	30	 **66** (60)	

[a] All reactions were carried out with $[Pd(PPh_3)_4]$ (5 mol%) and NaH (2.5 equiv) in MeOH at 60°C. [b] Yields of isolated products.

Experimental Section

General procedure for domino cyclization of propargylic bromides: To form compound **33a** (Table 1, entry 4), MeOH (0.5 mL) was added to NaH (60% suspension of mineral oil; 9.4 mg, 0.234 mmol) at 0°C under nitrogen, and the mixture was stirred at room temperature for 15 min. $[Pd(PPh_3)_4]$ (5.4 mg, 0.00468 mmol) and a solution of the propargyl bromide **19a** (48.0 mg, 0.0937 mmol) in MeOH (0.5 mL) were successively

added to the stirred mixture at room temperature, and the resulting mixture was stirred at 60 °C for 30 min and filtered through a short pad of silica gel with *n*-hexane/EtOAc (1:1). The filtrate was concentrated and purified by flash chromatography over silica gel with *n*-hexane/EtOAc (3:2) to give **33a** (36.0 mg, 89 % yield) as colorless crystals. M.p. 145–146 °C (*n*-hexane/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89 (dddd, J = 12.0, 12.0, 12.0, 9.0 Hz, 1H), 2.03 (dddd, J = 17.5, 9.0, 7.0, 5.0 Hz, 1H), 2.31–2.38 (m, 1H), 2.42 (s, 3H), 2.44 (s, 3H), 2.48 (dd, J = 12.0, 6.0 Hz, 1H), 2.64 (ddd, J = 12.0, 9.0, 5.0 Hz, 1H), 3.00–3.05 (m, 1H), 3.27 (ddd, J = 12.0, 10.5, 6.0 Hz, 1H), 3.59 (ddd, J = 12.0, 5.0, 5.0 Hz, 1H), 3.75 (dd, J = 10.5, 9.0 Hz, 1H), 5.78 (dd, J = 7.0, 5.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.65 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5 (2C), 23.8, 30.2, 44.3, 47.1, 56.0, 105.0, 127.2 (2C), 127.5 (2C), 129.6 (2C), 129.8 (2C), 133.5, 134.3, 135.9, 143.9, 144.1 ppm; IR (KBr): $\tilde{\nu}$ = 1597 (C=C), 1357 (NSO_2), 1152 cm^{-1} (NSO_2); MS (FAB): *m*/*z* (%): 433 (93) [*M*+H], 277 (100); HRMS (FAB): calcd for $C_{21}H_{25}N_2O_4S_2$ [*M*+H]: 433.1256; found: 433.1249.

Acknowledgements

This work was supported in part by Grants-in-Aid for Encouragement of Young Scientists (A) (H.O.) and for Scientific Research (B) (T.T.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Targeted Proteins Research Program. A.O. is grateful for Research Fellowships from the Japan Society for the Promotion of Science (JSPS) for Young Scientists. Appreciation is expressed to Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO).

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[17] Bicyclic product **33d** did not isomerize to the fused pyrrole of type **38** under the acidic conditions. This is presumably due to the lower reactivity of enamine moiety of **33d** that has a highly electron-withdrawing nosyl group on the enamine nitrogen.

[18] Isomerization reaction was promoted by $CDCl_3$ (stabilized by silver foil before use) or 3 N HCl, whereas commercial $CHCl_3$ was not effective for isomerization. These results can be attributed to the presence of EtOH (0.5 %) as the stabilizer in $CHCl_3$. Actually, addition of EtOH to $CDCl_3$ completely inhibited the isomerization reaction, presumably by suppressing acid formation.

[19] CCDC-764389 (**33d**) and 764390 (**44d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via

www.ccdc.cam.ac.uk/data_request/cif. The crystal structure of **43b** has already been reported in ref. [10a].

[20] The relative configuration of **44b** was also determined by NOE experiments (see the Supporting Information).

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Received: March 15, 2010
Published online: June 14, 2010

