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Direct Construction of Bicyclic Heterocycles by Palladium-Catalyzed Domino Cyclization of Propargyl Bromides

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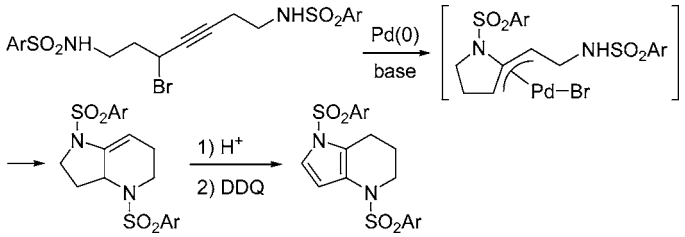
ABSTRACT



The palladium-catalyzed domino cyclization of propargyl bromides having two nucleophilic functional groups is described. Treatment of 1,7-diamino-5-bromohept-3-yne derivatives with catalytic $Pd(PPh_3)_4$ in the presence of NaH in MeOH gives the 2,7-diazabicyclo[4.3.0]non-5-enes in good yields. Interestingly, the regioselectivity of the reaction is completely controlled by the relative reactivity of the amine functional groups, irrespective of the position of the nucleophiles. The malonate derivative also undergoes domino cyclization to produce a hexahydroindole derivative.

Palladium-catalyzed reactions of propargylic compounds developed by Tsuji and co-workers are widely used as an efficient tool for the introduction of two nucleophiles into a substrate.[1,2] The reaction with dual nucleophiles such as acetoacetonates and diols forms cyclic products including furans and dioxanes.[1,3] Recent contributions in this area have revealed that a combination of nucleophilic attacks by an internal nucleophilic functional group and an appropriate external nucleophile can be a convenient approach to carbapenems,[4] furans,[5] indoles,[6] indenes,[7] and cyclic carbonates.[8] In contrast, there have been no reports of the direct

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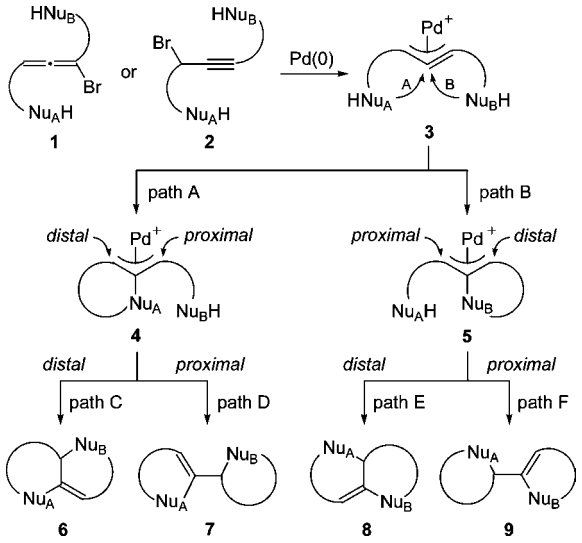
construction of bicyclic heterocycles by domino cyclization using propargylic substrates having two nucleophilic functional groups.

During the course of our studies directed toward elucidating efficient cyclization reactions of allenic compounds,[9] we found that bromoallenes can act as allyl dication equivalents in the presence of palladium(0) and alcohol. This reactivity has been shown to be extremely useful for the synthesis of medium-sized heterocycles[10] as well as bicyclic sulfamides[11] by successive bond formation. In light of this chemistry, we envisioned that the domino cyclization of bromoallenes **1** having two nucleophilic sites (Nu_A and Nu_B) might lead to bicyclic compounds by domino cyclization (Scheme 1).

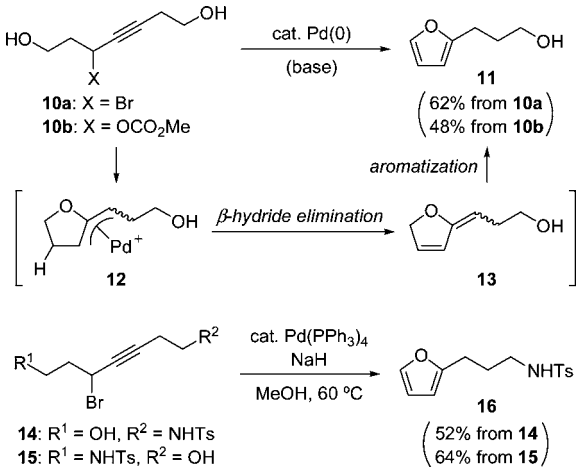
Scheme 1. Reaction Course of Palladium-Catalyzed Domino Cyclization of Allenyl/Propargyl Bromides **1** and **2**



However, since efficient chemoselective preparation of 1,3-disubstituted bromoallenes of the type **1** via conventional bromination methods has proven to be difficult,[12] we turned our attention to the reaction of propargyl bromides **2**, which can be considered as a synthetic equivalent of bromoallenes in the palladium-catalyzed reaction.[13] As shown in Scheme 1, this domino cyclization could afford four types of bicyclic products **6**−**9**, depending on (1) which nucleophilic site (Nu_A and Nu_B) would participate in the first cyclization (path A vs B) and (2) which carbon (distal or proximal) would be attacked on the second cyclization (path C vs D and E vs F). Herein we describe the domino cyclization of propargyl bromides **2** having two nitrogen functional groups to form fused azacycles of the type **6** and **8**. The remarkable effect of the nucleophilicity of N_A and N_B on the outcome as well as the stereochemical course of the reaction is also presented.

To avoid the regioselectivity issue during the first cyclization (path A vs B, Scheme 1), we investigated the reaction of propargyl bromide **10a** containing two hydroxy groups tethered by two carbon atoms (Scheme 2). Use of this starting material has the advantage of allowing the production of a highly symmetrical allenylpalladium intermediate. The bromide **10a** was readily prepared through the addition of the acetylide of a protected but-3-yn-1-ol to a hydroxypropanal derivative followed by bromination of the resulting protected propargyl alcohol with CBr_4 and PPh_3 in the presence of imidazole. Unfortunately, treatment of **10a** with $Pd(PPh_3)_4$ (5 mol %) in the presence of in situ generated NaOMe (standard conditions for cyclization of bromoallenes)[10,11] gave the furan derivative **11** in 62% yield. The reaction of the carbonate **10b** with $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %)/dppe (10 mol %) in dioxane also afforded **11** in 48% yield, without promoting the desired domino cyclization. Formation of the furan **11** can be rationalized through a β-hydride elimination from the π-allylpalladium intermediate **12** followed by aromatization of the diene **13**. Similar results were obtained with amino alcohol derivatives **14** and **15**, both leading to furan **16** in moderate yields. However, these unsuccessful results clearly show that the anion of the hydroxy group of **14** and **15** is more reactive than that of the tosylamide group, irrespective of their location (R^1 or R^2). Thus, both Nu_A and

Scheme 2. Formation of Furan Derivatives by Monocyclization[a]



[a] Reaction conditions: for **10a**, **14**, and **15**: $Pd(PPh_3)_4$ (5 mol %), NaH (2.5 equiv), MeOH, 60 °C; for **10b**: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), dppe (10 mol %), dioxane, 80 °C.

(8) (a) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616−619. (b) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874−4881.

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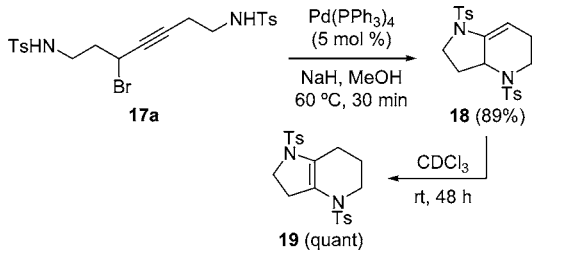
(12) For example, treatment of propargyl alcohols with $CuBr{\cdot}SMe_2$ in the presence of LiBr gave a mixture of allenyl/propargyl bromides.

(13) The reactivities of allenic and propargylic compounds are not necessarily the same. For example, propargyl bromides and carbonates are more reactive than bromoallenes toward S_N2 reactions and alcoholysis, respectively.[10b]

Nu_B with appropriate carbon tethers in the palladium complex **3** (Scheme 1) can readily react with the central carbon of the propargylic moiety.

Next, the reaction of diamine derivative **17a** was investigated (Scheme 3). Fortunately, treatment of **17a** with 5 mol

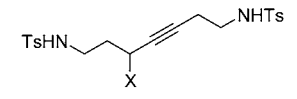
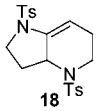
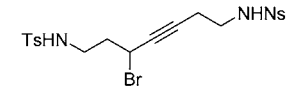
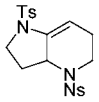
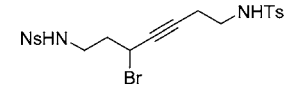
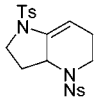
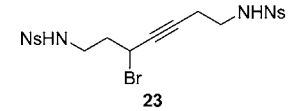
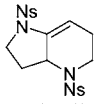
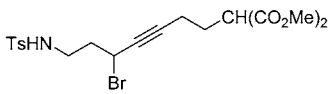
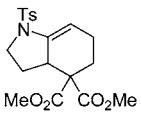
Scheme 3. Domino Cyclization of Diamine Derivatives **17a**



% of $Pd(PPh_3)_4$ in the presence of NaH (2.5 equiv) in MeOH afforded the desired bis-cyclized product **18** in 89% yield. This enamine is relatively unstable, and complete isomerization to the dihydropyrrole derivative **19** having an ethene diamide moiety proceeded in $CDCl_3$ within 48 h at room temperature.[14]

The results of the palladium-catalyzed domino cyclization using selected diamine derivatives are summarized in Table

Table 1. Domino Cyclization of Diamine and (Aminoalkyl)malonate Derivatives[a]

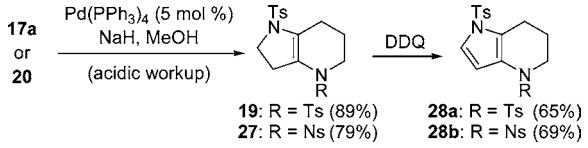
entry	substrate	time (min)	product (yield)[b]
			
1	**17a** (X = Br)	30	**18** (89%)
2	**17b** (X = OCO_2Me)	90[c]	(38%)
3	 **20**	5	 **21** (79%)
4	 **22**	5	 **21** (87%)
5	 **23**	5	 **24** (91%)
6	 **25**	30	 **26** (78%)

[a] Unless otherwise stated, the reactions were carried out with $Pd(PPh_3)_4$ (5 mol %), NaH (2.5 equiv) in MeOH at 60 °C. [b] Yields of isolated products. [c] The reaction was carried out with $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %)/dppe (10 mol %) in dioxane.

1. As shown in entries 1 and 2, the reaction of propargyl carbonate **17b** under aprotic conditions[15] gave a lower yield of **18** (38%) than the reaction of the bromide **17a** in MeOH. The reaction of the bromide **20** having tosyl- and nosylamide groups afforded the bicyclic product **21** in 79% yield (entry 3), in which the tosylamide group is incorporated into the five-membered ring.[16] Interestingly, the same product was obtained in 87% yield from the bromide **22** which has a nosylamide group on the carbon close to the bromine atom (entry 4). 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. When bis-nosylamide **23** was employed in the domino cyclization, the corresponding bicyclic product **24** was obtained in 91% yield (entry 5). The malonate derivative **25** was successfully converted to hexahydroindole dicarboxylate derivative **26** in 78% yield. This result can be partly attributed to steric hindrance of the malonate moiety which hampers the first cyclization.

To expand the synthetic utility of this domino cyclization, conversion to a fused pyrrole derivative was then investigated (Scheme 4). The domino cyclization of **17a** and **20** using

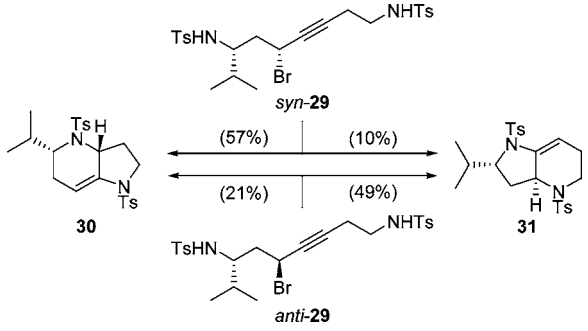
Scheme 4. Synthesis of Fused Pyrrole Derivatives



acidic workup (4% HCl) directly gave the dihydropyrrole-fused bicyclic compounds **19** and **27** both in good yields. DDQ-mediated oxidation of these compounds easily afforded the desired fused pyrroles **28**.

Finally, the stereochemical course of the domino cyclization was examined using *syn*- and *anti*-**29** derived from L-valine (Scheme 5). The reaction of *syn*-**29** under the

Scheme 5. Domino Cyclization of *syn*- and *anti*-**29**

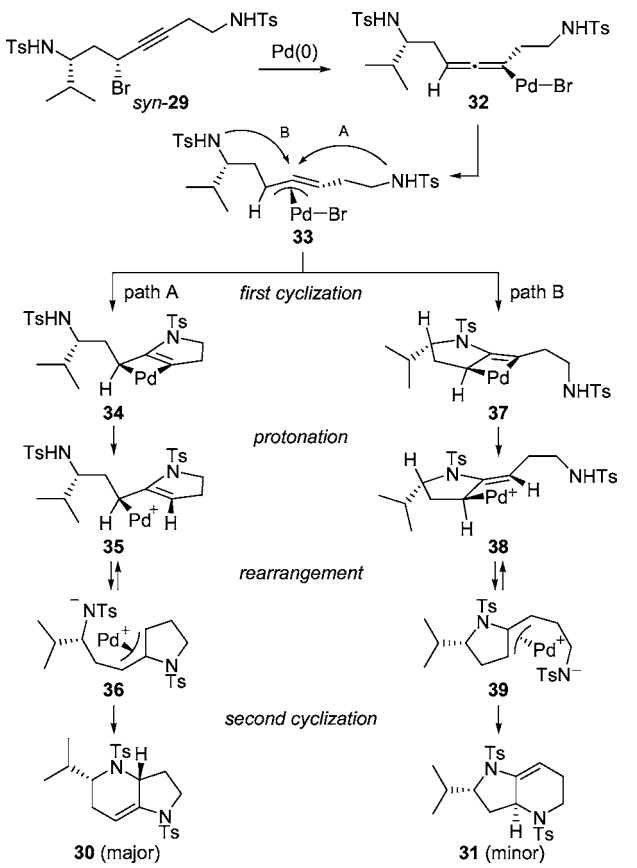


standard conditions using $Pd(PPh_3)_4$ (5 mol %) and in situ generated NaOMe in MeOH gave **30** (57%) and **31** (10%), both in a stereoselective manner.[17] Quite interestingly, the

isomeric *anti*-**29** afforded the same products, although the major isomer was **31** (**30**: 21%; **31**: 49%). These results suggest that the stereochemistry of the substrates is not reflected in that of the products, although it affects the regioselectivity, i.e., which nitrogen attacks the central carbon of the allenylpalladium intermediate in the first cyclization.

Formation of **30** and **31** from *syn*-**29** can be explained as follows (Scheme 6). Attack of palladium(0) to *syn*-**29** from the opposite face of the bromine atom gives an allenylpalladium(II) intermediate **32**. After formation of the π-propargylpalladium complex **33**,[18] the first cyclization by the less-hindered nitrogen atom on the methylene carbon (path A) would form a fused palladacyclobutene intermediate **34**.[19] Protonation of **34** leads to the allylpalladium complex **35**, which is in a state of equilibrium with the π-allylpalladium intermediate **36**. The second *anti*-cyclization from the resulting π-allylpalladium intermediate **36** by the more hindered nitrogen atom would give the major isomer **30** in a stereoselective manner.[20] On the other hand, the domino cyclization in the opposite order through the first cyclization by the more hindered nitrogen atom (path B) will form the minor isomer **31** in a similar manner. Although the production of the same isomers **30** and **31** from *anti*-**29** should involve inversion of the configuration through the sequence of these steps which requires further consideration,[21] these stereochemical outcomes demonstrate an interesting aspect of the palladium-catalyzed domino cyclization of propargyl bromides.

Scheme 6. Stereochemical Course of the Cyclization of *syn*-**29**



In conclusion, we have developed a novel domino cyclization of propargyl bromides having two nucleophilic sites catalyzed by palladium(0). The regioselectivity of the reaction depends on the relative reactivities of the nucleophilic moieties, irrespective of their location. This domino cyclization provides convenient access to fused bicyclic compounds such as hexa- or tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine derivatives as well as hexahydroindole derivatives.

Acknowledgment. This work was supported in part by a Grant-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.

Supporting Information Available: Representative experimental procedures, characterization data of all new compounds, and a crystallographic information file for **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) However, isolation and characterization of the bicyclic compounds of the type **18**, some of which are crystaline compounds, are possible.

(15) The reaction of **17b** under the standard conditions in MeOH promoted methanolysis to give propargyl alcohol in 77% yield.

(16) The structure of **21** was confirmed by acid-mediated isomerization, oxidation to **28b** (Scheme 4) followed by deprotection of the nosyl group. For more details, see the Supporting Information.

(17) The unambiguous structure assignment for **30** and **31** was made by X-ray analysis and NOE experiment (see the Supporting Information).

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(20) For related chirality transfer in the reaction of the propargylic compounds via palladacyclobutene intermediates, see: Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325−3327.

(21) For example, unfavorable steric repulsions around the isopropyl group in **36′** and **39′** (respective epimers of **36** and **39**) might hamper the second cyclization (see the graphic below), which assist isomerization of these intermediates to **36** and **39** via an inversion of configuration.