Asymmetric Catalysis

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Intramolecular Alkynylcyclopropanation of Olefins Catalyzed by Bi(OTf)$_3$: Stereoselective Synthesis of 1-Alkynyl-3-azabicyclo-[3.1.0]hexanes**

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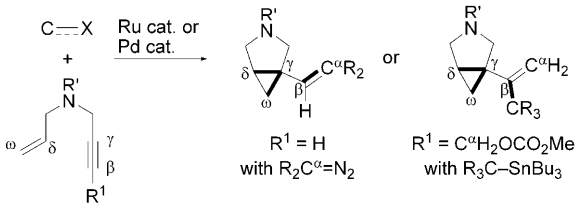
The development of efficient cyclization methods for the construction of nitrogen-containing heterocycles constitutes an ongoing challenge in the construction of natural and pharmaceutical materials. The cycloisomerization of enynes is one such method, for which transition metal catalysts, such as palladium, platinum, gold, ruthenium, and rhodium, have been found to effectively promote the reaction.[1] However, most of these procedures require high loading of expensive metal catalysts and ligands; moreover, accessible heterocyclic skeletons are limited. Therefore, the development of more practical catalyst systems for the synthesis of new heterocycles is desirable. To this end, we have recently reported the iron-catalyzed or bismuth-catalyzed intramolecular heterofunctionalization of olefins and alkynes; this provides various types of heterocycles in both an environmentally friendly and atom efficient manner.[2]

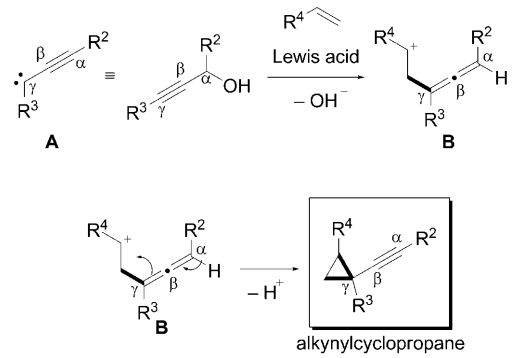
Nitrogen-containing heterocycles, such as 3-azabicyclo-[3.1.0]hexanes, are core structures of a variety of biologically active compounds.[3] Some efficient synthetic routes to this skeleton have been reported, which use stoichiometric quantities of organometallic reagents.[4] Recently, catalytic approaches to 3-azabicyclo[3.1.0]hexanes, which contain a vinylcyclopropane motif, have been developed using the transition-metal-catalyzed tandem carbometalation of 1,6-enynes with organotin[5] or diazoalkane[6] (Scheme 1). These vinylcyclopropane motifs are prized for their utility in ring-expansion reactions, affording a variety of heterocyclic ring sizes.[7] In contrast, the synthesis of analogous azabicyclohexanes with alkynyl substituents have been scarcely reported,[8] even though the alkynylcyclopropanes are versatile units for numerous chemical transformations[9] and are substructures in many natural products.[10]

To construct the skeleton, we envisaged that propargyl alcohol might act as a synthetic equivalent of propargyl



Scheme 1. Tandem carbometalation of 1,6-enynes using ruthenium or palladium catalysts.

carbene **A**, which is a useful active species for the alkynylcyclopropanation of olefins[11] (Scheme 2). It is known that propargyl alcohols undergo nucleophilic addition at the γ-position in the presence of a Lewis acid to form allenyl



Scheme 2. Propargyl alcohol acting as a synthetic carbene equivalent for the alkynylcyclopropanation of olefins.

intermediate **B**.[12] Trapping of the electrophilic carbocation by the internal allene results in formation of the expected alkynylcyclopropane. Thus, the overall mechanism is considered to be a formal addition reaction of propargyl carbene **A** to the olefin. However, the allene intermediate **B** is often supplemented with other unexpected nucleophiles,[13] spontaneously eliminates substituents,[12a,14] or sometimes oligomerizes. Indeed, when the model substrate *N*-tosyl-5-azaoct-7-en-2-yn-1-ol (**1a**) was treated with various Lewis acids (5 mol%), such as BF_3•OEt_2, $Sc(OTf)_3$, $Cu(OTf)_2$, $PtCl_2$, AgOTf, or TfOH, at 80 °C in 1,2-dichloroethane (DCE), only oligomeric products were formed [Eq. (1)]. However, upon further screening of the catalysts, we found that $Fe(OTf)_2$, $Fe(OTf)_3$, and $Bi(OTf)_3$ each produced the desired 1-(phenylethynyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (**2a**) in 30%, 28%, and 34% yields, respectively. It was noteworthy that bipyridine (bipy)

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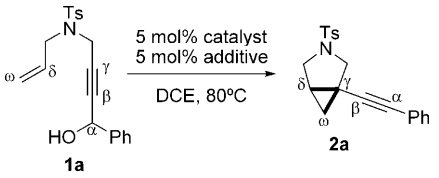


(1)

and 1,2-bis(diphenylphosphino)ethane (dppe) additives increased the yields to 42% and 40%, respectively. In contrast, 4-dimethylaminopyridine, 1,10-phenanthroline, and 2,2′:6′2″-terpyridine gave lower product yields. Similarly, high additive loading (greater than two equivalents relative to the bismuth catalyst) caused no reaction at all. In a control experiment, no formation of **2a** was observed using bipyridine alone and also in the absence of the $Bi(OTf)_3$ catalyst. The reaction was also found to be solvent dependent; 1,2-dichloroethane, toluene, and benzene were favorable for formation of **2a**, whereas acetonitrile, 1,4-dioxane, and nitromethane gave little or no product.

Next, with our optimized conditions in hand, we investigated the tolerance of the $Bi(OTf)_3$-catalyzed alkynylcyclopropanation with various azaenynols **1b**–**1w** (Table 1). Internal olefins **1b**, **1e**, **1h**, **1j**, **1l**, **1n**, **1o**, and **1q** reacted more efficiently under the optimized reaction conditions than terminal ones (**1d**, **1g**, **1i**, **1m**, and **1p**). Notably, these internal *E*-olefins provided only the *cis*-**2** stereoisomer between γ-alkynyl and ω-alkyl moieties (see Eq. (1) for assignment). The stereochemistry was determined from the coupling constant between the $C_{(\delta)}H$ and $C_{(\omega)}$ protons in the product ($^3J_{H(\delta)\text{-}H(\omega)}$ = ca. 4.0 Hz),[5b] and confirmed by an X-ray structure of the representative product **2l** (Figure 1). Furthermore, electron-rich olefins **1c**, **1f**, and **1k** enhanced the reaction efficiency, which proceeded at lower temperature (25 °C) and in the absence of an additive (Table 1, entries 2, 5, and 10). Alkyl substituents at the α-position of **1** inhibited the reaction, but a wide range of aryl attachments could successfully participate in the reaction; electron-withdrawing groups on the aryl ring were superior to electron-donating ones (Table 1, entries 3–7 vs. 8–11). Moreover, *ortho*-substitution of the aromatic ring did not interfere with the transformation (Table 1, entries 12–16).

This transformation is not limited to substrates have simple aryl attachments at the α-position. Valuable functional groups, such as heteroaryl (Table 1, entries 17 and 18), vinyl (entries 19 and 20), and alkynyl substituents (entry 21), could be introduced into the 1-alkynyl-3-azabicyclo-[3.1.0]hexane framework in satisfactory yields. Furthermore, this procedure was extended to the formation of 1-alkynyl-3-azabicyclo[4.1.0]heptane **2w** (Table 1, entry 22).

To gain an insight into the mechanism of the transformation of **1** into **2**, we studied the stereo-

Table 1: Scope of the bismuth-catalyzed dehydrative alkynylcyclopropanation of azaenynol **1**.

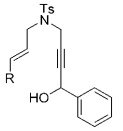
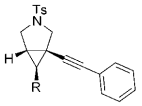
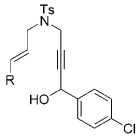
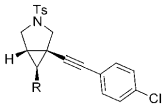
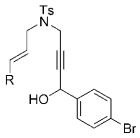
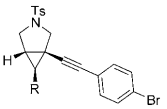
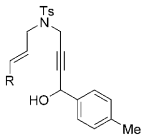
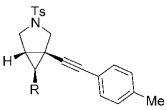
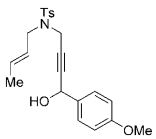
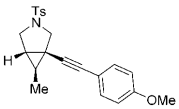
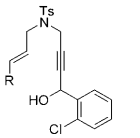
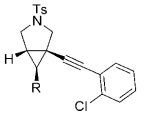
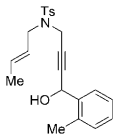
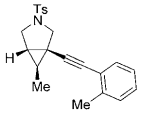
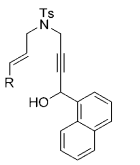
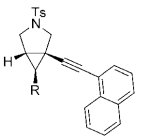
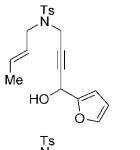
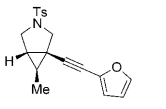
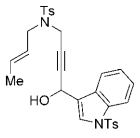
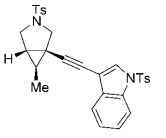
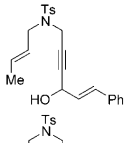
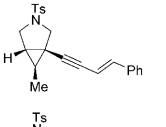
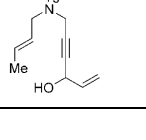
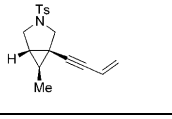
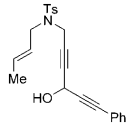
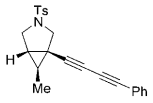
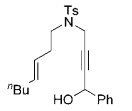
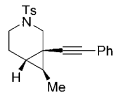
Entry	Substrate		*t* [h]	Product		Yield [%][a]
1		R = Me **1b**	1		**2b**	80
2[b]		R = Pr **1c**	1		**2c**	85
3		R = H **1d**	4		**2d**	52
4		R = Me **1e**	5		**2e**	77
5[b]		R = Pr **1f**	10		**2f**	80
6		R = H **1g**	24		**2g**	36
7		R = Me **1h**	5		**2h**	80
8		R = H **1i**	24		**2i**	26
9		R = Me **1j**	2		**2j**	65
10[b]		R = Pr **1k**	3		**2k**	70
11		**1l**	10		**2l**	52
12		R = H **1m**	12		**2m**	31
13		R = Me **1n**	5		**2n**	67
14		**1o**	3		**2o**	67
15		R = H **1p**	3		**2p**	36
16		R = Me **1q**	7		**2q**	62
17		**1r**	2		**2r**	23
18		**1s**	4		**2s**	48
19		**1t**	12		**2t**	54
20[c]		**1u**	18		**2u**	33

Table 1: (Continued)

Entry	Substrate		*t* [h]	Product		Yield [%][a]
21[d]		**1v**	1 week		**2v**	33
22[b]		**1w**	24		**2w**	75

[a] Yield of isolated product. [b] 25 °C; without bipyridine. [c] 80 °C; without bipyridine. [d] **1v** was recovered in 25 % yield.

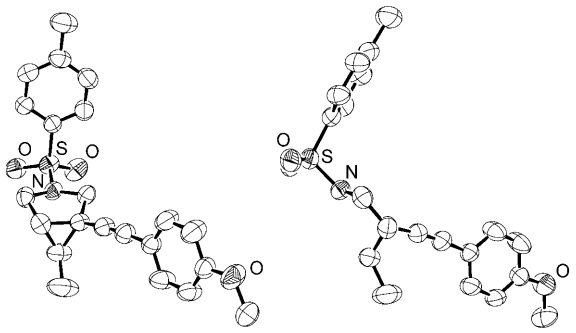
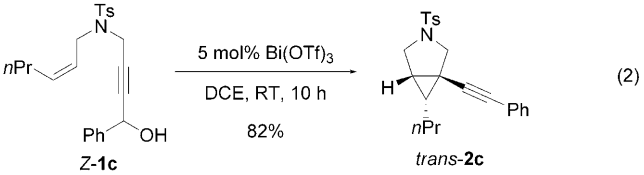


Figure 1. ORTEP showing two orthogonal views of **2l**. Ellipsoids are shown at 50 % probability. Hydrogen atoms are omitted for clarity.

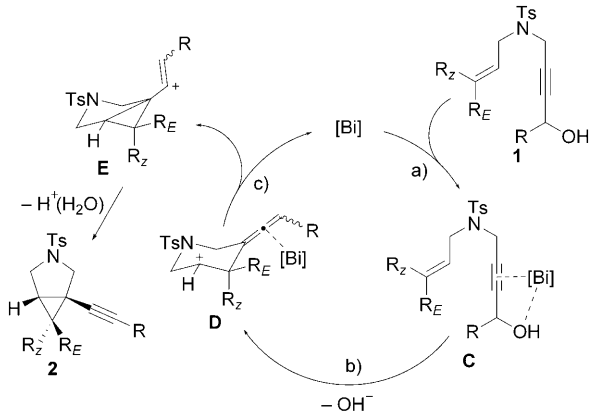
chemical course of the alkynylcyclopropanation, and found that the present reaction of azaenynols **1** containing 1,2-disubstituted olefins was stereospecific. Thus, *E*-olefin-substituted azaenynols **1** provided *cis*-**2** bicycles only as described in Table 1, whereas *Z*-substrate afforded *trans*-**2c** ($^3J_{H(\delta)\text{-}H(\omega)} = 7.7$ Hz) exclusively [Eq. (2)]. It was also confirmed that no isomerization between *E*-**1c** and *Z*-**1c**, and *cis*-**2c** and *trans*-**2c**, took place under identical conditions.



Z-**1c** *trans*-**2c** (2)

On the basis of these mechanistic studies, we propose a mechanism for the dehydrative alkynylcyclopropanation as follows (Scheme 3): a) Dual coordination of the alkyne and the oxygen of the hydroxy group to the bismuth catalyst gives complex **C**.[2f,15] b) Nucleophilic addition of the pendant olefin to the activated propargyl alcohol produces carbocation **D**, which contains a vinylidene moiety;[16] in the intermediate **D**, R_E and R_Z substituents would sit equatorially and axially, respectively.[17] c) A second cyclization from the vinylidene to the neighboring carbocation affords vinyl cation **E**; deprotonation gives 1-alkynyl-3-azabicyclo[3.1.0]alkane **2** with expulsion of water.

In conclusion, we have reported a bismuth-catalyzed dehydrative alkynylcyclopropanation of azaenynols to give 1-alkynyl-3-azabicyclo-[3.1.0]hexanes in good yield, wherein the propargyl alcohol unit formally acts as a propargyl carbene equivalent. This reaction tolerates a wide range of substituents at the propargyl position, including aryl, heteroaryl, vinyl, and alkynyl functional groups. Remarkably, the stereochemistry of theses products strongly depends on that of the starting azaenynols, that is, *cis*- and *trans*-1-alkynyl-3-azabicyclo-[3.1.0]hexanes were obtained stereoselectively from the reaction of *E*- and *Z*-azaenynols, respectively. Although the exact roles of the bismuth catalyst and bipyridine additive are not yet fully clear, the reaction proceeds efficiently only in the presence of bismuth triflates or iron triflates. Consequently, we concluded that the simple Lewis acid catalyzed pathway does not contribute to the present reaction. Mechanistic studies, and the extension of this procedure to other types of alkynylcyclopropanation reactions are in progress.



Scheme 3. Plausible reaction mechanism.

Experimental Section

General procedure for the reaction of **1b** with $Bi(OTf)_3$ catalyst: A solution of azaenynol **1b** (55.5 mg, 0.14 mmol) in 1,2-dichloroethane (0.7 mL) was added into a mixture of $Bi(OTf)_3$ (4.6 mg, 7.0 μmol), bipyridine (1.1 mg, 7.0 μmol), and 1,2-dichloroethane (0.7 mL) under N_2. After stirring for 1 h at 80 °C, the reaction mixture was cooled to room temperature, passed through a short silica gel column, and then concentrated. The crude product was purified by column chromatography on silica gel (60–230 mesh) with a hexanes/ethyl acetate eluent (5:1) to afford pure 1-phenylethynyl-6-methyl-3-tosyl-3-azabicyclo-[3.1.0]hexane (**2b**) in 80 % yield (39.3 mg).

2b was isolated as a white solid; m.p. 96.0–96.5 °C; R_f (SiO_2, hexanes/EtOAc = 5:1) = 0.28; ^{1}H NMR ($CDCl_3$, 270.05 MHz): $\delta =$ 1.22 (3H, t, $J = 5.9$ Hz), 1.29–1.35 (1H, m), 1.45 (1H, t, $J = 4.1$ Hz), 2.45 (3H, s), 3.12 (1H, dd, $J = 9.2$, 4.1 Hz), 3.15 (1H, d, $J = 9.1$ Hz), 3.59 (1H, d, $J = 9.1$ Hz), 3.71 (1H, d, $J = 9.1$ Hz), 7.27–7.36 (7H, m), 7.69 ppm (2H, d, $J = 8.2$ Hz); ^{13}C NMR ($CDCl_3$, 67.80 MHz): $\delta =$ 13.6, 21.3, 21.5, 23.9, 32.8, 49.6, 52.9, 81.2, 87.0, 123.0, 127.6, 128.0,

128.2, 129.7, 131.6, 133.0, 143.7 ppm; HRMS: *m/z* calc. for $C_{21}H_{21}NO_2S$: 351.1293, found: 351.1300.

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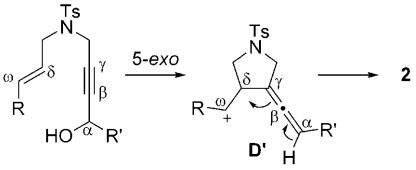
[16] An alternative mechanism that includes the formation of a five-membered intermediate **D′**, which has a carbocation at the ω-position, is also possible. However, the structure of **D′** cannot explain the stereospecificity of the transformation.



[17] A similar mechanism has been proposed in the gold-catalyzed cycloisomerization of 1,5-enynes. See Ref. [13b].

