Cyclization Reactions

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Gold-Catalyzed Tandem Cyclization of Dienol Silyl Ethers for the Preparation of Bicyclo[4.3.0]nonane Derivatives**

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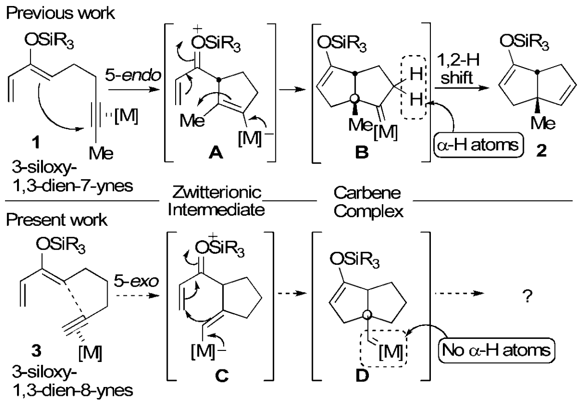
We previously reported the geminal carbo-functionalization reaction of alkynes on treatment of 3-siloxy-1,3-dien-7-ynes **1** with $[W(CO)_6]$ or $[ReCl(CO)_5]$ under photoirradiation to give bicyclo[3.3.0]octane derivatives **2** in good yield (Scheme 1).[1]

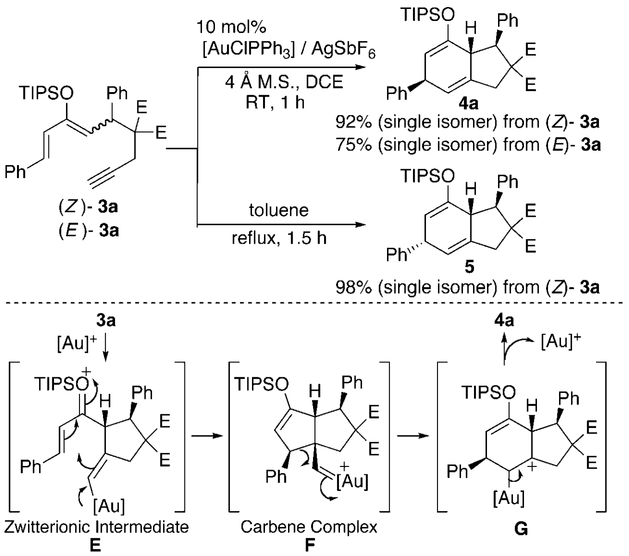


Scheme 1. Tandem cyclization of dienol silyl ethers.

The reaction was thought to proceed through nucleophilic attack of the silyl enol ether moiety to the electrophilically activated alkyne followed by attack of the generated alkenyl metallic species **A** to the α,β-unsaturated silyloxonium moiety at the position β to the metal to give bicyclic carbene complex intermediate **B**, which gave the product through 1,2-hydrogen shift with regeneration of the catalyst.[2] We then thought of the possibility of carrying out a similar geminal carbo-functionalization reaction by employing one-carbon-atom elongated substrates (3-siloxy-1,3-dien-8-ynes **3**) with the expectation that 5-exo attack of the silyl enol ether moiety followed by ring closure (geminal carbo-functionalization) would give bicyclo[3.3.0]octane derivative **D** having a carbene complex moiety as a substituent on the bridgehead carbon atom. As there is no α-hydrogen atom at the carbene complex moiety, 1,2-hydrogen shift is not possible and the behavior of this intermediate is intriguing (Scheme 1). We now report that 1,2-alkyl migration[3] occurred at the generated carbene moiety to give ring-expanded products by employing 3-siloxy-1,3-dien-8-yne derivatives as substrates, to stereoselectively obtain synthetically useful bicyclo[4.3.0]nonane derivatives, whose configuration was different from that of the Diels–Alder adduct.

We first examined the reaction of 3-siloxy-1,3-dien-8-yne **3a** with the geometry of the silyl enol ether moiety as (*Z*)[4] by using various electrophilic transition-metal catalysts. Although $[W(CO)_5(thf)]$ or $[ReCl(CO)_5]$ gave the products in reasonable yield (45% and 78%, respectively),[5] the cationic gold catalyst gave the best result. Thus, treatment of **3a** with 10 mol% of $[AuClPPh_3]/AgSbF_6$[6] in the presence of molecular sieves (4 Å) gave bicyclo[4.3.0]nonane derivative **4a**, a formal [4+2] cycloadduct, as a single stereoisomer in 92% yield (Scheme 2).[7,8] Interestingly, the configuration of the product was different from that of the thermal Diels–Alder adduct **5** obtained stereoselectively by heating a solution of (*Z*)-**3a** in toluene for 1.5 h.[9] Thus, two diastereoisomers[10] of the same bicyclo[4.3.0]nonane derivative were obtained selectively by choosing Au^I-catalyzed or thermal conditions.

Next, we examined the reaction of 3-siloxy-1,3-dien-8-yne derivative **3a** with the geometry of the silyl enol ether moiety as (*E*)[4] under thermal and Au^I-catalyzed conditions (Scheme 2). In this case, (*E*)-**3a** did not undergo thermal



Scheme 2. Au^I-catalyzed and thermal cyclization of dienynes **3a**. $E = CO_2Me$; TIPS = triisopropylsilyl; M.S. = molecular sieves; DCE = dichloroethane.

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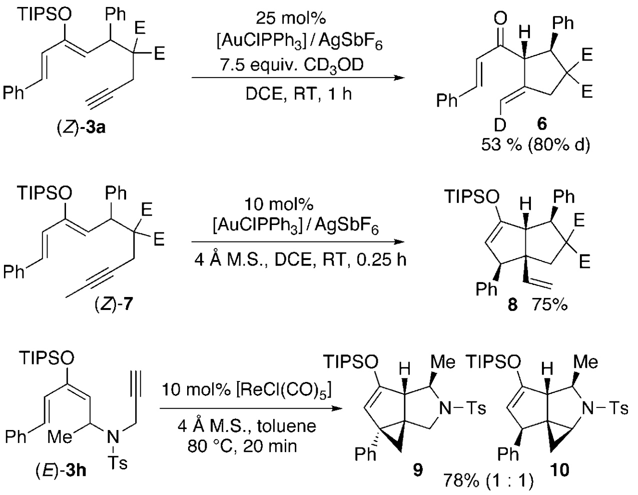
Diels–Alder reaction; however, treatment of (*E*)-**3a** with 10 mol% Au^I catalyst at room temperature afforded a good yield of the same product as obtained in the Au^I-catalyzed reaction of (*Z*)-**3a**.

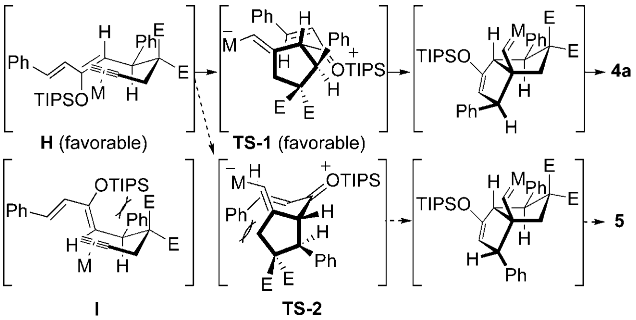
The proposed mechanism of the reaction is shown at the bottom of Scheme 2. First, zwitterionic intermediate **E** was generated by 5-exo nucleophilic attack of the silyl enol ether moiety to the electrophilically activated π-alkyne complex.[11] The alkenyl metallic species underwent intramolecular attack at the β position of the metal to the α,β-unsaturated silyl oxonium moiety to generate bicyclic unstable carbene complex **F**. Finally, the carbene moiety underwent 1,2-alkyl migration of the benzylic carbon atom, the electron density of which was higher than the other neighboring methylene carbon atom, to give the product with regeneration of the catalyst.

Support for the mechanism of the reaction was obtained by the following experiments (Scheme 3). Treatment of (*Z*)-**3a** with 25 mol% of [AuClPPh$_3$]/AgSbF$_6$ in the presence of 7.5 equivalents of CD$_3$OD gave monocyclic ketone **6**,[12] the hydrolyzed product of the *exo*-cyclized zwitterionic intermediate **E**, in which most of the deuterium was observed at the one side of the alkene. Furthermore, treatment of an internal alkyne derivative **7** with 10 mol% of cationic Au^I catalyst gave bicyclo[3.3.0]octane derivative **8**, geminal carbofunctionalization product, which was produced by 1,2-hydrogen shift at the carbene complex moiety. In addition, although the type of the metal catalyst is different, treatment of (*E*)-**3h** with 10 mol% [ReCl(CO)$_5$] gave tricyclic compounds **9** and **10**, which were produced by insertion of the carbene complex moiety into the neighboring C−H bonds in the carbene complex intermediate related to **F**.[13,14] These results supported the proposal that the reaction proceeded through *exo*-cyclization and 1,2-alkyl or 1,2-hydrogen shift occurred from the carbene complex intermediate containing a bicyclo[3.3.0]octane skeleton.



Scheme 3. Trapping of intermediates. E = CO$_2$Me; Ts = *p*-toluenesulfonyl.

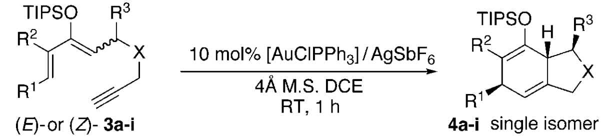
The stereoselectivity of the reaction could be explained as follows. Concerning the first cyclization, **H** was thought to be more favorable than **I** because of steric repulsion between the TIPS group and the phenyl substituent, and the second cyclization proceeded preferentially via transition state **TS-1**, because the phenyl group in another possible transition state **TS-2** is oriented toward the concave position (Scheme 4).[15]



Scheme 4. Transition states of gold-catalyzed tandem cyclization.

We next examined the generality of this Au^I-catalyzed stereoselective cyclization reaction (Table 1). The substrates **3** with phenyl or alkyl groups for R^1 and R^3 were cyclized to afford the corresponding bicyclic enol silyl ethers in good yield (Table 1, entries 1–3). Even the reaction of substrates without the geminal-diester moiety (**3d** and **3e**) also proceeded to afford the corresponding bicyclic enol silyl ethers albeit in somewhat lower yields (Table 1, entries 4 and 5). The substrates containing nitrogen or oxygen atoms in the tether were also cyclized to afford the corresponding bicyclic enol silyl ethers in good yield (Table 1, entries 6–9). All these products were obtained as a single diastereomer, whose configuration was different from that of the thermal Diels–Alder reaction.[16]

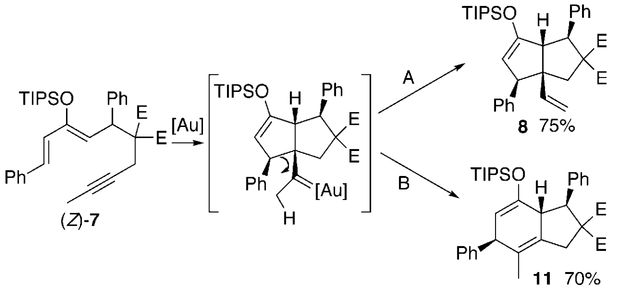
Table 1: Tandem cyclization of *E*- or *Z*-dienynes **3a–i**.



Entry	Substrate	R^1, R^2, R^3	X	Product (yield [%])
1	(*E*)-**3a**	Ph, H, Ph	C(CO$_2$Me)$_2$	**4a** (75)
2	(*E*)-**3b**	Ph, H, Me	C(CO$_2$Me)$_2$	**4b** (82)
3	(*E*)-**3c**	Me, H, Ph	C(CO$_2$Me)$_2$	**4c** (88)
4	(*Z*)-**3d**	Ph, H, H	CH$_2$	**4d** (45)
5	(*Z*)-**3e**	Ph, Me, H	CH$_2$	**4e** (76)
6	(*E*)-**3f**[a,b]	Ph, H, Ph	N−Ms	**4f** (72)
7	(*E*)-**3g**[a,c]	Ph, H, Me	N−Ts	**4g** (77)
8	(*E*)-**3h**[a,c]	Me, H, Me	N−Ts	**4h** (68)
9	(*Z*)-**3i**	Ph, H, Me	O	**4i** (66)

[a] Reaction temperature was 80°C. [b] Ms = methanesulfonyl. [c] Ts = *p*-toluenesulfonyl.

Interestingly, when the reaction of internal alkyne **7**, which gave 1,2-hydrogen shift product **8** on treatment with cationic Au^{I} catalyst, was carried out with 10 mol% of AuCl$_3$/AgSbF$_6$,[17] 1,2-alkyl migration occurred to give bicyclo[4.3.0]nonane derivative **11** in 70% yield (Scheme 5).[18] It is thought that, in case of the highly electron-deficient cationic Au^{III} carbene complex intermediate, 1,2-alkyl migration is accelerated by the highly electrophilic character of the carbene carbon atom, whereas in the moderately electron-deficient Au^{I} carbene complex, 1,2-hydrogen shift became the favorable reaction pathway.[19] Thus, two types of product could be obtained selectively by the appropriate choice of the Au^{I} or Au^{III} catalyst.



Scheme 5. 1,2-Hydrogen shift or 1,2-alkyl migration of the carbene intermediate. E = CO$_2$Me. Conditions: A) 10 mol% [AuClPPh$_3$]/AgSbF$_6$, 4 Å M.S., DCE, 80°C, 0.25 h; B) 10 mol% AuCl$_3$/AgSbF$_6$, 4 Å M.S., DCE, RT, 0.3 h.

In summary, we have developed gold-catalyzed geminal carbo-functionalization of 3-siloxy-1,3-dien-8-ynes **3** to give bicyclo[4.3.0]nonanes **4** stereoselectively through a ring-expansion reaction of the bicyclic carbene complex intermediates. The reaction gave synthetically useful bicyclo[4.3.0]nonane derivatives **4** whose configuration is different from that of the thermal Diels–Alder adduct.

Experimental Section

General procedure: 3-Siloxy-1,3-diene-8-yne (0.1 mmol) in degassed dichloroethane (1 mL) was added to a mixture of [AuClPPh$_3$] (0.01 mmol), AgSbF$_6$ (0.01 mmol), and activated 4 Å molecular sieves (100 mg). After the mixture was stirred for 1 h at room temperature, the reaction mixture was filtered through a short pad of silica gel, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (PTLC) to give the bicyclic compound.

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[1] a) H. Kusama, H. Yamabe, Y. Onizawa, T. Hoshino, N. Iwasawa, *Angew. Chem.* **2005**, *117*, 472–474; *Angew. Chem. Int. Ed.* **2005**, *44*, 468–470; b) Y. Onizawa, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2008**, *130*, 802–803; c) H. Kusama, Y. Onizawa, N. Iwasawa, *J. Am. Chem. Soc.* **2006**, *128*, 16500–16501.

[2] For recent reviews of electrophilic activation of alkynes, see: a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; b) C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380–2386; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328–2334; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346; d) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; e) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431–436; f) J. Marco-Contelles, E. Soriano, *Chem. Eur. J.* **2007**, *13*, 1350–1357; g) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159; h) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309; i) M. Álvarez-Corral, M. Muñoz-Dorado, I Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174–3198; j) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442.

[3] For recent reviews of 1,2-alkyl migration of carbene intermediates, see: B. Crone, S. F. Kirsch, *Chem. Eur. J.* **2008**, *14*, 3514–3522.

[4] See the Supporting Information for preparative methods.

[5] The reaction of **3a** with [W(CO)$_5$(thf)] proceeded to give the products as a mixture of diastereoisomers (**4a** 22% + 23%). The reaction of **3a** with [ReCl(CO)$_5$] proceeded to give the products as a mixture of silyl enol ether **4a** and its hydrolyzed product (9% + 69%).

[6] For recent reviews on gold-mediated homogeneous catalysis, see: a) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; b) P. Belmont, E. Parker, *Eur. J. Org. Chem.* **2009**, 6075–6089; c) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; d) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; e) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; f) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; g) J. Muzart, *Tetrahedron* **2008**, *64*, 5815–5849; h) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917–4938; i) H. C. Shen, *Tetrahedron* **2008**, *64*, 7847–7870; j) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; k) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; l) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; m) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; n) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555–4563.

[7] AgSbF$_6$ alone failed to catalyze the reaction of **3a**. Starting material **3a** was mostly recovered.

[8] For examples of transition-metal-catalyzed [4+2] cycloaddition of 1,3-dien-8-yne derivatives, see: a) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1995**, *60*, 2962–2963; b) R. Shintani, Y. Sannohe, T. Tsuji, T. Hayashi, *Angew. Chem.* **2007**, *119*, 7415–7418; *Angew. Chem. Int. Ed.* **2007**, *46*, 7277–7280; c) D. Motoda, H. Kinoshita, H. Shinokubo, K. Oshima, *Angew. Chem.* **2004**, *116*, 1896–1898; *Angew. Chem. Int. Ed.* **2004**, *43*, 1860–1862; d) B. Wang, P. Cao, X. Zhang, *Tetrahedron Lett.* **2000**, *41*, 8041–8044; e) S. R. Gilbertson, G. S. Hoge, D. G. Genov, *J. Org. Chem.* **1998**, *63*, 10077–10080; f) K. Kumar, R. S. Jolly, *Tetrahedron Lett.* **1998**, *39*, 3047–3048; g) A. Fürstner, K. Majima, R. Martín, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004; h) A. Fürstner, C. C. Stimson, *Angew. Chem.* **2007**, *119*, 9001–9005; *Angew. Chem. Int. Ed.* **2007**, *46*, 8845–8849.

[9] For an example of Diels–Alder reaction of 1,3-dien-8-yne derivatives, see: T. Stellfeld, U. Bhatt, M. Kalesse, *Org. Lett.* **2004**, *6*, 3889–3892.

[10] The relative configuration of **4a** and **5** was determined by observation of NOE spectra. For details, see the Supporting Information.

[11] a) K. Maeyama, N. Iwasawa, *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929; b) N. Iwasawa, K. Maeyama, H. Kusama, *Org. Lett.* **2001**, *3*, 3871–3873; c) H. Kusama, H. Yamabe, N. Iwasawa, *Org. Lett.* **2002**, *4*, 2569–2571; d) N. Iwasawa, T. Miura, K. Kiyota, H. Kusama, K. Lee, P. H. Lee, *Org. Lett.* **2002**, *4*, 4463–4466; for important example, see also: e) S. T. Staben, J. J. Kennedy-

Smith, D. Huang, B. K. Corkey, R. L. LaLonde, F. D. Toste, *Angew. Chem.* **2006**, *118*, 6137 – 6140; *Angew. Chem. Int. Ed.* **2006**, *45*, 5991 – 5994; f) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2003**, *9*, 2627 – 2635; g) K. C. Nicolaou, G. S. Tria, D. J. Edmonds, *Angew. Chem.* **2008**, *120*, 1804 – 1807; *Angew. Chem. Int. Ed.* **2008**, *47*, 1780 – 1783.

[12] The geometry of the deuterated double bond was confirmed by NOE experiments.

[13] Insertion of the gold-stabilized cationic intermediates into sp^3 C–H bonds is rare, see: Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809 – 2811, and references therein.

[14] We cannot completely rule out the possibility that in the gold-catalyzed reaction the second cyclization occurred (intermediate **E** in Scheme 2) at the α position of the metal followed by elimination of the gold catalyst.

[15] The configuration of the Diels–Alder adduct **5** could be explained by the consideration that the reaction proceeds through *s-cis* conformation of the siloxy diene moiety in **H**.

[16] The Diels–Alder reactions of (*Z*)-**3d**, (*Z*)-**3i**, and (*Z*)-**7** were examined to give corresponding adducts in 51 %, 99 %, and 97 % yields, respectively.

[17] For examples of difference of reactivity between Au^{I} and Au^{III}, see: a) A. W. Sromek, M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10500 – 10501; b) Y. Xia, A. S. Dudnik, V. Gevorgyan, Y. Li, *J. Am. Chem. Soc.* **2008**, *130*, 6940 – 6941; c) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553 – 11554; d) H. Rabaâ, B. Engels, T. Hupp, A. S. K. Hashmi, *Int. J. Quantum Chem.* **2007**, *107*, 359 – 365; e) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391 – 4394; f) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* **2006**, 4905 – 4909.

[18] When the reaction of (*Z*)- or (*E*)-**3a** was carried out with 10 mol % of $AuCl_3/AgSbF_6$, the reaction proceeded faster (10 min) than the reaction with $[AuClPPh_3]/AgSbF_6$ (1 h) to give the product **4a** in somewhat lower yield (32 % from (*Z*)-**3a**, 59 % from (*E*)-**3a**).

[19] For an example of ligand control of C–H versus aliphatic C–C migration reaction of Rh carbenoids, see: M. Vitale, T. Lecourt, C. G. Sheldon, V. K. Aggarwal, *J. Am. Chem. Soc.* **2006**, *128*, 2524 – 2525.