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The Skeletal Rearrangement of Gold- and Platinum-Catalyzed Cycloisomerization of *cis*-4,6-Dien-1-yn-3-ols: Pinacol Rearrangement and Formation of Bicyclo[4.1.0]heptenone and Reorganized Styrene Derivatives

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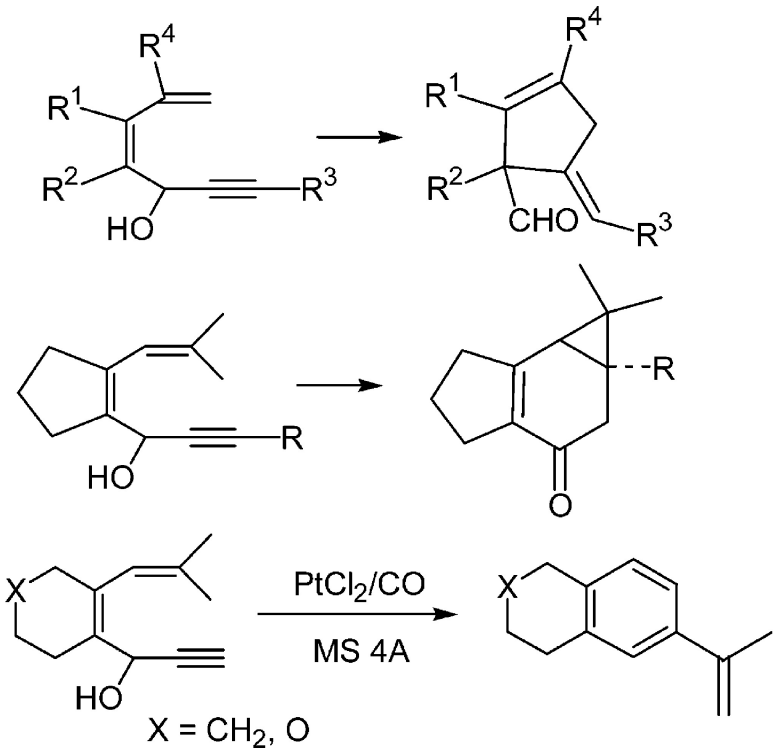

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The Skeletal Rearrangement of Gold- and Platinum-Catalyzed Cycloisomerization of *cis*-4,6-Dien-1-yn-3-ols: Pinacol Rearrangement and Formation of Bicyclo[4.1.0]heptenone and Reorganized Styrene Derivatives

Jhih-Meng Tang,[†] Sabyasachi Bhunia,[†] Shariar Md. Abu Sohel,[†] Ming-Yuan Lin,[†] Hsin-Yi Liao,[‡] Swarup Datta,[†] Arindam Das,[†] and Rai-Shung Liu*,[†]

Contribution from Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, ROC, and Department of Science Education, National Taipei University of Education, Taipei, Taiwan, ROC

Received August 16, 2007; E-mail: rsliu@mx.nthu.edu.tw

Abstract: With gold and platinum catalysts, *cis*-4,6-dien-1-yn-3-ols undergo cycloisomerizations that enable structural reorganization of cyclized products chemoselectively. The $AuCl_3$-catalyzed cyclizations of 6-substituted *cis*-4,6-dien-1-yn-3-ols proceeded via a 6-*exo*-*dig* pathway to give allyl cations, which subsequently undergo a pinacol rearrangement to produce reorganized cyclopentenyl aldehyde products. Using chiral alcohol substrates, such cyclizations proceed with reasonable chirality transfer. In the $PtCl_2$-catalyzed cyclization of 7,7-disubstituted *cis*-4,6-dien-1-yn-3-ols, we obtained exclusively either bicyclo-[4.1.0]heptenones or reorganized styrene products with varied substrate structures. On the basis of the chemoselectivity/structure relationship, we propose that bicyclo[4.1.0]heptenone products result from *6-endo-dig* cyclization, whereas reorganized styrene products are derived from the *5-exo-dig* pathway. This proposed mechanism is supported by theoretic calculations.

1. Introduction

Platinum- and gold-catalyzed cycloisomerization of acyclic 1,6- and 1,7-enynes[1−4] provides one-pot synthesis of complex carbocyclic molecules, which are not readily available from conventional syntheses. The values of such reactions are manifested by their applications to short synthesis of natural compounds.[5] Catalytic cycloisomerization of enynes often occurs with a skeletal rearrangement because a nonclassical carbocation participates as a reaction intermediate;[6,7] in such cases, the control of chemoselectivity becomes an important issue. Although the allyl cation is a synthetically useful intermediate because of both its thermodynamic stability and high electrophilicity,[8,9] this cationic species has been seldom employed in the cycloisomerization of enynes.[10,11] We seek to explore the cycloisomerization of enynes via allyl cations, which not only

[†] National Tsing-Hua University.
[‡] National Taipei University of Education.

(1) For recent reviews for gold and platinum catalysis, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (e) Hashmi, A. S. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990.
(2) For gold-catalyzed cycloisomerizations of enynes, see selected examples: (a) Nieto-Oberhuber, C.; Munoz, P. M.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (b) Luzung, M. R.; Markham, J. P.; Toste. F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (c) Horino, Y.; Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 11364. (d) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806. (e) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (f) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (g) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614. (h) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310.
(3) For $PtCl_2$-catalyzed cycloisomerization of enynes, see selected examples: (a) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (b) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (c) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (d) Méndez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (e) Mamane, V.; Gress, T.; Krause. H.; Fürstner. A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (f) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria. M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (g) Blaszykowski, C.; Harrak, Y.; Goncalves, M.-H.; Cloarec, J.-M.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771. (h) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345. (i) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367.
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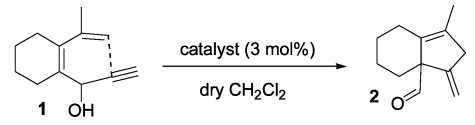
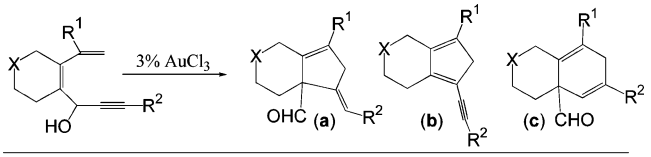
Table 1. Catalytic Transformation of Enyne 1 into Aldehyde 2 over Various Catalysts



entry[a]	catalyst	time	yield[b,c]
1	AuCl	0.5 hr	38%
2	$AuCl_3$	10 min	74%
3	$AuClPPh_3/AgOTf$	10 min	58%
4	AgOTf	10 min	15%
5	$AuClPPh_3/AgSbF_6$	10 min	59%
6	$AgSbF_6$	10 min	45%
7	$AuClPPh_3$	3 day	3%
8	$PtCl_2$	1 hr	41%
9	$PtCl_2/CO$	1 hr	49%
10	TfOH	22 hr	5%

[a] [substrate] = 0.5 M, 25 °C. [b] Yields are reported after separation from a silica column. [c] Starting alcohol **1** was completely consumed for all entries.

Table 2. Gold-Catalyzed Cyclization of *cis*-4,6-Dien-1-yn-3-ols



entry[a]	alcohols	mol %	time(min)	products (yields)[b]
	X = CH_2			
1	R^1 = Ph, R^2 = H (**3**)	3	10	**14a** (82%)
2	R^1 = Et, R^2 = H (**4**)	3	10	**15a** (67%)
	X = O			
3	R^1 = Me, R^2 = H (**5**)	3	5	**16a** (86%)
4	R^1 = Ph, R^2 = H (**6**)	3	5	**17a** (98%)
	X = CH_2			
5	R^1 = Ph, R^2 = Me (**7**)	3	10	**18a** (75%)
6	R^1 = Ph, R^2 = ^{n}Pr (**8**)	3	10	**19a** (70%), **19b** (10%)
7	R^1 = Ph, R^2 = Ph (**9**)	5	10	**20a** (68%), **20b** (6%)
	X = O			
9	R^1 = Me, R^2 = TMS (**10**)	10	10	**21a** (50%), 21c (11%)
10	R^1 = Ph, R^2 = ^{n}Bu (**11**)	5	10	**22a** (75%)
11	R^1 = Ph, R^2 = Ph (**12**)	10	10	**23a** (65%)
12	R^1 = Ph, R^2 =TMS (**13**)	10	10	**24a** (70 %), **24c** (11 %)

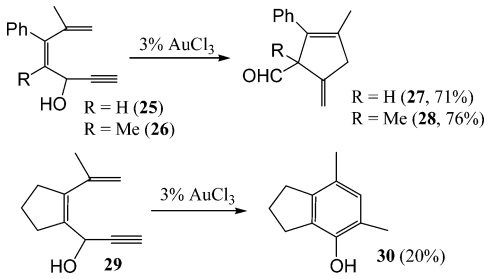
control the chemoselectivity but also provide unprecedented reaction routes. Here, we provide a full account[11] of gold- and platinum-catalyzed cycloisomerizations of *cis*-4,6-dien-1-yn-3-ols in various modes, which effect a skeletal rearrangement of cyclized products highly chemoselectively.

2. Results and Discussion

2.1. Cyclization of 6-Substituted *cis*-4,6-Dien-1-yn-3-ols. We first examined the cycloisomerization of *cis*-4,6-dien-1-yn-3-ol (**1**) with various acid catalysts, as this species is designed to generate an allyl cation. Table 1 shows the results on screening of various π-acid catalysts; the best result was obtained with $AuCl_3$ (3 mol %) in dry CH_2Cl_2 (25 °C, 10 min), which gave structurally reorganized aldehyde **2** in 74% yield. Here, the reaction periods refer to the complete consumption of starting alcohol **1**. Among other π-acid activators, $AuPPh_3$-OTf, $AuPPh_3SbF_6$, $AgSbF_6$, $PtCl_2/CO$, $PtCl_2$, and AuCl showed moderate activity to produce desired aldehyde **2** in 38−59% yields, whereas AgOTf, $AuClPPh_3$, and TfOH are virtually inactive toward cyclization in CH_2Cl_2 at 25 °C. The structural assignment of aldehyde **2** relies on its ^{1}H NOE effect;[12] this proposed structure is confirmed by an X-ray diffraction study[12] of its related aldehyde **24a** (see Table 2).

To examine the generality of this cycloisomerization, we prepared various *cis*-4,6-dien-1-yn-3-ols, **3**−**13**; the results are depicted in Table 2. In all cases, the resulting aldehydes **14a**−**24a** were produced efficiently using $AuCl_3$ catalyst (3−10 mol %) in dry CH_2Cl_2 at 25 °C. Entries 1−4 show the suitability of this cyclization for dienynols **3**−**6** bearing a terminal alkyne, which gave desired aldehydes **14a**−**17a** in 67−98% yields. The value of this cyclization is further shown by its applicability to internal alkyne substrates **7**−**13** containing methyl, *n*-propyl, *n*-butyl, phenyl, and trimethylsilyl substituents; the desired aldehydes **18a**−**24a** were produced efficiently with this gold catalyst, whereas byproducts **19b**, **20b**, **21c**, and **24c** were obtained in small proportions (<11%). Only one stereoisomer was obtained for cyclized products **18a**−**24a**, of which the alkenyl R^2 substituents lie away from the aldehyde according to X-ray data of compound **24a**.[12] Cyclopentadienyl alkynes **19b** and **20b** resulted from an acid-catalyzed Nazarov cyclization,[13] whereas cyclohexadienyl aldehydes **21c** and **24c** appear to arise from *7-endo-dig* cyclization/pinacol rearrangement.[14,15]

Scheme 1



As shown in Scheme 1, this $AuCl_3$ catalysis is extendible to acyclic dienynols **25** and **26** which provided aldehydes **27** and

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(10) For use of allylic cations for metal-catalyzed cycloisomerization of enynes, see: (a) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (b) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (c) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274. (d) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434.

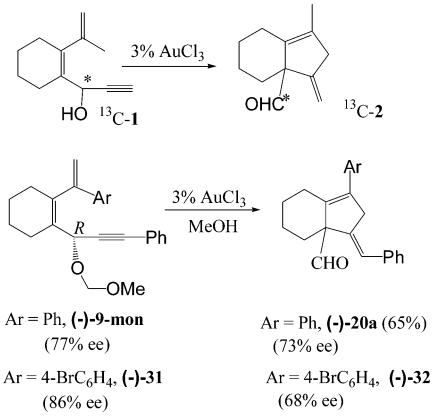
(11) Preliminary results of this work on the formations of reorganized styrene products, see: Lin, M.-Y.; Das, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9340.

(12) The ^{1}H NOE spectroscopy of key compounds and the X-ray crystallographic data of compound **26a** are provided in Supporting Information.

(13) Selected examples: (a) Nazarov, I. N.; Torgov, I. B.; Terekhova, L. N. *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* **1942**, 200. (b) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312. (c) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (d) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912 and ref 10b.

(14) The asymmetric syntheses in pinacol rearrangements deal exclusively with diastereomeric courses rather than the enantiospecificity in this study; see selected examples: (a) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143 (review). (b) Trost, B. M.; Brandi, A. *J. Am. Chem. Soc.*

Scheme 2



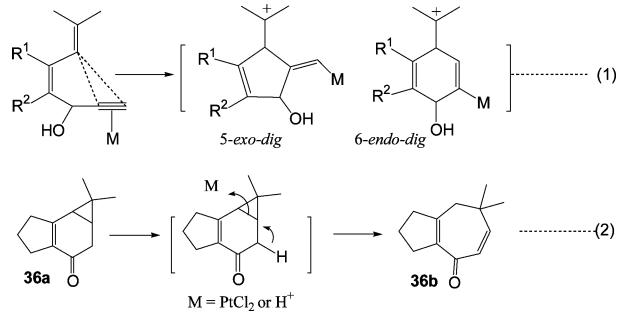
28 in 71% and 76% yields, respectively, but the analogous reaction is inapplicable to dienynol **29** bearing a cyclopentane, which underwent aromatization in dry CH_2Cl_2 to give phenol product **30** (20%) through a separate pathway[16] (Scheme 2).

We performed ^{13}C-labeling experiments to elucidate the mechanism of this structural reorganization. Gold catalysis of alcohol ^{13}C-**1** bearing 10% ^{13}C-content at the CH(OH) carbon gave aldehyde ^{13}C-**2** with the ^{13}C-content located at its aldehyde carbon. We prepared also chiral (*R*)-alcohols **9-mom** (77% ee) and **31** (87% ee)[17] bearing a methoxymethyl ether group; their cyclized aldehydes (−)-**20a** (73% ee) and (−)-**32** (68% ee) were obtained with only a small loss of enantiomeric purity. These observations indicate an atypical chirality transfer for this gold catalysis, which is astonishing because the adjacent chiral alcohol is normally ineffective to transfer the chirality in the related pinacol rearrangement.[14,15]

Scheme 3 shows a plausible mechanism to rationalize the gold-catalyzed skeletal rearrangement of species (−)-**9-mom**; this cycloisomerization involves atypical chirality transfer in pinacol-type rearrangement.[14−15] We envisage that the cyclization is initiated on the 6-*exo-dig* cyclization of Au-π-alkyne species **A** to form a stable allyl cation **B**. To rationalize the observed chirality transfer, we propose an equilibrium between conformational isomers **B′** and **B″** of the allyl cation **B**, which generate an enantiomeric pair of product **20a**, as depicted in path **a**. The occurrence of chirality transfer arises from the disparate rates of the 1,2-alkyl migration of the two conformers. Species **B″** is obviously more stable than **B′** because the latter has a large allyl strain[18] between the equatorial methoxymethyl ether and the bulky $AuCl_3^-$ fragment. The stereochemistry of this 1,2-alkyl migration (pinacol rearrangement) is proposed to proceed via addition of a new carbon−carbon bond to the *si*-face of the carbocation center of species **B″** to retain the chirality of the molecule.[14] Here, additional water is required to decompose the methoxymethyloxonium fragment in species **C**. An alternative mechanism (path **b**) involves formation of a cyclopropane ring via a through-space bond formation as shown by species **D**,[15] which ultimately produces aldehyde (−)-**20a** with the same configuration and the observed alkene geometry.

We have calculated the relative energies of the two conformers **B′** and **B″** using the B3LYP/LAN2DZ method.[19] As we expected, state **B″** has 5.97 kcal/mol lower energy than state **B′** because of a large 1,3-allyl strain in the latter.

2.2. Cyclization of 7,7-Disubstituted *cis*-4,6-Dien-1-yn-3-ols. To generate tertiary cations, we prepared three *cis*-4,6-dien-1-yn-3-ols **33**−**35**, used for either *5-exo-dig* or *6-endo-dig* enyne cyclization, as depicted in eq 1



. For such substrates, we observed substrate-dependent chemoselectivity and obtained skeletally rearranged cyclized products **36a**,**b**, **37**, and **38**, as shown in Table 3. Treatment of alcohol **33** with $PtCl_2$ (5 mol %) in hot toluene (90 °C, 1 h) produced bicyclo[4.1.0]heptenone **36a** and cycloheptadienone **36b** in 3% and 83% yields, respectively. The presence of CO (1 atm) increased the electrophilicity of $PtCl_2$[20] such that the cyclization proceeded under mild conditions, giving bicyclic ketone **36a** with yield up to 79% (entry 2). Transformation of species **36a** into cycloheptadienone **36b** is presumably catalyzed by acid with a mechanism proposed in eq 2. AuCl and $AuCl_3$ gave a messy mixture of products in CH_2Cl_2 (20 °C, 10−30 min), from which bicyclic ketone **36a** was obtained in small yields (<24%). Notably, $AuPPh_3SbF_6$ led to rapid decomposition of initial substrate **33** despite its high electrophilicity (entry 5). The cycloisomerization of alcohol substrate **34** bearing a cyclohexyl group proceeded efficiently using several π-acids including $PtCl_2$, $PtCl_2$/CO, AuCl, $AuCl_3$, and $Zn(OTf)_2$, giving styrene derivative **37** with yields exceeding 71% (entries 6−10). Its ^1H NMR spectroscopy revealed an isopropylidene shift. In such reactions, MS 4 Å was present for AuCl, $AuCl_3$, and Zn-

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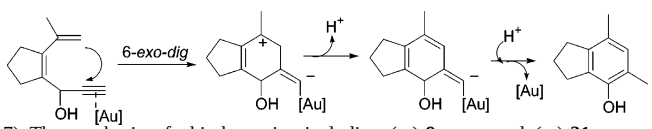
(15) For metal-catalyzed cycloisomerization of enynes involving pinacol rearrangement, see: (a) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310. (b) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398.

(16) The following scheme depicts the mechanism for aromatization of alcohol substrate **29** to compound **30**; here, we did not obtain aldehyde product via pinacol rearrangement because of its highly strained [3.3.0]-octene framework.



(17) The synthesis of chiral species including (−)-**9-mom** and (−)-**31** are provided in Supporting Information.

(18) (a) Hoffman, R. W. *Chem. Rev.* **1989**, 1841. (b) Broeker, J. L.; Hoffman, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006. (c) Allinger, N. L.; Hirsh, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968**, *90*, 5773.

(19) The procedure for theoretic calculation is provided in Supporting Information.

(20) For $PtCl_2$/CO catalytic system, see: (a) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (d) Chang, H.-K.; Datta, S.; Das, A.; Odedra, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4744. (e) Taduri, B. P.; Ran, Y.-F.; Huang, C.-W.; Liu, R.-S. *Org. Lett.* **2006**, *8*, 883.

Scheme 3

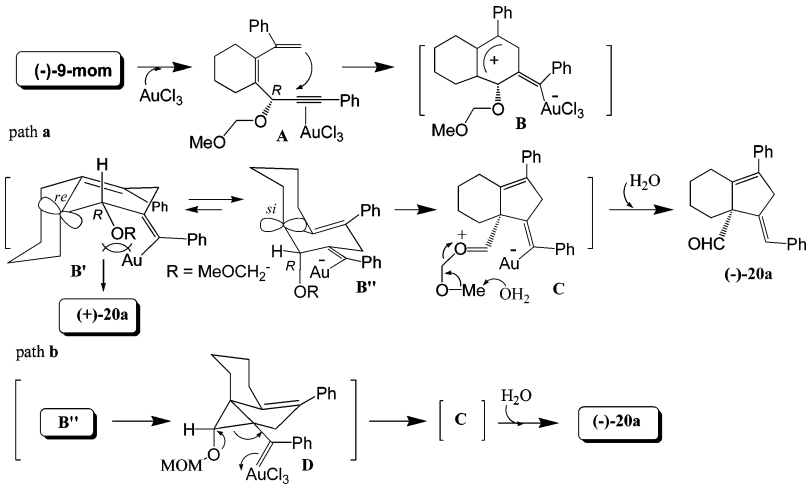
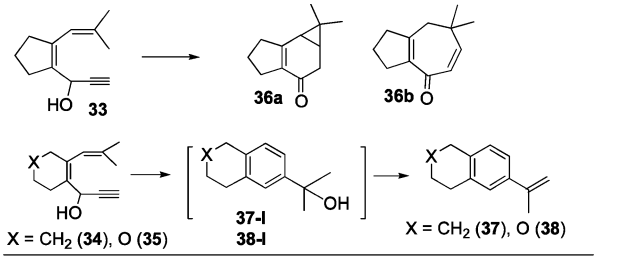


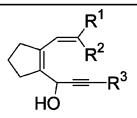
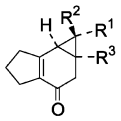
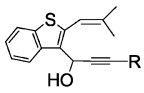
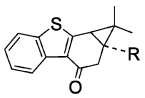
Table 3. Cyclization Chemoselectivities Using Various π-Acid Catalysts



substartes	catalyst[a]	condition[a,b]	yields[c,d]
(1) **33**	$PtCl_2$	toluene (90 °C, 1 h)	**36**a (3%), **36**b (83%)
(2) **33**	$PtCl_2$/CO	toluene (50 °C, 0.5 h)	**36a** (79%)
(3) **33**	AuCl	CH_2Cl_2 (20 °C, 10 min)	**36**a (15%)
(4) **33**	$AuCl_3$	CH_2Cl_2 (20 °C, 10 min)	**36a** (19%)
(5) **33**	$AuClPPh_3/AgSbF_6$	CH_2Cl_2 (20 °C, 2 h)	—
(6) **34**	$PtCl_2$	toluene (80 °C, 1 h)	**37** (78%)
(7) **34**	$PtCl_2$/CO	toluene (80 °C, 1 h)	**37** (87%)
(8) **34**	AuCl	CH_2Cl_2 (20 °C, 24 h)	**37** (71%)
(9) **34**	$AuCl_3$	CH_2Cl_2 (20 °C, 24 h)	**37** (83%)
(10) **34**	$Zn(OTf)_2$	toluene (80 °C, 1 h)	**37** (78%)
(11) **35**	$PtCl_2$/CO	toluene (80 °C, 0.5 h)	**38** (78%)

[a] 5 mol % for $PtCl_2$, AuCl, $AuCl_3$, $AuClPPh_3/AgSbF_6$ and 10 mol % for $Zn(OTf)_2$, [substrate] = 0.80−1.0 M. [b] MS 4Å was present for entries 8−10. [c] There are many byproducts in small quantities for entries 3−4 and 8−10. [d] Yields of products are given after separation from silica column.

Table 4. $PtCl_2$-Catalyzed Synthesis of Bicyclo[4.1.0]heptenones via Cyclization of Alcohols Bearing a Bridging Cyclopentane Ring

entry[a]	substrates	time	additive	products (yields)[b]
				
1	R^1, R^2 = -$(CH_2)_3$- R^3 = H (**39**)	0.5 h	—	**47** (80%)
2	R^1 = H, R^2 = Ph R^3 = H (**40**)	0.5 h	—	**48** (55%)
3	R^1 = Ph, R^2 = H R^3 = H (**41**)	3 h	—	messy
4	R^1 = R^2 = Me R^3 = Me (**42**)	3 h	MgO	**49** (78%)
5	R^1 = R^2 = Me R^3 = Ph (**43**)	4 h	MgO	**50** (85%)
				
6	R = H (**44**)	1 h	—	**51** (89%)
7	R = Me (**45**)	1 h	—	**52** (77%)
8	R = Ph (**46**)	1 h	—	**53** (82%)

[a] [substrate] = 0.8 M, 50 °C, 5 mol % $PtCl_2$, 1 atm CO, toluene, 0.5 h. [b] Yields were reported after separation from a silica column.

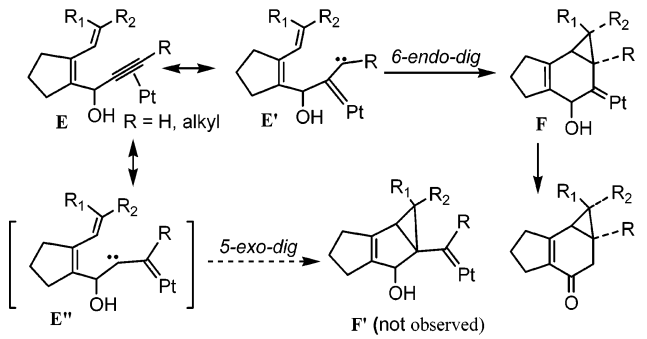
$(OTf)_2$ to ensure complete dehydration of the primary alcohol product (**I**). In the absence of MS 4 Å, we obtained alcohol product **37-I** in good yields (75−78%),[11] in addition to reorganized styrene **37** using AuCl or $AuCl_3$ catalysts; the structure of alcohol product **37-I** was characterized by ^{1}H NOE spectroscopy.[11] A similar platinum catalysis on oxacyclic substrate **35** gave a 78% yield of aromatized product **38,** of which the ^{1}H NOE spectroscopy verifies a novel 1,3-isopropylidene shift in this transformation.[21]

2.2.1. Formation of Bicyclo[4.1.0]heptenones. The preliminary results in Table 3 indicate that the ring sizes of alcohol substrates **33**−**35** affect the cyclization chemoselectivity. We prepared dienynol substrates **39**−**46** bearing a five-membered ring to assess the generality of bicyclo[4.1.0]heptenone synthesis using 5% $PtCl_2$/CO. For alcohol **39** bearing a cyclopentyl ring, the corresponding $PtCl_2$ catalysis gave desired ketones **47** in 80% yield. The stereoselectivity of this cyclization is shown by dienynol **40** bearing a *cis*-phenyl group, which selectively afforded bicyclic ketone **48**;[22] its structure was established with ^{1}H NOE spectroscopy.[12] In contrast, its *trans*-phenyl analogue **41** led to polymerization under similar conditions. In the presence of MgO additive,[23] this bicyclic ketone synthesis is

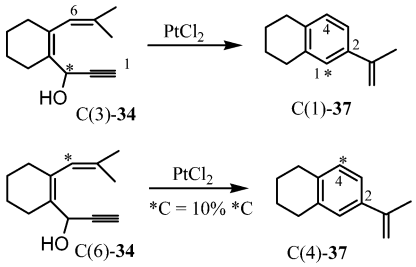
(21) Prior to our studies, a 1,3-alkylidene shift in the cycloisomerization of enynes is only reported for metathesis-type reactions,[1a,d] whereas a 1,2-alkylidene shift is only reported for one instance.[7]

(22) For stereoselective formation of cyclopropane products in metal-catalyzed cycloisomerization of enynes, see refs 2b, 3f,e, 4d, and (a) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (b) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (c) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546.

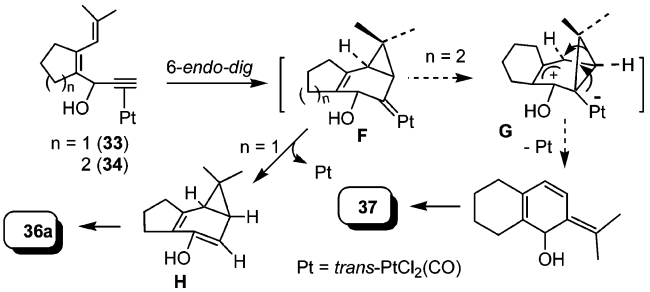
Scheme 4



Scheme 5



Scheme 6



extendible to dienynol analogues **42** and **43** bearing an internal alkyne (R^3 = Me, Ph); the yields of resulting ketones **49** and **50** were 78% and 85%, respectively. The benzothienyl species **44**−**46** are also suitable for this bicyclo[4.1.0]heptenone synthesis; the resulting ketones **51**−**53** were obtained in 77−89% yields. The five-membered rings of alcohols **39**−**40** and **42**−**46** apparently direct the cycloisomerization toward bicyclic ketone formation regardless of the types of tethered alkynes.

The cyclopentyl and benzothienyl groups of alcohols **33**, **39**−**40**, and **42**−**46** gave exclusively bicyclo[4.1.0]heptenones products **36a**, **47**−**48**, and **49**−**53** (Tables 3 and 4), regardless of the internal or terminal alkynes. The stereoselectivity in the production of bicyclo[4.1.0]heptenone **48** from alcohol **40** indicates that platinum-π-alkyne species **E** bears carbenoid character,[22] as represented by species **E′** (Scheme 4). This carbenoid captures its tethered olefin to form bicyclo[4.1.0]-heptenyl carbene **F,** which ultimately forms a bicyclo[4.1.0]-heptenone core via a 1,2-hydrogen shift. Although 5-*exo-dig* cyclization occurs more frequently than the 6-*endo-dig* route

(23) In the absence of MgO, the internal alkynes **42** underwent dehydration reaction to give the following byproduct:

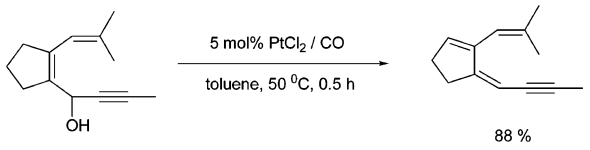
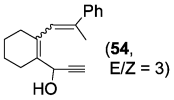
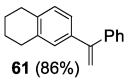
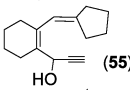
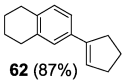
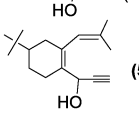
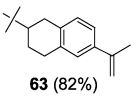
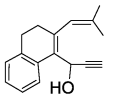
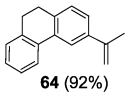
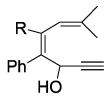
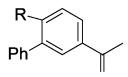
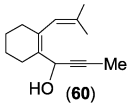
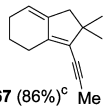
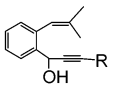
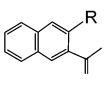
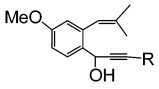
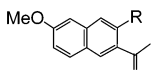
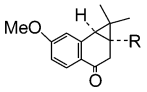
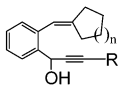
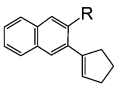
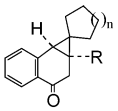


Table 5. $PtCl_2$-Catalyzed Synthesis of Stryrene Products *via* Cyclization of Alcohols Bearing a Bridging Cyclohexyl Ring

entry[a]	substrates	time (min)	products (yields)[b]
1	 (**54**, E/Z = 3)	25	 **61** (86%)
2	 (**55**)	30	 **62** (87%)
3	 (**56**)	35	 **63** (82%)
4	 (**57**)		 **64** (92%)
5	 R = H (**58**)	25	 **65** (78%)
6	R = Me (**59**)	20	**66** (82%)
7	 (**60**)	20	 **67** (86%)[c]

[a] [substrate] = 0.8 M, 80 °C, 5 mol % $PtCl_2$, 1 atm CO, toluene, 1 h. [b] Yields are given after separation from a silica column. [c] MgO was added.

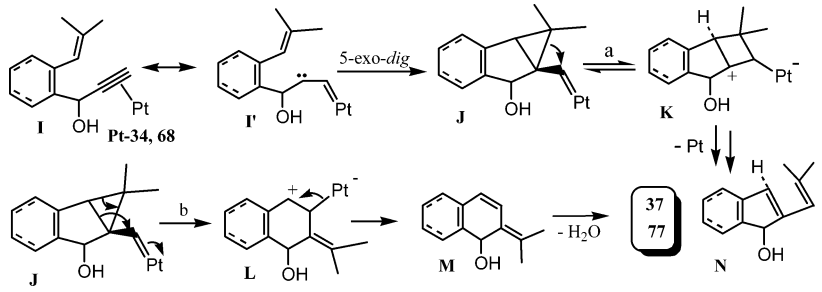
Table 6. Effects of the Alkyne on the $PtCl_2$-Catalyzed Cyclization of Alcohols Bearing a Bridging Benzene Ring

entries	substrates[a]	time (h)	products (yields)[b]		
					
1	R = H (**68**)	4	**77** (76%)	—	—
2	R = Me (**69**)	6	—	**78** (69%)	**79** (16%)
3	R = ^{n}Pr (**70**)	5	—	**80** (67%)	—
4	R = Ph (**71**)	3	—	**81** (81%)	—
					
5	R = H (**72**)	5	**82** (75%)	—	
6	R = Me (**73**)	6	—	**83** (65%)	
					
7	n = 1, R = H (**74**)	3	**84** (81 %)	—	
8	n = 1, R = Me (**75**)	4.5	—	**85** (74 %)	
9	n = 2, R = Me (**76**)	4	—	**86** (72 %)	

[a] [substrate] = 0.6 M, 60 °C, 5 mol % $PtCl_2$, 1 atm CO, toluene, 1 h. [b] Product yields are given after separation from a silica column.

in the cycloisomerization of 1,6-enynes containing a terminal alkyne,[24] the former is not suitable to alcohol substrate **E** containing a cyclopentyl group because the resulting carbene intermediate **F′** bears a strained [3.3.0]-octenol framework.

Scheme 7



2.2.2. Formation of Reorganized Styrene Derivatives. In the cycloisomerization of alcohols **34**−**35** to styrene derivatives **37**−**38**, as depicted in Table 3, this rearrangement proceeds via an atypical 1,3-isopropylidene migration. To assess the generality, we prepared various alcohol substrates **54**−**60** bearing either a cyclohexane or an acyclic framework; $PtCl_2$/CO (5%) was used as the catalyst (Table 5). Treatment of alcohols **54**−**55** gave styrene products **61**−**62** in 86−87% yields (entries 1−2); ^{1}H NOE spectra of cyclized products **63**−**64** (entries 3−4) confirm a 1,3-alkylidene migration. Acyclic alcohols **58** and **59** conformed to the same chemoselectivity to give styrene products **65**−**66** in good yields (78−82%). For alcohol **60** bearing an internal alkyne, this $PtCl_2$ catalysis led to undesired Nazarov cyclization to give cyclopentenyl derivative **67** in 86% yield, even in the presence of MgO additive. This information indicates that formation of species **67** was actually initiated by $PtCl_2$ rather than Brønsted acid.

As the Nazarov cyclization observed for alcohol **60** failed to clarify the preferred chemoselectivity of internal alkynes in the cyclohexyl system, we examined the cycloisomerization of substrates **68**−**76**, of which the benzene group is expected to inhibit Nazarov cyclization. The results in Table 6 clearly show the pronounced influence of the alkynyl substituent on the cyclization chemoselectivities; substrates **68**, **72**, and **74** bearing a terminal alkyne afforded styrene products **77**, **82**, and **84**, whereas their internal alkyne analogues **69**−**71**, **73**, and **75**−**76** gave bicyclo[4.1.0]heptenone products **78**, **80**−**81**, **83**, and **85**−**86** efficiently. We used the ^{1}H NOE effect to elucidate the structure of compound **78**. The reaction patterns here are distinct from those observed for alcohols **39**−**46** bearing a five-membered cyclopentane or benzothienyl ring, which provided only bicyclo[4.1.0]heptenones for both terminal and internal alkynes (see Table 4).

We prepared ^{13}C-enriched samples C(3)-**34** and C(6)-**34** with 10% ^{13}C content at the C(3)- and C(6)-carbons, respectively, of alcohol **34**. As depicted in Scheme 5, treatment of C(3)-**34** with $PtCl_2$ produced styrene C(1)-**37** with ^{13}C content at the C(1)-carbon according to ^{13}C−^{1}H HMQC and HMBC spectra,[25] whereas alcohol C(6)-**34** gave product C(4)-**37** with the ^{13}C content at the C(4)-carbon. These labeling results reconfirm the occurrence of a 1,3-isopropylidene shift for alcohol **34**.

Acylic alcohols **58**−**59** and the six-membered-rings containing alcohols **34**−**35**, **54**−**57**, **62**, **68**, and **74**, bearing a terminal alkyne, gave only reorganized styrene products **37**−**38**, **61**−**66**, **77**, **82**, and **84** (Tables 3 and 5−6). In our original mechanism[11] as depicted in Scheme 6, we proposed a 6-*endo-dig* cyclization for alcohol **34** ($n = 2$) to form intermediate **F**, which undergoes an atypical 1,2-cyclopropyl migration to generate species **G**, and ultimately produces reorganized styrene product **37**. However, our calculations (B3LYP/LAN2DZ) reveal that the two alcohols **33** ($n = 1$) and **34** have activation energies (11.9−12.3 kcal/mol) in the 1,2-hydrogen shifts (species **F**→ **H**) much lower than a 1,2-cyclopropyl shift (**F** → **G**).[26] This information suggests that 6-*endo-dig* cyclization is inapplicable to alcohol **34**, and thus we revise the mechanistic interpretation.

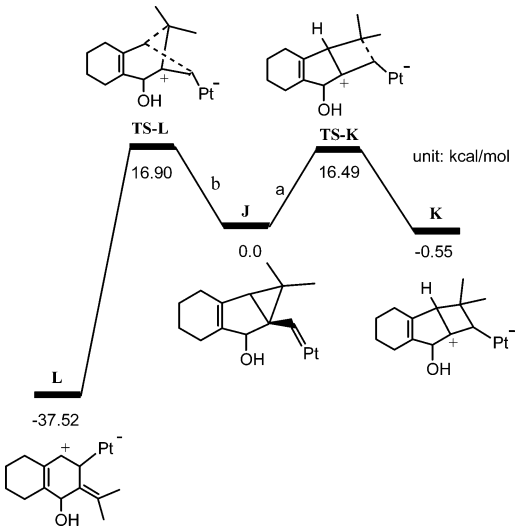
The cyclizations of alcohols **34** and **68** bearing both a six-membered ring and a terminal alkyne are expected to proceed via the common *5-exo-dig* cyclization,[24] as depicted in Scheme 7. The carbenoid character of the π-alkyne **I** is represented by species **I′**, which initiates *5-exo-dig* cyclization to form species **J**. This species is commonly proposed to undergo a 1,2-alkyl shift to form species **K** in the enyne metathesis-type reactions, but we obtained reorganized styrenes **37** and **77** rather than the metathesis product **N**.[27] Hence, we seek the mechanistic solution through calculation, and gratifyingly we find a new low-barrier rearrangement for species **J** (path **b**), to generate allyl or benzyl cation **L**, which ultimately provides the desired styrenes **37** and **77** through intermediate **M**.

We performed a theoretical calculation to estimate activation energies for path **a** and its competitive path **b** to compare their relative feasibility; the results are depicted in Scheme 8. According to the B3LYP/LANL2DZ calculation, path **a** has an activation energy of +16.49 kcal/mol, which is very close to that of +16.90 kcal/mol for path **b**. In addition, the proposed path **b** in Scheme 7 is supported by the transition-state structure (**TS-L**) connecting the intermediates **J** and **L** at the B3LYP/LANL2DZ level of theory. Notably, intermediate **L** given from path **b** is much more stable than species **K** (from path **a**) by a large margin (−36.97 kcal/mol) in energy; the metathesis route (path **a**) is thus unlikely to occur according to this energy profile.

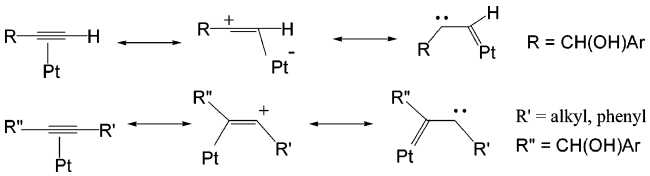
In Table 6, the alkynyl effects of alcohols **68**−**76** on their cyclization chemoselectivities are unclear at present. In gold catalysis,[28] there are reported similar observations that internal alkynes prefer 6-*endo-dig* cyclization, whereas terminal alkyne analogues lead to *5-exo-dig* routes. We propose tentatively that

(24) For the 5-*exo-dig* cyclizations of 1,6-enynes, see refs 2a, 3d, 4d, and selected examples: (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. (b) Nevado, C.; Cárdenas, J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627. (c) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, *698*. (d) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genet, J.-P. *Chem. Commun.* **2004**, 850.
(25) The ^{1}H−^{13}C-correlated HMQC and HMBC spectra of compound **37** were provided in the communication, see ref 11.
(26) See Scheme S1 in Supporting Information for the results of calculations.
(27) See refs 2a, 3c,g, 7, 20a, and selected examples: (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc*. **1998**, *120*, 8305. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc*. **2001**, *123*, 11863.
(28) Shapiro, N.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160.

Scheme 8



Scheme 9



such chemoselectivity is attributed to alternating the charge polarization of Pt-π-alkyne moiety, as depicted in Scheme 9. In both cases, the vinyl cations are generated preferably on the alkynyl carbon bearing a more electron-donating group. In the case of terminal alkynes, *5-exo-dig* route is more likely to occur than *6-endo-dig* for formation of a monocyclic product.

3. Conclusions

Gold and platinum catalysts implement catalytic cycloisomerizations of *cis*-4,6-dien-1-yn-3-ols in various modes and enable structural reorganization of cyclized products chemoselectively. For 6-substituted *cis*-4,6-dien-1-yn-3-ols, the $AuCl_3$-catalyzed cyclizations were initiated with a 6-*exo-dig* pathway to give allyl cations, which subsequently underwent a pinacol rearrangement to give a cyclopentenyl aldehyde core. We observed reasonable chirality using chiral alcohol substrates. For 7,7-disubstituted *cis*-4,6-dien-1-yn-3-ols, their $PtCl_2$-catalyzed cyclizations gave either bicyclo[4.1.0]heptenones or reorganized styrene products, depending on the types of substrate. On the basis of the chemoselectivity/structure relationship, we conclude that bicyclo[4.1.0]heptenone products result from *6-endo-dig* cyclization of alcohols bearing a five-membered ring, whereas reorganized styrene products are derived from *5-exo-dig* cyclization of alcohols bearing both a six-membered ring and a terminal alkyne.

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Supporting Information Available: Experimental procedures for synthesis of *cis*-4,6-dien-1-yn-3-ol substrates and catalytic operations, NMR spectra, spectral data of new compounds, and X-ray structural data of compound **24a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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