J|A|C|S
COMMUNICATIONS

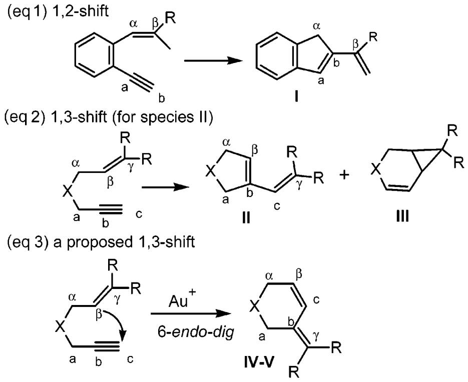
Metal-Catalyzed Cycloisomerization of Enyne Functionalities via a 1,3-Alkylidene Migration

Ming-Yuan Lin, Arindam Das, and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu 30043, Taiwan, Republic of China

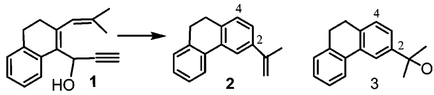
Received April 27, 2006; E-mail: rsliu@mx.nthu.edu.tw

Scheme 1



X = NTs, R = Me (**IV**) 96%; X=C(CO$_2$Me)$_2$, R=H (**V**) 70%

Scheme 2



catalyst[a]	condition[a]	yields[b]	catalyst	condition	yields
(1) PtCl$_2$	toluene 80 °C, 30 min	**2** (92%)	(4) AuCl	CH$_2$Cl$_2$, 20 °C 1 h	**3** (75%) **2** (6%)
(2) Zn(OTf)$_2$	toluene 80 °C, 1 h	**2** (60%)	(5) AuCl + MS 4Å	CH$_2$Cl$_2$, 20 °C 1 h	**2** (81%)
(3) Zn(OTf)$_2$ + MS 4Å	toluene 80 °C, 1 h	**2** (78%)	(6) AuCl$_3$	CH$_2$Cl$_2$, 20 °C 1 h	**3** (83%) **2** (6%)

[a] 5 mol% for PtCl$_2$, AuCl and AuCl$_3$, 10 mol% for Zn(OTf)$_2$, [substrate] = 0.80-1.0 M. [b] Yields of products are given after separation from silica column

Metal-catalyzed cycloisomerization of enynes often leads to skeletal rearrangement because “nonclassical” cations participate as reaction intermediates.[1] Among literature reports, migration of a 1,2- and 1,3-alkylidene fragment is very interesting in mechanistic and synthetic aspects (eqs 1 and 2 in Scheme 1).[2a,3] In such processes, the olefin double bond of the enyne substrate is cleaved and migrated to the alkyne carbon (eqs 1−3 in Scheme 1). Reports of a 1,3-alkylidene migration are limited strictly to formation of metathesis-type product **II**;[3] little is known for other processes.[3e] Echavarren recently proposed a 1,3-alkylidene migration in the cycloisomerization of 1,6-enynes using AuPPh$_3^+$ catalyst as depicted in eq 3.[3e,4] Unfortunately, this cyclization is only extensible to only two instances, **IV** and **V** (yields > 50%, eq 3), whereas most 1,6-enynes are catalyzed by this gold catalyst to give 1,3-diene **II**, cyclopropane derivative **III**, and other byproducts.[3e,4,5] Here we report a new metal-catalyzed cycloisomerization of *cis*-4,6-dien-1-yn-3-ols, for which the 1,3-alkylidene migration is unambiguously established by both ^{13}C-labeling experiments and product structures. This new cycloisomerization is applicable to a wide range of substrates.

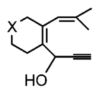
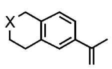
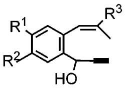
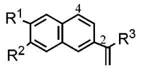
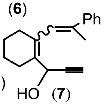
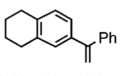
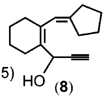
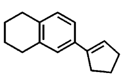
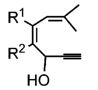
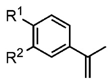
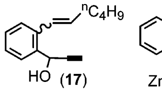
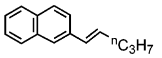
As shown in Scheme 2, treatment of *cis*-4,6-dien-1-yn-3-ol **1** with PtCl$_2$ (5 mol %) in hot toluene (80 °C, 30 min) produced styrene derivative **2** in 92% isolated yield. The ease and reliability with this catalytic reaction are manifested by the high efficiencies of other catalysts at optimum conditions: Zn(OTf)$_2$/MS 4 Å (10 mol %, 78% **2**) and AuCl/MS 4 Å (5 mol %, 81% **2**). In the absence of MS 4 Å, AuCl alone (5 mol %) gave tertiary alcohol **3** (CH$_2$Cl$_2$, 20 °C) in 75% yield in addition to species **2** (6%). AuCl$_3$ was equally active in catalytic activity at 20 °C (entry 6). The structures of compounds **2** and **3** were identified by ^{1}H NOE effect, which reveals that the vinyl and tertiary alcohols of compounds **2** and **3** are located at the C(2) rather than the expected C(4) carbon, clearly indicative of a 1,3-isopropylidene migration.[6]

We prepared various *cis*-4,6-dien-1-yn-3-ols **4**−**17** to generalize this catalytic cyclization, and all these substrates gave a single product efficiently, except alcohol **17**. For alcohols **4**−**10**, PtCl$_2$ was used as the catalyst because of its better chemoselectivity and cyclization efficiency. Entries 1−3 provide additional examples for cyclization of *cis*-4,6-dien-1-yn-3-ols **4**−**6**, which afforded styrene derivatives **18**−**20** in 78−82% yields. ^{1}H NOE effects confirmed the structures of compounds **19** and **20**. This cyclization works efficiently with alcohols **7** and **8** via alternation of their alkenyl substituents, giving desired styrene derivatives **21**−**22** in 86−87% yields. This catalytic reaction is extensible to acyclic substrates **9** and **10**, producing species **23** and **24** in 86 and 75% yields, respectively. The value of this catalytic reaction is again demonstrated by its applicability to 2-alkenylbenzylic alcohols **11**−**16**. We examined the catalytic cyclization of alcohol **11** with PtCl$_2$, AuCl, AuCl$_3$, and Zn(OTf)$_2$; PtCl$_2$/MS 4 Å gave isopropylidene product **25** in 64% yield in addition to a byproduct (6%), whereas AuCl$_3$/MS 4 Å gave desired **25** in low yield (25%) at 60 °C in DCE. In the presence of MS 4 Å, Zn(OTf)$_2$ and AuCl gave product **25** in respective yields of 81 and 70% (see Table S-1 in Supporting Information). Accordingly, Zn(OTf)$_2$/MS 4 Å was selected as the catalyst because of its best cyclization efficiency. Cyclization of these alcohols with Zn(OTf)$_2$ in hot toluene (90 °C, 3 h) yielded naphthalene derivatives **26**−**30** in 81−86% yields. We used ^{1}H NOE effects to elucidate the structures of **27**, **28**, and **30**,[6] which reveal that their alkenyl substituents are located at the C(2) carbon rather than the original C(4) carbon, consistent with a 1,3-shift. The cyclization of alcohol **17** bearing a disubstituted alkene, however, gave expected naphthalene **31** in low yield (33%).

We prepared ^{13}C-enriched samples C(6)-**1** and C(3)-**1** with 10% ^{13}C content at the C(6) and C(3) carbons of alcohol **1**, respectively (see Supporting Information). Treatment of C(6)-**1** with PtCl$_2$ produced styrene C(4)-**2** with the ^{13}C content at the C(4) carbon according to ^{13}C−^{1}H HMQC and HMBC spectra. Similarly, alcohol C(3)-**1** gave product C(1)-**2** with the ^{13}C content at the C(1) carbon.

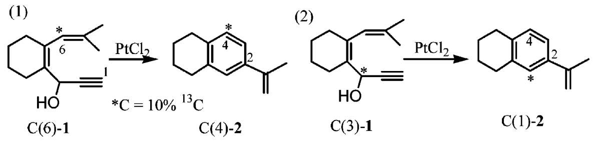
10.1021/ja062515h CCC: $33.50

Table 1. Metal-Catalyzed Cyclization of Various 4,6-Dien-1-yn-3-ols

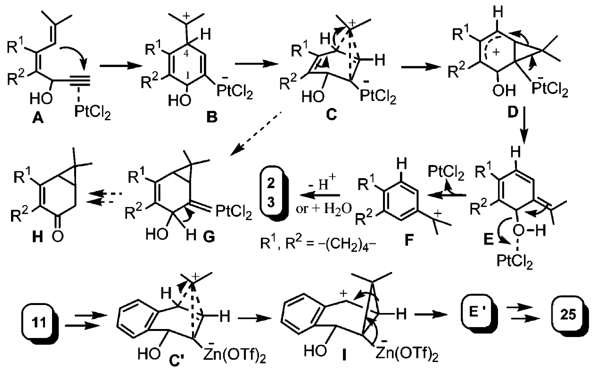
alcohols[a]	catalysts (yields)[c]	alcohols[b]	catalysts (yields)[c]
			
(1) X = CH_2 (**4**)	$PtCl_2$ (**18**, 78%)	(8) $R^1 = R^2$ = H, R^3 = Me (**11**)	$Zn(OTf)_2$ (**25**, 81%)
(2) X = O (**5**)	$PtCl_2$ (**19**, 78%)	(9) $R^1 = R^2$ = H, R^3 = Ph (**12**)	$Zn(OTf)_2$ (**26**, 84%)
(3) X = CH(*t*-Bu) (**6**)	$PtCl_2$ (**20**, 82%)	(10) R^1 = OMe R^2 = H, R^3 = Me (**13**)	$Zn(OTf)_2$ (**27**, 81%)
(4)  HO (**7**)	 $PtCl_2$ (**21**, 86%)	(11) R^2 = OMe, R^1 = H, R^3 = Me (**14**)	$Zn(OTf)_2$ (**28**, 84%)
(5)  HO (**8**)	 $PtCl_2$ (**22**, 87%)	(12) R^1,R^2= OCH_2O, R^1 = H, R^3 = Me (**15**)	$Zn(OTf)_2$ (**29**, 86%)
		(13) R^1=F R^2 = H, R^3 = Me (**16**)	$Zn(OTf)_2$ (**30**, 83%)
(6) R^1 = Me, R^2 = Ph (**9**)	$PtCl_2$ (**23**, 86%)	(14)  (**17**)	 $Zn(OTf)_2$ (**31**, 33%)
(7) R^1 = H, R^2 = Ph (**10**)	$PtCl_2$ (**24**, 75%)		

[a] 5 mol% $PtCl_2$, toluene, 80 °C, 30 min, [substrate] = 0.80 M. [b] 10 mol% $Zn(OTf)_2$, MS 4Å toluene, 90 °C, 2.5-3.5 h, [substrate] = 0.80 M. [c] Yields were reported after separation from a silica column.

Scheme 3



Scheme 4



These labeling results reconfirm the occurrence of a 1,3-isopropylidene shift for alcohol **1**.

The lack of byproducts, such as species **II** and **III** (Scheme 1), leads us to believe that this new cycloisomerization proceeds through an unprecedented mechanistic pathway. The low cyclization efficiency of alcohol **17** suggests the participation of a tertiary carbocationic intermediate generated from other alcohols **4**−**16**. As shown in Scheme 4, the mechanism involves an initial *6-endo-dig* cyclization of Pt(II)−π-alkyne **A** to give species **B**, which forms a nonclassical carbocation **C** via a through-space overlap of the tertiary cation with the electron-rich Pt−C═CH double bond.[7,8a] The participation of platinum carbenoid **G**, proposed by Echavarren in the gold example,[3e] is not evident here, but cyclohexenone **H** was obtained for an internal alkyne analogue using the $PtCl_2$ catalyst.[8−10] The key factor to accelerate the 1,3-isopropylidene shift is the formation of an allylic cation **D**, which causes the cleavage of the C(4) isopropyl σ-carbon bond of species **C**. Further cleavage of the cyclopropane ring of species **D** via dissociation of $PtCl_2$ regenerates cyclohexadienyl alcohol intermediate **E**, which in the presence of $PtCl_2$ gives tertiary benzylic cation **F** and ultimately leads to observed products **2** and **3**. In the case of benzylic alcohol substrate **11**, we envisage that the nonclassical carbocation **C′** forms a stable benzylic cation **I**, and ultimately afforded observed naphthalene **25** through formation of intermediate **E′**.

In summary, we report the metal-catalyzed cycloisomerization of *cis*-4,6-dien-1-yn-3-ols with an unusual skeletal rearrangement; this catalytic reaction is applicable to a wide range of substrates. Its 1,3-migration pathway is clearly established by suitable experimental evidences. Application of this new catalysis of a complex molecule is under current investigation.

Acknowledgment. The authors thank to the National Science Council, Taiwan, for supporting this work.

Supporting Information Available: Table for cyclization of alcohol **11** using various catalysts, formation of product **H** from internal alkyne analogues using the $PtCl_2$ catalyst, experimental procedure, NMR spectra (including HMQC, HMBC, and ^{13}C-labeling experiments), and spectra data of compounds **1**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) See selected reviews: (a) Ma, S.-M.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (b) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (d) Mendez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397. (e) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

(2) Recently, we reported a 1,2-alkylidene[2a] and 1,3-methylene transfer process,[2b] respectively, for cycloisomerization of 1,5-enynes and 6,6-disubstituted 3,5-dien-1-ynes using $TpRuPPh_3(CH_3CN)_2PF_6$ to generate initial ruthenium−vinylidene intermediates. The mechanism and reaction pattern of the two cyclizations are completely different from those observed for this new cyclization. See: (a) Madhushaw, R.; Lo, C.-Y.; Hwang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560. (b) Lian, J. J.; Odedra, A.; Wu, C.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 4186.

(3) Selected examples for metathesis-type products besides Grubbs' catalyst: (a) Trost, B. M.; Yanai, M.; Hoogstein, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294. (b) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104. (c) Mendez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc*. **2001**, *123*, 10511. (d) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc*. **2000**, *122*, 6785. (e) Nieto-Oberhuber, C.; Munoz, P. M.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402.

(4) In this $AuPPh_3^+$-based catalysis,[3e] the cycloisomerization proceeds at room temperatures; however, the chemoselectivity heavily depends on alternation of the alkenyl substituents, the connecting atom X.[3e]

(5) Diene products **IV** and **V** were also produced from Rh(1)-catalyzed cycloisomerization of 1,6-enynes via initial formation of rhodium−vinylidene intermediates; however, there is no skeletal rearrangement according to the ^2H-labeling experiments. See: Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 10180.

(6) Treatment of alcohol **1** with TfOH (10 mol %) in toluene (23 °C, 10 min) produced two new products distinct from **2** and **3**, and this information indicates that the catalytic activity of $Zn(OTf)_2$ is not caused by TfOH. See Scheme S2 in the Supporting Information.

(7) (a) Winstein, S.; Shtavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183. (b) Winstein, S.; Lewin, A. H.; Pande, K. C. *J. Am. Chem. Soc.* **1963**, *85*, 2324.

(8) (a) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244 and references therein. (b) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592. (c) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858.

(9) Our preliminary results reveal that product **H** was produced in 65% yield from an internal alkyne analogue **S3** (see Scheme S1 in Supporting Information).

(10) In the $PtCl_2$ catalysis, the methoxy derivative of alcohol **1** in hot toluene (80 °C, 30 min) gave naphthalene product **2** in 76% yield; this information suggests that propargyl $OPtCl_2^-$ is not involved in the reaction mechanism.

JA062515H