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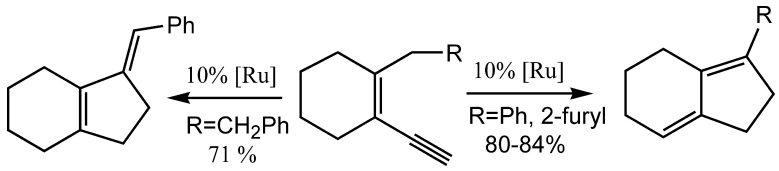

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Ruthenium-Catalyzed Cycloisomerization of *cis*-3-En-1-ynes to Cyclopentadiene and Related Derivatives through a 1,5-Sigmatropic Hydrogen Shift of Ruthenium−Vinylidene Intermediates

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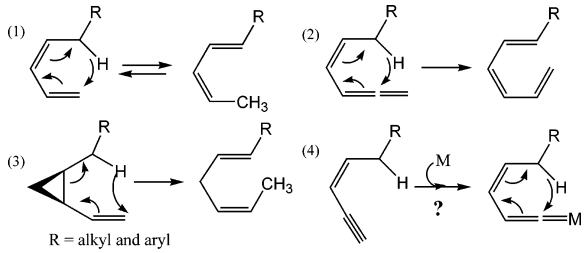
The [1,5]-sigmatropic hydrogen shift is a useful tool in organic synthesis,[1−4] and it has been employed frequently in the synthesis of complex bioactive molecules.[1] This process occurs very efficiently with *cis*-1,3-dienes,[1,2] *cis*-1-alkyl-2-vinylcyclopropanes[1,3] and *cis*-1-allen-4-enes[1,4] at suitable conditions (Scheme 1, eqs 1−3), but it proceeds sluggishly with *cis*-3-en-1-ynes even at elevated temperatures.[3a] One possible approach to realize the [1,5]-hydrogen shift of *cis*-3-en-1-ynes is to mimic the thermal rearrangement of *cis*-1-allen-4-enes, using a suitable metal species to generate metal−vinylidene intermediates (eq 4). To the best of our knowledge, examples of such reactions have never been documented, even though there is considerable interest in metal−vinylidene chemistry.[5] On the basis of this strategy, we report here a new ruthenium-catalyzed cycloisomerization of *cis*-3-en-1-ynes into cyclopentadiene and related derivatives, which are appealing building blocks to construct the skeletons of complex molecules.[6,7]

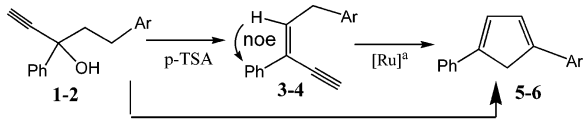
As shown in Scheme 2, treatment of 1-ethynyl-3-ols **1** and **2** with *p*-toluenesulfonic acid (p-TSA, 5 mol %) in hot toluene (110 °C, 12 h) gave *cis*-3-en-1-ynes **3** (91%) and **4** (92%), respectively. The *cis*-configuration of enynes **3**,**4** was confirmed by proton NOE spectra.[8] Heating a benzene solution (80 °C) of alcohol **1** (Ar = 2-methoxyphenyl, 0.15 M) with $TpRuPPh_3(CH_3CN)_2PF_6$[9] (10 mol %, Tp = tris(1-pyrazolyl)borate) for 4 h gave cyclopentadiene **5** in 51% yield and enyne **3** (40%). At a longer period (12 h, entry 2), the desired diene **5** was obtained up to 79% yield with complete consumption of enyne **3**. Entry 3 confirms that *cis*-enyne **3** is truly the active intermediate in the cyclization of alcohol **1** to diene **5**. Heating species **3** with the catalyst (10 mol %) in benzene (80 °C, 12 h) produced diene **5** in 80% yield; structural assignment of diene **5** was based on the ^{1}H NOE spectra.[8] Similarly, the alcohol **2** (Ar = 2-thienyl) and its *cis*-enyne derivative **4** were shown to be equally active in this catalytic cyclization; they each gave diene **6** in 65−66% yields (entries 4 and 5). The ruthenium catalyst has dual roles in catalytic activities: dehydration of 1-ethynyl-3-ols and cyclization of *cis*-enyne.

To examine the generality of this cycloisomerization, we used various 1-ethynyl-3-ols **7**−**16** (Table 1) in the catalytic cyclization because these alcohols are equally active as their dehydrated *cis*-enyne derivatives. Most of these alcohols bear aryl or heteroaryl substituents at their C(3) and C(5) carbons to ensure the formation of a single and thermally stable cyclopentadiene regioisomer.[10] Entries 1−3 reveal that the C(5)-phenyl substituent of alcohols **7** was catalytically as active as their 4-MeOPh and 4-CF_3Ph analogues **8** and **9**. This ruthenium catalyst is also active in the cyclizations of alcohols **10**−**11** bearing a furyl group and gave cyclopentadienes **27**−**28** in 62−65% yields. Entries 6−8 indicate the effects of alternating the C(3)-phenyl substituent of the alcohols **12**−**14**; the benzene group (**12**) produces a greater yield of cyclized product than do the reactions of its 4-tolyl (**13**) and 4-CF_3Ph counterparts (**14**). The value of this cyclization is highlighted by its applicability

Scheme 1



Scheme 2



entry	reactants	conditions[b]	products[c]
1	Ar = 2-MeOPh (**1**)	benzene (4 h)	**5** (51%); **3** (40%)
2	**1**	benzene (12 h)	**5** (79%)
3	Ar = 2-MeOPh (**3**)	benzene (12 h)	**5** (80%)
4	Ar = 2-thienyl (**2**)	benzene (12 h)	**6** (65%)
5	Ar = 2-thienyl (**4**)	benzene (12 h)	**6** (66%)

[a] [Ru] = 10 mol % $TpRuPPh_3(CH_3CN)_2PF_6$. [b] [substrate] = 0.15 M, 80 °C. [c] Yields were reported after separation from a silica column.

to the activation of a non-benzylic C−H bond, as represented by substrates **15** and **16**. The corresponding cylopentene products **32** and **33** were obtained in 71% and 53% yields, respectively (entries 9 and 10). The molecular structures of cyclopentadiene **29** and cyclopentene **33** were also characterized by X-ray diffraction studies.[8] The high efficiencies were maintained when this cyclization was applied to the synthesis of trisubstituted cyclopentene **34**−**35** (80−84%) and cyclopentene **36** (89%) from *cis*-enyne substrates **17**−**19**. Entries 14−17 show additional instances for cyclization of *cis*-enynes **20**−**23** via a non-benzylic C−H bond activation, and the cyclized products **37**−**39** and **34** were obtained in 71−79% yields. This new approach is very useful to construct bicyclic carbocyclic skeletons because only one regioisomer was formed exclusively (entries 11, 12, 14−17).

As shown in Scheme 3 (eq 1), the alkynyl deuterium of d_1-**3** produced the diene d_1-**5** bearing only 21% deuterium excess at the ***C***H=CPh carbon. The remaining three diene protons of d_1-**5** contained a total 0.42D content according to mass analysis.[11] The 1,5-hydrogen shift[2,6−7] of the cyclopentadiene framework hampers a precise interpretation of ^{2}H NMR labeling studies. Using a highly deuterated enyne d_3-**3** circumvented this problem. Equation 2 shows the deuterium distribution of diene d_3-**5** generated from this d_3-**3** enyne. The kinetic isotope effect of the CD_2 group of d_3-**5** inhibits this 1,5-hydrogen shift.[12] Notably, one C_eD_2Ph deuterium of species

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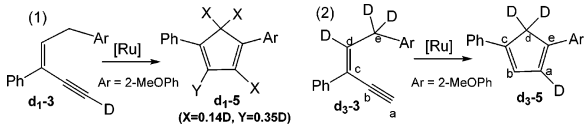
Table 1. Ruthenium-Catalyzed Cyclization of 1-Ethynyl-3-ols and *cis*-Enynes

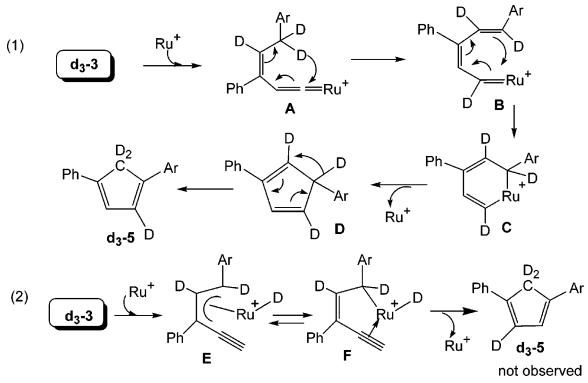
alcohols[a]	dienes[b]	enynes[a]	dienes[b]
(1) R = H (**7**)	**24** (70%)	(11) R = Ph (**17**)	**34** (80%)
(2) R = OMe (**8**)	**25** (66%)	(12) R = 2-(5-methyl-furyl (**18**)	**35** (84%)
(3) R = CF_3 (**9**)	**26** (67%)	(13) **19**	**36** (89%, a/b=1.8)
(4) R^1=R^2=H (**10**)	**27** (62%)	(14) **20**	**37** (71%)
(5) R^1=R^2= -(CH=CH)$_2$- (**11**)	**28** (65%)	(15) R = Ph (**21**)	**34** (79%)
(6) R = Ph (**12**)	**29** (80%)	(16) R = C≡CTBS (**22**)	**38** (76%)[c]
(7) R = 4-MePh (**13**)	**30** (48%)	(17) **23**	**39** (77%)
(8) R = 4-CF_3Ph (**14**)	**31** (60%)		
(9) R = H (**15**)	**32** (71%)		
(10) R = OMe (**16**)	**33** (53%)		

[a] 10 mol % catalyst, [substrate] = 0.15 M, benzene, 80 °C, 12 h. [b] Product yields were given after separation from a silica column. [c] Diene **38** was obtained in a 10:1 mixture of two isomers, and only the major isomer was shown.

Scheme 3



Scheme 4



***d*$_3$-3** relocates to the CD_2 fragment of diene ***d*$_3$-5**, and the other deuterium is present at the C_a-carbon of ***d*$_3$-5**. In this transformation, the alkynyl proton of ***d*$_3$-3** undergoes a 1,2-shift to relocate to the C_b-carbon of ***d*$_3$-5**.

Scheme 4 shows a plausible mechanism to rationalize the deuterium-labeling experiments. The 1,2-shift of the alkynyl hydrogen of ***d*$_3$-3** indicates the formation of ruthenium−vinylidene intermediate[5] **A**, which undergoes a subsequent 1,5-sigmatropic shift to generate ruthenahaxa-3,5-triene **B**. A subsequent 6π-electrocyclization[13] of species **B** gives ruthenacyclohexa-2,4-diene species **C**. Reductive elimination of this Ru(IV)-triene species produces cyclopentadiene **D** and ultimately yields the most stable regioisomer ***d*$_3$-5** via a 1,5-hydrogen shift. The deuterium distribution of ***d*$_3$-5** in Scheme 3 precludes an involvement of ruthenium-π-allyl **E** as a reaction intermediate, which equilibrates with its σ-allyl species **F** and would ultimately generate diene ***d*$_3$-5** bearing a deuterium distribution inconsistent with our observation.

Although *cis*-3-en-1-yne is a common and practical functionality,[14] cycloisomerization of this moiety into a cyclopentadiene or related framework is unprecedented before our findings. Here we report that $TpRuPPh_3(CH_3CN)_2PF_6$ implements the cycloisomerization of unactivated *cis*-3-en-1-ynes and efficiently produces stable cyclopentadiene and related derivatives. The mechanism of this cyclization is proposed to involve a [1,5]- sigmatropic hydrogen shift of ruthenium−vinylidene intermediates on the basis of deuterium-labeling experiments.

Acknowledgment. We thank the National Science Council, Taiwan, for supporting this work.

Supporting Information Available: NMR spectra, spectral data of compounds **1**−**39**, NMR spectra of ^{2}H-labeled ***d*$_3$-3** and ***d*$_3$-5**, ^{1}H NOE spectra of **3**, **5**, **37**, and **39**, and X-ray structural data of cyclized products **29** and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The ^{1}H NOE spectra of compounds **3**, **5**, **37**, and **39** and X-ray diffraction studies of compounds **29** and **33** are provided in Supporting Information.

(9) For formation of metal−vinylidene intermediates using this catalyst, see: Lian, J.-J.; Odedra, A.; Wu, C.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 4186 and our related work cited therein.

(10) Substituted cyclopentadienes readily undergo a [1,5]-hydrogen shift and form several regioisomers. In this study, the aromatic substituent of cyclized products tends to conjugate with diene functionality to give one single regioisomer, which is inactive toward intramolecular [4+2]-cycloaddition under catalytic conditions.

(11) The ***d*$_1$-5** and ***d*$_3$-5** samples were obtained at catalytic reactions at 30% conversion level (80 °C, 3 h). In the case of sample ***d*$_1$-5**, a loss of 23% deuterium content is caused by the proton exchange of the alkynyl proton of species ***d*$_1$-5** with residual water. This is a common phenomenon for metal−vinylidene chemistry; see our related work.[9]

(12) Heating diene ***d*$_3$-5** in hot benzene (80 °C, 16 h) led to a 96% and 91% recovery of this sample in the absence and presence of ruthenium catalyst, respectively. Its C_b−H proton content was decreased to 0.55H and 0.46H, respectively.

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