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Sequential Allenylidene/Vinylidene Cyclization for Stereoselective Construction of Bicyclic Carbocycles from Propargyl Alcohol

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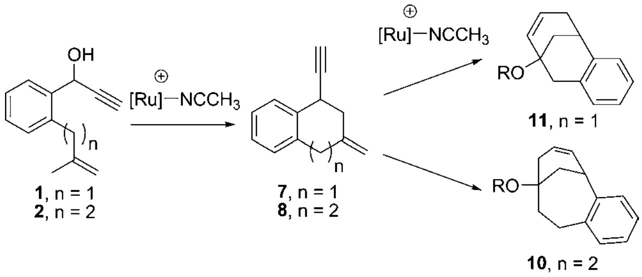
ABSTRACT



Consecutive cyclization reactions of phenyl propargyl alcohols 1 and 2 are catalyzed by [Ru]NCCH$_3^+$ ([Ru] = Cp(PPh$_3$)$_2$Ru) in cosolvent CHCl$_3$/MeOH at 60 °C, to afford the fused cyclic compounds 11a (R = Me) and 10a (R = Me), respectively.

Syntheses of six- or seven-membered carbocycle rings as building blocks or providers of rigid functional groups have attracted a great deal of attention.[1] Various methodologies[2−4] have been applied for constructing such ring systems. Transition metal catalyzed cycloisomerization, the cycloaddition reaction, and/or olefin metathesis[5] also provide valuable methods to access these ring systems.[6] Furthermore, the construction of more complicated ring systems, such as fused or bridged rings, is useful for synthesizing natural products.[7] To build these fused rings, photo-rearrangement[8]/thermal[9] rearrangement and the use of Lewis acids,[10] and transition metals,[11] have been

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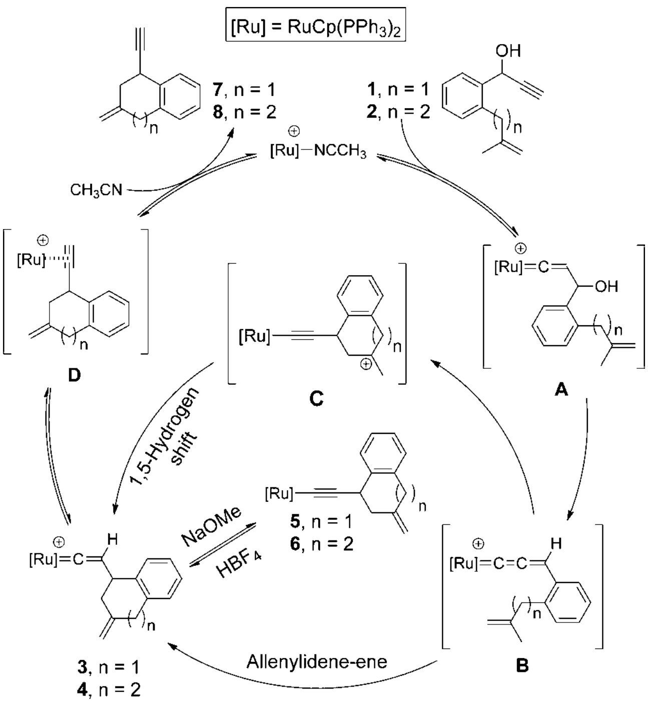
developed. These exhaustive efforts have resulted in elegant methods for intricate bicyclic systems.

Most transition-metal-catalyzed enyne cyclizations or skeleton rearrangements are accompanied by the consumption of an alkene or an alkyne moiety. It is relatively rare to have the product maintaining both unsaturated groups. We recently reported[12] the cyclization of propargylic alcohol tethered with a methyl-substituted allylic terminal affording a vinylidene complex with a five-membered ring containing an unsaturated methylene group on the ring. Presumably this enyne product may undergo further cyclization which unfortunately was not observed. As an extension of our previous study,[12] we further develop ruthenium-catalyzed cyclization reactions of aromatic 1,*n*-propargylic enynes ($n = 7$ or 8) affording a cyclized product retaining two unsaturated functionalities. The conservation of both olefinic and ethynyl moieties progresses to further cyclization. Herein, we report the sequential intramolecular cyclizations via allenylidene and vinylidene intermediates to form tricyclic compounds.

Heating the aromatic propargylic alcohol **1** bearing an alkene moiety at the *ortho*-position of the aromatic ring in CHCl$_3$ at 50 °C for 2 days in the presence of 20 mol % of [Ru]NCCH$_3^+$ gave the cyclization product **7** in 98% conversion and 92% isolated yield. The proposed mechanism is shown in Scheme 1. Formation of the γ-hydroxyvinylidene intermediate **A** is followed by a dehydration to give the allenylidene intermediate **B**. Subsequently, a C$-$C bond formation between the allenylidene ligand and the terminal carbon atom of the vinyl group takes place to form the vinylidene complex **3**. The vinylidene ligand in **3** is then replaced by CH$_3$CN to give **7**, thus finishing the catalytic cycle. In CH$_3$CN, however, no conversion of **1** to **7** was observed suggesting that formation of **A** is prohibited by a competitive coordination of CH$_3$CN. The cyclization of **2** with an additional methylene group is also catalyzed by [Ru]NCCH$_3^+$ affording **8** with a newly formed seven-membered ring in high yield, as also shown in Scheme 1.

Reactions of 1 equiv of [Ru]Cl with **1** and **2** form vinylidene complexes **3** and **4**, respectively, which are characterized by spectroscopic methods. In the 2D-HMBC NMR spectrum of **3**, the triplet peak at δ 346.16 with $^2J_{CP} = 15.5$ Hz, assigned to Cα, shows a correlation with the multiplet ^{1}H resonance at δ 3.82, assigned to CγH. The H,H-COSY NMR spectrum shows correlations of this ^{1}H resonance with two multiplet resonances at δ 2.68 and 2.34, assigned to the neighboring CH$_2$ group, clearly revealing the C$-$C bond formation described above. Complexes **3** and **4** are converted to acetylide complexes **5** and **6** by deprotonation, and protonations of **5** and **6** at 0 °C regenerate **3** and **4**, respectively.

Scheme 1. Proposed Mechanism for Formation of **7** and **8**



The cyclization step might proceed via addition of the unsaturated group to the electrophilic Cγ of the allenylidene ligand or by a concerted allenylidene-ene reaction pathway as shown in the lower part of Scheme 1.[13] The intramolecular attack of the alkene portion onto the electrophilic Cγ of the allenylidene ligand in **B**, resulting in a C$-$C bond formation, gives the acetylide complex **C** bearing a cationic charge at the methyl-substituted tertiary carbon of the six- or seven-membered ring. This is followed by a transfer of one of the methyl protons to Cβ of the acetylide ligand to give the vinylidene complex **3** or **4**. The presence of a tertiary carbocationic intermediate assists the cyclization process. The direct allenylidene-ene process is an alternative for this cyclization.

Heating a solution of **3** in CDCl$_3$/CH$_3$CN to reflux afforded the terminal enyne **7** and [Ru]NCCH$_3^+$. Complex **4** similarly gave **8**.[14] Cyclic enynes **7** and **8**, characterized by spectroscopic data, are isolated with 87$-$92% yields. In the ^{1}H NMR spectrum of **8**, two multiplet resonances at δ 4.83 and 4.80 are assigned to the olefinic methylene protons bonded to the seven-membered ring.

Treatment of **6** with allyl bromide afforded the vinylidene complex **9**, tethering an allyl group at Cβ. Complex **9**

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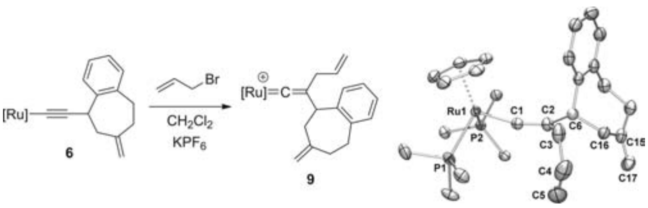
is stable; single crystals of **9** are obtained at ambient temperature in toluene/CH_2Cl_2 solution, and the structure is determined by a single crystal X-ray diffraction study. The seven-membered ring in the vinylidene ligand is clearly revealed in the crystal structure (see Scheme 2; details are given in the Supporting Information).

Scheme 2. Electrophilic Addition of **6** and Crystal Structure of **9**



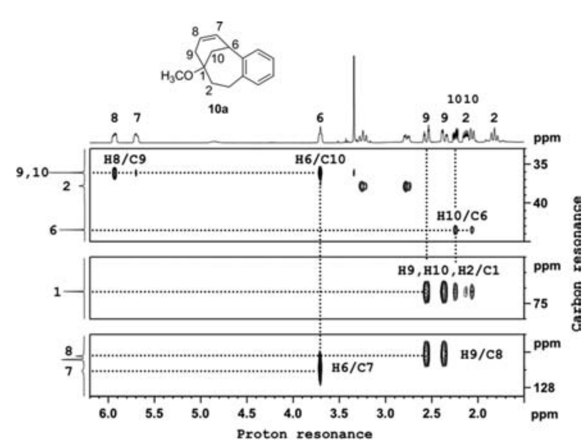


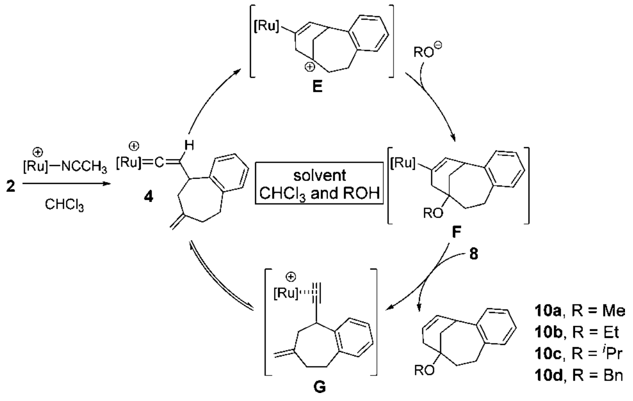
Figure 1. Part of 1,1-ADEQUATE 2D spectrum of **10a** with numbering of **10a**.

Interestingly, in a mixed solvent of $CHCl_3$/MeOH, sequential cyclization of **2** is directly catalyzed by 20 mol % of $[Ru]NCCH_3^+$ at 60 °C, giving the fused cyclic product **10a** in 92% yield. Treatment of **8** with $[Ru]NCCH_3^+$ in $CHCl_3$/MeOH also affords **10a** in high yield. Compound **10a** is also obtained from the treatment of **4** with $[Ru]NCCH_3^+$. 1,1-ADEQUATE[15] and H2BC[16] NMR techniques are used for determining the C−C connectivity of **10a**. Figure 1 shows part of the 1,1-ADEQUATE spectrum and numbering of **10a**. The ^{13}C resonance at δ 74.23, assigned to C^1, shows correlations with two ^1H resonances of the neighboring C^9H_2 group.

The ^{13}C resonance at δ 126.23 assigned to C^8 correlates with ^1H resonances at δ 2.56, 2.24 assigned to C^9H_2. These correlations support the proposed structure of **10a**. The cyclization of **2** in $CDCl_3/CD_3OD$ yields **10a-d₂**, where two olefinic protons at C^7, C^8 and the methoxy group are deuterated.

A plausible mechanism of the cascade cyclization of **2** is shown in Scheme 3. The first cyclization reaction of **2** yields **4** and **8** (Scheme 1). Then, nucleophilic addition of the olefinic moiety to Cα in **4** gives the cationic species **E**. Addition of a methoxide at the cationic carbon site affords **F**, which gives **10a** by protonation and **G** or **4** by addition of **8** or **2**, respectively, to the metal portion. Treatment of **2** with $[Ru]NCCH_3^+$ in three other different alcohols ROH (R = Et, ^{i}Pr, Bn) also affords **10b**−**d**, respectively. Yields of **10** decrease as the steric bulk of alcohol increases. Nevertheless, attempts to use allyl alcohol, acetone, and malononitrile as nucleophiles for the reaction failed to give any desired product.

Scheme 3. Proposed Mechanism of Cascade Cyclization of **2**



Using the same procedure as that used for the synthesis of **10a**, similar methoxide **11a**, containing two fused six-membered rings, is acquired from **1** (Scheme 4) in 73% yield. The EI mass spectrum of **11a** indicates the addition of a methoxy group. Surprisingly, in $CDCl_3/CD_3OD$, compound **11a-d₃** is obtained. In the ^1H NMR spectrum of **11a-d₃**, resonances of the methylene group of $C^{4'}$ (for numbering, see Scheme 4) disappear completely, and two partly overlapped olefinic peaks of $C^{2'}$ and $C^{3'}$ at δ 5.67, 5.61 decrease in intensity by approximately 30% and 70%. Thus, 1,1-ADEQUATE and H2BC are used again for the structure determination of **11a**. In the 1,1-ADEQUATE spectrum of **11a**, the ^1H resonance at δ 5.61, assigned to $C^{3'}H$, shows correlations with two ^{13}C resonances of the neighboring olefinic carbon at δ 127.79 ($C^{2'}$) and the methylene carbon at δ 34.88 ($C^{4'}$).

To our surprise, the ^{13}C resonance of the bridgehead carbon at δ 74.13 displays a correlation with the olefinic proton resonance at δ 5.76 ($C^{2'}H$). These data clearly reveal the location of the double bond in the newly formed ring. Thus, the mechanism for the formation of **11a**, shown in Scheme 4, is slightly modified from that of **10a**. Methanol addition to **3** leads to the protonated cationic

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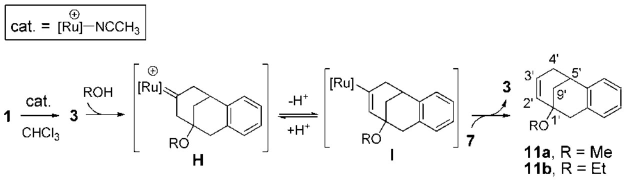
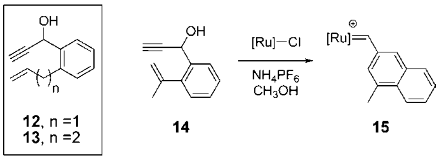
(15) For 1,1-ADEQUATE, see: (a) Reif, B.; Kock, M.; Kerssebaum, R.; Kang, H.; Fenical, W.; Griesinger, C. *J. Magn. Reson., Ser. A* **1996**, *118*, 282–285. (b) Kock, M.; Kerssebaum, R.; Bermel, W. *Magn. Reson. Chem.* **2003**, *41*, 65–69.

(16) For H2BC, see: Nyberg, N. T.; Duus, J. O.; Soerensen, O. W. *J. Am. Chem. Soc.* **2005**, *127*, 6154–6155.

Scheme 4. Cascade Cyclization of **1**



Scheme 5. Propargylic Enynes **12**, **13** and the Cyclization of **14**



ruthenium carbene species **H**. A subsequent reversible deprotonation and reprotonation process results in the formation of **I**, which is protonated to give **11a**.

The above-mentioned cyclization is indeed promoted by the methyl substituent on the vinyl group, since no cyclization is observed in two similar aromatic propargyl alcohols **12** and **13** with no methyl group (see Scheme 5) most likely due to a less stable secondary carbocation. When the tether olefinic carbon chain of the propargyl alcohol is made shorter while maintaining the methyl group, cyclization induced by a metal complex takes place again. Namely, the reaction of [Ru]Cl with **14** leads to the carbene complex **15** with a methyl substituted naphthyl group. For the conversions of **1** and **2** to **3** and **4**, respectively, the C–C bond formation takes place at Cγ; however, the cyclization of **14** to form **15** (Scheme 5), with the C–C bond formation at Cβ, might proceed through a different pathway.[17]

In conclusion, cascade cyclizations of aromatic propargylic alcohols **1** and **2** each with a methyl-substituted vinyl group are both catalyzed by [Ru]NCCH$_3^+$ leading to **11a** and **10a** with fused tricyclic rings in cosolvent CHCl$_3$/MeOH. Isolation of vinylidene and organic intermediates in the absence of MeOH and deuterium labeling studies reveal the mechanism. The cyclization reaction proceeds via an unobserved allenylidene complex acting as an enophile to afford the isolable vinylidene complexes, in which formation may proceed via a carbocationic intermediate or directly by the allenylidene-ene reaction. Subsequent intramolecular nucleophilic addition of the terminal double bond to Cα of the vinylidene ligand gives the tricyclic product. We developed a rapid and efficient cascade cyclization of aromatic propargylic enynes catalyzed by [Ru]NCCH$_3^+$ which is not commonly used as a catalyst to prepare complicated cyclized organic molecules.

Acknowledgment. We thank the National Science Council, Taiwan, ROC for financial support.

Supporting Information Available. Experimental methods, synthetic procedures, compound characterization data, NMR peak assignments, 1,1-ADEQUATE and H2BC NMR spectra, and X-ray data for complex **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Taduri, B. P.; Sohel, S. M. A.; Cheng, H.-M.; Lin, G.-Y.; Liu, R.-S. *Chem. Commun.* **2007**, 2530–2532.