ORGANIC LETTERS

2003
Vol. 5, No. 22
4149−4151

# On the Diastereoselectivity of Ru-Catalyzed [5 + 2] Cycloadditions

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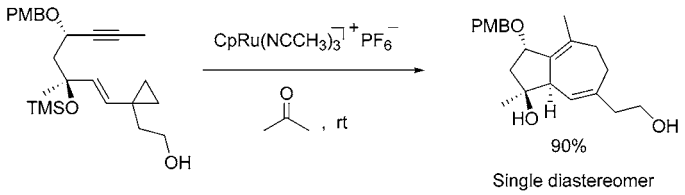
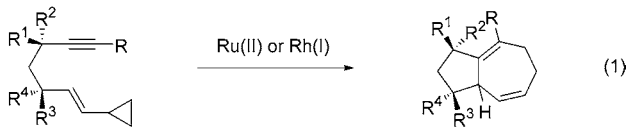
**Received August 23, 2003**

## ABSTRACT




**Ru-catalyzed cycloisomerization of cyclopropylenynes proceeds with good to high diastereoselectivities to form hexahydroazulenes.**

The development of new chemical reactions involving multiple bond formations and cleavage elevates the level of efficacy possible in modern organic synthesis. Cycloaddition reactions catalyzed by organotransition metal complexes[1] are of growing interest due to the efficient construction of complicated structures from much simpler starting materials in an atom-economical fashion.[2] Among these reactions, Rh(I)- and Ru(II)-catalyzed [5 + 2] cycloadditions of cyclopropylenynes, formally involving the formation of three carbon−carbon bonds and the cleavage of two carbon−carbon bonds, allow the formation of seven-membered rings (eq 1). For instance, Rh(I) complexes such as Wilkinson's catalyst ($RhCl(PPh_3)_3$) and (dicarbonyl)rhodium(I) chloride dimer ($[Rh(CO)_2Cl]_2$) have been utilized for [5 + 2] cycloadditions of cyclopropylenynes.[3]




(1)

Exceptional control over the direction of cyclopropane bond cleavage has been achieved through selection of appropriate substituents in the substrate and/or choice of the catalyst. Our initial work in this field was also inspired by the mechanistic implications of the Alder ene reaction[4] catalyzed by the cationic Ru complex $CpRu(MeCN)_3PF_6$.[5] Another major driving force came from the natural abundance of compounds with 5,7-fused bicyclic carbon skel-

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10.1021/ol0355884 CCC: $25.00 
**Published on Web 10/01/2003**

etons, especially represented among sesquiterpenoid natural products. Furthermore, many of these compounds display interesting biological activities. Figure 1 shows some relevant examples of (nor)sesquiterpenes with bicyclo[5.3.0]decane carbon frameworks.

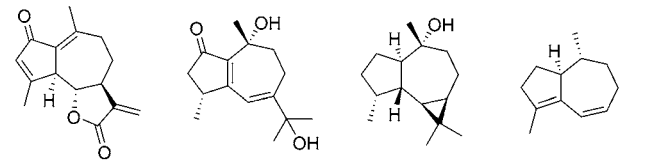


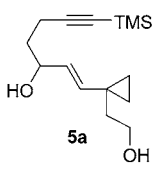
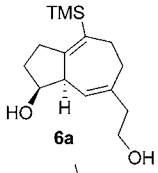
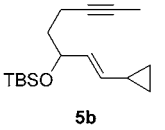
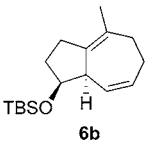
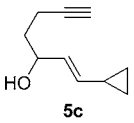
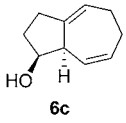
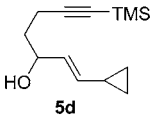
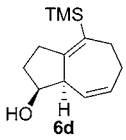
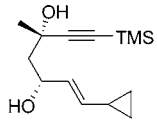
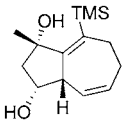
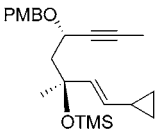
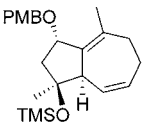
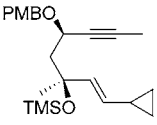
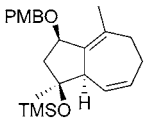
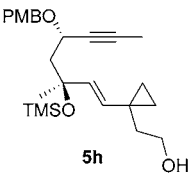
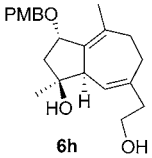
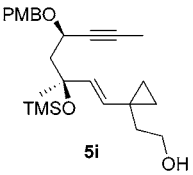
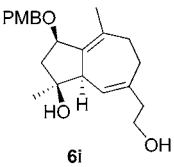
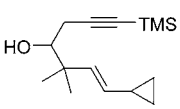
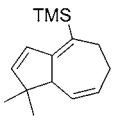

**Figure 1.** Representative natural products possessing 5,7-fused bicyclic moieties.

New strategies for concise total syntheses of such targets are highly desirable. One major concern in this endeavor is the diastereoselectivity of the key [5 + 2] cycloaddition step. Of particular significance is the question of how the relative stereochemistry of substituents in the tether can influence the configuration of the newly created stereogenic center at the bridgehead carbon atom. To shed light on this issue, we prepared a range of cycloaddition precursors with one or more substituents in the carbon tether and subjected them to a Ru-catalyzed [5 + 2] cycloaddition reaction. The results are shown in Table 1.

In all cases, besides good to excellent yields of the desired hydroazulene products, good to excellent diastereoselectivities were observed. Entries 1−4 show the influence of an allylic hydroxyl group (protected or unprotected) on the diastereoselectivity of the cycloaddition reaction. In all cases investigated so far, the bridgehead hydrogen atom and the hydroxyl group of the major cycloadduct show a trans relationship. A quarternary propargylic carbon atom with an additional allylic substituent gives rise to virtually complete diastereoselectivity in the product (entry 5). Interestingly, cycloisomerization of enyne **5e** under the usual conditions in acetone or DMF led to very slow reaction and significant decomposition. On the other hand, the reaction in dichloromethane proceeded much faster and gave an excellent yield at 15 °C. Switching to a quaternary allylic carbon atom and a propargylic PMB ether (entries 6−9) leads to equally diastereoselective reactions with only one diastereomer detectable in the product. In each case, the angular hydrogen and the homoallylic oxygen substituent are trans, as revealed by either the X-ray structure for diol **6e** or NOE experiments, as shown by some representative examples (Figure 2). Attempts to study the influence of a hydroxyl group on the carbon atom between the propargylic and allylic atoms in the tether led to only elimination product (entry 10).

The proposed mechanism of the cycloaddition involves the coordination of Ru(II) to both alkene and alkyne functions, followed by the formation of a ruthenacyclopentene. The coordination of alkyne to ruthenium is known

**Table 1.** Diastereoselective Cycloaddition of Cyclopropyl-enyne Substrates[a]

| | | | | |
|---|---|---|---|---|
| 1 |  **5a** |  **6a** | 75 | 5 : 1 |
| 2[d] |  **5b** |  **6b** | 92 | 5.1 : 1 |
| 3 |  **5c** |  **6c** | 86 | >10 : 1 |
| 4 |  **5d** |  **6d** | 75 | >20 : 1 |
| 5[e] |  **5e** |  **6e** | 84 | >20 :1 |
| 6 |  **5f** |  **6f** | 70[f] | >20 :1 |
| 7 |  **5g** |  **6g** | 75[g] | >20 : 1 |
| 8 |  **5h** |  **6h** | 90 | >20 : 1 |
| 9 |  **5i** |  **6i** | 70 | >20 : 1 |
| 10 |  **5j** |  **6j** | 38 (89[h]) | |

[a] Unless otherwise indicated, reactions were carried out in anhydrous acetone with 10 mol % $CpRu(MeCN)_3PF_6$ at room temperature. [b] Isolated yield. [c] Determined by $^1H$ NMR. [d] DMF was used as a solvent. [e] Reaction was run in dichloromethane at −80 to 15 °C. [f] Product shown (65%) + desilylated product (5%). [g] Product shown (42%) + desilylated product (33%). [h] Yield based on recovered starting material.

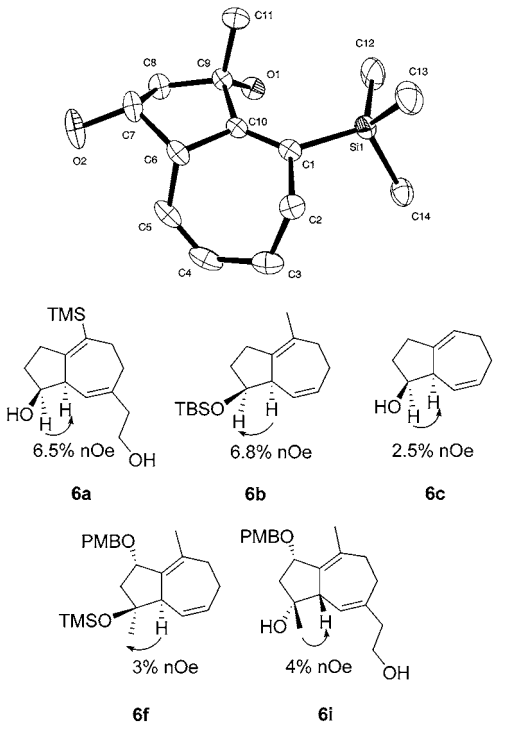
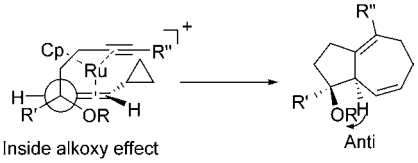



**Figure 2.** X-ray structure of **6e** and representative NOE data.

to promote nucleophilic addition.[6] One way to look at the interaction between cationic ruthenium species and alkene is that the alkene is nucleophilic toward the ruthenium alkyne complex. Presumably, the $\sigma$-donation of the alkene $\pi$-bond to cationic Ru species is more important for the coordination of the alkene to Ru than the back-bonding of the d orbital of the metal to alkene. The observation that the angular hydrogen is anti to the homoallylic OR subsitutent in the major diasteromeric cycloadduct is in agreement with the Stork/Houk-Jäger "inside alkoxy" model.[7] If the $\sigma^*_{CO}$ orbital overlaps with the alkene $\pi$ orbital, the alkene becomes less prone to donate electrons to Ru, which in turn destabilizes the transition state. Conversely, if the $\sigma^*_{CO}$ orbital is orthogonal to the alkene $\pi$ orbital (alkoxy group is "inside"), the overlap of the $\sigma^*_{CO}$ orbital with the $\pi$ orbital of alkene is minimized. Meanwhile, the electron-donating $\sigma_{CH}$ or $\sigma_{CR'}$ will stabilize the transition state. Scheme 1 shows the most reactive conformation which leads to the major diastereomer.

**Scheme 1.** Mechanistic Rationale for Diastereoselectivity




In summary we have demonstrated that high diastereoselectivities can be achieved in the Ru-catalyzed intramolecular [5 + 2] cycloaddition of cyclopropylenynes. The notably high diastereoselectivity favoring the angular hydrogen to be anti to the homoallylic oxygen substituent can be understood by the proposed mechanism involving ruthenacyclopentene intermediates, which further elucidate the mechanism of the Ru-catalyzed intramolecular [5 + 2] cycloadditions. In addition to the virtues of atom economy and a remarkable increase in molecular complexity, this beneficial feature of the cycloaddion reaction enhances the prospect for its successful application in the synthesis of challenging molecular targets.

**Acknowledgment.** We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences (GM33049), for their generous support of our programs. H.C.S. is a Stanford Graduate Fellow. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California−San Francisco supported by the NIH Division of Research Resources.

**Supporting Information Available:** Experimental details and characterization data for all cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0355884

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