those with trisubstituted double bonds. We further suggest that the regio- and stereochemistry of the major products of these reactions are determined by the relative energetics of various organopalladium intermediates produced during the reactions.

Acknowledgment. We wish to thank the Burroughs-Wellcome Corp. for financial support of this work.

Supplementary Material Available: Experimental and spectroscopic data for all products and calculated Boltzmann distributions of various tetrahydropyran and furan products (18 pages). Ordering information is given on any current masthead page.

On the Origin of Diastereoselection in the Cyclization of Enynes on Low-Valent Zirconium Centers. Substituent and Torsional Effects on Annulation Stereochemistry

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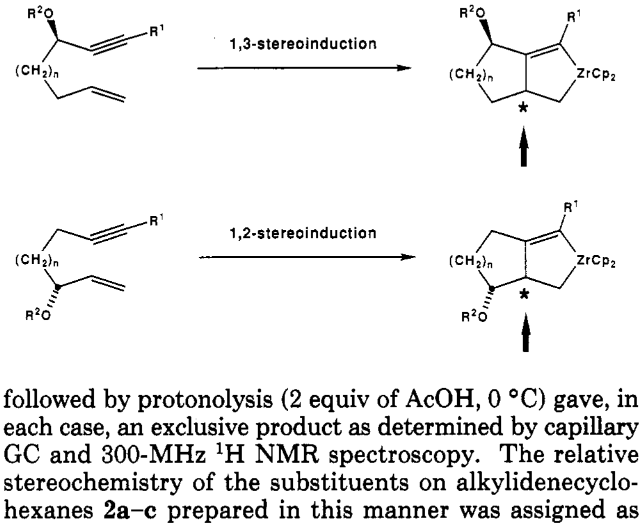
Summary: A variety of substituted enynes have been found to undergo reductive cyclization mediated by zirconocene complexes with excellent degrees of stereoselection.

Sir: Stereoselective processes have played a central role in the synthesis of compounds possessing medicinal and/or theoretical significance. In principle, low-valent transition metal templates should provide a propitious environment for performing transformations of this variety. In a series of seminal papers, Magnus[2] and Schore[3] have revealed several topological features which govern stereoselection in the cobalt-promoted bicyclization of enynes.[4] Despite the activity in the latter area, relatively little is known regarding the influence of peripheral stereocontrol elements on Group IV based cyclization of simple enynes (Scheme I).[5] In this communication we report our observations on the stereoselective annulation of oxygen-substituted enynes by zirconocene reagents.[6]

Scheme I



We initiated this investigation by examining the relative influence of propargylic and allylic substituents on the stereochemical outcome of representative alkylidenecyclohexane annulations. In this connection, three propargylic enynes and two allylic enynes were studied.[7] Cyclization of the propargylic enynes **1a–c** in the presence of Cp$_2$Zr(n-Bu)$_2$[8,9] (−78 °C, 0.5 h then 25 °C, overnight) followed by protonolysis (2 equiv of AcOH, 0 °C) gave, in each case, an exclusive product as determined by capillary GC and 300-MHz ^{1}H NMR spectroscopy. The relative stereochemistry of the substituents on alkylidenecyclohexanes **2a–c** prepared in this manner was assigned as trans on the basis of the following spectroscopic data. The coupling constants observed for the silyloxy methine resonances (H_a) in the cyclohexanes **2a–c** were invariably small in magnitude (ca. 0–3 Hz) as would be expected for equatorially disposed protons. By way of contrast, the allylic methine hydrogens (H_b) of **2a–c** exhibited both large (ca. 6.0 Hz) and small couplings characteristic of axial protons. Additional evidence for the trans relative orientation of the silyloxy and methyl substituents as well as for the *Z* geometry of the alkylidine moiety was provided by nuclear Overhauser enhancement difference (NOED) spectroscopy. Significant positive NOEs were observed between the vinylic methines and the peripheral methyl substituents of the cyclization products **2a–c**. In addition, no observable NOEs were observed between H_a and H_b nor between the vinylic methine and H_b in these products.

These data are again consistent with the existence of a trans relationship between H_a and H_b, the equatorial

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[1] Fellow of the Alfred P. Sloan Foundation, 1989–1991.

[2] (a) Magnus, P.; Becker, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 7495. (b) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483. (c) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (d) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. (e) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477.

[3] Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224.

[4] A recent account concerned with the influence of internal ligands as regiocontrol elements in Co$_2$(CO)$_8$ mediated cyclizations has also appeared: Krafft, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 968.

[5] Recently, RajanBabu et al. have reported the stereoselective cyclization of two 7-substituted-5-[(*tert*-butyldimethylsilyl)oxy]hept-1-en-6-ynes to the corresponding 1-(silyloxy)-2-alkylidenecyclopentane derivatives via low-valent metallocenes. In these instances, the *cis*-alkylidenecyclopentane isomers were formed as the major products: RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128.

[6] Part 4 in the series Synthetic Applications of Low Valent Metallocene Complexes. For part 3, see: Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.*, in press. For part 2, see: Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1989**, *111*, 4495.

[7] The propargylic and allylic substrates utilized in this study were prepared via the addition of the requisite 1-lithioalkyne or vinylmagnesium bromide respectively to the appropriate aldehyde followed by silylation (t-BuMe$_2$SiOTf/i-Pr$_2$NEt, CH$_2$Cl$_2$, 0 °C).

[8] Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

[9] The direct cyclization of the propargylic alcohol **1c** and the allylic alcohols **5b** and **9b** could be conveniently effected by way of the corresponding lithium alkoxides. Accordingly, addition of n-BuLi (3 equiv) to the substrate alcohol (1 equiv) and zirconocene dichloride (1 equiv, THF, −78 °C, 0.5 h then 25 °C overnight) followed by protonolysis (3 equiv of AcOH, 0 °C) furnished the corresponding cycloalcanols in high (70–81%) yield.

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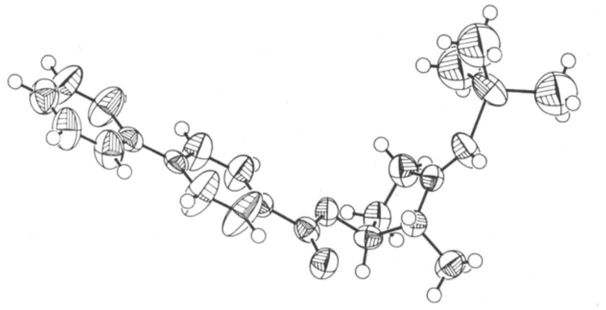
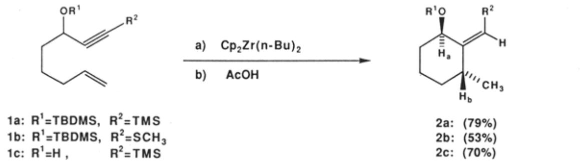
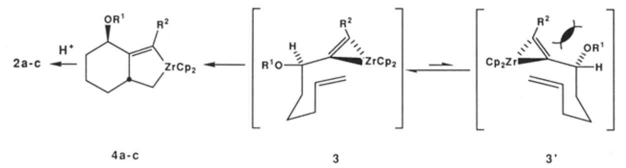


Figure 1. ORTEP diagram of **11c**.

disposition of the C-3 methyl substituent, and *Z* alkene geometry.

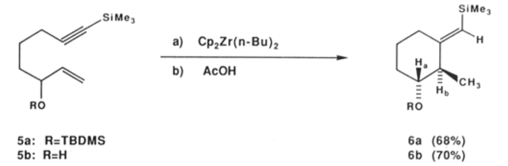
The foregoing stereochemical results are in concordance with the following mechanistic analysis. Reductive elimination of butane from $Cp_2Zr(n\text{-}Bu)_2$ followed by enyne complexation[10] should generate the transient zirconacyclopropenes **3a–c** for which there are two extreme precyclization conformers (e.g., **3** and **3′**). Conformers corresponding to **3′** are expected to be strongly disfavored energetically as a consequence of allylic 1,3-nonbonded interactions between the proequatorial oxygen bearing moiety and the zirconacyclopropenyl substituent. Accordingly, cyclization will be favored via conformers corresponding to **3**, in which allylic 1,3-strain is minimized, to provide the exo substituted zirconacyclopentenes **4a–c**.

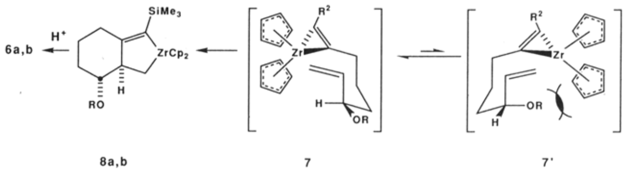




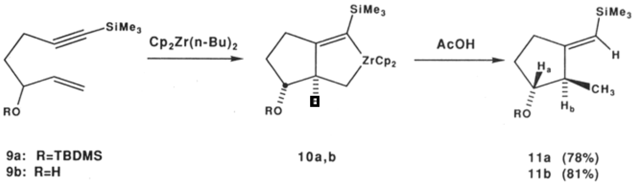
Cyclization of the allylically substituted enynes **5a,b**[7] [$Cp_2Zr(n\text{-}Bu)_2$, 0.5 h, −78 °C then 25 °C, overnight] followed by protonolysis (2 equiv of AcOH, 0 °C) gave the trans homoallylic ether **6a** and the alcohol **6b** as the exclusive stereoisomers in 68% and 70% isolated yield, respectively. In the case of **6a**, both the silyloxy methine and allylic methine protons (H_a and H_b, respectively) exhibited one large [9.0 Hz (H_a), 8.9 Hz [H_b)] and one small [3.0 Hz (H_a), 1.4 Hz (H_b)] coupling constant. Moreover, no observable NOE was detected between H_a and H_b but a prominent NOE was observed between the C-2 methyl substituent and the vinylic methine. These internally consistent data strongly support the designated stereochemical and geometrical assignments for **6a**. The homoallylic alcohol **6b** exhibited closely analogous splitting patterns and NOE behavior.

Although allylic 1,3-strain is not a significant factor governing the formation of **6a** and **6b**, an alternative mechanistic model can be advanced. As in the case of the zirconacyclopropenes **3a–c**, two extreme precyclization conformers (e.g., **7** and **7′**) can be envisaged. Conformer **7′** is expected to be significantly higher in energy than **7** as a result of an unfavorable nonbonded interaction involving the allyl ether moiety and a cyclopentadienyl ligand bound to the zirconium atom. Cyclization via **7** leads to the exo-substituted zirconacyclopentenes **8a,b** and ultimately to **6a** and **6b**.





We next directed our attention to the utilization of zirconocene-mediated bicyclizations for the annulation of alkylidenecyclopentane derivatives.[5] In this study two allylic enynes were examined.[7] Cyclization of the allylic enynes **9a** and **9b** as before[8,9] led to the formation of the trans alkylidenecyclopentanes **11a,b** as the exclusive isomers in high yield. In these instances, evidence for relative stereochemistry derived both from NOE spectroscopy and single-crystal X-ray analysis. As in the case of the alkylidenecyclohexanes **6a** and **6b**, the splitting patterns and chemical shift data for the alkylidenecyclopentanes **11a** and **11b** were closely analogous. As before, no observable NOE was detected between H_a and H_b. In addition, a significant NOE was observed between the C-2 methyl substituent and the vinylic methine for both **11a** and **11b**.



In the instance of **11b**, the trans relationship of the pendant methyl and hydroxy substituents as well as the *E* geometry of the alkylidene moiety were ultimately confirmed via single-crystal X-ray analysis of the corresponding 4-phenylbenzoate ester **11c** (Figure 1).

In summary, several conformational features which regulate stereoinduction in zirconocene-promoted enyne cyclizations have been elucidated. Additional examples of metallocene-based diastereoselection as well as the utilization of homochiral ketals in reductive enyne cyclizations will be reported in due course.

Acknowledgment. Support for this research by a grant from the National Institutes of Health is gratefully acknowledged. We are indebted to Ray Larsen of the Department of Chemistry, Montana State University, for obtaining the crystal structure of **11c** (Figure 1), and to Dr. L. J. Sears for providing mass spectral data.

Supplementary Material Available: Spectral data for compounds **1a–c**, **2a–c**, **5a**, **5b**, **6a**, **6b**, **9a**, **9b**, **11a**, and **11b** (5 pages). Ordering information is given on any current masthead page.

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[10] (a) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870 and references therein. (b) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544.