with the picture that the substituent (Me, R) develops no significant nonbonded interactions with the alkene-Pd(II) substituent in either conformation. Starting from 7, conformation B presents pseudo-1,3-diaxial interaction between the Me (R) and the alkene-Pd(II) substituents, accounting for a modest preference for the product (trans) from conformation A.

Using the corresponding reactant conformations from 8–11 (C and D, Figure 2), conformer D is predicted to be favored when R is bulkier than R (substrates 8 and 10) because of unfavorable interaction between R and the alkene-Pd(II) unit. The sensitivity is high, leading to the 2,5-cis products with a preference of 6:1 (from 8) to 11:1 (from 10). When R is bulkier than R (9 and 11), conformation C is favored and with even a stronger preference, now producing the 2,5-trans products 18 (9:1) and 22 (> 90:1). The simple picture in Figure 2 suggests that R and the alkene-Pd(II) unit are eclipsed in conformation D, a significant repulsion when R is large.

We imagine the application of this methodology in a selective general synthesis of 2,5-disubstituted tetrahydrofurans when a removable substituent at C-3 is used to induce the desired selectivity.

Acknowledgment. We are pleased to acknowledge support in the form of a grant from the Public Health Service (NIH GM 31352). We thank Dr. D. Little for collecting the mass spectral data and Dr. D. van Engen for the X-ray diffraction structure determinations.

Supplementary Material Available: Experimental procedures, spectral data for new compounds, data tables for X-ray diffraction structure determinations, and three ORTEP diagrams (31 pages). Ordering information is given on any current masthead page.

---

Effects of Substitution on Intramolecular Alkoxypalladation Carbonylation Reactions

Michael McCormick, Robert Monahan III, Jose Soria, David Goldsmith,* and Dennis Liotta*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received June 13, 1989

Summary: Intramolecular alkoxypalladation carbonylation reactions can be efficiently carried out on a variety of alkenols, including those with trisubstituted double bonds. It is suggested that the regio- and stereochemistry of the major products of these reactions are determined by the relative energetics of various organopalladium intermediates produced during these reactions.

Sir: As part of a program aimed at the preparation of physiologically active ionophores, we required a versatile method for the stereoselective construction of some of the common subunits of naturally occurring carboxylic acid ionophores, specifically, substituted tetrahydrofurans and tetrahydropyran ionophores. In this regard we were particularly intrigued by the reports of Semmelhack and co-workers, who demonstrated that alkenols undergo efficient palladium-catalyzed cyclizations to produce these units. However, since the alkenols reported in these studies contained only a small number of substitution patterns at or around the olefinic groups, we decided to examine the scope and limitations of this process with several alkenols possessing a variety of substitution patterns. In this communication we report the results of this study (see Table I).

Intramolecular alkoxypalladation carbonylation reactions are highly regio- and stereoselective when the double bond in question is unsymmetrical. Under these circumstances the additions proceed in a strict trans, Markovnikov fashion (e.g., entries 1 and 4–6). As the double bond becomes more heavily substituted, the observed rates of the cyclization decrease to the point that, with most trisubstituted double bonds, no cyclization is observed by using standard conditions (i.e., 0.05–0.20 equiv of PdCl₂, 3.00 equiv of CuCl₂, methanol, carbon monoxide atmosphere). However, addition of 0.1–0.2 equiv of triethylamine results in a substantial increase in the rates of cyclization, perhaps by converting the olefin-palladium chloride complex from a chloro-bridged dimer to an olefin-palladium–amine monomer. Whatever the underlying cause, this observation substantially extends the scope

---

(1) For a review of this subject, see: Boivin, T. L. Tetrahedron 1987, 43, 3209.
(4) A general experimental procedure is provided in the supplementary material. All products were fully characterized by using standard spectroscopic techniques. Product regio- and stereochemistries were unequivocally assigned by exhaustive NOE studies and by 3¹C NMR chemical shift correlations.
of these palladium-catalyzed cyclizations.

In substrates possessing 1,2-disubstituted olefins where there is a possibility of forming either five- or six-membered ring products, the olefin geometry exerts a substantial influence on the product distribution. In accord with previous findings, (E)-olefins (e.g., entry 7) give tetrahydropyrans and (Z)-olefins (e.g., entries 2, 3, 8, and 9) lead to tetrahydrofurans as the major reaction products.

Semmelhack and Bodurow have proposed that these reactions proceed via transition states arising from conformations that minimize nonbonded interactions. In arrangements such as these, the presence of a (Z)-alkyl substituent results in a substantial conformational bias in favor of the conformers depicted as A in Scheme I. In general, the formation of the cyclic ether products should be geometrically much more feasible from A-type chairlike conformations than from the B type. In the B-type conformations for the formation of the five-membered ring products, an unfavorable interaction occurs between the methyl group and the developing olefin–palladium substituent compared to the "trans" arrangement for these groups in the A conformation. Most of the cyclization data reported here and elsewhere may be rationalized by using these conformational arguments. Also consistent with this hypothesis is the observation that 5 and 19 cyclized at a significantly slower rate than did 3 and 17 (26 h for 5, 7 h for 3, 52 h for 19, 18 h for 17), presumably because in the cyclizations of 5 and 19 unfavorable steric interactions exist between the pseudoaxial substituent on the carbinol carbon and the olefinic (Z)-alkyl group (i.e., R₁ and R₂ in the A' conformation).

One of the most striking features of these palladium-catalyzed cyclizations is illustrated by the following example. Alkenol 1 (Scheme II) exhibits very low stereoselectivity in electrophile-induced cyclizations, yet it undergoes a highly stereoselective intramolecular alkoxy-palladation carbonylation reaction (i.e., 2 is the only observed product). In general, electrophile-induced cyclizations are most readily understood in the context of kinetically controlled processes. Since little, if any, conformational bias is expected for 1, we wondered if the regioselectivity and stereoselectivity of these palladium-catalyzed reactions, although seemingly consistent with kinetic rationales, might actually be the result of thermodynamic control.

As one probe of this hypothesis, we performed a thorough molecular mechanics conformational search of each of the possible products derived from several of the cyclizations shown in Table I to determine the global minimum of each. The energy differences in favor of the observed products are only of the order of 1.2 kcal/mol, a difference insufficient to account for the high selectivity. In addition, the unobserved tetrahydropyrans were found to have the lowest steric energies. We therefore conclude that the relative energies of the possible isomers cannot be the determining factor for the observed stereocontrol.

The explanation of the stereoselectivity exhibited in the alkoxy-palladation cyclization reactions most likely hinges on the relative steric demands of reversibly formed palladium intermediates. A full understanding of the steric course of these reactions must await a thorough mechanistic study. We have demonstrated, however, that intramolecular alkoxy-palladation carbonylation reactions can be efficiently carried out on a variety of alkenols, including

---

(8) Molecular modeling studies were performed using version 2.94 of MODEL (K. Steliou/W. C. Still).
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.

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

Eric C. Lund and Tom Livinghouse*1

Department of Chemistry, Montana State University, Bozeman, Montana 59717

Received June 9, 1989

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

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, Magnus2 and Schore3 have revealed several topological features which govern stereoselection in the cobalt-promoted bicyclization of enynes. 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

We initiated this investigation by examining the relative influence of propargylic and allylic substituents on the stereochmical outcome of representative alkyldiene-cyclohexane annulations. In this connection, three propargylic enynes and two allylic enynes were studied.7 Cyclization of the propargylic enynes 1a–e in the presence of Cp2Zr(n-Bu)2 (–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

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.

(4) A recent account concerned with the influence of internal ligands as regiocontrol elements in Cp2(CO)2 mediated cyclizations has also appeared: Krafft, M. E. J. Org. Chem. 1988, 53, 968.
(5) Recently, RajanBabu et al. have reported the stereoselective cyclization of two 1-substituted-5-{[tert-butyldimethylsilyl]oxy}hepta-1-en-8-ynes to the corresponding 1-(silyloxy)-2-alkyldenecyclopentane derivatives via low-valent metalloenes. In these instances, the cis-alkyldiene-cyclopentane 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, 7125.
(7) The propargylic and allylic substrates utilized in this study were prepared via the addition of the requisite 1-alkylalkyne or vinylmagnesium bromide respectively to the appropriate aldehyde followed by silylation (t-BuMe2SiOTf/i-Pr2NEt, CH2Cl2, 0 °C).
(9) The direct cyclization of the propargylic alcohol 1a 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 cycloalkanols in high (70–81%) yield.

0022-3263/89/1954-4487$01.50/0 © 1989 American Chemical Society