with the picture that the substituent (Me, R_1) 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_2) 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_1 is bulkier than R_2 (substrates **8** and **10**) because of unfavorable interaction between R_1 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_2 is bulkier than R_1 (**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_2 and

the alkene–Pd(II) unit are eclipsed in conformation D, a significant repulsion when R_2 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.

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

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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 tetrahydropyrans.[1] 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.[2,3] 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, Markov-

Scheme I
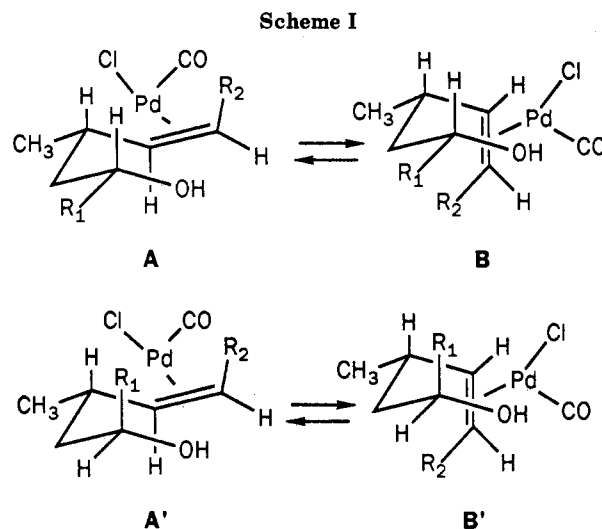
nikov fashion (e.g., entries 1 and 4–6). As the double bond becomes more heavily substituted, the observed rates of the cyclization decrease to the point that, with most trisubstituted double bonds, no cyclization is observed by using standard conditions (i.e., 0.05–0.20 equiv of PdCl$_2$, 3.00 equiv of CuCl$_2$, methanol, carbon monoxide atmosphere).[4] 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.[5] Whatever the underlying cause, this observation substantially extends the scope

(1) For a review of this subject, see: Boivin, T. L. *Tetrahedron* **1987**, *43*, 3309.

(2) (a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (b) Semmelhack, M. F.; Fewkes, E. Herndon, J. W.; Knaus, G. Le, H. T. M.; Sanner, M. *Chem. Scr.* **1985**, *25*, 131. (c) Semmelhack, M. L.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034. (d) Semmelhack, M. L.; Bozell, J. J.; Wulff, W.; Spiess, E.; Zask, A. *Ibid.* **1982**, *104*, 5850. (e) Semmelhack, M. L.; Keller, L.; Sato, T.; Spiess, E. *J. Org. Chem.* **1982**, *47*, 4382. (f) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171. (g) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.*, previous communication in this issue.

(3) See also: Holmes, C. P.; Bartlett, P. A. *J. Org. Chem.* **1989**, *54*, 98.

(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 ^{13}C NMR chemical shift correlations.

(5) Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973.
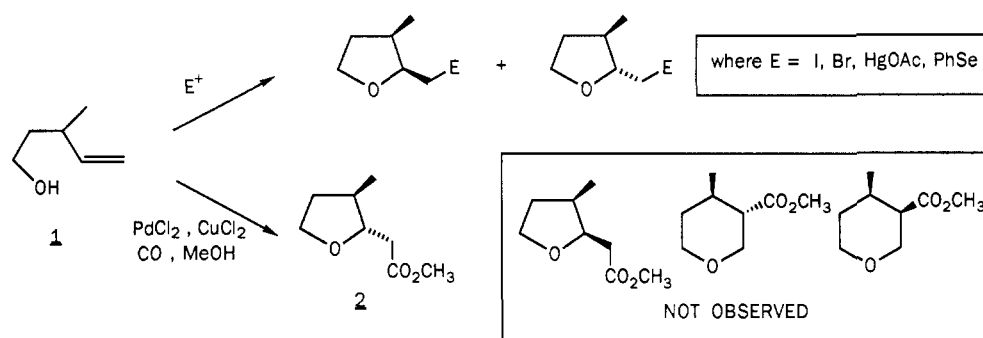
Scheme II

Table I

entry	substrate	product(s)	% yield
1			87
2			85
3			87
4			85 (3:1)
5			65
6			66
7			75 (1:4)
8			80
9			84

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.[2a] 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.[2a]

Semmelhack and Bodurow have proposed that these reactions proceed via transition states arising from conformations that minimize nonbonded interactions.[2a,g] 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.[6] 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[2] 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 rates 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., R_1 and R_2 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,[7] yet it undergoes a highly stereoselective intramolecular alkoxypalladation 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.[7] 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.[8] 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 alkoxypalladation 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 alkoxypalladation carbonylation reactions can be efficiently carried out on a variety of alkenols, including

(6) MM2 calculations indicate that in alkenols, such as **3** and **5**, the conformations in which the (Z)-methyl group approximately eclipses the allylic C–H bond is favored by at least 1.4 kcal/mol.

(7) Reitz, A.; Nortey, S. O.; Maryanoff, B. E.; Monahan, R.; Liotta, D. *J. Org. Chem.* **1987**, *52*, 4191.

(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.

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]

We initiated this investigation by examining the relative influence of propargylic and allylic substituents on the stereochemical outcome of representative alkylidene-cyclohexane 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 $Cp_2Zr(n\text{-Bu})_2$[8,9] (−78 °C, 0.5 h then 25 °C, overnight)

Scheme I
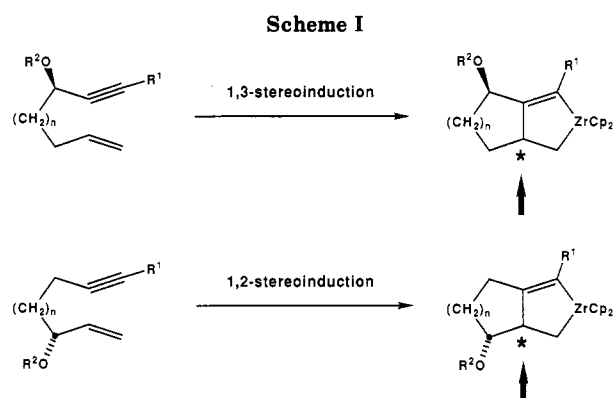
followed by protonolysis (2 equiv of AcOH, 0 °C) gave, in each case, an exclusive product as determined by capillary GC and 300-MHz ^{1}H NMR spectroscopy. The relative stereochemistry of the substituents on alkylidenecyclohexanes 2a–c prepared in this manner was assigned as trans on the basis of the 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

(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.