benzofuran acetate **6e** (28%) (entry 10). Substrate **2b** provided better generality for cyclization than **2a**, presumably due to a difference in thermal stability between the two complexes. For example, the reaction of **2b** with methyl 4,4-dimethylpentynoate (entry 11) and diphenylacetylene (entry 12) resulted in efficient benzofuran formation, while **2a** decomposed under identical conditions with the same alkynes.

Considering our earlier work on the carbene–alkyne cycloaddition with in situ protection,[2g,16] the role of $BF_3 \cdot Et_2O$, Ac_2O, and Et_3N is apparently more than that of an acetylation reagent. Presumably, it also promotes the cycloaddition. The Lewis acid would strongly coordinate to the very basic alkylthio group, which could increase the electrophilicity of the metal–carbene carbon bond, favoring CO dissociation and then alkyne coordination.[17] The synthetic utility of this reaction is illustrated is illustrated in Scheme II by formation of the key intermediate (**10**) in the synthesis of **15**. The reaction of **2b** with an alkoxyalkyne **9**[2g] under the conditions described above provided the benzofuran acetate **10** in 33% yield. During this process, the (trimethylsilyl)oxy group was eliminated, producing an olefin. Direct conversion of the acetate to the methyl ether was effected with NaH and methyl iodide in THF (**11**, 75%).[18] The Wacker procedure [$PdCl_2$, Cu_2Cl_2, DMF, H_2O, O_2 gas, 25 °C][19] converted the olefin to the ketone **12** in 75% yield. Selective cleavage of the ethyl ether [$BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C to 25 °C; **13**, 70%],[2g] followed by a Claisen-type condensation [EtOAc, NaH, THF, reflux, 5 h] and acid treatment [1 N, HCl, MeOH, 25 °C],[2g,8] produced the furochromane **14** in 56% overall yield. Treatment of **14** with Raney Ni [absolute EtOH] replaced the methylthio group with hydrogen, generating visnagan (**15**)[20] in 60% yield.

In summary, we have demonstrated the first use of [(alkylthio)arylcarbene]chromium complexes for the alkynecarbene cycloaddition to form the 1,4-dihydrothioquinones. The application of the process to the synthesis of visnagan illustrates the potential utility of the reaction of sulfur-substituted carbene complexes with alkynes in organic synthesis.

Supplementary Material Available: Characterization data (^1H NMR, IR, mass spectra, and combustion analyses) on all new compounds and X-ray crystallographic data for compound **7** (12 pages). Ordering information is given on any current masthead page.

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[16] Yamashita, A.; Scahill, T. A.; Toy, A. *Tetrahedron Lett.* **1985**, *26*, 2969.

[17] (a) Alternatively, the Lewis acid may coordinate to CO ligands to remove electron density from the metal–carbene ligand center, favoring CO dissociation. This is the case in the literature where there are no strong Lewis bases available to the acid. (i) Nolan, S. P.; de la Vega, R. L.; Hoff, C. D. *J. Am. Chem. Soc.* **1986**, *108*, 7852. (ii) Waymouth, R. M.; Grubbs, R. H. *Organometallics* **1988**, *7*, 1631. Increasing electron density on the metal center could intercept carbon monoxide insertion: Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915. (b) Treatment of pentacarbonyl(methyl- or phenylmethoxycarbene)chromium (or molybdenum, tungsten) with boron trihalides in alkanes is known to afford thermolabile trans halogen methyl- or phenylcarbyne tetracarbonyl complexes of chromium (or Mo, W). (i) Fischer, E. O.; Kreis, G.; Kreiter, C. G.; Muller, J.; Huttner, G.; Lorenz, H. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 564. (ii) Fischer, E. O.; Kreis, G.; Kreissl, F. R.; Kalbfuus, W.; Winkler, E. *J. Organomet. Chem.* **1974**, *65*, C53–C56. However, the carbyne formation from the methylthio-substituted carbene complex with Lewis acid is not known. Since the products from the reaction of **2a** and **2b** with alkynes did not loose the methylthio group, the carbyne formation from **2a,b** with Lewis acid can be eliminated. The role of the Lewis acid, combined with Ac_2O and Et_2N seems to be coordination to the basic sulfur and/or the weakly basic CO groups.

[18] Yamashita, A.; Toy, A. *Synth. Commun.* **1989**, *19*, 755.

[19] Tsuji, J.; Nagashima, H.; Sato, K. *Tetrahedron Lett.* **1982**, *23*, 3085.

[20] MP 145 °C (undepressed on admixture with a natural specimen, mp 140–142 °C). The physical behavior of the product was the same as that of the authentic sample (purchased from Aldrich Co.).

[21] Satisfactory spectral data (high resolution mass, IR and ^1H NMR) were obtained for all new compounds, **2a**, **3a**, **3b**, **5a–e**, **6a–f**, **7**, **8**, **10**, **11**, **12**, **13**, **14**, **15**, and **16**. Combustion analyses were obtained for **5a–e**, **6a–f**, **7**, **8**, **10**, **11**, **12**, **13**, **14**, and **15**. These data are recorded as supplementary material. The X-ray crystallographic data for compound **7** were submitted to *Acta Crystallographr.* for publication.

Stereoselective Formation of Tetrahydrofuran Rings via Intramolecular Alkoxycarbonylation of Hydroxyalkenes

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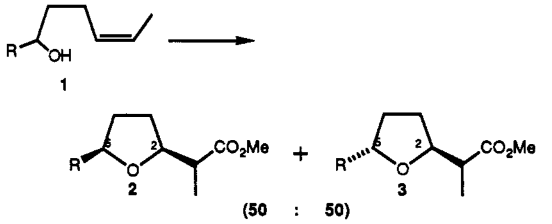
Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received May 30, 1989

Summary: Starting from 5-hydroxy-1-pentenes, palladium-catalyzed intramolecular alkoxycarbonylation produces 2,5-disubstituted tetrahydrofurans in good yield. In the simplest cases, mixtures of cis- and trans-2,5-substitution are obtained. With a methyl group at C-4, the mixture is 1:1 or 2:1 depending on the relative configuration of the Me. With a methyl or phenyl group at C-3, the selectivity is much higher, producing either cis-2,5- or trans-2,5-disubstituted furans in >9:1 selectivity. In the best case, with a 3-phenyl derivative, the selectivity is >99%. The formation of cis or trans isomers depends on the configuration at C-3 in a predictible way.

Sir: Methods of preparation of substituted oxygen heterocycles have attracted attention since furan and pyran rings appear frequently in polyether antibiotics and other biologically active natural products.[1] Tetrahydrofurans bearing 2,5-substituents have been synthesized stereoselectively in some cases, but there are few completely satisfactory general methods.[1,2] We have been attracted to a palladium-catalyzed cyclization process for hydroxyalkenes with concomitant chain extension with CO (alkoxycarbonylation).[3,4] The process (eq 1) is efficient for



(eq 1)

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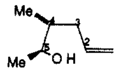
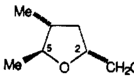
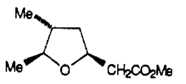
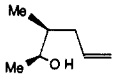
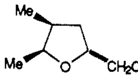
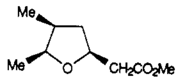
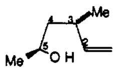
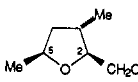
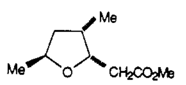
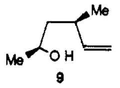
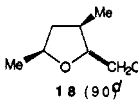
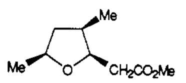
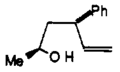
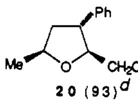
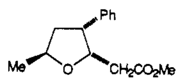
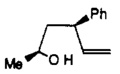
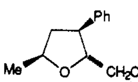
[1] For a review, see: Boivin, T. L. *Tetrahedron* **1987**, *43*, 3309.

[2] For a recent successful example and leading references, see: Mulholland, R. L., Jr.; Chamberlin, A. R. *J. Org. Chem.* **1988**, *53*, 1082.

[3] For a review of palladium-promoted nucleophile addition to alkenes, including oxygen nucleophiles, see: Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415.

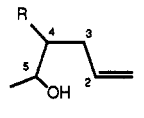
0022-3263/89/1954-4483$01.50/0

Table I. Cyclizations of Hydroxyalkenes with Pd(II) and CO

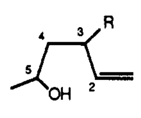
entry	reactant alcohol	yield,[a] %	product(s) (% of total)[b]	
1	 6	85%	 12 (50)	 13 (50)
2	 7	87%	 14 (62)[c]	 15 (38)
3	 8	88%	 16 (87)[c]	 17 (13)
4	 9	90%	 18 (90)[d]	 19 (10)
5	 10	73%	 20 (93)[d]	 21 (7)
6	 11	76%	 22 (100)[d]	

[a] The yield is based on the weight of a distilled sample before separation of diastereoisomers. [b] The ratio is based on integration of the ^{1}H NMR signal at ca. δ 4.0 ppm due to the H at C-5. [c] The assignment of configuration is based on ^{1}H NMR analysis.[6] [d] The structural assignment is based on an X-ray diffraction study of the corresponding acids prepared by hydrolysis.

tetrahydropyrans[3,4c–f] and tetrahydrofurans.[4a,b] While 2,6-disubstituted tetrahydropyrans are formed with a strong preference for the cis arrangement,[5] in the several examples of tetrahydrofuran formation, mixtures of cis and trans 2,5-disubstituted products (e.g., 2 and 3) are produced.[4a,b] The results are rationalized based on steric interactions in the appropriate reactant conformations.[4a,b] We have been interested in influencing the stereoselectivity in tetrahydrofuran formation by introducing substituents in the alkoxyalkene chain (in 4 and 5). In this paper we report examples which point to a strong and useful effect, allowing highly selective formation of cis or trans 2,5-disubstituted tetrahydrofurans.



4



5

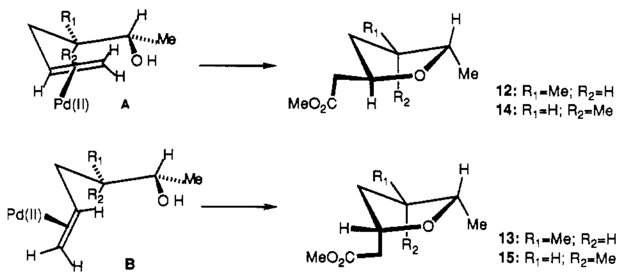


Figure 1. Reactant conformations of 4-substituted hydroxyalkenes.

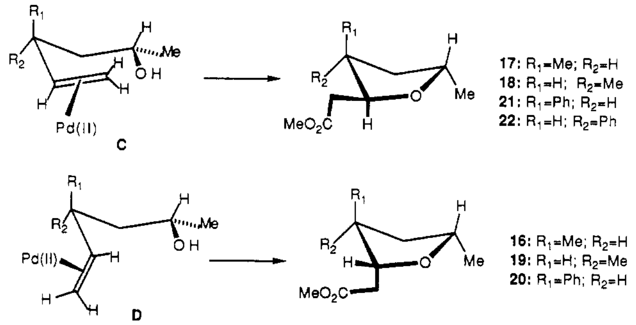


Figure 2. Reactant conformations of 3-substituted hydroxyalkenes.

Table I displays the results with a series of racemic substrates 6–11 which were chosen to compare the dependence on position (6/7 vs 8/9), configuration (6 vs 7, etc.), and substituent size (Me vs Ph) on the selectivity in the formation of products 12–22.[6-8]

Entries 1 and 2 allow the conclusion that a substituent at C-4 has a small effect on the selectivity. A stronger effect is seen for the methyl group at C-3 (8/9) and amplified with the larger substituent in 10/11. There is a parallel trend within each pair of diastereoisomeric hydroxy alkenes (9 > 8; 11 > 10). With position, configuration, and size effects reinforcing (entry 6), the process gives >99% the 2,5-trans isomer. The other configuration of the directing substituent also leads to highly selective cyclization (entry 5), giving the 2,5-cis isomer in >11:1 preference.

The selectivity can be rationalized in a simple way from conformations (A and B, Figure 1) of the intermediate palladium(II) complex.[4a,b] It is assumed that transition states arising from conformations with minimum nonbonded interactions are more favored. As shown in Figure 1, two reactant conformations might be written starting with compound 6 (R_1 = Me; R_2 = H) or 7 (R_1 = H; R_2 = Me). The equimolar mixture arising from 6 is consistent

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(4) (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.* (Nobel Symposium) **1985**, *25*, 131. (c) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034. (d) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *Ibid.* **1982**, *104*, 5850. (e) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. *J. Org. Chem.* **1982**, *47*, 4382. (f) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, 3171.

(5) For efforts to influence the configuration of the products in tetrahydropyran formation, see: Holmes, C. P.; Bartlett, P. A. *J. Org. Chem.* **1989**, *54*, 98.

(6) **General Procedure.** A mixture of hydroxyalkene (1.00 mmol), cupric chloride (2.20 mmol) and palladium bis(acetonitrile) dichloride (0.10 mmol; 0.40 mmol for entries 5 and 6) in 3 mL of methyl alcohol under 1.1 atm of CO was stirred at 23 °C until TLC showed the reaction was complete (3.5 h for entries 1–4; 10 h for entries 5 and 6). After removal of the methyl alcohol, the residue was triturated with pentane (ethyl acetate for entries 5 and 6), and the pentane solution was concentrated to give the crude organic products. Short-path vacuum distillation provided a colorless liquid. For further characterization data, see the supplementary material. In addition to the X-ray diffraction studies confirming the structures of **18**, **20**, and **22**, a correlation was established for the ^{1}H NMR chemical shifts of the H at C-5. The signal appears 0.1–0.2 ppm more downfield when the proton is cis to the acetic ester side chain.

(7) Compounds 6 and 7 were previously reported: Felkin, H.; Claude, F.; Roussi, G. *Bull. Chim. Fr.* **1970**, 3704. We used a general procedure: Linstrumelle, G.; Lorne, R.; Dang, H. P. *Tetrahedron Lett.* **1978**, 4069.

(8) Compounds 8 and 9 were prepared as a mixture as reported by Hill, E. A.; Myers, M. M. *J. Organomet. Chem.* **1979**, *173*, 1. The isomers were then separated by preparative GC. Compounds 10 and 11 were prepared in the same way, starting from cinnamyl chloride, separated by preparative GC, and fully characterized. The relative configurations were assigned by reasoning backwards from the confirmed (X-ray) structures.

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.

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

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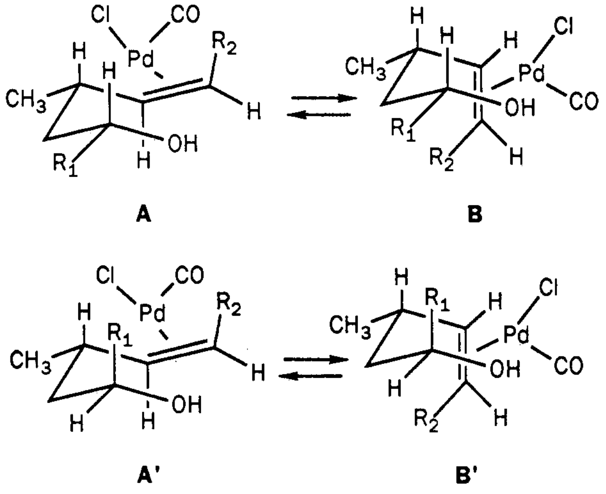
Department of Chemistry, Emory University, Atlanta, Georgia 30322

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 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).

Scheme 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 $PdCl_2$, 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

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(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.

0022-3263/89/1954-4485$01.50/0