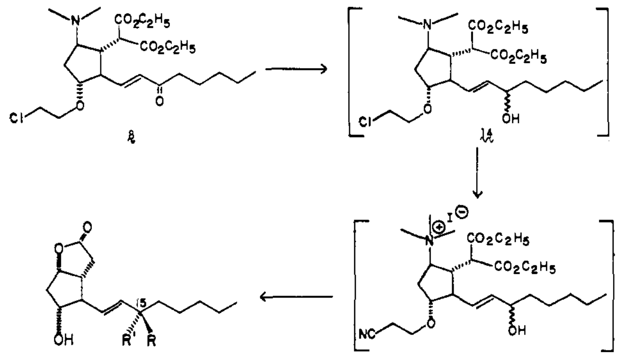
excess borohydride and lithium alkoxide were quenched by the addition of acetone and ammonium carbonate, and solvent was removed under reduced pressure and replaced with deoxygenated DMF. To this solution was added sodium cyanide (2.0 mol equiv) in DMF and the mixture was warmed to 75 °C for 18 h to allow conversion of chloride to nitrile. The solution was cooled to room temperature and excess methyl iodide was introduced to produce quaternary salt **15.** Volatile material (methyl iodide, acetonitrile) was removed under reduced pressure and decyanoethylation, hydrolysis, decarboxylation, and lactonization were accomplished through the action of aqueous potassium hydroxide in the same manner as previously described for the **5** → **6** conversion. Extraction from dilute acid afforded, after preparative layer chromatography, the racemic lactone diol **7**[18] along with an approximately equal portion of **7a,** epimeric at C-15, in 75–80% combined yield from enone **8.**



As previously stated, **7** has been converted to a variety of natural prostaglandins in high yield, and synthesis of this material thereby constitutes a synthesis of the natural products. We believe that this synthesis is the simplest and most efficient reported to date, affording **7** in ~35% overall yield in four chemical steps from cyclopentadiene.

Two obstacles remain to be overcome. At this time synthetic **7** consists of a racemic mixture of diastereomers. Although the C-15 epimers are separable by chromatography, and it has previously been established that 15-epi material may be recycled by oxidation-reduction,[19] we find this to be an aesthetically unpalatable procedure. Although we have not yet conducted experiments in this area, we believe that it may be possible to direct the reduction of **8** to the desired isomer[20] by varying either the alkyl portions of the ester or the protecting group attached to the hydroxyl at C-11. Secondly, it should be noted that preparation of optically active materials should present no great difficulty. We believe that resolution of the very inexpensive amine **3** will prove to be an extremely simple task, and from this point no further resolution should be necessary.

A unique feature of this synthesis is the unambiguous establishment of four contiguous stereocenters about a cyclopentane ring from a single amino directing functionality. This sequence of reactions firmly establishes that carbopalladation and alkoxypalladation occur via stereospecific trans addition to the olefinic linkage, and that ketovinylation proceeds with *retention* of configuration of the migrating group attached to palladium. We believe that the principles delineated herein will prove invaluable to organic synthesis; further studies involving carbopalladation and natural product synthesis are in progress.

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(7) Correct exact mass data have been obtained for this compound.

(8) Yields refer to spectrally homogeneous material of >95% purity.

(9) Despite the fact that the reactions described here are not catalytic with respect to palladium, it should be pointed out that palladium may be easily recovered from each of these reactions by simple filtration through Celite and subsequently recycled.

(10) Identified by comparison (TLC, GC, IR, NMR, mass spectrum) with an authentic sample prepared by hydrogenation (H_2, 5% Pd/C, ethyl acetate) of unsaturated lactone i, kindly supplied by Mr. R. J. Pariza.

1

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(12) Stereochemistry of ketovinylation was predicted to be the same as that of carbonylation; see L. F. Hines and J. K. Stille, *J. Am. Chem. Soc.*, **94**, 485 (1972).

(13) Conveniently prepared from 1,3-diethoxypropene and *n*-pentyl bromide: R. A. Holton, manuscript in preparation.

(14) Ketovinylation of monocyclic complexes similar to **4** requires refluxing benzene or toluene; see ref 4. Presumably the strain inherent in **12** is responsible for this remarkably facile ketovinylation.

(15) Although **8** was a single isomer, unambiguous assignment of stereochemistry at this stage was not possible. The assigned stereochemistry of **8** rests on its ultimate conversion to **7.**

(16) In our hands, neither zinc borohydride (DME, 25 °C) nor sodium borohydride (C_2H_5OH, −78 °C) gave satisfactorily clean 1,2 reduction of **8.**

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(18) Identical (IR, TLC, NMR, mass spectrum) with an authentic sample kindly supplied by Dr. G. L. Bundy, Upjohn Co. We thank Dr. Bundy and Upjohn for their generosity.

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(20) For an elegant solution to this problem, see E. J. Corey, K. B. Becker, and R. K. Varma, *J. Am. Chem. Soc.*, **94**, 8616 (1972).

(21) Du Pont Assistant Professor of Chemistry.

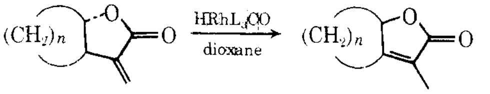
Robert A. Holton[21]
R. B. Wetherill Laboratory of Chemistry
Purdue University, West Lafayette, Indiana 47907
Received July 18, 1977

Mechanism of the Palladium-Catalyzed Synthesis of α-Methylene Lactones from Carbon Monoxide and Acetylenic Alcohols

Sir:

We have found that our palladium-catalyzed synthesis of α-methylene lactones[1] proceeds with kinetic control of the double-bond location, we have proposed a mechanism to explain this and other observations, and we have demonstrated its feasibility by isolating and interconverting the proposed organopalladium intermediates in complexes containing stabilizing ligands.

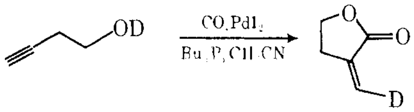
Although the isomerization of the double bond of damsin during its attempted hydrogenation[2] showed the thermodynamic instability of some α-methylene lactones, we required knowledge of the position of such isomerization equilibria, if established, for the products of our catalytic reactions. We have thus treated the simple fused-ring lactones **1a** and **1b** with $HRh(Ph_3P)_3CO$, known to be an excellent double-bond isomerization catalyst (eq 1).[3] In both cases isomerization to the corresponding butenolides **2a**[4] and **2b** is complete.[5] It is thus apparent that an effective double-bond isomerization



1a, $n = 4$ **b**, $n = 5$ **2a**, $n = 4$ **b**, $n = 5$ (1)

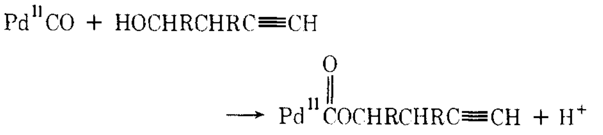
catalyst must *not* be present during the catalytic synthesis of **1a** and **1b** from CO and the corresponding ethynyl alcohols; i.e., the invariably exo position of the double bond results from kinetic control.

Before writing a mechanism for this reaction it is also necessary to know the origin of the two hydrogens on the *exo*-methylene group. The appropriate labeling study and kinetic studies to be mentioned below were carried out using a slightly modified (PdI_2, 1 equiv of Bu_3P, CH_3CN solvent) version of the original $PdCl_2$/thiourea/acetone catalyst system.[1] Catalytic results are comparable, but, as it remains homogeneous for many turnovers, the modified version is far better suited for mechanistic study. Its use on a deuterium-labeled substrate alcohol establishes that the labile deuterium is, stereospecifically, incorporated cis to the carbonyl in the *exo*-methylene group (eq 2).[6]



(2)

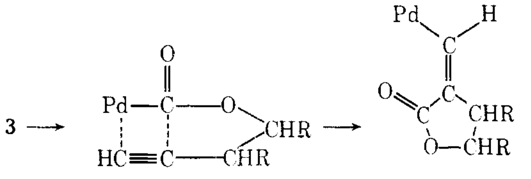
A mechanism which explains both of the preceding observations begins with nucleophilic attack by the alcohol end of a butynol on a carbonyl ligand coordinated to palladium (II) (eq 3). A carbonyl ligand coordinated to a Pd^{II} would be expected to be very susceptible to nucleophilic attack. There are numerous precedents for reactions of this sort.[7]



$$Pd^{II}CO + HOCHRCHRC{\equiv}CH \longrightarrow Pd^{II}\overset{\overset{\displaystyle O}{\|}}{C}OCHRCHRC{\equiv}CH + H^+ \quad (3)$$

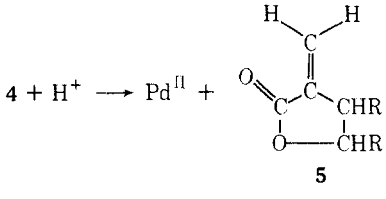
3

We propose that the carboalkoxy species **3** next adds intramolecularly to the triple bond. Numerous precedents suggest that this addition will proceed with cis stereochemistry.[8-11] Control of the direction of addition to the triple bond results, as cis addition in the direction opposite to that shown in eq 4 would form a highly strained six-membered ring containing a trans double bond.



4 (4)

Finally, cleavage of **4** with the H^+ formed in reaction 3 generates the product α-methylene lactone **5** (eq 5), and coordination of another equivalent of carbon monoxide regenerates the Pd^{II} carbonyl and returns to the beginning of the catalytic cycle (eq 6).



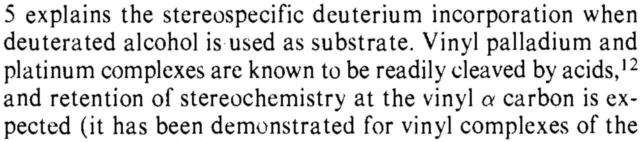
5 (5)

$$Pd^{II} + CO \longrightarrow Pd^{II}CO \quad (6)$$

This mechanism accounts for the selective synthesis of an α-methylene group and, as required, does not involve any intermediates, such as palladium hydrides, which would be expected to isomerize the double bond. Furthermore, reaction 5 explains the stereospecific deuterium incorporation when deuterated alcohol is used as substrate. Vinyl palladium and platinum complexes are known to be readily cleaved by acids,[12] and retention of stereochemistry at the vinyl α carbon is expected (it has been demonstrated for vinyl complexes of the isoelectronic Rh^{I} [13]).

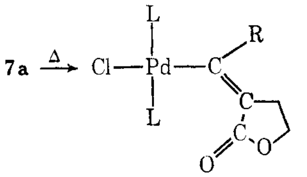
Somewhat similar mechanisms have been written by a number of workers for related palladium-catalyzed processes, e.g., by Fenton[14] for the intermolecular hydrocarboxylation of olefins and by Heck[15] for the intermolecular carboxyalkylation of acetylenes. However, there is little hard evidence to support these proposals.[16] There has, for example, been no report of the reaction of an isolable, well-characterized carboalkoxy palladium complex with an acetylene, either inter- or (as required in the present case) intramolecular.

We set out to provide such an example by making a compound analogous to the proposed mechanistic intermediate **3** under aprotic conditions so that the cleavage step, reaction 5, could not occur. We initially employed an internal acetylene, as well as bulky triphenylphosphine ligands, in order to slow down the rate of the insertion step, reaction 4. Treatment of 3-pentyn-1-ol with phosgene and addition of the resulting chloroformate **6a** to $Pd(Ph_3P)_4$ yields the expected[17,18] neutral carboalkoxy palladium complex **7a** (88%) (eq 7).[19] After a few minutes in boiling xylene, **7a** undergoes an intramolecular acetylene insertion, as in reaction 4 of the proposed mechanism, to give **8a** (50%) (eq 8).[20] Only after the addition of acid can cleavage, analogous to that in reaction 5 in the catalytic cycle, proceed, giving the known[21,22] α-[(*E*)-ethylidene]-γ-butyrolactone (**9a**, 45%) (eq 9).

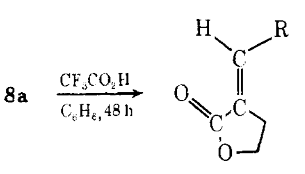


$$PdL_4 + ClCO_2CH_2CH_2C{\equiv}CR \xrightarrow[\text{toluene}\ 4\ \text{h}]{80\ ^\circ\text{C}} L{-}\underset{\underset{\displaystyle Cl}{|}}{\overset{\overset{\displaystyle CO_2CH_2CH_2C\equiv CR}{|}}{Pd}}{-}L \quad (7)$$

6a, $R = CH_3$ **7a**, $R = CH_3$



8a, $R = CH_3$ (8)



9a, $R = CH_3$ (9)

To carry out a similar sequence of reactions with R = H leading to α-methylene-γ-butyrolactone (**9b**) itself, the use of a protecting group is necessary, as the reaction of the chloroformate **6b** (R = H) of 3-butyn-1-ol with PdL_4 occurs preferentially at the triple bond. Treatment of 4-(trimethylsilyl)-3-butyn-1-ol[23] with phosgene yields the chloroformate **6c** (R = $SiMe_3$) with its triple bond protected, and **6c** adds smoothly to PdL_4 to form **7c** (R = $SiMe_3$) (87%).[24] Removal of the protecting trimethylsilyl group without disturbing the carboalkoxy palladium system is difficult (a number of standard methods fail) but can be accomplished by an adaptation of the fluoride ion method[25] (fortunately the affinity of F^- for Pd^{II} is quite low). Stirring **7c** with KF and dicyclohexyl-18-crown-6 in CH_2Cl_2 gives **7b** (R = H) and, quite rapidly at room temperature, **8b** (R = H) (60%).[26,27] Acid cleavage (CF_3CO_2H/C_6H_6) readily gives α-methylene-γ-butyrolactone (**9b**, R = H).

Complexes **7** and **8** represent stabilized, independently synthesized analogues of the proposed catalytic intermediates **3** and **4**. The fact that they react as suggested in reactions 4 and 5 strongly supports the mechanism proposed, reactions 3–6 above. Preliminary kinetic results[28] indicate that the rate, expressed in turnovers per unit time, is first order in CO pressure and independent of substrate concentration above 1 M. Under normal catalytic conditions the rate-determining step is therefore reaction 6, uptake of carbon monoxide by palladium(II).

The observation that both the insertion and the cleavage steps are much slower for the internal-acetylene-derived **7a** and **8a** than for the terminal-acetylene-derived **7b** and **8b** suggests that the catalyst system will be much more effective for the synthesis of α-methylenelactones than for α-alkylidenelactones. Work in progress generally bears out this prediction. However, conversion of appropriate actylenic alcohols to chloroformates, addition to Pd^0, insertion, and acid cleavage offer a potential two-flask stoichiometric synthesis of α-alkylidenelactones.

Acknowledgment. We thank Hoffmann-La Roche for microanalytical services and Matthey-Bishop for a generous loan of $PdCl_2$. This investigation was supported by Grant No. CA 18546 and by training grants (to T.M. and V.V.) awarded by the National Cancer Institute, DHEW.

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(6) The deuterium label in the alcohol is 69% (by integration of the NMR spectrum) incorporated into the downfield methylene proton at δ 6.2 in $CDCl_3$. The presumption that the downfield proton is cis to the lactone carbonyl is supported by our observation that it shifts 2.62 times as much as the upfield methylene proton upon addition of $Eu(fod)_3$.

(7) See, for example, J. E. Byrd and J. Halpern, *J. Am. Chem. Soc.*, **93**, 1634 (1971), and references therein.

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(19) ^1H NMR (C_6D_6): δ 1.46 (t, 3 H), 1.78 (m, 2 H), 3.20 (t, 2 H). IR: 1660, 1096 cm^{-1}.

(20) ^1H NMR (C_6D_6): δ 1.48 (m, 2 H), 1.82 (m, 3 H), 3.39 (t, 2 H). IR: 1725, 1610 cm^{-1}.

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(24) ^1H NMR ($CDCl_3$): δ 0.06 (s, 9 H), 1.72 (t, 2 H), 2.75 (t, 2 H). IR: 2180, 1665 cm^{-1}.

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(26) The use of anhydrous KF gives **8b** directly in good yield: apparently the acetylide ion resulting from the cleavage inserts rapidly and protonation by adventitious water then gives **8b**. The use of $KF{\cdot}2H_2O$ results in protonation before insertion: a 3300-cm^{-1} IR band assigned to the intermediate **7b** can be observed for a few hours, but then disappears as the bands characteristic of **8b** continue to grow.

(27) ^1H NMR of **8b** (C_6D_6): δ 1.45 (m, 2 H), 3.20 (t, 2 H), 7.32 (tt, 1 H). IR of **8b**: 1734, 1599 cm^{-1}.

(28) Kinetic data are obtained from initial rates measured by GLC sampling during the initial homogeneous phase of the reaction. Eventually turnovers per unit time decrease and palladium metal is deposited.

(29) Dreyfus Teacher-Scholar, 1976, and Sloan Fellow, 1977–1979.

Timothy F. Murray, Vijaya Varma, Jack R. Norton*[29]
Department of Chemistry, Princeton University
Princeton, New Jersey 08540
Received July 8, 1977

New Ferraboranes. Structural Analogues of Hexaborane(10) and Ferrocene. A Complex of Cyclic $B_5H_{10}^-$, a Counterpart of $C_5H_5^-$

Sir:

We report the preparation and characterization of two isomers of a new metalloborane, $(\eta^5\text{-}C_5H_5)FeB_5H_{10}$, which are isoelectronic, and in one case also isostructural, with $(\eta^5\text{-}C_5H_5)_2Fe$ (ferrocene). The reaction of anhydrous $FeCl_2$ with $Na^+C_5H_5^-$ and $Na^+B_5H_8^-$ in tetrahydrofuran at 25 °C afforded violet crystals of 2-$(\eta^5\text{-}C_5H_5)FeB_5H_{10}$ (I), whose proposed structure is shown in Figure 1. This compound was isolated in low yield as a moderately air-sensitive solid by extraction with methylene chloride followed by chromatography on a silica gel column. Large quantities of ferrocene and small amounts of other ferraboranes, currently under investigation, were also obtained. The fact that I is the major ferraborane product is in sharp contrast with the reaction of $CoCl_2$, $Na^+C_5H_5^-$, and $Na^+B_5H_8^-$ which generated a host of three- and four-boron metalloboranes but gave no detectable five-boron products.[1]

The characterization of I was accomplished from its electron-impact mass spectrum, which exhibited a parent ion with the major cutoff at *m/e* 186, the chemical ionization mass

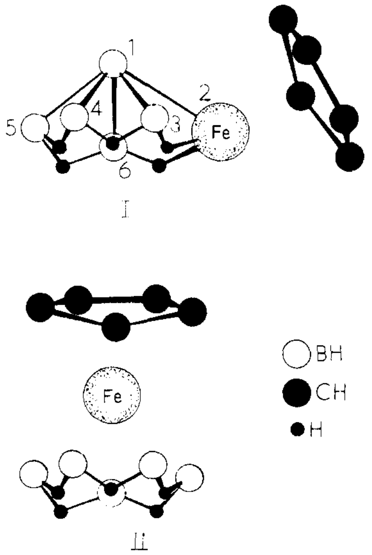

Figure 1. Proposed structures of 2-$(\eta^5\text{-}C_5H_5)FeB_5H_{10}$ (I) and 1-$(\eta^5\text{-}C_5H_5)FeB_5H_{10}$ (II). Connecting lines between iron and boron are omitted in II to emphasize the sandwichlike arrangement of ligands.