Palladium-Catalyzed Oxidative Cyclization of 1,5-Dienes – A Mechanistic Investigation

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Nucleophilic attack of acetate ion on an olefinic bond of dichloro(η^4-*cis*-1,2-divinylcyclohexane)palladium has been shown by NMR spectroscopy to lead to a σ,π-palladium(II) complex. This complex, which is also formed from nucleophilic attack on *cis*-1,2-divinylcyclohexane in the presence of palldium(II) acetate, spontaneously undergoes migratory insertion of the remaining olefinic bond into the palladium–carbon σ bond. This is followed by β-elimination to yield (1*R**,6*S**,7*S**)-7-acetoxy-9-methylenebicyclo[4.3.0]nonane together with some rearranged products. The insertion has been shown to be favored by acidic reaction conditions.

In the presence of palladium(II) compounds, 1,5-dienes are attacked by nucleophiles such as alkoxide ions,[1] carbanions,[2] amines[2b,3] and carboxylates,[3a,4] to yield σ,π-palladium(II) complexes, which in turn may be reduced,[1b,2,4] oxidized,[5] or treated either with carbon monoxide followed by methanol[6] or with base[2a] to yield organic derivatives.

We have recently found that a variety of 1,5-dienes undergo oxidative cyclization to yield acetoxymethylenecyclopentanes,[7] the reaction being catalyzed by the palladium(0) reoxidation system $Pd(OAc)_2/MnO_2$/*p*-benzoquinone with acetic acid as the solvent. This is of great synthetic interest,[8] particularly since asymmetric induction has proved possible,[9] enabling the preparation of a variety of substituted and annelated cyclopentanes.

In a previous investigation, we have demonstrated that palladium diene complexes are likely intermediates in these cyclizations.[10] It was shown that the olefinic bond of the complex is attacked by acetate ion from the side opposite palladium; however, the expected σ,π-complex was thought to be too reactive to be isolated. The regiochemistry of the reaction was shown to be governed by the conformation of the diene complexes, slight differences in coordination to the metal atom causing different reactivities of the two olefinic bonds. It was thus possible to explain the sometimes high stereoselectivity observed.

Provided nucleophilic addition proceeds to yield a σ,π-palladium complex, our oxidative cyclization differs from previously reported[1–4] palladium-catalyzed additions of nucleophiles to 1,5-dienes in that this complex is not stable under the present reaction conditions, but undergoes spontaneous insertion of the palladium–carbon σ bond into the second olefinic bond. We therefore sought to determine which factors were responsible for the formation of cyclized products and to obtain more information about the individual steps of the reaction by detecting other intermediates. The results of this mechanistic investigation are presented in this paper.

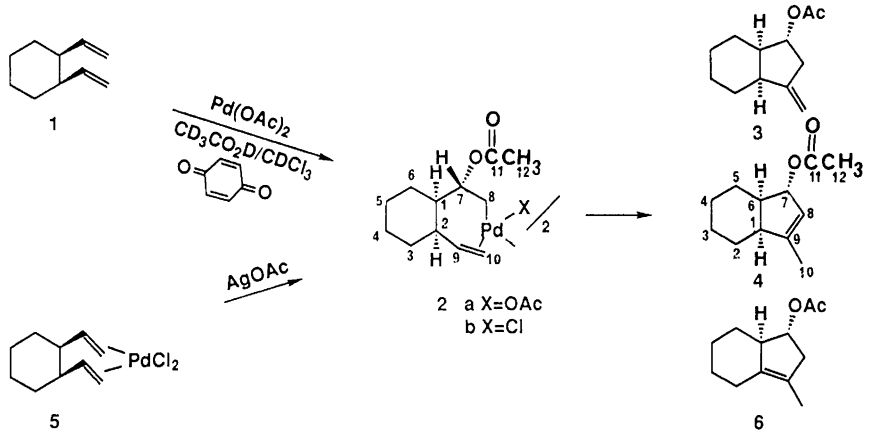
Results

The cyclization of *cis*-1,2-divinylcyclohexane (**1**) in acetic acid-d_4/chloroform-*d* (1/1 v/v*) using one equivalent of palladium acetate was followed over a period of time at 10 °C by ^{1}H NMR spectroscopy. A stack plot diagram showing the spectrum of the reaction mixture at 100 min intervals is presented in Fig. 1. This diagram shows signals (e.g. multiplets at δ 5.87 and 5.0) of gradually decreasing intensity belonging to the free diene. After only 50 min, an intermediate with absorptions at δ 5.52 (q), 4.62 (dd), 4.2 (d), 3.88 (m) and 3.45 (m) started to form and at the same time signals attributed to the product obtained from the catalytic reaction, **3** (at δ 4.95, 4.85, 2.88, 2.62 and 2.40),† and an isomer, **4** (at δ 5.43, 5.30, 2.60 and 1.74), appeared. The signals attributed to the intermediate disappeared after 14 h and, after two days at ambient temperature, the signals attributed to compound **4** disappeared, whereas **3** was stable under these conditions.

In order to simulate more closely the catalytic reaction conditions, the above reaction was performed in the presence of one equivalent of *p*-benzoquinone to give the stack plot diagram shown in Fig. 2. This change in reaction conditions did not cause any major changes in the product pattern except that compound **3** was not indefinitely stable. It is noteworthy that the peak attributed to benzoquinone

* This solvent mixture was used in place of neat acetic acid to increase the solubility of the intermediates.

† The small chemical shift differences compared with those previously reported[7] are attributed to the different medium used in this study.



(at δ 6.82) decreases as a new peak at δ 6.69 (originating from hydroquinone) increases with time.

The intermediate observed in these reactions is thought to be a σ,π-complex (**2a**), the chemical shifts being close to those expected for this structure.[11] However, owing to its rapid decomposition and low concentration, its structure proved difficult to verify.

Since a diolefin–palladium complex is most probably an intermediate in the cyclization, the reaction of acetate ion with a preformed diene complex was considered to constitute a model for the catalytic reaction. Therefore, one equivalent of silver acetate was added to dichloro(η^4-*cis*-1,2-divinylcyclohexane)palladium (**5**)[10] in dichloromethane at −50 °C, which caused the immediate precipitation of silver chloride. From this reaction, a palladium complex with a ^{1}H NMR spectrum similar to that of complex **2a** (signals at δ 5.65, 4.75, 4.45, 4.02 and 3.47 in $CDCl_3$) was isolated. It is therefore believed that this complex (**2b**) is similar to the σ,π-complex (**2a**) observed in the cyclization of diene **1**, the small chemical shift differences being due to the different bridging groups and, possibly, to the different solvents used.

Palladium–carbon σ bonds are reduced by sodium borohydride[12] to yield products containing a hydrogen atom in place of palladium. In order to verify further the structure of the assumed σ,π-complex, the product mixture obtained from **5** and silver acetate was reacted with sodium borohydride. Surprisingly, the expected reduction product[1b,2,4]

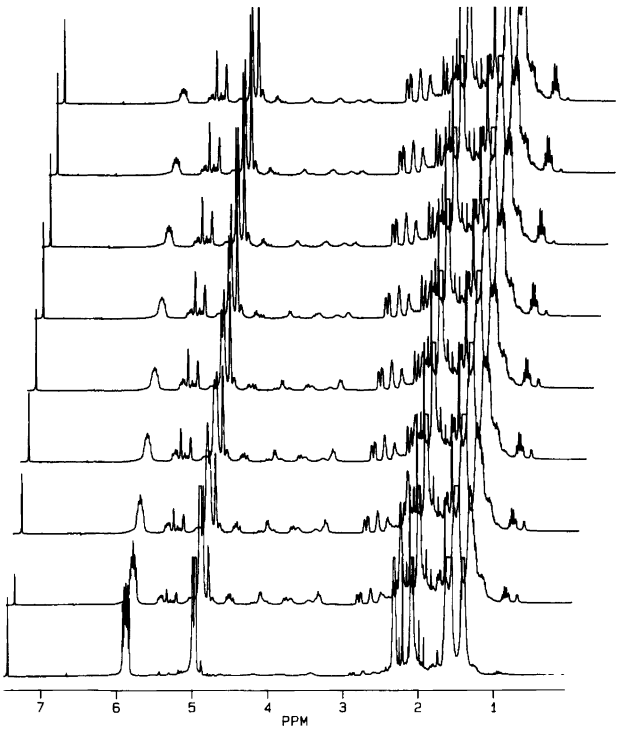


Fig. 1. ^{1}H NMR (400 MHz) spectral stack plot for the cyclization of *cis*-1,2-divinylcyclohexane using $Pd(OAc)_2$ (1 equiv.) in $CD_3COOD/CDCl_3$. Spectra were recorded at ca. 100 min intervals.

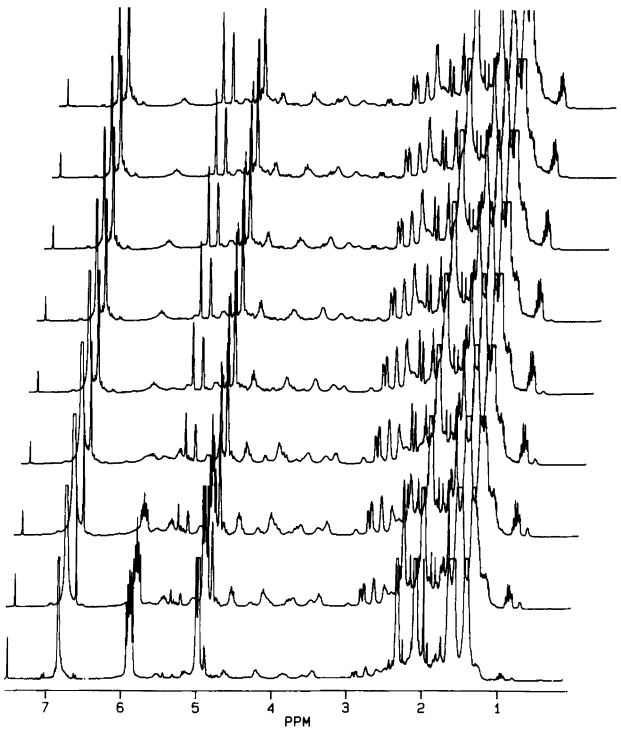


Fig. 2. ^{1}H NMR (400 MHz) spectral stack plot for the cyclization of *cis*-1,2-divinylcyclohexane in the presence of *p*-benzoquinone (1 equiv.) using $Pd(OAc)_2$ (1 equiv.) in $CD_3COOD/CDCl_3$. Spectra were recorded at ca. 100 min intervals.

was not observed; instead, cyclization followed by isomerization took place to yield the allylic acetate **4** and/or the rearranged product **6**.

In the catalytic reaction, (1*R**,6*S**,7*S**)-7-acetoxy-9-methylenebicyclo[4.3.0]nonane is formed in high yield with no sign of isomerization of the exocyclic double bond.[7] In the present investigation, however, the rearranged products (**4** and **6**) were the major products observed. The formation of **4** and **6** under stoichiometric conditions can be explained by palladium(0)-catalyzed isomerization of initially formed **3**, since such rearrangements have been observed previously in the presence of a stoichiometric amount of palladium[7] as well as under catalytic conditions using $PdCl_2/CuCl_2$ as an oxidant (yielding **6**).[13,14] That the rearrangement is caused by Pd^0 is supported by the facile rearrangement of **3** upon treatment with palladium-on-charcoal, previously activated with hydrogen, and the resistance to rearrangement in the presence of Pd^{II}, which caused no change to **3** during 20 h ($PdCl_2$ requires 1 h at 70 °C to rearrange **3** to **6**).

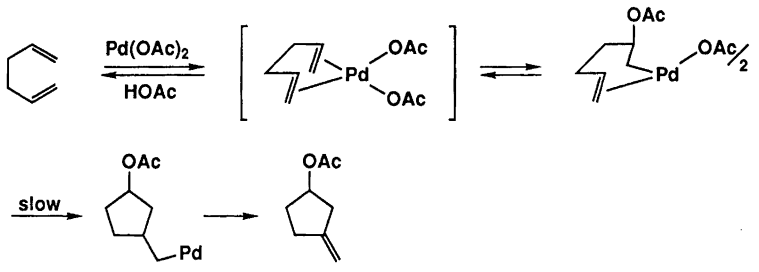
Discussion

Oxidative cyclization of 1,5-dienes using a catalytic amount of $Pd(OAc)_2$ is thought to proceed via several steps: formation of a diolefin–palladium complex, nucleophilic attack of acetate to give a σ,π-complex, insertion of the remaining double bond into the palladium–carbon σ bond and, finally, β-elimination of palladium hydride (Scheme 1).[14] Previous work has suggested that a diolefin complex is, indeed, an intermediate.[10] The results presented in this paper support this assertion since it is shown that a 1,5-diene complex is attacked by acetate ion to yield, eventually, the cyclized product observed under catalytic conditions. Prior to formation of the cyclized product, this reaction yields a thermally unstable product which was isolated and shown by NMR spectroscopy to be a σ,π-complex, similar to the short-lived intermediate observed in the NMR study of the cyclization of **1** (Figs. 1 and 2). This is the first time a σ,π-complex has been observed as an intermediate in this reaction, providing support for the mechanism shown in Scheme 1. The reaction involves *trans* Markovnikov addition of the nucleophile and the metal across one double bond to yield a σ,π-complex followed by migratory insertion. The rate-determining step is thought to be the migratory insertion, since no signs of a cyclized palladium σ-complex have been observed. Attempts to detect this intermediate using 2-methyl-1,5-hexadiene as the diene, where the methyl group is expected to prevent the final β-elimination, were also unsuccessful, yielding only recovered starting material.

The reaction under study is thus analogous to those previously reported for palladium–diene complexes,[1-4] in that a σ,π-complex is formed. The difference is that insertion of the olefinic bond into the palladium–carbon σ bond of **2** takes place readily. Analogous insertion reactions have previously been observed upon addition of phosphine or pyridine ligands to complexes obtained from norbornadiene[15] and upon photolysis.[16] In the present case, the insertion is probably facilitated by the acidic medium, as supported by the accumulation of σ,π-complex when silver acetate is used as a nucleophile in place of acetic acid. This seems reasonable since insertion of carbon monoxide is known to be accelerated by Lewis acids[17] as well as by protic acids.[18] The facile migratory insertion in this particular case is probably also due to the favorable geometry of the σ,π-complex,[19] as is evident from inspection of molecular models. The reason for the formation of **4** and/or **6**, rather than the normally observed products of reduction,[1b,2,4] upon treatment of the σ,π-complex with sodium borohydride is, however, unclear.

Reaction of metal–diene complexes with silver acetate has previously been studied in a small number of cases.[15b,20,21] With platinum, products resulting from acetate attack on an olefinic bond or monomeric diene acetate complexes were obtained.[15b] With palladium, only dimeric chloro-bridged σ,π-complexes were observed since monomeric diacetate complexes are labile. In the cases studied, these complexes, derived from *exo*-attack of acetate on the olefinic bond, were stable, migratory insertion taking place only after addition of donor ligands such as a diphosphine or pyridine.[15]

The distribution of isomers **4** and **6** obtained from cyclizations under stoichiometric conditions is difficult to explain since preliminary studies show that it is sensitive to many reaction conditions. The allylic acetate **4** is believed to be the thermodynamically stable product, as verified by molecular dynamics calculations which suggest this isomer to be the global minimum, 3.9 kJ lower in energy than isomer **6**.[22] In principle, however, it is possible that the allylic acetate is formed by a different route, involving palladium hydride-catalyzed cyclization to (1*R**,6*S**)-7-



Scheme 1.

methylbicyclo[4.3.0]non-7-ene[23] followed by palladium-catalyzed allylic oxidation.[24] The present investigation does not, however, favor this route since no trace of this hydrocarbon was observed by NMR spectroscopy.

The different product patterns obtained under different conditions illustrate the general problem with the approach of using stoichiometric models in mechanistic studies of catalytic reactions. Since the concentrations of reactive intermediates are different, side reactions absent in the catalytic reactions may well be observed in the stoichiometric model reactions. Although the different steps of the reaction under study may well be identical, conclusive evidence is often difficult to obtain. In the present case, however, we believe that the difference in product pattern is a result of the different concentrations of Pd(0), resulting in a much higher selectivity in the catalytic case.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 FT spectrometer (400 and 100.6 MHz, respectively) with Me_4Si as an internal standard. Palladium(II) acetate from Engelhardt and *cis*-1,2-divinylcyclohexane from Fluka were used as received. CH_2Cl_2 was distilled from P_2O_5 and stored over molecular sieves.

NMR tube reactions. To $Pd(OAc)_2$ (22 mg, 0.1 mmol) in a 1/1 (v/v) mixture of HOAc-d_4 and $CDCl_3$ (total vol = 1 ml) was added *cis*-1,2-divinylcyclohexane (16 µl, 0.1 mmol) at 10 °C. The NMR experiment was run at 10 °C over 14 h. The spectra consisted of 100 scans each and were obtained every 100 min. They were plotted as a 'stack plot' diagram.

A reaction, similar to that described above, was performed, except with addition of benzoquinone (11 mg, 0.1 mmol).

*Reaction of dichloro(*cis*-1,2-divinylcyclohexane)palladium with silver acetate.* To dichloro(η^4-*cis*-1,2-divinylcyclohexane)palladium[10] (48 mg, 0.15 mmol) in CH_2Cl_2 (5 ml) at −50 °C (acetone/dry ice) was added AgOAc (26 mg, 0.15 mmol). After being stirred for 2 h at the same temperature, the yellow–grey mixture was filtered at approximately 0 °C. The solid was warmed to room temperature, whereupon it changed color from grey to black, and then extracted with CH_2Cl_2 to give a light green solution. The ^{1}H NMR spectrum showed a mixture of a σ,π-complex (**2b**) and **4**, which after some days precipitated Pd(0) to give pure **4**. A small amount of **3** was observed, but that also disappeared after some days.

Compound **2b**: ^{1}H NMR ($CDCl_3$, 297 K): δ 5.65 (dd, $J_{9,10t}$ = 14.5 Hz, $J_{9,10c}$ = 8.5 Hz, 1 H, H^9), 4.75 (d, 1 H, $J_{9,10t}$ = 14.5 Hz, H^{10t}), 4.45 (d, 1 H, H^{10c}), 4.02 (dd, $J_{8a,8b}$ = 13.5 Hz, $J_{7,8a}$ = 4.0 Hz, 1 H, H^{8a}), 3.47 (m, 2 H, H^7, H^{8b}), 2.52 (m, 1 H, H^2), 2.32 (m, 1 H, H^1), 2.15 (s, 3 H, H^{12}). ^{13}C NMR ($CDCl_3$, 297 K):* δ 171.1 (1 C, C^{11}), 118.0 (1 C, C^9), 78.8 (1 C, C^7), 68.2 (1 C, C^{10}), 53.4 (1 C, C^8), 42.5, 39.3 (2 C, C^1, C^2), 25.2, 24.4, 20.7, 20.6 (4 C, C^3, C^4, C^5, C^6), 21.2 (1 C, C^{12}).

Compound **4**: ^{1}H NMR ($CDCl_3$, 297 K): δ 5.42 (m, $J_{8,10}$ = 1.5 Hz, $J_{8,7}$ = $J_{8,1}$ = 2.0 Hz, 1 H, H^8), 5.30 (m, $J_{7,10}$ = 1.5 Hz, $J_{7,8}$ = $J_{6,7}$ = 2.0 Hz, 1 H, H^7), 2.60 (m, 1 H, H^1), 2.24 (m, 1 H, H^6), 2.05 (s, 1 H, H^{12}), 1.74 (m, 1 H, H^{10}). ^{13}C NMR ($CDCl_3$, 297 K): δ 171.5 (1 C, C^{11}), 151.8 (1 C, C^9), 122.8 (1 C, C^8), 83.0 (1 C, C^7), 44.7, 43.9 (2 C, C^1, C^6), 29.7, 27.4, 25.3, 23.1 (4 C, C^2, C^3, C^4, C^5), 21.4 (1 C, C^{12}), 15.1 (1 C, C^{10}).

Reaction of the mixture **2b** *and* **4** *with* $NaBH_4$. To 12 mg of the mixture of compounds **2b** and **4** (obtained from reaction of dichloro(*cis*-1,2-divinylcyclohexane)palladium and silver acetate and containing 10.2 mg (0.03 mmol) of **2b** as deduced from NMR integration of mixture) in tetrahydrofuran (1 ml) was added $NaBH_4$ (4.2 mg, 0.11 mmol). Immediately, the green–brown solution gave a black precipitate [Pd(0)] and a clear yellow solution. The precipitate was filtered and, after 30 min, the residue extracted with hexane (yield: 8 mg). The ^{1}H NMR spectrum showed primarily rearranged product **6**.[7]

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