The Origin of Stereoselectivity in the Palladium-Catalyzed Oxidative Cyclization of 1,5-Dienes

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Dichloro\((trans\text{-}1,2\text{-divinylcyclohexane})\)palladium reacts with nucleophiles such as acetate ion, methanol, methoxide ion, chloride ion and amines to yield \(\sigma,\pi\) complexes obtained by attack at only one of the two olefinic bonds of the diene complex. The different reactivity of the olefinic groups is thought to explain the stereoselectivity observed in the palladium-catalyzed oxidative cyclization of 1,5-dienes.

Nucleophilic attack at olefinic bonds coordinated to palladium constitutes a key step in many catalytic reactions\(^1\) and has therefore stimulated extensive mechanistic\(^2\) and theoretical investigations.\(^3\) In palladium complexes of dienehins, it is of interest to study the effect of structure on the reactivity in order to explain the regiochemistry. Several examples of regioselective nucleophile addition to dienehins are known; however, in most cases, large structural differences exist.\(^4,5\) In such cases, the selectivity has been attributed to differences in strain\(^6,7\) or to in-plane coordination of one of the double bonds.\(^8\)

Previous studies have shown that oxidative cyclization, in the presence of the Pd(II)-regenerating catalyst system Pd(OAc)\(_2\)/p-benzoquinone/MnO\(_2\), of cis- and trans-1,2-divinylcyclohexane gives one stereoisomer from each reaction [eqns. (1) and (2)].\(^9\) Structural studies on the palladium diene complexes dichloro\((cis\text{-}1,2\text{-divinylcyclohexane})\)palladium have shown that the cyclohexane ring assumes a chair conformation, the cis isomer flipping while the diene is at least partially coordinated to palladium.\(^7\) For the cis derivative, we were able to demonstrate that the palladium diene complex is an intermediate in the catalytic reaction and that minor structural differences in the two olefinic groups result in different reactivities, i.e., only attack at the equatorial olefinic group in the palladium complex leads to product. For trans-1,2-divinylcyclohexane, a structural study of its palladium complex demonstrated that only one olefinic group could be attacked to give one product. It was not clear, however, whether the selectivity in both reactions originated in the nucleophilic attack, the first step shown in Scheme 1, since it is possible that two \(\sigma,\pi\)-complexes could form of which only one develops into product. This hypothesis is not unrealistic since the second step, which is the insertion of the carbon-palladium bond into the remaining double bond, has severe geometrical restrictions\(^8\) and, furthermore, has been shown to be the rate-determining step.\(^9,10\) However, since cis-1,2-

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\(\text{cis-1,2-divinylcyclohexane is prochiral, containing enantiotopic olefinic groups, nucleophilic addition to either the equatorial or axial olefinic groups in the palladium complex is expected to lead to enantiomeric } \sigma,\pi\text{-complexes, since flipping of the cyclohexane ring should occur prior to insertion, at least under conditions where insertion is slow. If this is also true under catalytic conditions, different reactivities of the } \sigma,\pi\text{-complexes can be excluded as the origin of the selectivity. That the selectivity originates in the nucleophilic attack is supported by the structural investigation of dichloro\((cis\text{-}1,2\text{-divinylcyclohexane})\)palladium which shows the metal to be closer to the equatorial olefinic bond, explaining its higher reactivity. In the } trans\text{ complex, however, the metal is equidistant to the two olefinic bonds. In this case, nucleophilic attack at the two olefinic bonds results in diastereomeric } \sigma,\pi\text{-complexes which should be distinguishable by NMR spectroscopy. Since the origin of selectivity is expected to be the same for both } cis\text{ and } trans\text{ complexes, it is the purpose of this paper to demonstrate that only one } \sigma,\pi\text{-complex is observed from nucleophilic addition to the } trans\text{ complex.}

**Results and discussion**

Reaction of dichloro\((trans\text{-}1,2\text{-divinylcyclohexane})\)pall-
Scheme 1.

Dium with silver acetate resulted in the formation of only one σ,π-complex, 1a (see Table 1 for 1H NMR chemical shifts), suggesting that the selectivity resides in the nucleophilic attack. Determination of the coupling constants (J = 11 Hz) indicates that it is this σ,π-complex which goes on to form the product observed in the catalytic reaction (2b). This is supported by the formation of an isomer of 2b after allowing 1a to stand at −5°C for 3.5 months. It is possible that the product that is observed is really an average of two σ,π-complexes which are in fast equilibrium with one another, as shown in Scheme 1. However, low-temperature NMR studies (−50°C) disfavor this possibility.

In order to test whether this selectivity for olefinic groups is general, the nucleophiles methoxide, methanol, diethylamine and butylamine were employed. (Attempts to employ these nucleophiles in the catalytic reaction failed since both methanol and diethylamine were found to attack benzoquinone.) Reaction of dichloro(trans-1,2-divinylcyclohexane)palladium with sodium methoxide was performed at −50°C, analogous to the reaction with silver acetate, to give a single σ,π-complex (1b), as determined from 1H NMR spectroscopy. Since the complex was highly unstable, it was not possible to obtain further characterization.

Reaction of dichloro(trans-1,2-divinylcyclohexane)palladium with methanol, performed at room temperature, initially showed the formation of two σ,π-complexes, one of which disappeared within minutes. Since the 1H NMR coupling pattern for the peak corresponding to the internal olefinic proton was similar in both complexes, and to that in 1a, it is believed that nucleophilic attack occurs to the same olefinic bond. (Nucleophilic attack at the other olefinic bond is expected to produce a product with a different coupling pattern.) Neither of the complexes could be the methoxy derivative 1b since no methoxy peak was observed in the 1H NMR spectrum. The complex which remained is believed to be 1c. This could form as a by-product from formation of a methoxy σ,π-complex (which, for some reason, is highly unstable), which is probably a dimer and therefore loses a chloride ion which could act as the nucleophile. This type of substitution has been observed previously in the formation of the chloro-substituted σ,π-complex derived from 5-vinyl-2-norbornene. This also explains why no chloride complex was observed initially in the reactions with silver acetate and sodium methoxide (AgCl and NaCl precipitate out of solution). After 3.5 months, however, 1a disappears and 1c is formed, along with an isomer of 2b. In this case, hydrogen chloride could form as a by-product (after β-elimination) from formation of the cyclized product (isomer of 2b). If all the hydrogen chloride that formed reacted, then the ratio 2b/1c should be one, which was indeed observed. This latter result also supports our assertion that an equilibrium may exist between two σ,π-complexes (as shown in Scheme 1, but in this case with chloride ion attacking the same olefinic group), since 1a was converted into either the cyclized product (an isomer of 2b), or 1c (i.e., 1c is not derived from 'unchanged' starting material). As to the other σ,π-complex formed in the methanol reaction, that which disappears over time, it is uncertain as to the nature of the nucleophile, but could be hydroxide ion from water contamination of the methanol.

In the reactions of dichloro(trans-1,2-divinylcyclohexane)palladium with diethylamine and butylamine, one σ,π-complex derived from attack of amine, was observed; however, in both cases, the complex (thought to be 3a and 3b, respectively) is derived from nucleophilic attack at the terminal olefinic position. This regiochemistry of amines with terminal dienes is that generally observed in palladium as well as in platinum complexes, although the

Table 1. 1H NMR chemical shifts of σ,π-complexes (ppm[J=11(Hz)]).^a

<table>
<thead>
<tr>
<th></th>
<th>H-7</th>
<th>H-8t</th>
<th>H-8c</th>
<th>H-9</th>
<th>H-10a/H-10b</th>
<th>H-2</th>
</tr>
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<tbody>
<tr>
<td>1b</td>
<td>5.35</td>
<td>4.0 [14]</td>
<td>3.7 [8.5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>5.95 [5+8+14.5]</td>
<td>4.35 [14.5]</td>
<td>4.3 [8]</td>
<td></td>
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^aCDCl3. ^Assignment uncertain. ^From reaction with NEt3H.

* It is uncertain whether chloro group is cis or trans to the olefinic group.

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formation of the imino group seems to be particular to these reactions. (Preliminary studies on the reaction of dichloro(1,5-hexadiene)palladium with diethylamine also showed the formation of an imino group, although reaction with benzylamine was found to give the expected addition product\(^4\)). Complex 1c was also observed in both reactions. Owing to the difficulty in obtaining either 3a or 3b pure of 1c, reaction of diethylamine with the cis diene complex, dichloro(cis-1,2-divinylcyclohexane)palladium, was attempted. Fortunately, no 1c formed and the imino product 4 could be isolated pure and characterized by twodimensional NMR spectroscopy. The characteristic peaks in the NMR spectra of 4 are derived from the imino group, whose \(^1\)H peak (H-10) resonates at 8.3 ppm and whose \(^1\)C peak (C-10) resonates at 172.6 ppm, values similar to what one would expect from an aldehyde. Another characteristic feature of the \(^1\)H NMR spectrum is the four different peaks for the methylene protons of the imino group, this being due to the fact that one ethyl group is cis and the other trans to the imino proton (reflected also in the presence of the two methyl resonances), as well as in the diastereotopic nature of the methylene protons. The \(^1\)H NMR spectrum remained unchanged when run at low temperature, suggesting that the cyclohexane ring does not interconvert between its two chair conformations, as observed for the palladium diene complex.\(^7\)

Although 4 was shown to decompose over time, it was stable in the presence of D\(_2\)O, in which solvent the \(^1\)H NMR spectrum showed the replacement of H-17 with D. It was also stable in the presence of acid (CF\(_3\)COOH); however, in the presence of base (K\(_2\)CO\(_3\)), H-17 was removed causing a slight shift in the peaks of the \(^1\)H NMR spectrum. Further characterization of the complex was not possible owing to its instability. In all reactions, bis(amine)PdCl\(_2\) formed, but this was easily removed by addition of CF\(_3\)COOH. Another product, the aldehyde 5, showing the characteristic peak at low field (8.7 ppm) in the \(^1\)H NMR spectrum, was observed as a minor product from reaction of the trans diene complex with diethylamine. It is believed that water (whose source is unknown) or amine, which is later replaced by water, attacks the terminal olefinic position of the diene complex. This product was removed by extraction with hexane.

The formation of complexes 3a, 3b and 4 is unclear, although it is thought to arise from \(\beta\)-elimination of the initial addition product, followed by rearrangement and oxidation. This is supported by the formation of Pd(0). Why \(\beta\)-elimination occurs in these cases and not in those reactions with amines reported earlier is uncertain.

Conclusions

From the study of dichloro(trans-1,2-divinylcyclohexane)palladium with silver acetate, we have shown that the origin of the selectivity in the oxidative cyclization reaction (2) [and probably also that in reaction (1)] is derived from the nucleophilic addition and not from the insertion. This selectivity for coordinated olefinic groups which differ only in their stereochemistry was also shown to be general for the nucleophiles chloride, diethylamine and butylamine, and probably also for methoxide, and reflects the subtle nature of chemical reactivity.

Experimental

\(^1\)H and \(^1\)C NMR spectra were run on either a Bruker AC 250 FT spectrometer (250 and 62.9 MHz) or on a Bruker AM 400 FT spectrometer (400 and 100.6 MHz). Microanalyses were performed by Micro Kemi AB, Uppsala, Sweden.

Dichloro(cis- and trans-1,2-divinylcyclohexane)palladium were prepared as previously described.\(^7\) cis- and trans-1,2-divinylcyclohexane were purchased from Fluka. Silver acetate, purchased from J. T. Baker Chemical Co., lithium chloride and methanol, purchased from Merck, and butylamine, purchased from Aldrich, were all used as received. Diethylamine, from Aldrich, was distilled over KOH. Sodium methoxide was prepared by addition of metallic sodium to methanol, followed by removal of the remaining methanol.

Toluene was distilled from sodium–benzophenone and stored over molecular sieves, hexane was fractionally distilled, and dichloromethane was distilled over P\(_2\)O\(_5\).

Reaction of dichloro(trans-1,2-divinylcyclohexane)palla-
**STEROSELECTIVITY IN CYCLIZATION**

**Reaction of dichloro(trans-1,2-divinylcyclohexane) palladium with sodium methoxide.** To dichloro(trans-1,2-divinylcyclohexane)palladium (48 mg, 0.15 mmol) in CH₂Cl₂ (5 ml) at −50°C (acetone−dry ice) was added NaOMe (10 mg, 0.19 mmol). After 2 h of stirring at same temperature, the solvent was removed and the residue was extracted with CH₂Cl₂. The solid was characterized as 1b by ¹H NMR spectroscopy. ¹H NMR (CDCl₃−TMS, 250 MHz, 297 K): δ 5.35 (m, 1 H, H-7), 4.0 (d, J = 14 Hz, 1 H, H-8) 3.7 (d, J = 8.5 Hz, 1 H, H-8c), 3.35 (s, 3 H, H-11) 3.1 (d, J = 10.5 Hz, J = 3.5 Hz, 1 H), 2.0−0.9 (m).

**Reaction of dichloro(trans-1,2-divinylcyclohexane)palladium with methanol.** Dichloro(trans-1,2-divinylcyclohexane)palladium (48 mg, 0.15 mmol) was dissolved in MeOH (5 ml) and left stirring for 45 min. The methanol was removed and the orange residue was extracted with CH₂Cl₂. The product, initially obtained as a mixture with another α, π-complex which later disappeared (see the text), was characterized as 1c by ¹H NMR spectroscopy. (This reaction was also run in MeOH-d₆ and followed by ¹H NMR spectroscopy). ¹H NMR (CDCl₃−TMS, 250 MHz, 287 K): δ 6.0 (dd, J = 5.5 Hz, J = 14.5 Hz, J = 8.5 Hz, 1 H, H-7), 4.35 (d, J = 14.5 Hz, 1 H, H-8), 4.15 (d, J = 8.5 Hz, 1 H, H-8c), 3.0 (m, 1 H), 2.0−0.9 (m).

**Reaction of dichloro(trans-1,2-divinylcyclohexane)palladium with diethylamine (1 molar equivalent).** To dichloro (trans-1,2-divinylcyclohexane)palladium (30 mg, 0.10 mmol) in CH₂Cl₂ (5 ml) was added diethylamine (10 µl, 0.10 mmol). After four days of stirring at room temperature, the solution was filtered [the precipitate being primarily Pd(0)], to leave an orange residue (yield = 22 mg).

The solid was characterized by ¹H and ¹³C NMR spectroscopy as a mixture of 1c, 3a, 5 and (NEt₃)₂PdCl₂, the last of which was prepared independently from (PhCN)PdCl₂ and two molar equivalents of NEt₃H.

**Compound 3a:** ¹H NMR (CDCl₃−TMS, 250 MHz, 297 K): δ 8.2 (d, J = 10 Hz, 1 H, H-10), 7.8 (br, 1 H, H-17), 6.2 (dd, J = 15.5 Hz, J = 15.5 Hz, J = 8.0 Hz, 1 H, H-7), 5.0 (d, J = 8.0 Hz, 1 H, H-8), 4.95 (d, J = 8.0 Hz, 1 H, H-8c), 4.6 ( sextet, J = 7 Hz, 1 H, H-13a), 3.85 ( sextet, J = 7 Hz, 1 H, H-11a), 3.65 (sextet, J = 7 Hz, 1 H, H-11b), 3.45 (s, J = 12 Hz, 1 H, H-9), 3.3 (sextet, J = 7 Hz, 1 H, H-13b), 3.2 (q, 4 H, H-15), 1.7 (t, J = 7 Hz, 3 H, H-12), 1.55 (t, J = 7 Hz, 6 H, H-16), 1.2 (t, J = 7 Hz, 3 H, H-14). ¹³C NMR [(CD₃)₂CO, 100.6 MHz, 287 K]: δ 173 (C-10), 117 (C-7), 79.5 (C-8), 54.1 (C-11), 47.2 (C-13), 46.7 (C-9), 44.3 (C-3), 43.2 (C-15), 41.3 (C-2), 27.4−25.8 (C-3, C-4, C-5, C-6), 14.5, 14.0 (C-12, C-14), 12.5 (C-16). (Assignments uncertain since peaks due to 1c are also present, but are based on those from 4). The ¹H NMR spectrum for 1c has been described previously (in reaction with methanol).

**Compound 5:** (the ¹H NMR data were taken from the reaction with two molar equivalents of diethylamine). ¹H NMR (CDCl₃−TMS, 250 MHz, 297 K): δ 9.75 (dd, J = 10 Hz, J = 4.0 Hz, 1 H, H-10), 5.55 (m, 1 H, H-7), 5.0 (m, 2 H, H-8), 2.6 (dd, J = 17 Hz, J = 4.0 Hz, J = 1.5 Hz, 1 H, H-9b), 2.1 (dd, J = 17 Hz, J = 17 Hz, J = 8.0 Hz, 1 H, H-9a), 1.8−0.9 (m). ¹³C NMR (CDCl₃−TMS, 62.9 MHz, 297 K): δ 173 (C-10), 116 (C-7), 83 (C-8) (Remaining values are uncertain).

**NET₃H₂PdCl₂:** ¹H NMR (CDCl₃−TMS, 250 MHz, 297 K): δ 5.0 (m, 2 H), 2.4 (m, 2 H), 1.6 (t, 6 H). ¹³C NMR [(CD₃)₂CO, 100.6 MHz, 297 K]: δ 50.0, 48.4, 15.1, 14.9.

**Reaction of dichloro(trans-1,2-divinylcyclohexane)palladium with diethylamine (2 molar equivalent).** To dichloro (trans-1,2-divinylcyclohexane)palladium (30 mg, 0.10 mmol) in CH₂Cl₂ (5 ml) was added diethylamine (20 µl, 0.20 mmol). After 3 h, a ¹H NMR experiment was run which showed (NEt₃H)₂PdCl₂ and 5.

**Reaction of dichloro(trans-1,2-divinylcyclohexane)palladium with butyramine.** To a solution of dichloro (trans-1,2-divinylcyclohexane)palladium (24 mg, 0.08 mmol) in CDCl₃ (5 ml) was added butyramine (8 µl, 0.08 mmol) and the reaction was followed by ¹H NMR spectroscopy over several days. After 13 days, all starting material had disappeared, leaving a mixture of 3b, 1c and [NH₂(CH₂)₃−CH₂]₂PdCl₂, the last of which was prepared independently by reaction of (PhCN)PdCl₂ with butyramine.

**Compound 3b:** ¹H NMR (CDCl₃−TMS, 250 MHz, 297 K): δ 8.5 (m, 1 H, H-10), 6.11 (dd, J = 4.0 Hz, J = 8.5 Hz, J = 14.5 Hz, 1 H, H-7), 4.65 (d, J = 8.5 Hz, 1 H, H-8c), 4.4 (d, J = 14.5 Hz, 1 H, H-8c), 3.4 (1 H), 3.1 (1 H).

*For H-3, 'a' refers to axial and 'e' refers to equatorial.

¹H It is uncertain whether H-10 is trans to C-11 or to C-13.
$[\text{NH}_2(\text{CH}_3)\text{CH}_2]_2\text{PdCl}_2$: $^1$H NMR (CDCl$_3$-TMS, 250 MHz, 287 K): $\delta$ 3.0–2.6 (m, 4 H), 1.65 (m, 2 H), 0.9 (t, 3 H).

Reaction of dichloro(cis-1,2-divinylcyclohexane)palladium with diethylamine. To a solution of dichloro(cis-1,2-divinylcyclohexane)palladium (31 mg, 0.10 mmol) in CH$_2$Cl$_2$ (5 ml) was added diethylamine (10.35 ml, 0.10 mmol). After 29 days of stirring at room temperature, a black precipitate was filtered off to leave a yellow solution. The solvent was removed to give 4 with a smaller amount of (NEt$_2$)$_2$PdCl$_2$.

Compound 4 was characterized by $^1$H and $^{13}$C NMR spectroscopy (confirmed by DEPT, $^{1}$H–$^{1}$H COSY and $^{1}$H–$^{13}$C COSY NMR experiments). $^1$H NMR (CDCl$_3$-TMS, 250 MHz, 297 K): $\delta$ 8.35 (d, $J_{6,10} = 12$ Hz, 1 H, H-10), 8.0 (br, 1 H, H-17), 5.8 (dd, $J_{3,16} = 15$ Hz, $J_{3,8} = 8.5$ Hz, 1 H, H-7), 5.2 (d, $J_{10,8} = 15$ Hz, 1 H, H-8), 5.0 (d, $J_{16,8} = 8.5$ Hz, 1 H, H-8c), 4.7 (sextet, $J = 7$ Hz, 1 H, H-13a), 4.1 (dd, $J_{9,10} = 12$ Hz, $J_{9,9} = 10.5$ Hz, 1 H, H-9), 3.95 (sextet, $J = 7$ Hz, 1 H, H-11a), 3.7 (sextet, $J = 7$ Hz, 1 H, H-11b), 3.35 (sextet, $J = 7$ Hz, 1 H, H-13b), 3.15 (m, 4 H, H-15), 2.7 (d, $J_{9,9} = 10.5$ Hz, 1 H, H-2), 2.4, 2.0 (CH$_3$), 1.7, 1.1 (CH$_3$), 1.8, 1.2 (CH$_2$), 1.6, 1.4 (CH$_2$) (8 H, H-3, H-4, H-5, H-6), 1.6 (t, $J = 7$ Hz, 3 H, H-12), 1.4 (t, $J = 7$ Hz, 6 H, H-16), 1.2 (t, $J = 7$ Hz, 3 H, H-14). $^{13}$C NMR (CDCl$_3$-TMS, 100.6 MHz, 297 K): $\delta$ 172.6 (C-10), 118.3 (C-7), 82.0 (C-8), 54.1 (C-11), 46.7 (C-13), 45.7 (C-9), 44.6 (C-1), 42.8 (C-15), 37.5 (C-2), 28.4, 28.1, 25.2, 20.5 (C-3, C-4, C-5, C-6), 13.7, 13.0 (C-12, C-14), 11.3 (C-16).

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References


10. That the insertion is the rate-determining step has been shown previously in similar cases by product analysis [Ref. 4(a)], as well as by kinetic measurements: Evans, D. J. and Kane-Maguire, L. A. P. J. Organomet. Chem. 312 (1986) C24.


12. Compound 6 in Ref. 9.

13. It is possible that CuCl$_2$ [Heumann, A., Regler, M. and Waegell, B. Angew. Chem., Int. Ed. Engl. 18 (1979) 866 and 867; Heumann, A., Regler, M. and Waegell, B. Tetrahedron Lett. 24 (1983) 1971] could be used instead of benzoquinone as the oxidizing agent since it was found to be stable in methanol; this reaction, however, was not tried.


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